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October 14, 2019

ATTORNEY DOCKET NO.: JHU3260-8
Parent Application No.: 15/362,632
Parent Filing Date: November 28, 2016
Parent Inventors: Atul Bedi and Rajani Ravi

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Presented for filing is a new **Continuation** patent application of:

INVENTORS : Atul Bedi and Rajani Ravi

TITLE : COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

The prior application is assigned of record to **THE JOHNS HOPKINS UNIVERSITY**, by virtue of an assignment recorded by the U.S. Patent and Trademark Office on February 7, 2017 at Reel 041196, Frame 0155.

Attached are the following papers, including all those required for a filing date under 37 C.F.R. § 1.53(b):

Pages of Specification	74
Pages of Claims	3
Pages of Abstract	1
Sheets of Drawing	75
Pages of Declaration (from Parent)	2

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331323-001301

This request includes Three (3) sheets and the following:

- Application Data Sheet (9 pages); and
- Sequence Listing in .txt format entitled "JHU3260-8_ST25.txt" (459 KB).

Under 35 USC § 120, this application is a **continuation** application of U.S. Application Serial No. 15/362,632 filed November 28, 2016, now issued as U.S. patent 10,442,860; which is a divisional application of U.S. Application Serial No. 15/231,309 filed August 8, 2016, now issued as U.S. patent 9,850,306; which is a continuation application of U.S. Application Serial No. 14/645,282 filed March 11, 2015, now issued as U.S. patent 9,441,044; which is a continuation application of U.S. Application Serial No. 13/582,717 filed October 17, 2012, now issued as U.S. patent 8,993,524; which is a 35 USC § 371 National Stage application of International Application No. PCT/US2011/027317 filed March 4, 2011, now expired; which claims the benefit under 35 USC § 119(e) to U.S. Application Serial No. 61/435,671 filed January 24, 2011 and to U.S. Application Serial No. 61/311,255 filed March 5, 2010, both now expired. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

Applicant claims **SMALL ENTITY** status in the above-identified application. Pursuant to 37 CFR. § 1.27, a verified statement claiming small entity status is not required.

The filing fee is calculated as follows:

	Number Filed		Number Extra		Rate			Fee	
					Large Entity	Small Entity		Large Entity	Small Entity
Total Claims	**20**-20	=	**0**	X		$50	=		$ .00
Independent Claims	**1**-3	=	**0**	X		$230	=		$ .00
Multiple Dependent Claims Present: ____ Yes __x__ No						$410			N/A
Fee for Each Additional 66 Sheets in Excess of 133 Pages						$200			$ 200.00
					FILING FEE				$ 75.00
					SEARCH FEE				$ 330.00
					EXAM FEE				$ 380.00
					SURCHARGE FEE				$ 80.00
					TOTAL FEE				**$1,065.00**

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331323-001301

PLEASE DEFER THE PAYMENT OF THE FILING FEES. The Commissioner is hereby authorized to charge the minimal fees, if any, associated with obtaining a filing date for this application to Deposit Account 07-1896, referencing the Attorney Docket number shown above.

If this application is found to be INCOMPLETE, or if it appears that a telephone conference would helpfully advance prosecution, please telephone the undersigned at (858) 677-1456.

Please send all correspondence to: **USPTO Customer No. 100899**.

Respectfully submitted,

DLA Piper LLP (US)

October 14, 2019
Date

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LAH:ag
Enclosures

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1. Amino acid sequences of transforming growth factor beta receptor type II (TGF-β-RII) or TGF-β-RIIB or a fragment thereof:

(i) Transforming growth factor beta receptor type II (TGF-β-RII) (SEQ ID NO: 79):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQVTGI SLLPPLGVAI
SVIIIFYCYR VNRQQKLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNTE
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARLT AQCVAERFSE
LEHLDRLSGR SCSEEKIPED GSLNTTK

[Italic – Extracellular domain of Transforming growth factor beta Receptor II (TGFβ RII)]
[Underlined = TGFβ RII Extracellular domain (ECD) region that binds TGF-β)]

(ii) Transforming growth factor beta receptor type IIB (TGF-β-RIIB) (SEQ ID NO: 80):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK S**DVEMEAQKD EIICPSCNRT AHPLRHI**NND
MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
SNPDLLLVIF QVTGISLLPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
CAIILEDDRS DISSTCANNI NHNTELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH
VISWEDLRKL GSSLARGIAH LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
SLRLDPTLSV DDLANSGQVG TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR
CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
WDHDPEARLT AQCVAERFSE LEHLDRLSGR SCSEEKIPED GSLNTTK

[Italic – Extracellular domain of Transforming growth factor beta Receptor IIB (TGFβ RIIB)]
[Underlined = TGFβ RIIB Extracellular domain (ECD) region that binds TGF-β)]

2. Truncated mutants of Transforming growth factor beta Receptor II (TGF-β-RII) or TGF-β-RIIB comprising the Extracellular domain (ECD) region that binds TGF-β

(i) TGF-β R-II (ΔC terminus): TGFβ RII lacking the last 38 amino acids from the C-terminus (SEQ ID NO: 81):

MGRGLLRGLW PLHIVLWTRI ASTIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQVTGI SLLPPLGVAI
SVIIIFYCYR VNRQQKLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNTE
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC WDHDPEARL

FIG. 1A

TGF-β R-IIB (ΔC terminus): TGFβ RIIB lacking the last 38 aa from the C-terminus (SEQ ID NO: 82):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK S**DVEMEAQKD EIICPSCNRT AHPLRHI**NND*
MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
*SNPDLLLVIF Q*VTGISLLPP LGVAISVIII FYCYRVNRQQ KLSSTWETGK TRKLMEFSEH
CAIILEDDRS DISSTCANNI NHNTELLPIE LDTLVGKGRF AEVYKAKLKQ NTSEQFETVA VKI FP
YEEYASWKTE KDIFSDINLK HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH
VISWEDLRKL GSSLARGIAH LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL
SLRLDPTLSV DDLANSGQVG TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR
CNAVGEVKDY EPPFGSKVRE HPCVESMKDN VLRDRGRPEI PSFWLNHQGI QMVCETLTEC
WDHDPEARL

(ii) TGF-βR-II (Δcyt): TGFβRII lacking the kinase domain & juxtamembrane region (SEQ ID NO: 83):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST*
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
*CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQ*VTGI SLLPPLGVAI
SVIIIFYCYR VNRQQKLSS

TGF-βR-IIB (Δcyt): TGFβRIIB lacking the kinase domain & juxtamembrane region (SEQ ID NO: 84):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK S**DVEMEAQKD EIICPSCNRT AHPLRHI**NND*
MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
*SNPDLLLVIF Q*VTGISLLPP LGVAISVIII FYCYRVNRQQ KLSS

(iii) TGF-β R-II containing the N-terminus region including the extracellular domain (SEQ ID NO: 85):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST*
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQ

TGF-β R-IIB containing the N-terminus region including the extracellular domain (SEQ ID NO: 86):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK S**DVEMEAQKD EIICPSCNRT AHPLRHI**NND*
MIVTDNNGAV KFPQLCKFCD VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI
TLETVCHDPK LPYHDFILED AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT
SNPDLLLVIF Q

(iv) TGF-β R-II containing the extracellular domain that binds TGF-β (SEQ ID NO: 87):

TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP
QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS
DECNDNIIFS EEYNTSNPD

TGF-β R-IIB containing the extracellular domain that binds TGF-β (SEQ ID NO: 88):

*TIPPHVQK S**DVEMEAQKD EIICPSCNRT AHPLRHI**NND MIVTDNNGAV KFPQLCKFCD*
VRFSTCDNQK SCMSNCSITS ICEKPQEVCV AVWRKNDENI TLETVCHDPK LPYHDFILED
AASPKCIMKE KKKPGETFFM CSCSSDECND NIIFSEEYNT SNPD

(v) TGF-β R-II containing the region of the extracellular domain that binds TGF-β (SEQ ID NO: 89):

PQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD
FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

FIG. 1B

3. Kinase-deficient mutants, deletion mutants, or point mutants of Transforming growth factor beta Receptor II (TGFβ-RII) or TGFβ-RIIB or a fragment thereof which binds TGF-β

(i) Transforming growth factor beta Receptor II containing point mutations:

Amino acid sequence of TGF-β R-II (K277R) contains a point mutation in its ATP-binding site and is inactive as a kinase (SEQ ID NO: 90):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST*
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
*CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQ*VTGI SLLPPLGVAI
SVIIIFYCYR VNRQQKLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNTE
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVRIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
LEHLDRLSGR SCSEEKIPED GSLNTTK

(ii) Transforming growth factor beta Receptor II containing deletions in the amino acid sequence (deletion mutants): Transforming growth factor beta Receptor II (Δi)

TGF-β R-II (Δi2) contains a deletion of amino acids 498 to 508 and is inactive as a kinase (SEQ ID NO: 91):

MGRGLLRGLW PLHIVLWTRI AS*TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST*
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
*CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPDL LLVIFQ*VTGI SLLPPLGVAI
SVIIIFYCYR VNRQQKLSST WETGKTRKLM EFSEHCAIIL EDDRSDISST CANNINHNTE
LLPIELDTLV GKGRFAEVYK AKLKQNTSEQ FETVAVKIFP YEEYASWKTE KDIFSDINLK
HENILQFLTA EERKTELGKQ YWLITAFHAK GNLQEYLTRH VISWEDLRKL GSSLARGIAH
LHSDHTPCGR PKMPIVHRDL KSSNILVKND LTCCLCDFGL SLRLDPTLSV DDLANSGQVG
TARYMAPEVL ESRMNLENVE SFKQTDVYSM ALVLWEMTSR CNAVGEVKDY EPPFGSKVRE
HPCVESMKD**A** **S**GIQMVCETL TECWDHDPEA RLTAQCVAER FSELEHLDRL SGRSCSEEKI
PEDGSLNTTK

4. Amino acid sequences of transforming growth factor beta receptor type III (TGF-β-RIII) or or a fragment thereof.

5. Hybrid or fusion proteins containing amino acid sequences of transforming growth factor beta receptor type II (TGF-β-RII) and TGF-β-RIII.

6. Hybrid or fusion proteins containing amino acid sequences of transforming growth factor beta receptor type IIB (TGF-β-RIIB) and TGF-β-RIII.

Linker sequence used in fusion proteins (SEQ ID NO: 104):

GGGGSGGGGSGGGGS

FIG. 1C

Fusion proteins comprising Anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-HER2/neu heavy chain + TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 1):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKG
RFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST**
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSR
SGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-HER2 antibody variable region
Plain: Anti-HER2 antibody constant region
Italic: *Linker*
Bold: **TGFβRII ectodomain**

FIG. 2

Fusion proteins comprising Anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + TGFβ-RII ECD fusion amino acid sequence
(SEQ ID NO: 2):

QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSR
LSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST**
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-EGFR1 light chain amino acid sequence (SEQ ID NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region
Plain: Anti-EGFR antibody constant region
Italic: *Linker*
Bold: **TGFβRII ectodomain**

FIG. 3

Fusion proteins comprising Anti-CD20 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-CD20 heavy chain+ TGFβ-RII ECD fusion amino acid sequence
(SEQ ID NO: 3):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST**
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CD20 light chain amino acid sequence (SEQ ID NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: Anti-CD20 antibody variable region
Plain: Anti-CD20 antibody constant region
Italic: *Linker*
Bold: **TGFβRII ectodomain**

FIG. 4

Fusion proteins comprising anti-VEGF antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-VEGF heavy chain+ TGFβ-RII ECD fusion amino acid sequence
(SEQ ID NO: 4):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADFKR
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST**
CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK
CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-VEGF Light chain sequence (SEQ ID NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-VEGF antibody variable region
Plain: Anti-VEGF antibody constant region
Italic: *Linker*
Bold: **TGFβRII ectodomain**

FIG. 5

Fusion proteins comprising anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-CTLA-4 heavy chain + TGFβ-RII Extracellular domain fusion amino acid sequence (SEQ ID NO: 5):

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGK *GGGGSGGGGSGGGGS* **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CTLA-4 light chain (SEQ ID NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 antibody heavy chain variable region

Plain: Anti-CTLA-4 antibody heavy chain constant region

Italic: *Linker*

Bold: **TGFβRII ectodomain**

FIG. 6

Fusion proteins comprising IL-2, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

IL-2 + Fc + TGFβ-RII Extracellular domain (SEQ ID NO: 6):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**EEM**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFSEEYNTSNPD

TGFβ-RII Extracellular domain + Fc + IL-2 (SEQ ID NO: 7):

TIPPHVQK SVNNDMIVTD NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP
QEVCVAVWRK NDENITLETV CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS
DECNDNIIFS EEYNTSNPD *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

Bold: **TGFβRII ectodomain**
Italic: *Linker (Optional; other linker sequences)*
Plain: Fc
Underlined: IL-2 fragment
(Note: Can replace linker *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L in Fc)

FIG. 7

Fusion proteins comprising anti-CD25 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-CD25 (Daclizumab) heavy chain and TGFβ-RII Extracellular domain (SEQ ID NO: 8):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGGSGGGGS* **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: Anti-CD25 antibody

Italic: *Linker*

Bold: **TGFβRII ectodomain**

FIG. 8A

Anti-CD25 (Basiliximab) heavy chain and TGFβ-RII Extracellular domain
(SEQ ID NO: 9):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDYGY YFDFWGQGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK *GGGGSGGGGSGGGGS* **TIPPHVQK SVNNDMIVTD**
NNGAVKFPQL CKFCDVRFST CDNQKSCMSN CSITSICEKP QEVCVAVWRK NDENITLETV
CHDPKLPYHD FILEDAASPK CIMKEKKKPG ETFFMCSCSS DECNDNIIFS EEYNTSNPD

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE

Plain: Anti-CD25 antibody
Italic: *Linker*
Bold: **TGFβRII ectodomain**

FIG. 8B

Fusion proteins comprising anti-CD4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD).

Anti-CD4 heavy chain and TGFβ-RII Extracellular domain (SEQ ID NO: 10):

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRF**
STCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITLETVCHDPKLPYHDFILEDAASPKCIMK
EKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Plain: Anti-CD4 antibody (variable region – underlined)

Italic: *Linker*

Bold: **TGFβRII ectodomain**

FIG. 9

Fusion proteins comprising PD-1 Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain).

PD-1 ectodomain + Fc + TGFβRII ectodomain (SEQ ID NO: 11):

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVW
RKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYN
TSNPD

TGFβRII ectodomain + Fc + PD-1 ectodomain (SEQ ID NO: 12):

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVW
RKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYN
TSNPD *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

Underlined: PD-1 ectodomain

Italic: *Linkers*

Plain: IgG1 Fc

Bold: **TGFβRII ectodomain**

(Note: The first linker sequence *GGGGSGGGGSGGGGS* is optional and may be replaced with *EPKSCDK* SEQ ID NO: 105 or deleted)

FIG. 10

Fusion proteins comprising Transforming growth factor-beta receptor II (TGFβ-RII) ectodomain, Fc, and Receptor activator of nuclear factor–κB (RANK) Ectodomain:

TGFβRII ectodomain – Fc - RANK ectodomain (SEQ. ID. NO: 13):

TIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVW
RKNDENITLETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYN
TSNPD*GGGGSGGGGSGGGGS*THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* QI
APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain – Fc - TGFβRII ectodomain (SEQ. ID. NO: 14):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
*GGGGSGGGGSGGGGS*THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGS**TIPPHVQKS**
VNNDMIVTDNNGAVKFPQLCKFCDVRFSTCDNQKSCMSNCSITSICEKPQEVCVAVWRKNDENITL
ETVCHDPKLPYHDFILEDAASPKCIMKEKKKPGETFFMCSCSSDECNDNIIFSEEYNTSNPD

Bold: TGFβRII ectodomain

Plain: IgG1 Fc

Italics: Linker

Underlined: RANK ectodomain

(optional linker 1 may be deleted or replaced with another linker such as IEGRDMD (SEQ. ID. NO:106) or EPKSCDK (SEQ.ID. NO: 105))

FIG. 11

(i) Full-length PD-1 or fragment thereof (SEQ ID NO: 92):

1 MQIPQAPWPV VWAVLQLGWR *PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS*

61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT

121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS

181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP

241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL

Italic: PD-1 ectodomain
Underlined Italic: ligand-binding domain

(ii) PD-1 extracellular domain (ectodomain) or fragment thereof (SEQ ID NO: 93):

PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

(iii) PD-1 extracellular domain (ectodomain) ligand-binding region (SEQ ID NO: 94):

DSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQ

(iv). Mutant of PD-1 or a fragment thereof which binds Programmed Death-1 ligand [PD-L1 (B7-H1) or PD-L2 (B7-DC)]

FIG. 12

Fusion proteins comprising Anti-HER2/neu antibody and PD-1 Ectodomain.

Anti-HER2/neu heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 15):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKG
RFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV**

Anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSR
SGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-HER2/neu Variable region

Plain: Anti-HER2/neu Constant region

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 13

Fusion proteins comprising Anti-EGFR1 antibody and PD-1 Ectodomain.

Anti-EGFR heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 16):

QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSR
LSINKDNSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS**
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

Anti-EGFR light chain amino acid sequence (SEQ ID NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSG
SGTDFTLSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-EGFR Variable region

Plain: Anti-EGFR Constant region

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 14

Fusion proteins comprising Anti-CD20 antibody and PD-1 Ectodomain.

Anti-CD20 heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 17):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV**

Anti-CD20 light chain amino acid sequence (SEQ ID NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: Anti-CD20 Variable region
Plain: Anti-CD20 Constant region
Italic: *Linker*
Bold: **PD-1 ectodomain**

FIG. 15

Fusion proteins comprising Anti-VEGF antibody and PD-1 Ectodomain.

Anti-VEGF heavy chain + PD-1 ectodomain fusion amino acid sequence
(SEQ ID NO: 18):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADFKR
RFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS**
ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV

Anti-VEGF Light chain sequence (SEQ ID NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPSRFSGSG
SGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: Anti-VEGF Variable region
Plain: Anti-VEGF Constant region
Italic: *Linker*
Bold: **PD-1 ectodomain**

FIG. 16

Fusion proteins comprising anti-human CTLA-4 antibody and PD-1 Ectodomain.

Anti-(human CTLA-4) (human γ1-chain)-PD-1 ectodomain fusion protein, disulfide with human κ-chain, dimer

Anti-CTLA-4 heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 19):

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **PGWFLDSPDR**
PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG
QDCRFRVTQL PNGRDFHMSV VRARRNDSGT YLCGAISLAP KAQIKESLRA ELRVTERRAE
VPTAHPSPSP RPAGQFQTLV

Anti-CTLA-4 light chain (SEQ ID NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 Variable region

Plain: Anti-CTLA-4 Constant region

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 17

Fusion proteins comprising anti-CD25 antibody and PD-1 Ectodomain.

Anti-CD25 (Daclizumab) heavy chain and PD-1 ectodomain (SEQ ID NO: 20):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGGSGGGGS*
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNT
SESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR
RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: Anti-CD25 antibody
Italic: *Linker*
Bold: **PD-1 ectodomain**

FIG. 18A

Anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 21):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDYGY YFDFWGQGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK *GGGGSGGGGSGGGGS*
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNT
SESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRAR
RNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRPAGQFQTLV

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE

Plain: Anti-CD25 antibody

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 18B

Fusion proteins comprising IL-2, Fc, and PD-1 ectodomain.

IL-2 + Fc + PD-1 ectodomain (SEQ ID NO: 22):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

PD-1 ectodomain + Fc + IL-2 (SEQ ID NO: 23):

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

Underlined: IL-2 fragment
Italic: *Linker*
Plain: Fc
Bold: **human PD-1 ectodomain**
(Note: Can replace optional linker 1 *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 19

Fusion proteins comprising anti-CD4 antibody and PD-1 Extracellular domain

Anti-CD4 heavy chain and PD-1 Extracellular domain (SEQ ID NO: 24):

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Plain: Anti-CD4 antibody (Variable region – underlined)

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 20

Fusion proteins comprising PD-1 Ectodomain, Fc, and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ectodomain):

RANK ectodomain – Fc - PD-1 ectodomain (SEQ. ID. NO: 25):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV

PD-1 ectodomain – Fc - RANK ectodomain (SEQ. ID. NO: 26):

PGWFLDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDR
SQPGQDCRFRVTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVP
TAHPSPSPRPAGQFQTLV*GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* QI APPCTSEKHY EHLGRCCNKC
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Bold: PD-1 ectodomain

Italics: Linker (optional: may delete linker 1 or replace with IEGRDMD (SEQ. ID. NO: 106) or EPKSCDK (SEQ. ID. NO: 105))

Plain: IgG1 Fc

Underlined: RANK ectodomain

FIG. 21

Moieties that bind Receptor activator of nuclear factor–κB (RANK) ligand

(i) Full-length RANK (TNFRSF11A) or fragment thereof (SEQ. ID. NO: 95):

1 MAPRARRRRP LFALLLLCAL LARLQVAL**QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
61 TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW
121 SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
181 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPGLIILLLF ASVALVAAII FGVCYRKKGK
241 ALTANLWHWI NEACGRLSGD KESSGDSCVS THTANFGQQG ACEGVLLLTL EEKTFPEDMC
301 YPDQGGVCQG TCVGGGPYAQ GEDARMLSLV SKTEIEEDSF RQMPTEDEYM DRPSQPTDQL
361 LFLTEPGSKS TPPFSEPLEV GENDSLSQCF TGTQSTVGSE SCNCTEPLCR TDWTPMSSEN
421 YLQKEVDSGH CPHWAASPSP NWADVCTGCR NPPGEDCEPL VGSPKRGPLP QCAYGMGLPP
481 EEEASRTEAR DQPEDGADGR LPSSARAGAG SGSSPGGQSP ASGNVTGNSN STFISSGQVM
541 NFKGDIIVVY VSQTSQEGAA AAAEPMGRPV QEETLARRDS FAGNGPRFPD PCGGPEGLRE
601 PEKASRPVQE QGGAKA

Bold: RANK extracellular domain (RANK ligand-binding domain)

(ii) RANK extracellular domain (ectodomain) or fragment thereof (SEQ. ID. NO: 96):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

(iii) Peptide sequences in RANKL binding domains of RANK or peptides containing key RANKL-binding residues of RANK (SEQ. ID. NO: 97):

1 MAPRARRRRP LFALLLLCAL LARLQVAL**QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
61 TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VC*DTGKA*LVA VVAGNSTTPR RCACTAGYHW
121 S*QDCECCRRN* TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
181 RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Bold: RANK extracellular domain (RANK ligand-binding domain)
RANK peptide sequences (Underlined) and residues (Italics) involved in binding RANKL.

(iv). Mutant of RANK or a fragment thereof which binds Receptor activator of nuclear factor–κB (RANK) ligand (RANKL)

(v) Full-length Osteoprotegerin (OPG, TNFRSF11B) or fragment thereof (SEQ. ID. NO: 98):

1 MNKLLCCALV FLDISIKWTT Q**ETFPPKYLH YDEETSHQLL CDKCPPGTYL KQHCTAKWKT**
61 VCAPCPDHYY TDSWHTSDEC LYCSPVCKEL QYVKQECNRT HNRVCECKEG RYLEIEFCLK
121 HRSCPPGFGV VQAGTPERNT VCKRCPDGFF SNETSSKAPC RKHTNCSVFG LLLTQKGNAT
181 HDNICSGNSE STQKCGIDVT LCEEAFFRFA VPTKFTPNWL SVLVDNLPGT KVNAESVERI
241 KRQHSSQEQT FQLLKLWKHQ NKAQDIVKKI IQDIDLCENS VQRHIGHANL TFEQLRSLME
301 SLPGKKVGAE DIEKTIKACK PSDQILKLLS LWRIKNGDQD TLKGLMHALK HSKTYHFPKT
361 VTQSLKKTIR FLHSFTMYKL YQKLFLEMIG NQVQSVKISC L

Bold: RANK ligand-binding domain

FIG. 22

Fusion proteins comprising Anti-HER2/neu antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-HER2/neu heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 27):

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISA
DTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAA
LGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
KVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-HER2/neu light chain amino acid sequence (SEQ. ID. NO: 70):

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSRSGTDFT
LTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-HER2 antibody variable region

Plain: Anti-HER2 antibody constant region

Italics: Linker

Bold: RANK ectodomain

FIG. 23

Fusion proteins comprising Anti-EGFR1 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-EGFR1 heavy chain + RANK ECD fusion amino acid sequence (SEQ. ID. NO: 28):

QVQLKQSGPGLVQPSQSLSITCTVSGFSLTNYGVHWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSINKD
NSKSQVFFKMNSLQSNDTAIYYCARALTYYDYEFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-EGFR1 light chain amino acid sequence (SEQ. ID. NO: 71):

DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTDFT
LSINSVESEDIADYYCQQNNNWPTTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-EGFR antibody variable region
Plain: Anti-EGFR antibody constant region
Italics: Linker
Bold: RANK ectodomain

FIG. 24

Fusion proteins comprising Anti-CD20 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-CD20 heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 29):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKGKATLTA
DKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD20 light chain amino acid sequence (SEQ. ID. NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGSGTSYSL
TISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Underlined: Anti-CD20 antibody variable region

Plain: Anti-CD20 antibody constant region

Italics: Linker

Bold: RANK ectodomain

FIG. 25

Fusion proteins comprising anti-VEGF antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-VEGF heavy chain+ RANK ECD fusion amino acid sequence (SEQ. ID. NO: 30):

EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTYAADF
KRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP**
CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

Anti-VEGF Light chain sequence (SEQ. ID. NO: 73):

DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPSRFSGSGSG
TDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Underlined: Anti-VEGF antibody variable region
Plain: Anti-VEGF antibody constant region
Italics: Linker
Bold: RANK ectodomain

FIG. 26

Fusion proteins comprising anti-human CTLA-4 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-CTLA-4 heavy chain + RANK ECD fusion sequence (SEQ. ID. NO: 31):

QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYTMHWVRQA PGKGLEWVTF ISYDGNNKYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAIYYCARTG WLGPFDYWGQ GTLVTVSSAS
TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS
VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT
KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ
GNVFSCSVMH EALHNHYTQK SLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC**
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CTLA-4 light chain (SEQ. ID. NO: 74):

EIVLTQSPGT LSLSPGERAT LSCRASQSVG SSYLAWYQQK PGQAPRLLIY GAFSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIKRT VAAPSVFIFP
PSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTL
TLSKADYEKH KVYACEVTHQ GLSSPVTKSF NRGEC

Underlined: Anti-CTLA-4 antibody variable region

Plain: Anti-CTLA-4 antibody constant region

Italics: Linker

Bold: RANK ectodomain

FIG. 27

Fusion proteins comprising anti-CD25 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-CD25 and RANK ectodomain - Heavy chain (SEQ. ID. NO: 32):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC**
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD25 - Light chain (SEQ. ID. NO. 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: Anti-CD25 antibody
Italics: Linker
Bold: RANK ectodomain

FIG. 28A

Fusion proteins comprising anti-CD25 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

Anti-CD25 and RANK ectodomain - Heavy chain (SEQ. ID. NO: 33):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDYGY YFDFWGQGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC**
EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR
RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR
PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Anti-CD25 – Light chain (SEQ. ID. NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGEC

Plain: Anti-CD25 antibody
Italics: Linker
Bold: RANK ectodomain

FIG. 28B

Fusion proteins comprising IL-2, Fc, and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD).

IL2 – Fc – RANK ECD (SEQ. ID. NO: 34):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT*GGGGSGGGGSG*
*GGGS*THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC**
TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW
SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK
RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ECD – Fc – IL-2 (SEQ. ID. NO: 35):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
*GGGGSGGGGSGGGGS*THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK*GGGGSGGGGSGGGGS*APTSSSTKKTQLQLEHLLLDLQMILNGINNYKN
PKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMC
EYADETATIVEFLNRWITFCQSIISTLT

Bold: RANK ectodomain

Italics: Linker (Optional; any linker sequence)

Plain: Fc

Underlined: IL2 fragment that binds CD25 (IL-2Rα)

(Can replace linker 1 with EPKSCDK (SEQ. ID. NO: 105) or IEGRDMD (SEQ. ID. NO: 106))
(Can replace underlined aa in Fc: E with D and M with L)

FIG. 29

Fusion protein comprising anti-CD4 antibody and Receptor activator of nuclear factor–κB (RANK) Extracellular domain (ECD)

Anti-CD4 heavy chain and RANK Extracellular domain (SEQ ID NO: 36):

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG**

Anti-CD4 light chain (SEQ ID NO: 77):

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Italic: *Linker*

Bold: **PD-1 ectodomain**

FIG. 30

(i) Full-length human PD-1 ligand 1 (B7-H1; PDCD1L1; PDL1; CD274) protein or a fragment thereof (SEQ ID NO: 99):

MRIFAVFIFM TYWHLLNAFT VTVPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME
DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG
ADYKRITVKV NAPYNKINQR ILVVDPVTSE HELTCQAEGY PKAEVIWTSS DHQVLSGKTT
TTNSKREEKL FNVTSTLRIN TTTNEIFYCT FRRLDPEENH TAELVIPELP LAHPPNERTH
LVILGAILLC LGVALTFIFR LRKGRMMDVK KCGIQDTNSK KQSDTHLEET

(ii) PD-L1 extracellular binding domain (ectodomain) or fragment thereof (SEQ ID NO: 100):

AFT VTVPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME DKNIIQFVHG
EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG ADYKRITVKV
NAPYNKINQR ILVVDPVTSE HELTCQAEGY PKAEVIWTSS DHQVLSGKTT TTNSKREEKL
FNVTSTLRIN TTTNEIFYCT FRRLDPEENH TAELVI

(iii) Human PD-1 ligand 2 [PD-L2 (B7-DC)] or a fragment thereof.

(iv). Mutant of Programmed Death-1 ligand [PD-L1 (B7-H1) or PD-L2 (B7-DC)] or a fragment thereof which binds Programmed Death-1 (PD-1).

Sequence used in fusion proteins (SEQ ID NO: 101):

RIFAVFIFM TYWHLLNAFT VTVPKDLYVV EYGSNMTIEC KFPVEKQLDL AALIVYWEME
DKNIIQFVHG EEDLKVQHSS YRQRARLLKD QLSLGNAALQ ITDVKLQDAG VYRCMISYGG
ADYKRITVKV NAPYNKINQR ILVVDPVTSE HELTCQAEGY PKAEVIWTSS DHQVLSGKTT
TTNSKREEKL FNVTSTLRIN TTTNEIFYCT FRRLDPEENH TAELVIPELP LAHPPNERTH
LVILGAILLC LGVALTFIFR LRKGRMMDVK KCGIQDTNSK KQSDTHLEET

Bold: **PD-L1 extracellular domain (ectodomain)**

Underlined Bold: **Ligand Binding domain**

FIG. 31

Fusion proteins comprising anti-tumor necrosis factor (TNFα) antibody and PD-1 ligand 1 or PD-1 ligand 2

Anti-TNFα heavy chain + PD-L1 (SEQ ID NO: 37):

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-TNFα light chain (SEQ ID NO: 78):

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGKAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNFα antibody variable region

Plain: anti-TNFα antibody constant region

Italic: *Linker*

Bold: **human PD-1 ligand 1 (PD-L1)**

(Note: Fc region **KKAE** SEQ ID NO: 107 can be replaced with **KRVE** SEQ ID NO: 108 or **KKVE** SEQ ID NO: 109)

FIG. 32

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand: (TNFR2 ECD + IgG Cγ1 + PD-L1)

TNFR2 ECD + IgG Cγ1 + PD-L1 (SEQ ID NO: 38):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Fusion proteins comprising PD-1 ligand, Fc, and TNFR2 Extracellular ligand binding domain: (PD-L1 + IgG Cγ1 + TNFR2 ECD)

PD-L1 + IgG Cγ1 + TNFR2 ECD (SEQ ID NO: 39):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQ
FVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
PYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFR
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET *GGGGSGGGGSGGGGS EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD

Underlined: TNFR2 ligand-binding domain
Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)
Italic: *Linker (Linker 1 is optional and may be replaced with another linker such as EPKSCDK* (SEQ. ID. NO: 105) *or GGGGSGGGGSGGGGS* (SEQ. ID. NO: 104))
Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-L1**

FIG. 33

Fusion proteins comprising anti-CD20 antibody and PD-1 ligand 1 (PD-L1).

Anti-CD20 heavy chain + PD-L1 sequence (SEQ ID NO: 40):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD20 light chain sequence (SEQ ID NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: anti-CD20 antibody variable region

Plain: anti-CD20 antibody constant region

Italic: *Linker*

Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-L1**

FIG. 34

Fusion proteins comprising anti-CD25 antibody and PD-1 ligand 1 (PD-L1).

Anti-CD25 (Daclizumab) heavy chain and PD-L1 (SEQ ID NO: 41):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECK
FPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNA
ALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHEL
TCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYC
TFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: anti-CD25 antibody

Italic: *Linker* (optional and may be replaced)

Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-L1 (underlined)**

FIG. 35A

Anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 42)

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDYGY YFDFWGQGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECK
FPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQRARLLKDQLSLGNA
ALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSEHEL
TCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYC
TFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE

Plain: anti-CD25 antibody

Italic: *Linker*

Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-L1 (underlined)**

FIG. 35B

Fusion proteins comprising IL-2, Fc, and PD-1 ligand 1 (PD-L1)

Fusion protein: hPD-1 ligand 1 + Fc + IL-2 (SEQ ID NO: 43):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEE
DLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKV
NAPYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTT
TNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFR
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK *GGGGSGGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT

Fusion protein: IL-2 + Fc + PD-1 ligand 1 (SEQ ID NO: 44):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPLEEVLNL
AQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTLT
GGGGSGGGGSGGGGS
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEED
LKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEE
T

Underlined: IL-2 fragment
Italic: *Linker (optional)*
Plain: Fc
Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)**
(Note: Can replace linker 1 *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 36

Fusion protein comprising anti-CD4 antibody and PD-1 ligand 1 (PD-L1)

Anti-CD4 heavy chain and PD-1 ligand 1 (SEQ ID NO: 45)

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Anti-CD4 light chain (SEQ ID NO: 77)

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Plain: Anti-CD4 antibody constant region

Italic: *Linker*

Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)**

FIG. 37

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from PD-1 ligand (PD-L1)

Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + PD-L1 (SEQ ID NO: 46):

*MGVLLTQRTLLSLVLALLFPSMASM*AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGI
GNGTQIYVIDPEPCPDSD *QEPKSCDK*THTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
**RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET**

Fusion proteins comprising the extracellular domain of PD-1 ligand (PD-L1), Immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4.

PD-L1 + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 47):

**MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQ
FVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
PYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFR
LRKGRMMDVKKCGIQDTNSKKQSDTHLEET** *GGGGSGGGGSGGGGS*
*QEPKSCDK*THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP
QVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDSD

Underlined Italic: *Oncostatin M Signal Peptide (-25 to -1)*
Underlined: CTA-4 extracellular domain (1-125)
Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)
Italic: *Linker (optional)*
Bold: **human PD-1 ligand 1 (PD-1L) or extracellular binding domain of PD-1L (underlined)**
(Note: Optional C to S conversion in IgG sequence (bold underlined))
(Note: The linker *QEPKSCDK* SEQ ID NO: 110 can be replaced with *EPKSCDK* SEQ ID NO: 105 or another linker sequence)

FIG. 38

Fusion proteins comprising a sequence of transforming growth factor-β (TGF-β), Immunoglobulin Fc (IgG Cβ1), and a sequence of PD-1 ligand (PD-L1)

TGFβ-1 + Fc + PD-L1 (SEQ ID NO: 48):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQF
VHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAP
YNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRI
NTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGR
MMDVKKCGIQDTNSKKQSDTHLEET

Fusion protein comprising a sequence of PD-1 ligand (PD-L1), Immunoglobulin Fc (IgG Cγ1), and a sequence of Transforming growth factor beta (TGF- β)

PD-L1 + Fc + TGFβ-1 (SEQ ID NO: 49):

MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQ
FVHGEEDLKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNA
PYNKINQRILVVDPVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLR
INTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKG
RMMDVKKCGIQDTNSKKQSDTHLEET *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: TGFβ-1
Italic: *Linker (optional)*
Plain: Fc
Bold: **human PD-1 ligand 1 or extracellular binding domain of PD-1L (underlined)**
(Note: Can replace linker *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 39

(i) Transforming growth factor-beta (TGF-β1, TGF-β2, or TGF-β3 or a fragment thereof:

TGF-β1 full sequence (SEQ ID NO: 102):

1 MPPSGLRLLP LLLPLLRLLV LTPGRPAAGL STCKTIDMEL VKRKRIEAIR GQILSKLRLS
61 SPPSQGEVPP VPLPEAVLAL YNSTRDRVAG ESAEPEPEPE ADYYAKEVTR VLMVENTNKI
121 YEKVKKSPHS IYMLFNTSEL REAVPEPVLL SRAELRLLRL KLKAEQHVEL YQKYSNDSWR
181 YLSNRLLAPS DTPEWLSFDV TGVVRQWLSH GGEVEGFRLS AHCSCDSKDN TLQVDINGFS
241 SSRRGDLATI HGMNRPFLLL MATPLERAQH LHSSRQRRAL DTNYCFSSTE KNCCVRQLYI
301 DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW SLDTQYSKVL ALYNQHNPGA SAAPCCVPQA
361 LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS

Underlined: Mature (active) TGF-β1 sequence (Ala 279 – Ser 390; 112 aa).

(ii) Mature (active) TGF-β1 sequence (Ala 279 – Ser 390; 112 aa)
(SEQ ID NO: 103):

AL DTNYCFSSTE KNCCVRQLYI DFRKDLGWKW IHEPKGYHAN FCLGPCPYIW
SLDTQYSKVL ALYNQHNPGA SAAPCCVPQA LEPLPIVYYV GRKPKVEQLS NMIVRSCKCS

FIG. 40

Fusion proteins comprising an antibody that binds TNF-α, and a sequence of transforming growth factor-β (TGF-β).

Anti-TNFα heavy chain + TGF-β1 (SEQ ID NO: 50):

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-TNFα light chain (SEQ ID NO: 78):

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGKAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNFα antibody variable region

Plain: anti-TNFα antibody constant region

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

(Note: **KKAE** SEQ ID NO: 107 can be replaced with **KRVE** SEQ ID NO: 108 or **KKVE** SEQ ID NO: 109)

FIG. 41

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and a sequence from transforming growth factor-β (TGF-β)

TNFR2 ECD + IgG Cγ1 + TGF-β1 (SEQ ID NO: 51):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Fusion proteins comprising a sequence from transforming growth factor-β (TGF-β), Fc, and TNFR2 Extracellular ligand binding domain:

TGF-β1 + IgG Cγ1 + TNFR2 ECD (SEQ ID NO: 52):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD

Underlined: TNFR2 ligand-binding domain

Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

(Note: Can replace linker 1 with *GGGGSGGGGSGGGGS* SEQ ID NO: 104 or *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 42

Fusion proteins comprising anti-CD20 antibody and a sequence from transforming growth factor-β (TGF-β)

Anti-CD20 heavy chain + mature TGFβ1 sequence (SEQ ID NO: 53):

QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIGAIYPGNGDTSYNQKFKG
KATLTADKSSSTAYMQLSSLTSEDSAVYYCARSTYYGGDWYFNVWGAGTTVTVSAASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD20 light chain sequence (SEQ ID NO: 72):

QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSNLASGVPVRFSGSGS
GTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

Underlined: anti-CD20 antibody variable region

Plain: anti-CD20 antibody constant region

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

FIG. 43

Fusion proteins comprising anti-CD25 antibody and a sequence from transforming growth factor-β (TGF-β).

Anti-CD25 (Daclizumab) heavy chain and TGF-β1 (SEQ ID NO: 54):

QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY INPSTGYTEY
NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG GVFDYWGQGT LVTVSSASTK
GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL PPSRDELTKN
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN
VFSCSVMHEA LHNHYTQKSL SLSPGK *GGGGSGGGGSGGGGS* **ALDTNYCFSSTEKNCCVRQLY**
IDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLP
IVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75):

DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT SNLASGVPAR
FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG TKVEVKRTVA APSVFIFPPS
DEQLKSGTAS VVCLLNNFYP REAKVQWKVD NALQSGNSQE SVTEQDSKDS TYSLSSTLTL
SKADYEKHKV YACEVTHQGL SSPVTKSFNR GEC

Plain: anti-CD25 antibody

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

FIG. 44A

Anti-CD25 (Basiliximab) heavy chain and TGF-β1 (SEQ ID NO: 55):

QLQQSGTVLA RPGASVKMSC KASGYSFTRY WMHWIKQRPG QGLEWIGAIY PGNSDTSYNQ
KFEGKAKLTA VTSASTAYME LSSLTHEDSA VYYCSRDYGY YFDFWGQGTT LTVSSASTKG
PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL
SSVVTVPSSS LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP ELLGGPSVFL
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV
VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPQVYTLP PSRDELTKNQ
VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV
FSCSVMHEAL HNHYTQKSLS LSPGK *GGGGSGGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHAN
FCLGPCPYIWSLDTQYSKVLALYNQHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQ
LSNMIVRSCKCS

Anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76):

QIVSTQSPAI MSASPGEKVT MTCSASSSRS YMQWYQQKPG TSPKRWIYDT SKLASGVPAR
FSGSGSGTSY SLTISSMEAE DAATYYCHQR SSYTFGGGTK LEIKRTVAAP SVFIFPPSDE
QLKSGTASVV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE

Plain: anti-CD25 antibody

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

FIG. 44B

Fusion proteins comprising IL-2, Fc, and a sequence from transforming growth factor-β (TGF-β).

TGF-β1 + Fc + IL-2 (SEQ ID NO: 56):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T

IL-2 + Fc + TGF-β1 (SEQ ID NO: 57):

APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCLEEELKPL
EEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNRWITFCQSIISTL
T *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: IL-2 fragment
Italic: *Linker (optional)*
Plain: Fc
Bold: **Mature (active) human TGF-β1**
(Note: Can replace linker 1 *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 45

Fusion protein comprising anti-CD4 antibody and a sequence from transforming growth factor-β (TGF-β).

Anti-CD4 heavy chain and TGF-β1 (SEQ ID NO: 58)

Heavy chain fusion protein:

QVQLQEAGPGLVKPSETLSLTCSVSGGSISGDYYWFWIRQSPGKGLEWIGYIYGSGGGTNYNPSLN
NRVSISIDTSKNLFSLKLRSVTAADTAVYYCASNILKYLHWLLYWGQGVLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Anti-CD4 light chain (SEQ ID NO: 77)

Light chain:

SYELSQPRSVSVSPGQTAGFTCGGDNVGRKSVQWYQQKPPQAPVLVIYADSERPSGIPARFSGSNS
GNTATLTISGVEAGDEADYYCQVWDSTADHWVFGGGTRLTVLGRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

Underlined: Anti-CD4 antibody variable region

Plain: Anti-CD4 antibody constant region

Italic: *Linker*

Bold: **Mature (active) human TGF-β1**

FIG. 46

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from a sequence from transforming growth factor-β (TGF-β)

Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + TGF-β1 (SEQ ID NO: 59):

*MGVLLTQRTLLSLVLALLFPSMASM*AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGI
GNGTQIYVIDPEPCPDSD*QEPKSCDK* THTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS
**ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS**

Fusion proteins comprising a sequence from transforming growth factor-β (TGF-β), Immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4

TGF-β1 + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 60):

**ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS** *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDSD

Underlined Italic: *Oncostatin M Signal Peptide (-25 to -1)*
Underlined: CTLA-4 extracellular domain (1-125)
Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)
Italic: *Linker (optional)*
Bold: **Mature (active) human TGF-β1**
(Note: Optional C to S conversion in IgG sequence (bold underlined))
(Note: The linker *QEPKSCDK* SEQ ID NO: 110 can be replaced with *EPKSCDK* SEQ ID NO: 105 or another linker sequence)

FIG. 47

Fusion proteins comprising an antibody that binds TNF-α, and a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK)

Anti-TNFα heavy chain + RANK ectodomain (SEQ ID NO: 61):

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSAITWNSGHIDYADSVEG
RFTISRDNAKNSLYLQMNSLRAEDTAVYYCALVSYLSTASSLDYWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVD**KKAE**PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG**

Anti-TNFα light chain (SEQ ID NO: 78):

DIQMTQSPSSLSASVGDRVTITCRASQGIRNYLAWYQQLPGKAPKLLIYAASTLQSGVPSRFSGSG
SGTDFTLTISSLQPEDVATYYCQRYNRAPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

Underlined: anti-TNFα antibody variable region

Plain: anti-TNFα antibody constant region

Italic: *Linker*

Bold: **RANK ectodomain**

(Note: **KKAE** SEQ ID NO: 107 can be replaced with **KRVE** SEQ ID NO: 108 or **KKVE** SEQ ID NO: 109)

FIG. 48

Fusion proteins comprising TNFR2 Extracellular ligand binding domain, Fc, and a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK)

TNFR2 ECD + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 62):

LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY**
EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS
DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK), Fc, and TNFR2 Extracellular ligand binding domain:

RANK ectodomain + IgG Cγ1 + TNFR2 ECD (SEQ ID NO: 63):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG
GGGGSGGGGSGGGGS THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
LPAQVAFTPYAPEPGSTCRLREYYDQTAQMCCSKCSPGQHAKVFCTKTSDTVCDSCEDSTYTQLWN
WVPECLSCGSRCSSDQVETQACTREQNRICTCRPGWYCALSKQEGCRLCAPLRKCRPGFGVARPGT
ETSDVVCKPCAPGTFSNTTSSTDICRPHQICNVVAIPGNASMDAVCTSTSPTRSMAPGAVHLPQPV
STRSQHTQPTPEPSTAPSTSFLLPMGPSPPAEGSTGD

Underlined: TNFR2 ligand-binding domain

Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)

Italic: *Linker*

Bold: **RANK ectodomain**

(Note: Can replace linker 1 with *GGGGSGGGGSGGGGS* SEQ ID NO: 104 or *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 49

Fusion proteins comprising the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK)

Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 64):

*MGVLLTQRTLLSLVLALLFPSMASM*AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQA
DSQVTEVCAATYMMGNELTFLDDSICTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGI
GNGTQIYVIDPEPCPDSD*QEPKSCDK* THTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
GGGGSGGGGSGGGGS **QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG**

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK), Immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4

RANK ectodomain + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 65):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG *EPKSCDK*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
AMHVAQPAVVLASSRGIASFVCEYASPGKATEVRVTVLRQADSQVTEVCAATYMMGNELTFLDDSI
CTGTSSGNQVNLTIQGLRAMDTGLYICKVELMYPPPYYLGIGNGTQIYVIDPEPCPDSD

Underlined Italic: *Oncostatin M Signal Peptide (-25 to -1)*
Underlined: CTLA-4 extracellular domain (1-125)
Plain: human IgG1 heavy chain constant region (IgG Cγ1 domain = H, CH2, CH3)
Italic: *Linker (optional)*
Bold: **RANK ectodomain**
(Note: Optional C to S conversion in IgG sequence (bold underlined))
(Note: The linker *QEPKSCDK* SEQ ID NO: 110 can be replaced with *EPKSCDK* SEQ ID NO: 105 or another linker sequence)

FIG. 50

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK), Fc, and a sequence from transforming growth factor-β (TGF-β).

TGF-β1 + Fc + RANK ectodomain (SEQ ID NO: 66):

ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS* **QI APPCTSEKHY**
EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK VCDTGKALVA
VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS
DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain + Fc + TGF-β1 (SEQ ID NO: 67):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW
NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ
HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA
RKPPNEPHVY LPG *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
R**E**E**M**TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK *GGGGSGGGGSGGGGS*
ALDTNYCFSSTEKNCCVRQLYIDFRKDLGWKWIHEPKGYHANFCLGPCPYIWSLDTQYSKVLALYN
QHNPGASAAPCCVPQALEPLPIVYYVGRKPKVEQLSNMIVRSCKCS

Underlined: Mature (active) human TGF-β1
Italic: *Linker (optional)*
Plain: Fc
Bold: **RANK ectodomain**
(Note: Can replace linker 1 *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 51

Fusion proteins comprising a RANKL-binding sequence of receptor activator of nuclear factor-kB (RANK), Fc, and a sequence from PD-1 ligand 1

PD-1L1 + Fc + RANK ectodomain (SEQ ID NO: 68):

RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEED
LKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEE
T *GGGGSGGGGSGGGGS*
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK *GGGGSGGGGSGGGGS* QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP
CGPDEYLDSW NEEDKCLLHK VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN
TECAPGLGAQ HPLQLNKDTV CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS
DAVCSSSLPA RKPPNEPHVY LPG

RANK ectodomain + Fc + PD-1L1 (SEQ ID NO: 69):

QI APPCTSEKHY EHLGRCCNKC EPGKYMSSKC TTTSDSVCLP CGPDEYLDSW NEEDKCLLHK
VCDTGKALVA VVAGNSTTPR RCACTAGYHW SQDCECCRRN TECAPGLGAQ HPLQLNKDTV
CKPCLAGYFS DAFSSTDKCR PWTNCTFLGK RVEHHGTEKS DAVCSSSLPA RKPPNEPHVY LPG
GGGGSGGGGSGGGGS
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR**E**E**M**TKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK *GGGGSGGGGSGGGGS*
RIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMTIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEED
LKVQHSSYRQRARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVD
PVTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPE
ENHTAELVIPELPLAHPPNERTHLVILGAILLCLGVALTFIFRLRKGRMMDVKKCGIQDTNSKKQSDTHLEE
T

Bold: PD-1L1 (May use PD-1L1 extracellular domain – underlined)
Italic: *Linker (optional)*
Plain: Fc
Underlined: RANK ectodomain
(Note: Can replace linker 1 *GGGGSGGGGSGGGGS* SEQ ID NO: 104 with *EPKSCDK* SEQ ID NO: 105)
(Note: Can replace underlined aa in Fc: **E** with D and **M** with L)

FIG. 52

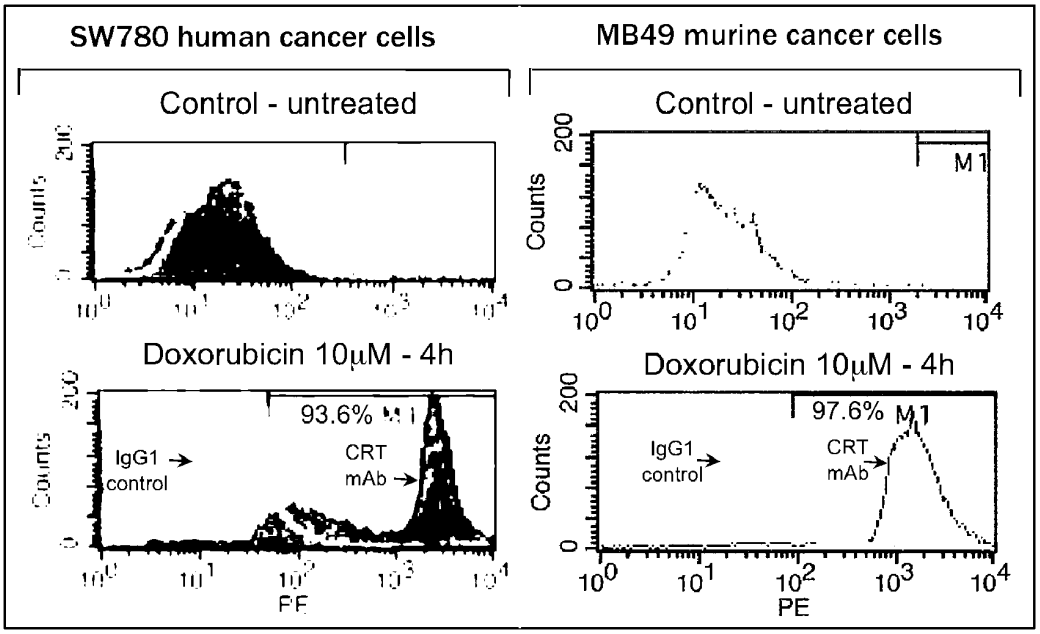


FIG. 53A

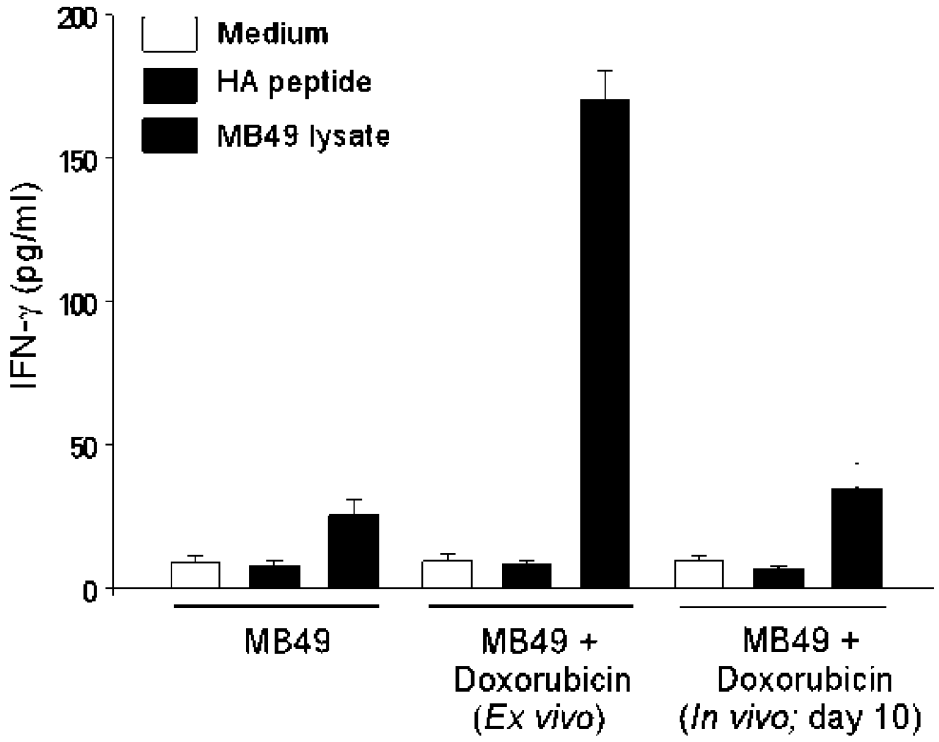


FIG. 53B

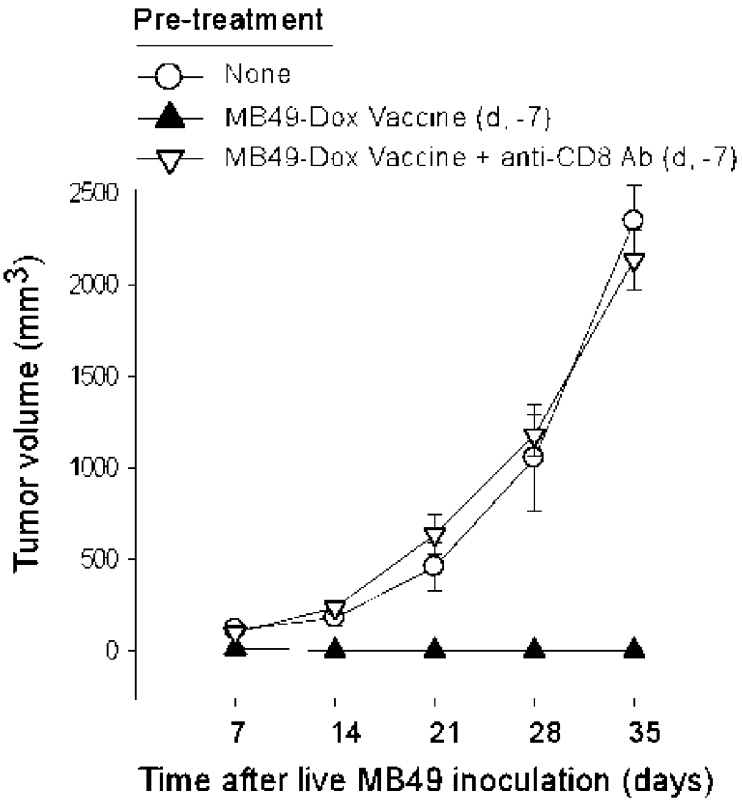


FIG. 53C

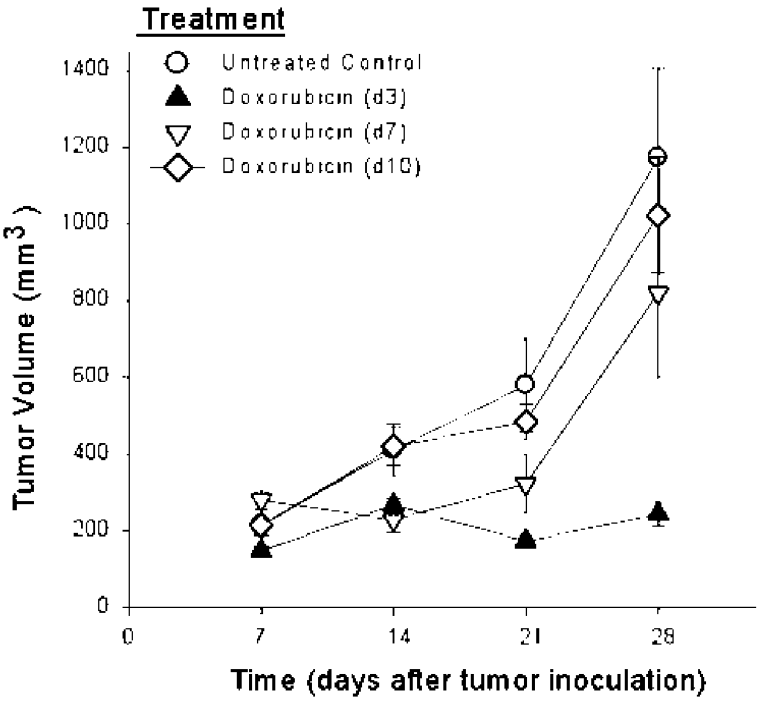


FIG. 53D

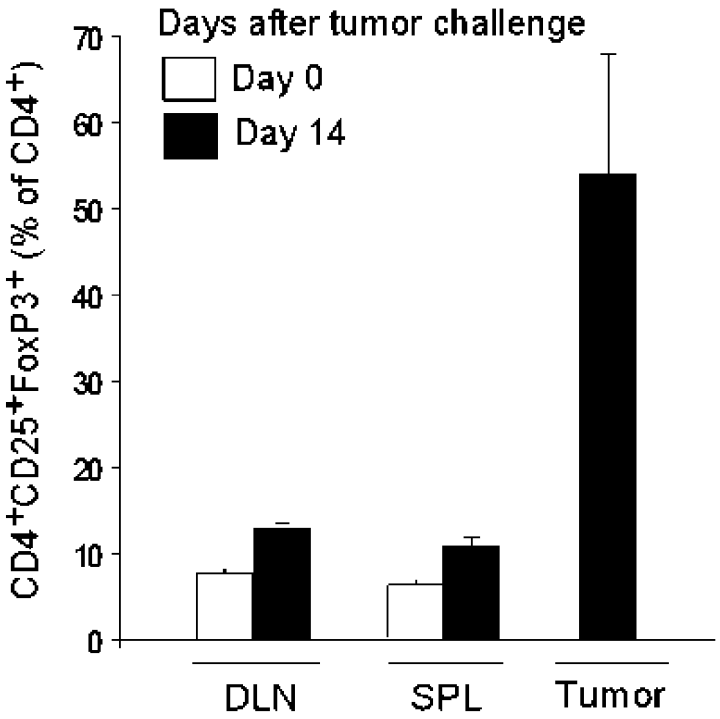


FIG. 53E

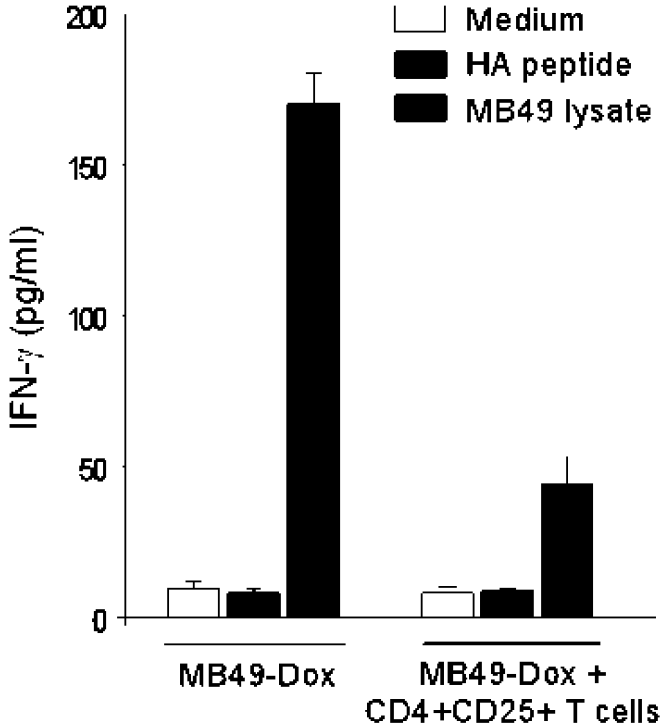


FIG. 53F

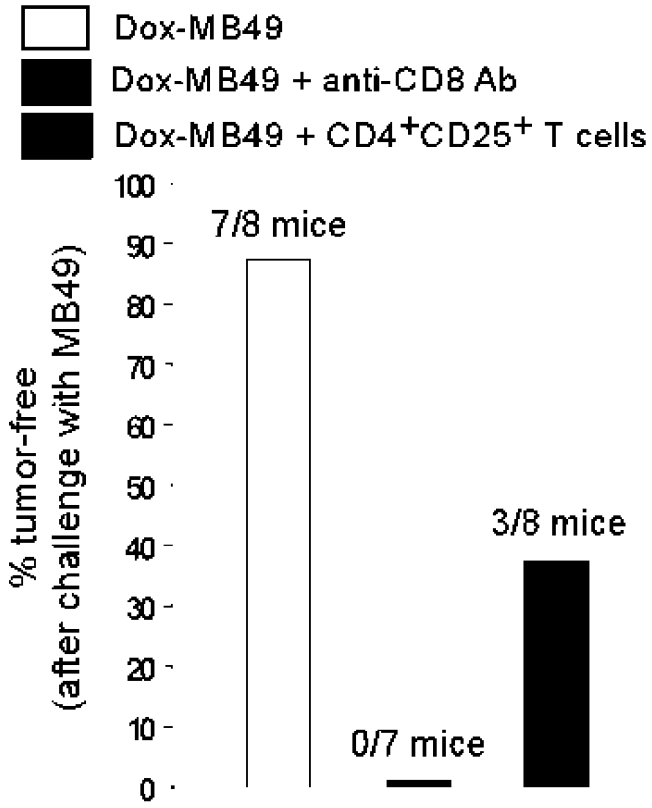

Dox-MB49
Dox-MB49 + anti-CD8 Ab
Dox-MB49 + CD4+CD25+ T cells
% tumor-free
(after challenge with MB49)
100
90
80
70
60
50
40
30
20
10
0
7/8 mice
0/7 mice
3/8 mice

FIG. 53G

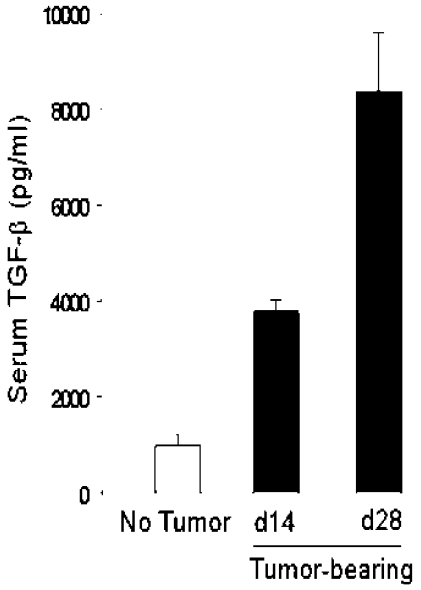


FIG. 54A

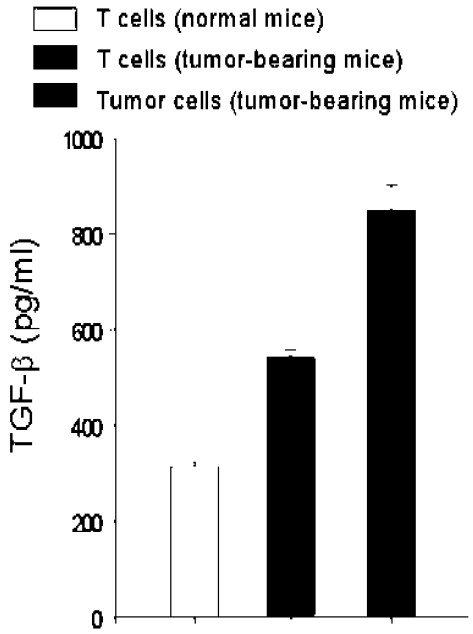


FIG. 54B

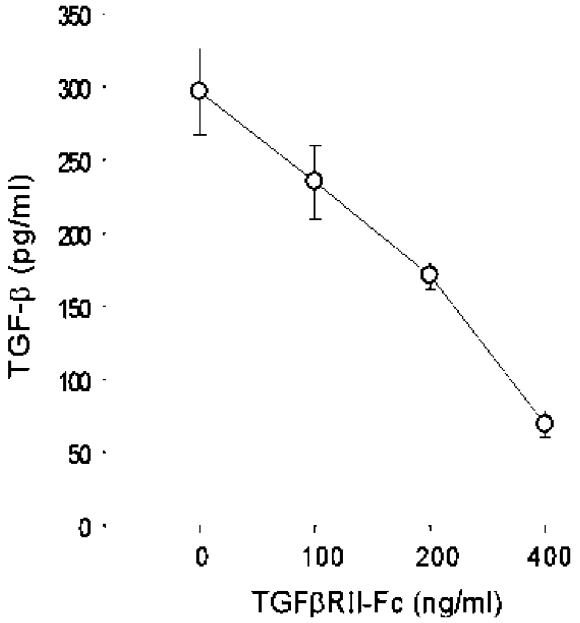


FIG. 54C

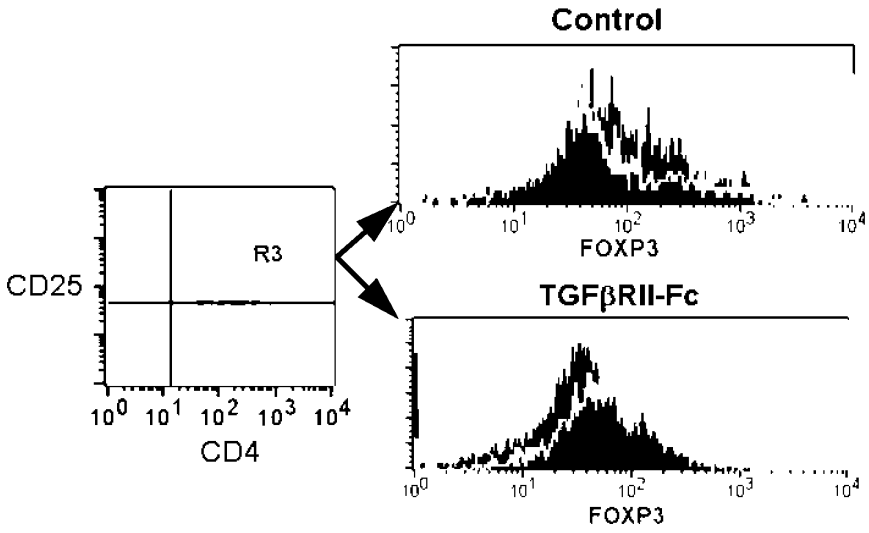


FIG. 54D

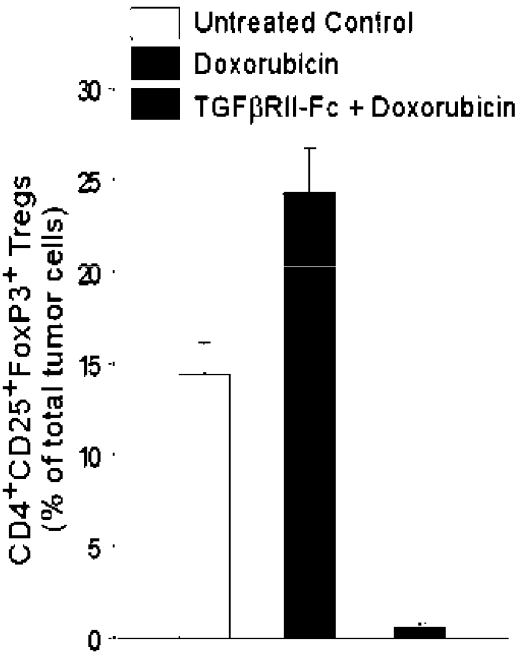


FIG. 54E

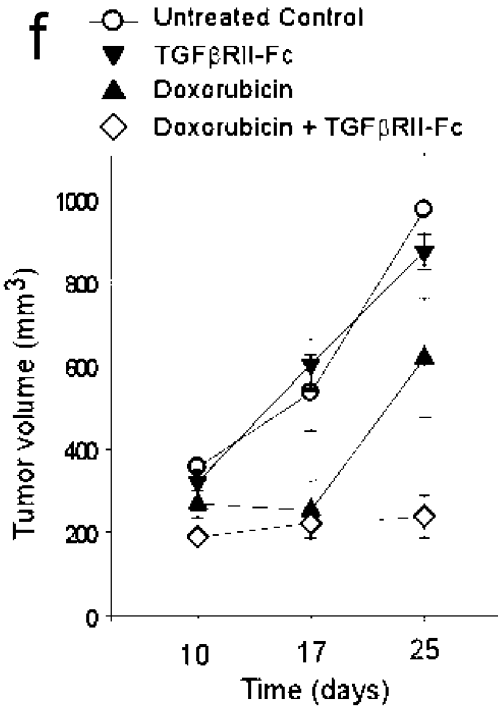


FIG. 54F

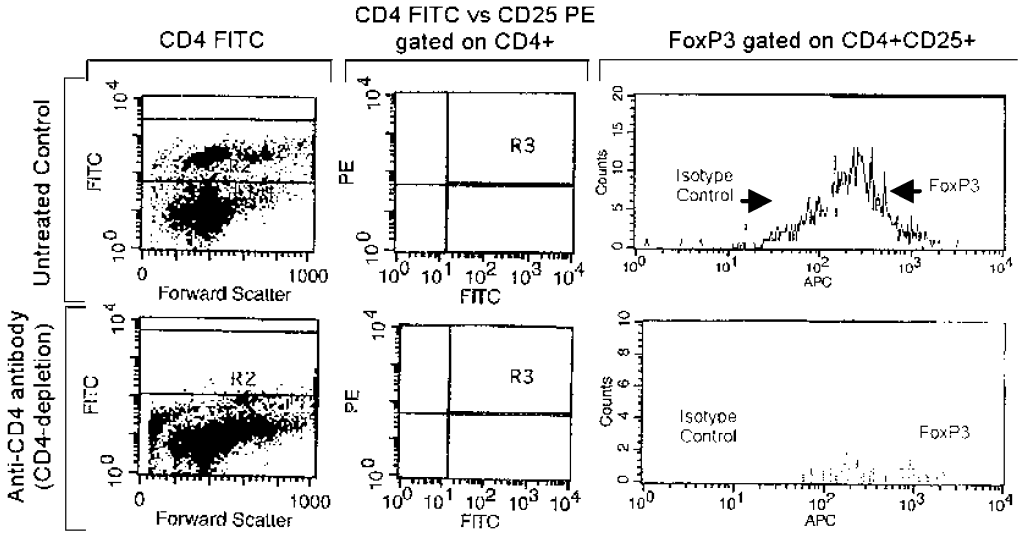


FIG. 55A

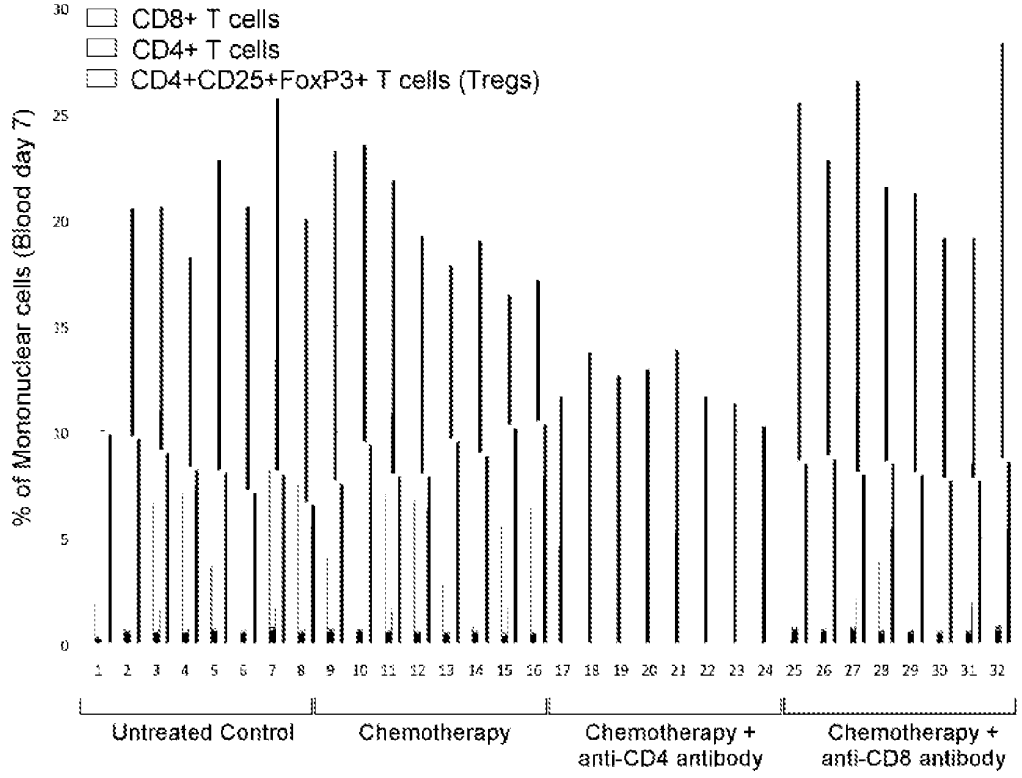


FIG. 55B

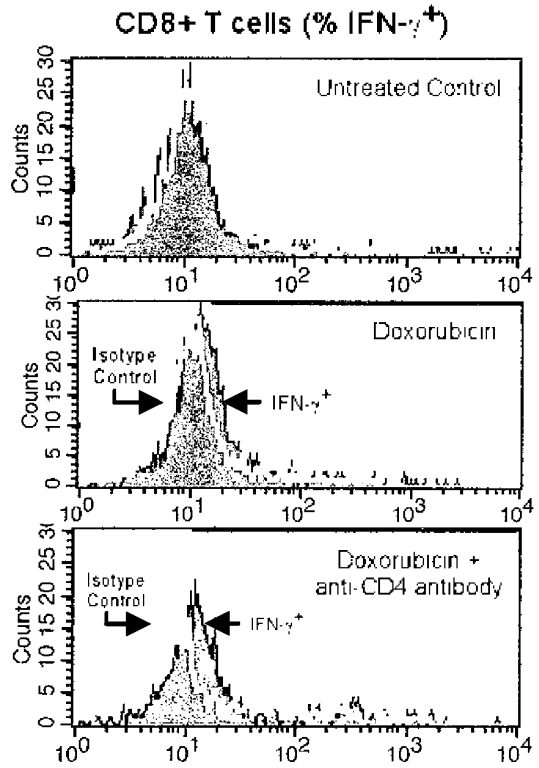


FIG. 55C

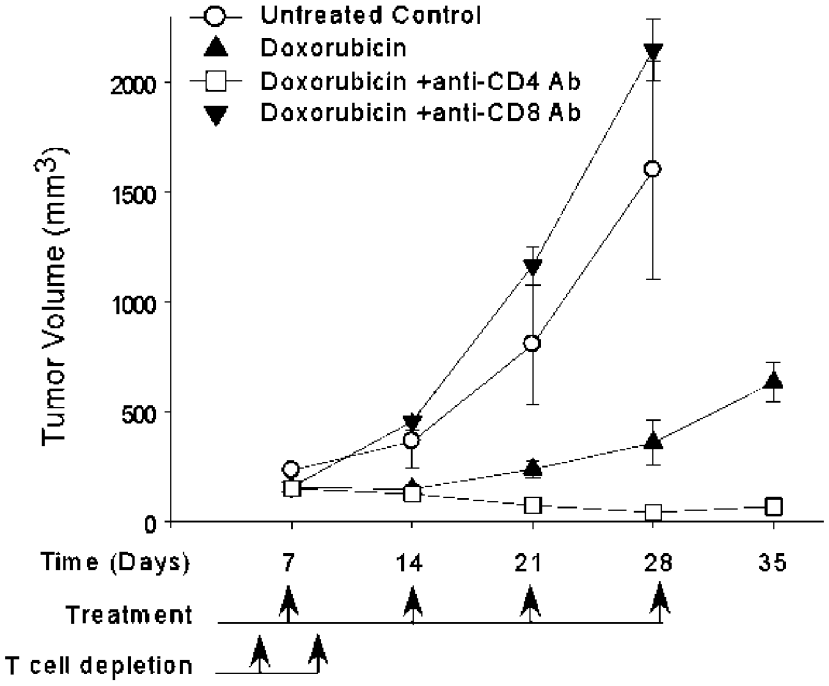


FIG. 55D

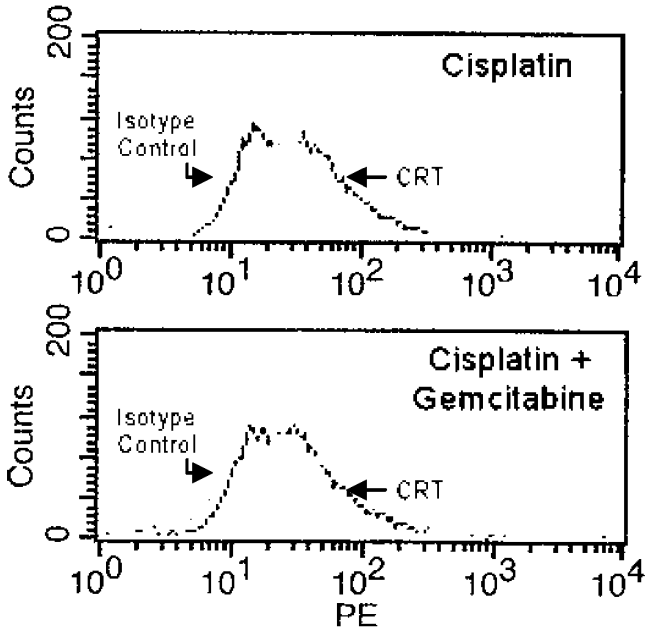


FIG. 56A

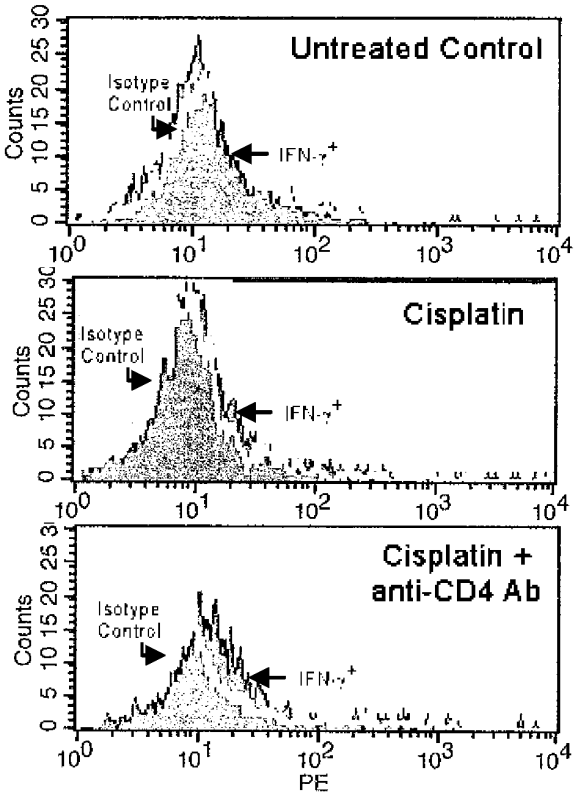


FIG. 56B

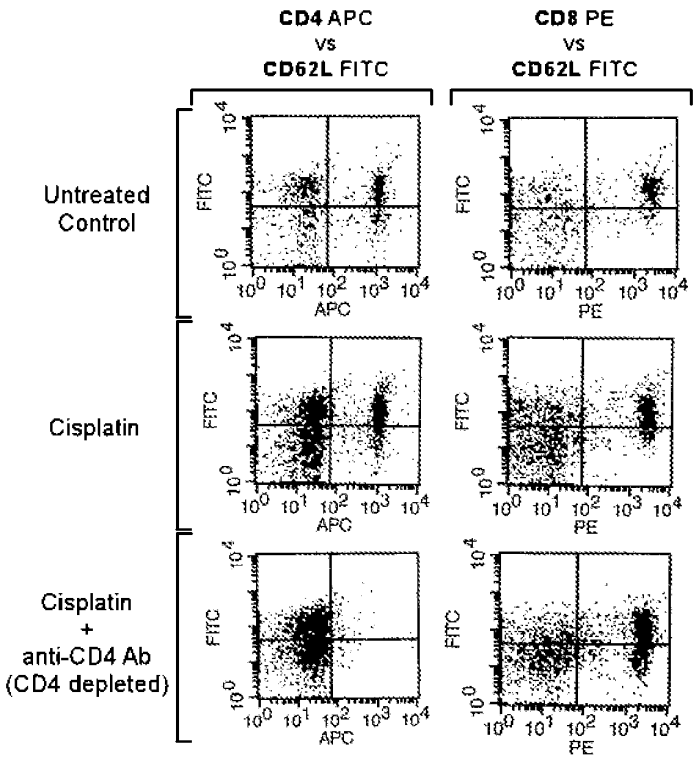


FIG. 56C

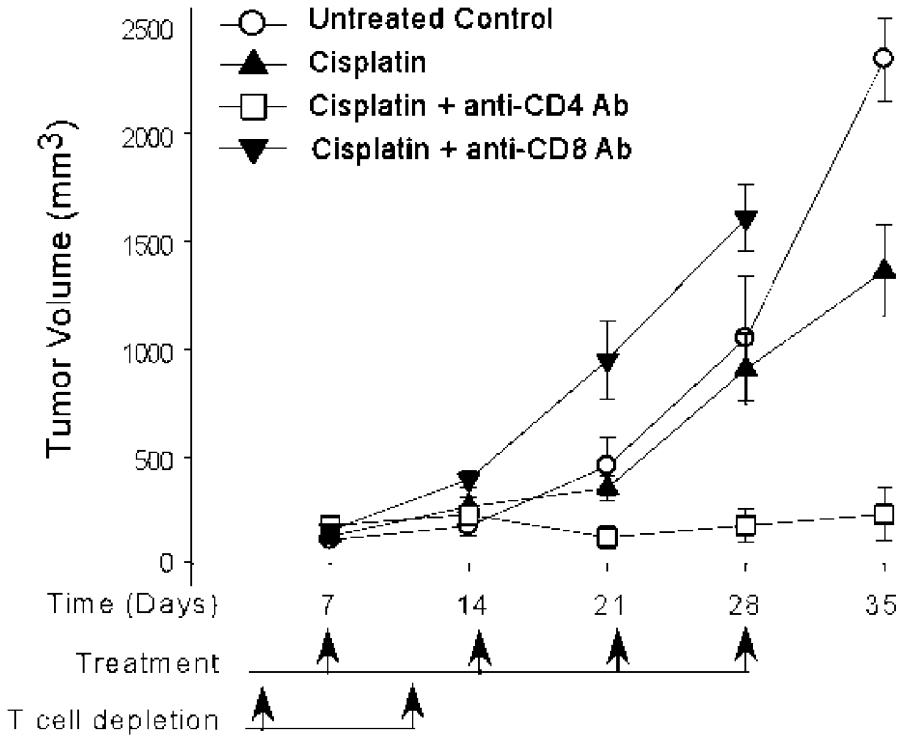


FIG. 56D

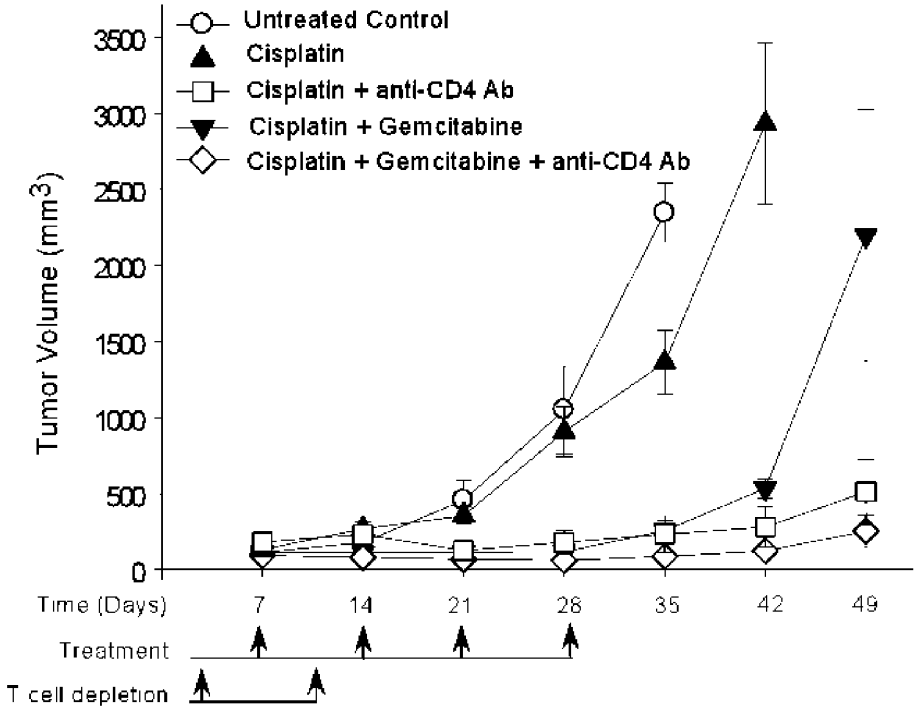


FIG. 56E

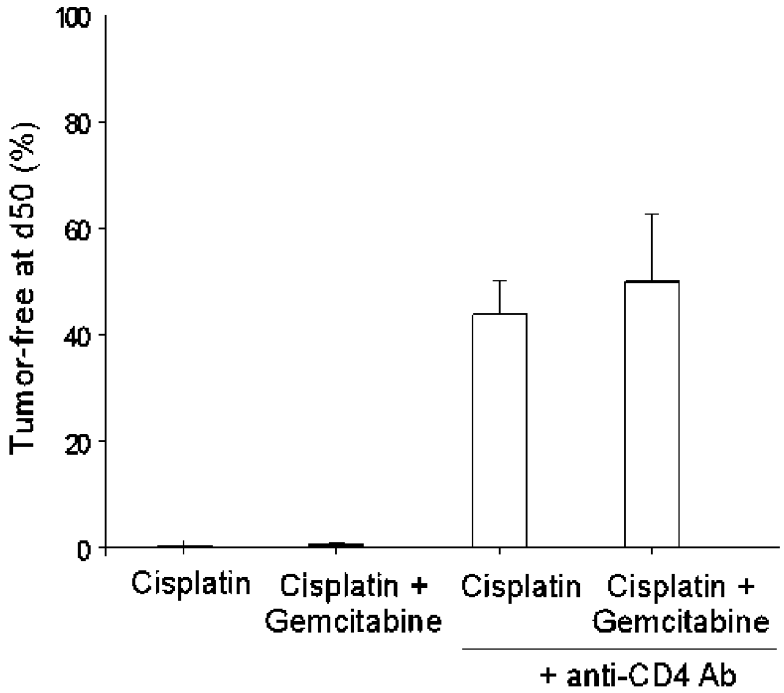


FIG. 56F

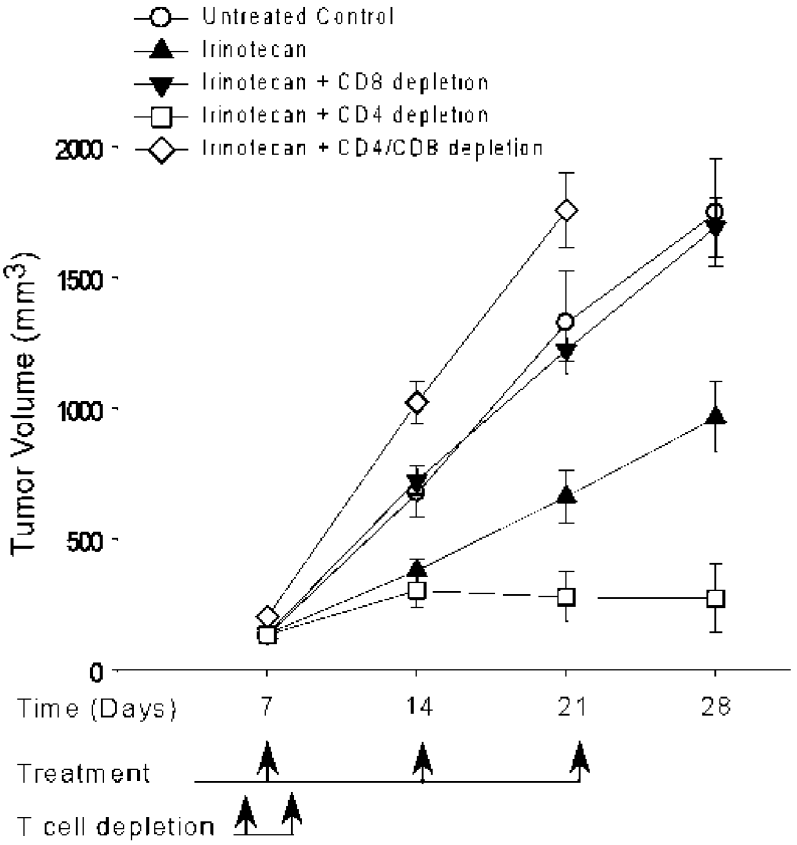


FIG. 57A

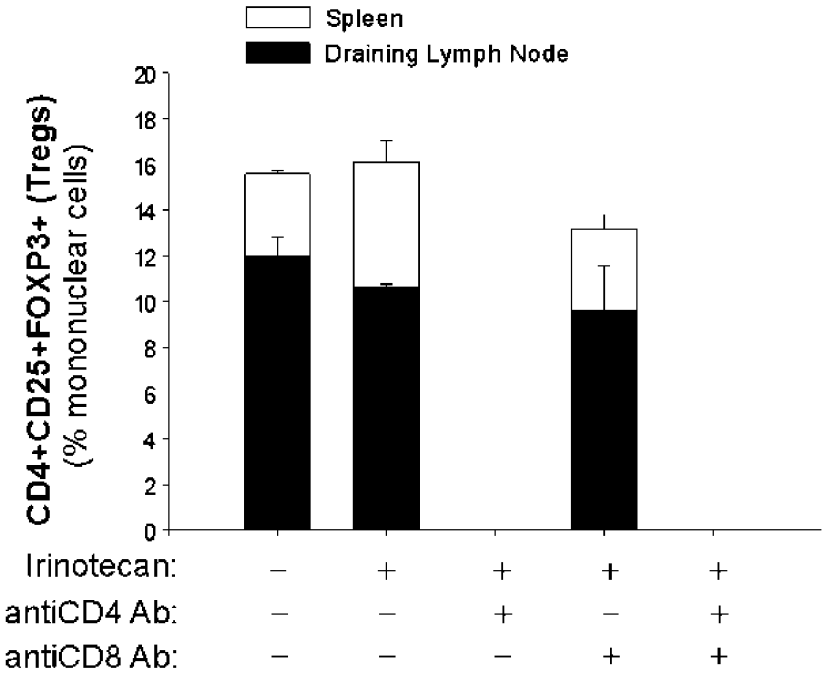


FIG. 57B

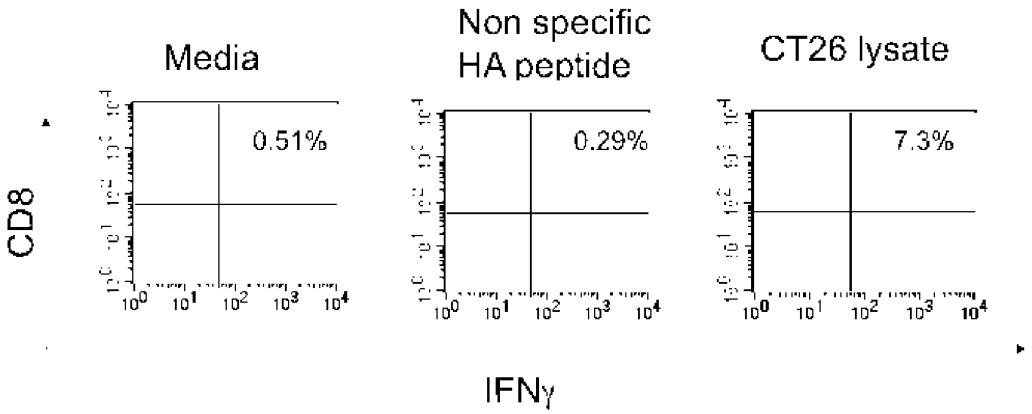


FIG. 57C

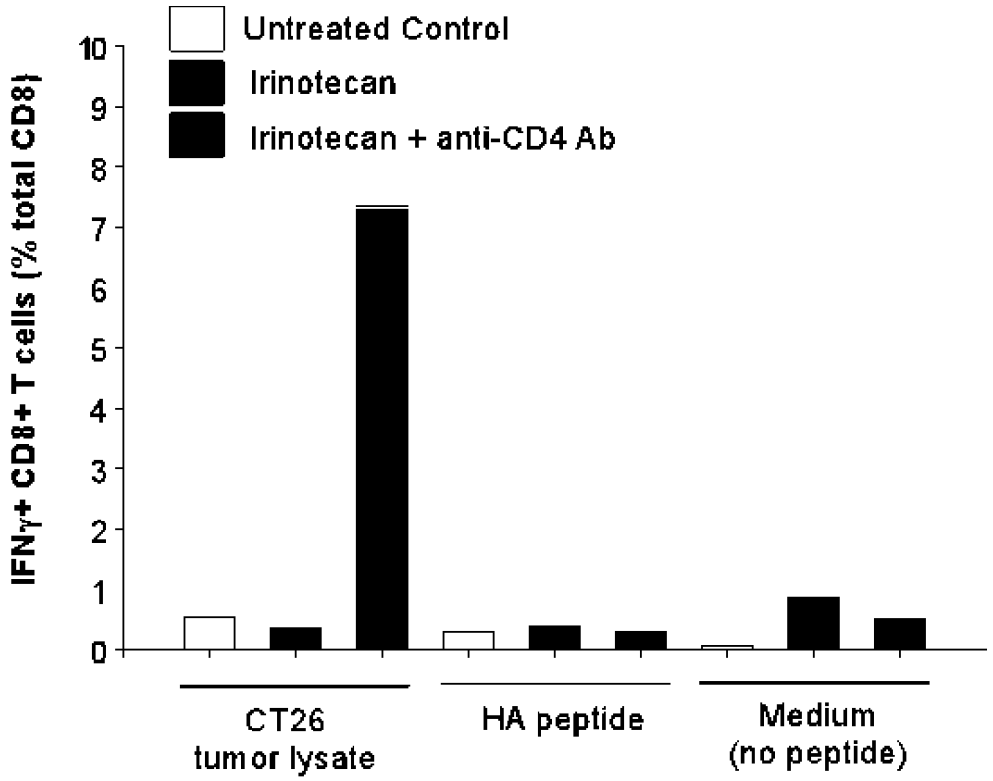


FIG. 57D

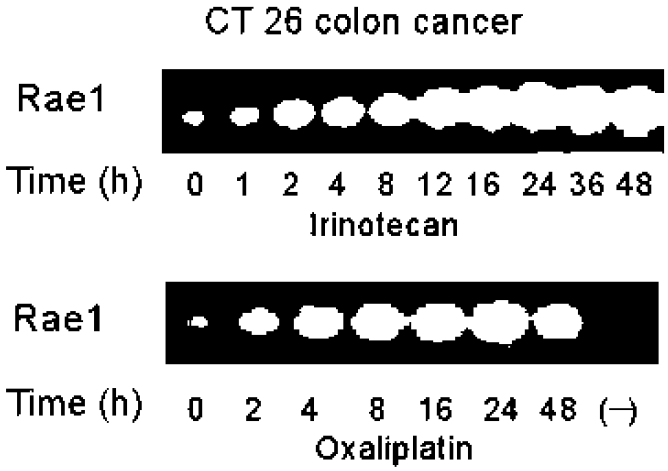


FIG. 57E

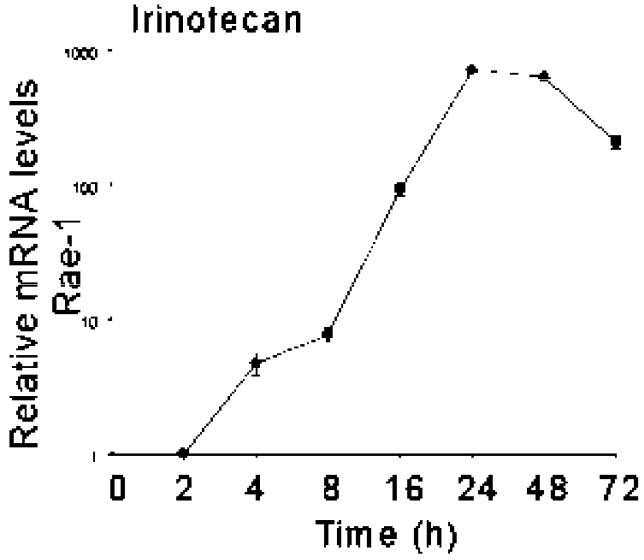


FIG. 57F

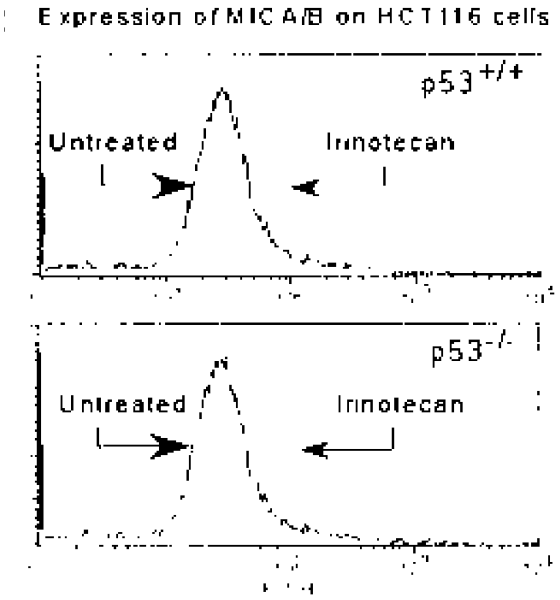


FIG. 57G

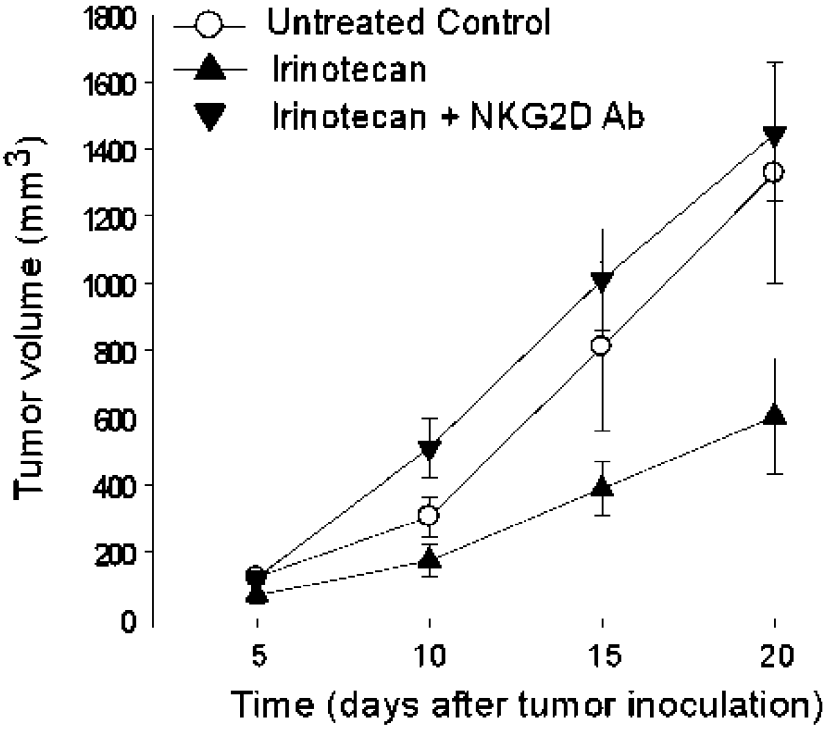


FIG. 57H

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

ABSTRACT OF THE DISCLOSURE

The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-β)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

Bicara Ex. 1006, Page 80 of 498
Bicara v. JHU - PGR2026-00025

What is claimed is:

1. An isolated molecule comprising:

(a) a targeting moiety that specifically binds Interleukin-6 (IL-6)/Interleukin-6 Receptor (IL6R) complex; and

(b) an immunomodulatory moiety that specifically binds Transforming growth factor-beta (TGFβ).

2. The molecule of claim 1 wherein:

(a) the targeting moiety specifically binds Interleukin-6 Receptor (IL6R); and

(b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFβR) or a fragment thereof.

3. The molecule of claim 1, wherein the targeting moiety comprises an antibody, antibody fragment, antigen-binding domain of an immunoglobulin, single chain variable fragment (scFv), Fc-containing polypeptide, or fusion protein that specifically binds IL6R or a fragment thereof.

4. The molecule of claim 3, wherein the targeting moiety comprises the amino acid sequence corresponding to the heavy chain or light chain of an antibody that specifically binds IL6R.

5. The molecule of claim 2, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor selected from the group consisting of SEQ ID NO: 79-91.

6. The molecule of claim 5, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFβRII) or a binding fragment thereof.

Bicara Ex. 1006, Page 81 of 498
Bicara v. JHU - PGR2026-00025

7. The molecule of claim 6, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87 or a binding fragment thereof.

8. The molecule of claim 2, wherein said immunomodulatory moiety is fused to the heavy chain or light chain of said targeting moiety comprising an antibody or to the C-terminus or N-terminus of said targeting moiety.

9. The molecule of claim 2, wherein the targeting moiety is fused to the immunomodulatory moiety via a linker.

10. The molecule of claim 2, further comprising a linker at the CH3 region of the Fc.

11. The molecule of claim 10, wherein the linker is $(GGGGS)_n$ and wherein n is 1, 2, 3, 4, 5, 6, 7 or 8.

12. The isolated molecule of claim 11, wherein the linker comprises the amino acid sequence GGGGSGGGGSGGGGS (SEQ ID NO: 104).

13. A method of preventing or treating a neoplastic disease or cancer comprising administration to a subject in need thereof a molecule of claim 1.

14. The method of claim 13, further comprising administering an additional cancer therapy.

15. The method of claim 14, wherein the cancer therapy is selected from the group consisting of a chemotherapeutic molecule, immunotherapeutic molecule, immune checkpoint inhibitor, antibody, targeted therapeutic agent, small molecule kinase inhibitor, hormonal agent, ionizing radiation, or immune cell therapy.

16. The method of claim 13, further comprising administering a vaccine.

17. A composition comprising a molecule of claim 1 and an immune cell, wherein the cells are contacted *ex vivo* or *in vivo* with the molecule.

Bicara Ex. 1006, Page 82 of 498
Bicara v. JHU - PGR2026-00025

18. A composition for the treatment of a neoplastic disease comprising immune cells contacted with a molecule of claim 1.

19. A method of preventing or treating an autoimmune or inflammatory disease comprising administration to a subject in need thereof a molecule of claim 1.

20. A method of preventing or treating a neoplastic, inflammatory, or genetic bone disease comprising administration to a subject in need thereof a molecule of claim 1.

Bicara Ex. 1006, Page 83 of 498
Bicara v. JHU - PGR2026-00025

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation application of U.S. Application Serial No. 15/362,632 filed November 28, 2016, now issued as U.S. patent 10,442,860; which is a divisional application of U.S. Application Serial No. 15/231,309 filed August 8, 2016, now issued as U.S. patent 9,850,306; which is a continuation application of U.S. Application Serial No. 14/645,282 filed March 11, 2015, now issued as U.S. patent 9,441,044; which is a continuation application of U.S. Application Serial No. 13/582,717 filed October 17, 2012, now issued as U.S. patent 8,993,524; which is a 35 USC § 371 National Stage application of International Application No. PCT/US2011/027317 filed March 4, 2011, now expired; which claims the benefit under 35 USC § 119(e) to U.S. Application Serial No. 61/435,671 filed January 24, 2011 and to U.S. Application Serial No. 61/311,255 filed March 5, 2010, both now expired. The disclosure of each of the prior applications is considered part of and is incorporated by reference in the disclosure of this application.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of targeted immunomodulatory antibodies and fusion proteins for cancer therapy and more specifically to composition and methods for targeted immunostimulatory or immunosuppressive antibodies and fusion proteins to counteract or induce immune tolerance of cancer cells.

BACKGROUND INFORMATION

[0003] The immune system provides the human body with a means to recognize and defend itself against microorganisms and substances recognized as foreign or potentially harmful. While passive immunotherapy of cancer with monoclonal antibodies and passive transfer of T cells to attack tumor cells have demonstrated clinical efficacy, the goal of active therapeutic vaccination to induce these immune effectors and establish

immunological memory against tumor cells has remained challenging. Several tumor-specific and tumor-associated antigens have been identified, yet these antigens are generally weakly immunogenic and tumors employ diverse mechanisms to create a tolerogenic environment that allows them to evade immunologic attack. Strategies to overcome such immune tolerance and activating robust levels of antibody and/or T cell responses hold the key to effective cancer immunotherapy.

SUMMARY OF THE INVENTION

[0004] The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counteract or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-β)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

[0005] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule, and the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF-β); (ii) Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2); (iii) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); (iv) Transforming growth factor-beta receptor (TGF-βR); (v) Programmed death-1 (PD-1); and (vi) Receptor activator of nuclear factor-κB (RANK).

Bicara Ex. 1006, Page 85 of 498
Bicara v. JHU - PGR2026-00025

[0006] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, or CD40.

[0007] In one aspect, the targeting moiety specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: (i) CD4; (ii) CD25 (IL-2α receptor; IL-2αR); (iii) cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); (iv) Interleukin-10 (IL-10); (v) Transforming growth factor-beta receptor (TGF-βR); (vi) Transforming growth factor-beta (TGF-β); (vii) Programmed Death-1 (PD-1); (viii) Programmed death-1 ligand (PD-L1 or PD-L2); (ix) Receptor activator of nuclear factor-κB (RANK); or (x) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL).

[0008] In one aspect, the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF-β); (ii) Programmed death-1 ligand (PD-L1 or PD-L2); or (iii) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL).

[0009] In one aspect, the immunomodulatory moiety includes a molecule that binds TGF-β. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Transforming growth factor-beta receptor TGF-βRII, TGF-βRIIb, or TGF-βRIII. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of TGF-β.

[0010] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial

growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0011] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Programmed Death-1 (PD-1), Programmed death-1 ligand 1 (PD-L1), or Programmed death-1 ligand 2 (PD-L2). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes PD-1 ectodomain, immunoglobulin Fc region, and TGFβRII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 11 or 12.

[0012] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and TGFβRII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 13 or 14.

[0013] In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Programmed death-1 ligand 1 (PD-L1).

Bicara Ex. 1006, Page 87 of 498
Bicara v. JHU - PGR2026-00025

[0014] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24.

[0015] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Programmed Death-1 (PD-1). In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and PD-1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 25 or 26.

[0016] In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Receptor activator of nuclear factor-κB ligand (RANKL).

[0017] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36.

Bicara Ex. 1006, Page 88 of 498
Bicara v. JHU - PGR2026-00025

[0018] In one aspect, the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the immunomodulatory moiety increases the function of PD-1.

[0019] In one aspect, the targeting moiety specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 37. In another aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2), and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from PD-L1. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 38 or 39.

[0020] In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25, or CD4, and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 40, 41, 42, 43, 44, or 45.

[0021] In one aspect, the targeting moiety includes the extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 46 or 47.

[0022] In one aspect, the targeting moiety includes transforming growth factor-β (TGF-β) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1

Bicara Ex. 1006, Page 89 of 498
Bicara v. JHU - PGR2026-00025

ligand 2 (PD-L2). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 48 or 49.

[0023] In one aspect, the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In an additional aspect, the immunomodulatory moiety activates the signaling function of transforming growth factor-β (TGF-β) receptor.

[0024] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from TGF-β. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 50. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from transforming growth factor-β (TGF-β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 51 or 52.

[0025] In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25 (IL-2α receptor; IL-2αR), or CD4, and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 53, 54, 55, 56, 57 or 58.

[0026] In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 59 or 60.

[0027] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or

ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from an extracellular RANKL-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 61. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from an extracellular RANK-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 62 or 63.

[0028] In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 64 or 65.

[0029] In one aspect, the targeting moiety includes a sequence from transforming growth factor-β (TGF-β) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 66 or 67.

[0030] In one aspect, the targeting moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 68 or 69.

[0031] In various aspects, the molecule is fused or directly linked to one or more antigen, antigenic determinant, or epitope.

Bicara Ex. 1006, Page 91 of 498
Bicara v. JHU - PGR2026-00025

[0032] In another embodiment, the present invention provides a composition including the molecule of the invention and a cell, wherein the cell is a tumor cell, immune cell, or dendritic cell.

[0033] In another embodiment, the present invention provides a method of counteracting or overcoming immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

[0034] In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof one or more molecule of the invention. In various aspects, the subject is administered one or more molecule of the invention in combination with another anticancer therapy. In one aspect, the anticancer therapy includes a chemotherapeutic molecule, antibody, small molecule kinase inhibitor, hormonal agent or cytotoxic agent. In another aspect, the anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

[0035] In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof an antibody that targets and depletes CD4+ regulatory T cells (Tregs) in combination with another cytotoxic anticancer therapy. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In various aspects, the cytotoxic anticancer therapy includes a chemotherapeutic molecule, tumor-targeted antibody, small molecule kinase inhibitor, hormonal agent or tumor-targeted cytotoxic agent. In another aspect, the cytotoxic anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

[0036] In another embodiment, the subject is administered one or more molecule of the invention in combination with any vaccine. In another aspect, the vaccine includes a tumor antigen, tumor-associated antigen, tumor epitope, tumor antigen-containing fusion protein, tumor cell, or dendritic cell. In another aspect, the vaccine includes a pathogen

Bicara Ex. 1006, Page 92 of 498
Bicara v. JHU - PGR2026-00025

antigen, pathogen-associated antigen, pathogen epitope, or pathogen antigen-containing fusion protein.

[0037] In another embodiment, the present invention provides a method for treating immune cells wherein the cells are contacted *ex vivo* or *in vitro* with a molecule of the invention. In another embodiment, the present invention provides a method of treatment of a neoplastic disease. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

[0038] In another embodiment, the present invention provides a method of inducing or promoting immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

[0039] In another embodiment, the present invention provides a method of preventing or treating an autoimmune or inflammatory disease including administering to a subject in need thereof one or more molecule of the invention. In one aspect, the subject is administered one or more molecule of the invention in combination with another anti-inflammatory or immunosuppressive therapy. In another embodiment, the present invention provides a method of treatment of immune cells wherein the cells are contacted *ex vivo* or *in vitro* with a molecule of the invention. In another embodiment, the present invention provides a method of treating an autoimmune or inflammatory disease or preventing rejection of grafted cells or tissue. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] Figures 1A-1C show exemplary amino acid sequences of transforming growth factor beta receptor type II (TGF-β-RII) or TGF-β-RIIB or a fragment thereof, including (i) Transforming growth factor beta receptor type II (TGF-β-RII) (SEQ ID NO: 79); and (ii) Transforming growth factor beta receptor type IIB (TGF-β-RIIB) (SEQ ID NO: 80).

[0041] Also shown in Figures 1A-1C are exemplary truncated mutants of Transforming growth factor beta Receptor II (TGF-β-RII) or TGF-β-RIIB including the Extracellular

Bicara Ex. 1006, Page 93 of 498
Bicara v. JHU - PGR2026-00025

domain (ECD) region that binds TGF-β, including (i) TGF-β R-II (ΔC terminus): TGFβ RII lacking the last 38 amino acids from the C-terminus (SEQ ID NO: 81) and TGF-β R-IIB (ΔC terminus): TGFβ RIIB lacking the last 38 aa from the C-terminus (SEQ ID NO: 82); (ii) TGF-βR-II (Δcyt): TGFβRII lacking the kinase domain & juxtamembrane region (SEQ ID NO: 83) and TGF-βR-IIB (Δcyt): TGFβRIIB lacking the kinase domain & juxtamembrane region (SEQ ID NO: 84); (iii) TGF-β R-II containing the N-terminus region including the extracellular domain (SEQ ID NO: 85) and TGF-β R-IIB containing the N-terminus region including the extracellular domain (SEQ ID NO: 86); (iv) TGF-β R-II containing the extracellular domain that binds TGF-β (SEQ ID NO: 87) and TGF-β R-IIB containing the extracellular domain that binds TGF-β (SEQ ID NO: 88); and (v) TGF-β R-II containing the region of the extracellular domain that binds TGF-β (SEQ ID NO: 89).

[0042] In addition, Figures 1A-1C also show exemplary kinase-deficient mutants, deletion mutants, or point mutants of Transforming growth factor beta Receptor II (TGFβ-RII) or TGFβ-RIIB or a fragment thereof which binds TGF-β, including (i) Transforming growth factor beta Receptor II containing point mutations - amino acid sequence of TGF-β R-II (K277R) contains a point mutation in its ATP-binding site and is inactive as a kinase (SEQ ID NO: 90); and (ii) Transforming growth factor beta Receptor II containing deletions in the amino acid sequence (deletion mutants) - Transforming growth factor beta Receptor II (Δi) - TGF-β R-II (Δi2) contains a deletion of amino acids 498 to 508 and is inactive as a kinase (SEQ ID NO: 91).

[0043] Figure 2 shows exemplary fusion proteins including anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-HER2/neu heavy chain + TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 1) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70).

[0044] Figure 3 shows exemplary fusion proteins including anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-EGFR1 heavy chain + TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 2) and anti-EGFR1 light chain amino acid sequence (SEQ ID NO: 71).

Bicara Ex. 1006, Page 94 of 498
Bicara v. JHU - PGR2026-00025

[0045] Figure 4 shows exemplary fusion proteins including anti-CD20 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-CD20 heavy chain+ TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 3) and anti-CD20 light chain amino acid sequence (SEQ ID NO: 72).

[0046] Figure 5 shows exemplary fusion proteins including anti-VEGF antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-VEGF heavy chain+ TGFβ-RII ECD fusion amino acid sequence (SEQ ID NO: 4) and anti-VEGF Light chain sequence (SEQ ID NO: 73).

[0047] Figure 6 shows exemplary fusion proteins including anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including Anti-CTLA-4 heavy chain + TGFβ-RII Extracellular domain fusion amino acid sequence (SEQ ID NO: 5) and Anti-CTLA-4 light chain (SEQ ID NO: 74).

[0048] Figure 7 shows exemplary fusion proteins including IL-2, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including IL-2 + Fc + TGFβ-RII Extracellular domain (SEQ ID NO: 6) and TGFβ-RII Extracellular domain + Fc + IL-2 (SEQ ID NO: 7). The linker GGGGSGGGGSGGGGS (SEQ ID NO: 104) is optional and can be replaced with EPKSCDK (SEQ ID NO: 105) or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0049] Figures 8A-8B show exemplary fusion proteins including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-CD25 (Daclizumab) heavy chain and TGFβ-RII Extracellular domain (SEQ ID NO: 8) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 8A); and anti-CD25 (Basiliximab) heavy chain and TGFβ-RII Extracellular domain (SEQ ID NO: 9) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76).

Bicara Ex. 1006, Page 95 of 498
Bicara v. JHU - PGR2026-00025

[0050] Figure 9 shows exemplary fusion proteins including anti-CD4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), including anti-CD4 heavy chain and TGFβ-RII Extracellular domain (SEQ ID NO: 10) and anti-CD4 light chain (SEQ ID NO: 77).

[0051] Figure 10 shows exemplary fusion proteins including Programmed Death-1 (PD-1) Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain), including PD-1 ectodomain + Fc + TGFβRII ectodomain (SEQ ID NO: 11) and TGFβRII ectodomain + Fc + PD-1 ectodomain (SEQ ID NO: 12). The linker sequence EPKSCDK (SEQ ID NO: 105) is optional and can be deleted or replaced with another linker.

[0052] Figure 11 shows exemplary fusion proteins including Receptor activator of nuclear factor-kB (RANK) Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain), including RANK ectodomain + Fc + TGFβRII ectodomain (SEQ ID NO: 13) and TGFβRII ectodomain + Fc + RANK ectodomain (SEQ ID NO: 14). The linker sequence EPKSCDK (SEQ ID NO: 105) is optional and can be deleted or replaced with another linker.

[0053] Figure 12 shows exemplary immunomodulatory moiety that binds Programmed Death-1 ligand 1 (PD-L1 or B7-H1) or Programmed Death-1 ligand 2 (PD-L2 or B7-DC), including full-length PD-1 or fragment thereof (SEQ ID NO: 92), PD-1 extracellular domain (ectodomain) or fragment thereof (SEQ ID NO: 93), and PD-1 extracellular domain (ectodomain) ligand-binding region (SEQ ID NO: 94).

[0054] Figure 13 shows exemplary fusion proteins including anti-HER2/neu antibody and PD-1 Ectodomain, including anti-HER2/neu heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 15) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70).

[0055] Figure 14 shows exemplary fusion proteins including anti-EGFR1 antibody and PD-1 Ectodomain, including anti-EGFR heavy chain + PD-1 ectodomain fusion amino

Bicara Ex. 1006, Page 96 of 498
Bicara v. JHU - PGR2026-00025

acid sequence (SEQ ID NO: 16) and anti-EGFR light chain amino acid sequence (SEQ ID NO: 71).

[0056] Figure 15 shows exemplary fusion proteins including anti-CD20 antibody and PD-1 Ectodomain, including anti-CD20 heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 17) and anti-CD20 light chain amino acid sequence (SEQ ID NO: 72).

[0057] Figure 16 shows exemplary fusion proteins including anti-VEGF antibody and PD-1 Ectodomain, including anti-VEGF heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 18) and anti-VEGF Light chain sequence (SEQ ID NO: 73).

[0058] Figure 17 shows exemplary fusion proteins including anti-human CTLA-4 antibody and PD-1 Ectodomain, including anti-CTLA-4 heavy chain + PD-1 ectodomain fusion amino acid sequence (SEQ ID NO: 19) and anti-CTLA-4 light chain (SEQ ID NO: 74).

[0059] Figures 18A-18B show exemplary fusion proteins including anti-CD25 antibody and PD-1 Ectodomain, including anti-CD25 (Daclizumab) heavy chain and PD-1 ectodomain (SEQ ID NO: 20) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 18A), and anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 21) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76) (FIG. 18B).

[0060] Figure 19 shows exemplary fusion proteins including IL-2, Fc, and PD-1 ectodomain, including IL-2 + Fc + PD-1 ectodomain (SEQ ID NO: 22) and PD-1 ectodomain + Fc + IL-2 (SEQ ID NO: 23). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0061] Figure 20 shows exemplary fusion proteins including anti-CD4 antibody and PD-1 ectodomain, including anti-CD4 heavy chain and PD-1 ectodomain (SEQ ID NO: 24) and anti-CD4 light chain (SEQ ID NO: 77).

Bicara Ex. 1006, Page 97 of 498
Bicara v. JHU - PGR2026-00025

[0062] Figure 21 shows exemplary fusion proteins including Receptor activator of nuclear factor-kB (RANK) Ectodomain, Fc, and PD-1 ectodomain, including RANK ectodomain + Fc + PD-1 ectodomain (SEQ ID NO: 25) and PD-1 ectodomain + Fc + RANK ectodomain (SEQ ID NO: 26). The linker sequence EPKSCDK (SEQ ID NO: 105) is optional and can be deleted or replaced with another linker.

[0063] Figure 22 shows exemplary immunomodulatory moiety that binds Receptor activator of nuclear factor-kB (RANK) ligand (RANKL) including full-length RANK or fragment thereof (SEQ ID NO: 95), extracellular ligand-binding domain or ectodomain of RANK (SEQ ID NO: 96), RANKL-binding sequences or residues of RANK (SEQ ID NO: 93), or RANKL-binding sequences of Osteoprotegerin (OPG) (SEQ ID NO: 98).

[0064] Figure 23 shows exemplary fusion proteins including anti-HER2/neu antibody and RANK Ectodomain, including anti-HER2/neu heavy chain + RANK ectodomain fusion amino acid sequence (SEQ ID NO: 27) and anti-HER2/neu light chain amino acid sequence (SEQ ID NO: 70).

[0065] Figure 24 shows exemplary fusion proteins including anti-EGFR1 antibody and RANK Ectodomain, including anti-EGFR heavy chain + RANK ectodomain fusion amino acid sequence (SEQ ID NO: 28) and anti-EGFR light chain amino acid sequence (SEQ ID NO: 71).

[0066] Figure 25 shows exemplary fusion proteins including anti-CD20 antibody and RANK Ectodomain, including anti-CD20 heavy chain + RANK ectodomain fusion amino acid sequence (SEQ ID NO: 29) and anti-CD20 light chain amino acid sequence (SEQ ID NO: 72).

[0067] Figure 26 shows exemplary fusion proteins including anti-VEGF antibody and RANK Ectodomain, including anti-VEGF heavy chain + RANK ectodomain fusion amino acid sequence (SEQ ID NO: 30) and anti-VEGF Light chain sequence (SEQ ID NO: 73).

[0068] Figure 27 shows exemplary fusion proteins including anti-human CTLA-4 antibody and RANK Ectodomain, including anti-CTLA-4 heavy chain + RANK

ectodomain fusion amino acid sequence (SEQ ID NO: 31) and anti-CTLA-4 light chain (SEQ ID NO: 74).

[0069] Figures 28A-28B show exemplary fusion proteins including anti-CD25 antibody and RANK Ectodomain, including anti-CD25 (Daclizumab) heavy chain and RANK ectodomain (SEQ ID NO: 32) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 28A), and anti-CD25 (Basiliximab) heavy chain and RANK ectodomain (SEQ ID NO: 33) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76) (FIG. 28B).

[0070] Figure 29 shows exemplary fusion proteins including IL-2, Fc, and RANK ectodomain, including IL-2 + Fc + RANK ectodomain (SEQ ID NO: 34) and RANK ectodomain + Fc + IL-2 (SEQ ID NO: 35). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0071] Figure 30 shows exemplary fusion proteins including anti-CD4 antibody and RANK ectodomain, including anti-CD4 heavy chain and RANK ectodomain (SEQ ID NO: 36) and anti-CD4 light chain (SEQ ID NO: 77).

[0072] Figure 31 shows exemplary immunomodulatory moiety that binds Programmed Death-1 (PD-1) including a PD-1 ligand 1 (PD-L1 or B7-H1) or PD-1 ligand 2 (PD-L2 or B7-DC) or a fragment thereof (for example, SEQ ID NO: 101), full-length human PD-1 ligand 1 (B7-H1; PDCD1L1; PD-L1; or CD274) protein or a fragment thereof (SEQ ID NO: 99), and PD-L1 extracellular binding domain (ectodomain) or fragment thereof (SEQ ID NO: 100).

[0073] Figure 32 shows exemplary fusion proteins including anti-tumor necrosis factor (TNFα) antibody and PD-1 ligand, including anti-TNFα heavy chain + PD-1L (SEQ ID NO: 37) and anti-TNFα light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO: 107) can be replaced with KRVE (SEQ ID NO: 108) or KKVE (SEQ ID NO: 109).

Bicara Ex. 1006, Page 99 of 498
Bicara v. JHU - PGR2026-00025

[0074] Figure 33 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand, including TNFR2 ECD + IgG Cγ1 + PD-L1 (SEQ ID NO: 38) and PD-L1 + IgG Cγ1 -TNFR2 ECD (SEQ ID NO: 39).

[0075] Figure 34 shows exemplary fusion proteins including anti-CD20 antibody and PD-1 ligand 1 (PD-L1), including anti-CD20 heavy chain + PD-L1 sequence (SEQ ID NO: 40) and anti-CD20 light chain sequence (SEQ ID NO: 72).

[0076] Figures 35A-35B show exemplary fusion proteins including anti-CD25 antibody and PD-1 ligand 1 (PD-L1), including anti-CD25 (Daclizumab) heavy chain and PD-L1 (SEQ ID NO: 41) and anti-CD25 (Daclizumab) light chain (SEQ ID NO: 75) (FIG. 35A), and anti-CD25 (Basiliximab) heavy chain and PD-1 ectodomain (SEQ ID NO: 42) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76) (FIG. 35B).

[0077] Figure 36 shows exemplary fusion proteins including IL-2, Fc, and PD-1 ligand 1 (PD-L1), including fusion protein hPD-1 ligand 1 + Fc + IL-2 (SEQ ID NO: 43) and fusion protein IL-2 + Fc + PD-1 ligand 1 (SEQ ID NO: 44). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0078] Figure 37 shows exemplary fusion proteins including anti-CD4 antibody and PD-1 ligand 1 (PD-L1), including anti-CD4 heavy chain and PD-1 ligand 1 (PD-L1) (SEQ ID NO: 45) and anti-CD4 light chain (SEQ ID NO: 77).

[0079] Figure 38 shows exemplary fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from PD-1 ligand (PD-L1) including Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + PD-L1 (SEQ ID NO: 46) and PD-1L1 + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 47). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPKSCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence.

Bicara Ex. 1006, Page 100 of 498
Bicara v. JHU - PGR2026-00025

[0080] Figure 39 shows exemplary fusion proteins including a sequence of transforming growth factor-β (TGF-β), Immunoglobulin Fc (IgG Cγ1), and a sequence of PD-1 ligand (PD-L1) including TGFβ-1 + Fc + PD-L1 (SEQ ID NO: 48), and PD-1L1 + Fc + TGFβ-1 (SEQ ID NO: 49). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0081] Figure 40 shows exemplary immunomodulatory moiety that binds Transforming growth factor-beta receptor (TGF-βR) including Transforming growth factor-beta (TGF-β1, TGF-β2, or TGF-β3 or a fragment thereof, TGF-β1 full sequence (SEQ ID NO: 102), and mature (active) TGF-β1 sequence (Ala 279 – Ser 390; 112 amino acids) (SEQ ID NO: 103).

[0082] Figure 41 shows exemplary fusion proteins including an antibody that binds TNF-α, and a sequence of transforming growth factor-β (TGF-β), including anti-TNFα heavy chain + TGF-β1 (SEQ ID NO: 50) and anti-TNFα light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO: 107) can be replaced with KRVE (SEQ ID NO: 108) or KKVE (SEQ ID NO: 109).

[0083] Figure 42 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain (TNFR2 ECD), immunoglobulin Fc (IgG Cγ1), and a sequence from transforming growth factor-β (TGF-β) including TNFR2 ECD + IgG Cγ1 + TGF-β1 (SEQ ID NO: 51), and TGF-β1 + IgG Cγ1 + TNFR2 ECD (SEQ ID NO: 52).

[0084] Figure 43 shows exemplary fusion proteins including anti-CD20 antibody and a sequence from transforming growth factor-β (TGF-β), including anti-CD20 heavy chain + mature TGFβ1 sequence (SEQ ID NO: 53) and anti-CD20 light chain sequence (SEQ ID NO: 72).

[0085] Figures 44A-44B show exemplary fusion proteins including anti-CD25 antibody and a sequence from transforming growth factor-β (TGF-β), including anti-CD25 (Daclizumab) heavy chain and TGF-β1 (SEQ ID NO: 54) and anti-CD25 (Daclizumab)

Bicara Ex. 1006, Page 101 of 498
Bicara v. JHU - PGR2026-00025

light chain (SEQ ID NO: 75) (FIG. 44A), and anti-CD25 (Basiliximab) heavy chain and TGF-β1 (SEQ ID NO: 55) and anti-CD25 (Basiliximab) light chain (SEQ ID NO: 76) (FIG. 44B).

[0086] Figure 45 shows exemplary fusion proteins including IL-2, Fc, and a sequence from transforming growth factor-β (TGF-β), including TGF-β1 + Fc + IL-2 (SEQ ID NO: 56) and IL-2 + Fc + TGF-β1 (SEQ ID NO: 57). The linker GGGGSGGGGSGGGGS SEQ ID NO: 104 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence well known in the art. Certain amino acid sequences can be replaced in Fc, including underlined E with D and underlined M with L.

[0087] Figure 46 shows exemplary fusion proteins including anti-CD4 antibody and a sequence from transforming growth factor-β (TGF-β), including anti-CD4 heavy chain and TGF-β (SEQ ID NO: 58) and anti-CD4 light chain (SEQ ID NO: 77).

[0088] Figure 47 shows exemplary Fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from transforming growth factor-β (TGF-β) including Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + TGF-β1 (SEQ ID NO: 59), and TGF-β1 + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 60). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPKSCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence.

[0089] Figure 48 shows exemplary fusion proteins including an antibody that binds TNF-α, and a sequence of RANK ectodomain, including anti-TNFα heavy chain + RANK ectodomain (SEQ ID NO: 61) and anti-TNFα light chain (SEQ ID NO: 78). The sequence KKAE (SEQ ID NO: 107) can be replaced with KRVE (SEQ ID NO: 108) or KKVE (SEQ ID NO: 109).

[0090] Figure 49 shows exemplary fusion proteins including TNFR2 Extracellular ligand binding domain (TNFR2 ECD), immunoglobulin Fc (IgG Cγ1), and a sequence from RANK ectodomain including TNFR2 ECD + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 62), and RANK ectodomain + IgG Cγ1 + TNFR2 ECD (SEQ ID NO: 63).

Bicara Ex. 1006, Page 102 of 498
Bicara v. JHU - PGR2026-00025

[0091] Figure 50 shows exemplary Fusion proteins including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from RANK ectodomain including Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 64), and RANK ectodomain + IgG Cγ1 + CTLA-4 ECD (SEQ ID NO: 65). The IgG sequence shown can have optional C to S conversion in (bold underlined). The linker QEPKSCDK SEQ ID NO: 110 is optional and can be replaced with EPKSCDK SEQ ID NO: 105 or another linker sequence.

[0092] Figure 51 shows exemplary fusion proteins including a sequence from transforming growth factor-β (TGF-β), immunoglobulin Fc (IgG Cγ1), and a sequence from RANK ectodomain including TGF-β + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 66), and RANK ectodomain + IgG Cγ1 + TGF-β (SEQ ID NO: 67).

[0093] Figure 52 shows exemplary fusion proteins including a sequence from PD-1 ligand (PD-L1), immunoglobulin Fc (IgG Cγ1), and a sequence from RANK ectodomain including PD-L1 + IgG Cγ1 + RANK ectodomain (SEQ ID NO: 68), and RANK ectodomain + IgG Cγ1 + PD-L1 (SEQ ID NO: 69).

[0094] Figures 53A-53G show Regulatory T cells (Treg) accumulate in the tumor microenvironment and counteract the ability of chemotherapy to activate $CD8^+$ T cell-mediated antitumor immunity. (FIG. 53A) Surface exposure of calreticulin (CRT) in response to treatment of human (SW780) and murine (MB49) cancer cells with doxorubicin (10 μM) for 4h. The surface exposure of CRT was determined by immunofluorescence cytometry of untreated control or doxorubicin-treated cells stained with Dylight-labeled anti-CRT antibody or an isotype control (IgG1) antibody. (FIG. 53B) Priming of tumor-reactive immune responses by MB49 tumor cells treated with doxorubicin *ex vivo* or *in vivo*. $5x10^6$ MB49 cells that were pre-treated *ex vivo* with doxorubicin (10 μM) for 4h were injected into one flank of syngeneic immunocompetent C57BL/6 mice. Alternatively, C57BL/6 mice were injected with $5x10^5$ live MB49 tumor cells and then administered intratumoral doxorubicin (10 μg) at 10d following tumor inoculation. Tumor-reactive immune responses were determined by measuring production of IFN-γ by draining lymph node (DLN) cells in response to *in vitro* re-challenge with

either MB49 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (FIG. 53C) Vaccination with doxorubicin-treated tumor cells induces $CD8^+$ T cell-mediated antitumor immunity that prevents tumor formation following re-challenge with live tumor cells. MB49 cells ($5x10^6$) that were pre-treated *in vitro* with doxorubicin (10 μM) for 4h were injected subcutaneously into one flank of syngeneic immunocompetent C57BL/6 mice. Naïve or vaccinated mice were challenged with untreated live MB49 tumor cells injected into the opposite flank with or without pre-treatment with an anti-CD8 antibody (Clone GK2.43)(5 μg x 2 doses, iv) to deplete $CD8^+$ T cells. (FIG. 53D) Delayed administration of chemotherapy in mice with pre-established tumors decreases its immunogenicity and antitumor efficacy. C57BL/6 mice were injected with $5x10^5$ live syngeneic MB49 tumor cells and then administered intratumoral doxorubicin (10 μg) at d3, d7, or d10 following tumor inoculation. (FIG. 53E) Tumors foster the accumulation of $CD4^+CD25^+FoxP3^+$ cells (Tregs) in their microenvironment. Flow cytometric analyses of the percentage of $CD4^+CD25^+Fox^P3^+$ cells (Tregs) among $CD4^+$ T lymphocytes isolated from the spleen, draining lymph nodes (DLN), and tumors of immunocompetent C57BL/6 mice at d0 and d14 after subcutaneous inoculation of $5x10^5$ live MB49 tumor cells. (FIG. 53F) Tregs infiltrating the tumor microenvironment suppress priming of tumor-reactive immune responses by doxorubicin-treated tumor cells. Naïve C57BL/6 mice were vaccinated with $5x10^6$ doxorubicin-killed MB49 cells with or without intravenous adoptive transfer of $5x10^6$ $CD4^+CD25^+$ cells isolated from tumors and DLN of tumor-bearing mice via immunomagnetic separation. Tumor-reactive immune responses were determined by measuring production of IFN-γ by draining lymph node (DLN) cells in response to *in vitro* re-challenge with either MB49 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (FIG. 53G) Tregs infiltrating the tumor microenvironment suppress the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death. Naïve C57BL/6 mice were vaccinated with $5x10^6$ doxorubicin-killed MB49 cells (left flank) with or without pre-treatment with either an anti-CD8 antibody (Clone GK2.43)(5 μg x 2 doses, iv) to deplete $CD8^+$ T cells or adoptive transfer of $5x10^6$ $CD4^+CD25^+$ cells isolated from tumors and DLN of tumor-bearing mice. Protective antitumor immunity in vaccinated mice was

Bicara Ex. 1006, Page 104 of 498
Bicara v. JHU - PGR2026-00025

determined by assessment of tumor growth upon challenge with untreated live MB49 tumor cells injected into the opposite flank.

[0095] Figures 54A-54F show inhibition of TGF-β in the tumor microenvironment reduces 'adaptive' FoxP3$^+$ regulatory T cells and enhances the antitumor efficacy chemotherapy. (FIG. 54A) Tumor growth results in a progressive increase in the level of serum TGF-β. Levels of TGF-β in serum of mice at d0, d14, and d28 following inoculation of $5x10^5$ live MB49 tumor cells were evaluated utilizing ELISA. (FIG. 54B) Tumor cell-autonomous expression of TGF-β is the dominant source of elevated TGF-β in tumor-bearing mice. Tumor cells or draining lymph node cells isolated from either tumor-bearing mice or their tumor-free counterparts were cultured *ex vivo* in serum-free medium for 24h and the amount of TGF-β/10^6 cells in supernatants was measured by ELISA. (FIG. 54C) TGFβRII:Fc sequesters TGF-β in supernatants of MB49 tumor cells in a concentration-dependent manner. MB49 tumor cells were cultured in the presence of graded concentrations of TGFβRII:Fc (0-400 ng/ml) for 24h followed by measurement of TGF-β (pg/ml/10^6 cells) in supernatants via ELISA. (FIG. 54D) TGF-β induces 'adaptive' FoxP3$^+$ regulatory T cells in the tumor microenvironment. At 5d following inoculation of MB49 tumor cells, mice were either left untreated (control) or treated with TGFβRII:Fc (1μg intratumoral; twice weekly) for 3 weeks followed by flow cytometric analyses of intracellular FoxP3 expression in CD4$^+$CD25$^+$ T cells infiltrating the tumors. (FIGS. 54E, 54F). Sequestration of intratumoral TGF-β with TGFβRII:Fc reduces CD4$^+$CD25$^+$FoxP3$^+$ Tregs in tumor tissue and improves the antitumor efficacy of doxorubicin. MB49 tumor-bearing mice were administered doxorubicin (5mg/kg i.p. weekly x 3) with or without twice weekly treatment with TGFβRII:Fc (1μg intratumoral). The percentage of CD4$^+$CD25$^+$FoxP3$^+$ cells (Tregs) among tumor cells was assessed by flow cytometry (FIG. 54E), and tumor volume was monitored to determine the effect of counteracting tumor-induced TGF-β-mediated immune tolerance on the *in vivo* antitumor efficacy of doxorubicin (FIG. 54F).

[0096] Figures 55A-55D show that anti-CD4 antibody-mediated depletion of CD4$^+$ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive CD8$^+$ T

Bicara Ex. 1006, Page 105 of 498
Bicara v. JHU - PGR2026-00025

cells and enhances the antitumor efficacy of chemotherapy. (FIG. 55A) *In vivo* depletion of tumor-infiltrating $CD4^+CD25^+FoxP3^+$ T cells by treatment of tumor-bearing mice with anti-CD4 antibody. C57BL/6 mice injected with 5 $x10^5$ MB49 tumor cells s.c. were left untreated (control) or administered an anti-CD4 antibody (Clone GK1.5) i.p. at 5d and 9d following tumor challenge. $CD4^+CD25^+FoxP3^+$ T cells infiltrating tumors isolated from mice at d16 following tumor challenge were detected by flow cytometry. (FIG. 55B) Target-specific depletion of either $CD4^+$ T cells, $CD4^+CD25^+FoxP3^+$ T cells, or $CD8^+$ T cells by treatment of tumor-bearing mice with anti-CD4 antibody or anti-CD8 antibody. C57BL/6 mice injected s.c. with 5 $x10^5$ MB49 tumor cells were left untreated or treated with doxorubicin (5mg/kg i.p. weekly x 3) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Flow cytometric analyses of peripheral blood mononuclear cells isolated from mice at d16 following tumor challenge determined the percentage of $CD4^+$ T cells or $CD8^+$ T cells among total mononuclear cells, and the percentage of $CD4^+CD25^+FoxP3^+$ T cells among total $CD4^+$ T cells. (FIG. 55C) Depletion of $CD4^+$ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive $CD8^+$ T cells. C57BL/6 mice injected s.c. with 5 $x10^5$ MB49 tumor cells were left untreated or treated with doxorubicin (5mg/kg i.p. weekly x 3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN-γ expression in $CD8^+$ T cells from the tumor and draining lymph node in response to *in vitro* stimulation with MB49 cell lysates. (FIG. 55D) Depletion of $CD4^+$ regulatory T cells augments the *in vivo* antitumor efficacy of chemotherapy via activation of tumor-reactive $CD8^+$ T cells. C57BL/6 mice injected s.c. with 5 $x10^5$ MB49 tumor cells were left untreated or treated with doxorubicin (5mg/kg i.p. weekly x 3) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Tumor volume was monitored to determine the effect of depleting either $CD4^+$ T cells or $CD8^+$ T cells on the *in vivo* antitumor efficacy of doxorubicin.

Bicara Ex. 1006, Page 106 of 498
Bicara v. JHU - PGR2026-00025

[0097] Figures 56A-56F show anti-CD4 antibody-mediated depletion of $CD4^+$ regulatory T cells augments and sustains the antitumor effect of chemotherapy by enabling activation of adaptive antitumor immunity. (FIG. 56A) Surface exposure of calreticulin (CRT) in response to treatment of MB49 cancer cells with either cisplatin or the combination of cisplatin and gemcitabine for 4h. The surface exposure of CRT was determined by immunofluorescence cytometry of untreated control or chemotherapy-treated cells stained with Dylight-labeled anti-CRT antibody or an isotype control (IgG1) antibody. (FIGS. 56B, 56C) Depletion of $CD4^+$ regulatory T cells enables cisplatin-induced activation of tumor-reactive IFN-γ^+CD8^+ T cells and effector memory ($CD8^+CD62L^-$) T cells. C57BL/6 mice injected s.c. with 5 $x10^5$ MB49 tumor cells were left untreated or treated with cisplatin (0.5mg/kg i.p. weekly x 4) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN-γ expression in $CD8^+$ T cells from the tumor and draining lymph node (DLN) in response to *in vitro* stimulation with MB49 cell lysates (FIG. 56B). The percentage of effector memory T_{EM} cells was determined by flow cytometric analyses of $CD8^+CD62L^-$ cells (FIG. 56C). (FIGS. 56D, 56E and 56F) Depletion of $CD4^+$ regulatory T cells augments the *in vivo* antitumor efficacy of chemotherapy via activation of tumor-reactive $CD8^+$ T cells. C57BL/6 mice injected s.c. with 5 $x10^5$ MB49 tumor cells were left untreated or treated with either cisplatin (0.5mg/kg) or the combination of cisplatin and gemcitabine (i.p. weekly x 4) beginning at d7 following tumor inoculation, with or without administration of either anti-CD4 antibody (Clone GK1.5) or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Tumor volume was monitored to determine the effect of depleting either $CD4^+$ T cells or $CD8^+$ T cells on the *in vivo* antitumor efficacy of chemotherapy and the percentage of mice exhibiting complete tumor-regression by d50 following tumor inoculation. Establishment of adaptive antitumor immunity following regression of primary tumors was determined by re-challenging mice with live MB49 tumor cells in the opposite flank.

Bicara Ex. 1006, Page 107 of 498
Bicara v. JHU - PGR2026-00025

[0098] Figures 57A-57H show that Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of $CD4^+$ regulatory T cells to stimulate $CD8^+$ T cell-mediated tumor regression. (FIG. 57A) Genotoxic chemotherapeutic agents induce expression of mouse NKG2D ligands (Rae-1) on cancer cells. Kinetics of the upregulation of Rae1 transcripts in mouse CT26 colon cancer cells was determined by quantitative real-time PCR following treatment with irinotecan (25 μg/ml) or oxaliplatin (10 μg/ml). Quantitative RT-PCR was carried out using Rae-1 specific primers [sense, 5'-CTAGTGCCACCTGGGAATTCA-3' (SEQ ID NO: 111); anti-sense, 5'-CATCATTAGCTGATCTCCAGCTCA-3'(SEQ ID NO: 112)] and probe [5'-6-FAM-CATCAGTGACAGTTACTTCTTCACCTTCTACACAGAGA-Tamra-3' (SEQ ID NO: 113)]. (FIG. 57B) Genotoxic chemotherapeutic agents induce p53-independent cell surface expression of human NKG2D ligands (MHC-I-related A and B molecules – MICA/MICB) on cancer cells. Isogenic p53-proficient ($p53^{+/+}$) or p53-deficient ($p53^{-/-}$) HCT116 cells were treated with irinotecan (25 μg/ml) for 16h or left untreated. Irinotecan-induced upregulation of cell surface expression of MICA/B was determined by flow cytometryic analysis of tumor cells labeled with an anti-human MICA/B MAb (R&D Systems). (FIG. 57C) and (FIG. 57D) Induction of NKG2D ligands contributes to the antitumor effect of chemotherapy *in vivo*. Immunocompetent Balb/C mice injected s.c. with 2 $x10^5$ syngeneic CT26 tumor cells were treated with irinotecan (50 mg/kg i.p weekly x 3) beginning at d5 following tumor inoculation, with or without pre-treatment with an NKG2D blocking antibody (CX5, eBIOscience) (200 μg i.p.) at 16h before each dose of chemotherapy. Tumor volume was monitored to determine the effect of NKG2D blockade on the *in vivo* antitumor efficacy of irinotecan. (FIG. 57E) *In vivo* depletion of $CD4^+CD25^+FoxP3^+$ T cells by treatment of tumor-bearing mice with anti-CD4 antibody. Balb/C mice injected with 2 $x10^5$ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly x 3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. $CD4^+CD25^+FoxP3^+$ T cells in spleen and draining lymph node isolated from mice at d16 following tumor challenge were detected by flow cytometry. (FIG. 57F) Depletion of $CD4^+$ regulatory T cells facilitates irinotecan-induced activation of tumor-

Bicara Ex. 1006, Page 108 of 498
Bicara v. JHU - PGR2026-00025

reactive IFN-γ^+CD8^+ T cells. Balb/C mice injected with 2 $x10^5$ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly x 3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) at d5 and d9 following tumor inoculation. Tumor-reactive immune responses were determined by flow cytometric analyses of IFN-γ expression in $CD8^+$ T cells from the tumor and draining lymph node (DLN) in response to *in vitro* stimulation with either CT26 cell lysates, an irrelevant peptide (Hemagglutinin-HA), or medium alone. (FIG. 57G) and (FIG. 57H) Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of $CD4^+$ regulatory T cells to stimulate $CD8^+$ T cell-mediated tumor regression. Balb/C mice injected with 2 $x10^5$ CT26 tumor cells s.c. were left untreated or treated with irinotecan (50 mg/kg i.p weekly x 3) beginning at d7 following tumor inoculation, with or without administration of anti-CD4 antibody (Clone GK1.5) and/or anti-CD8 antibody (Clone GK2.43) at d5 and d9 following tumor inoculation. Tumor volume was monitored to determine the effect of depleting $CD4^+$ T cells and/or $CD8^+$ T cells on the *in vivo* antitumor efficacy of irinotecan.

DETAILED DESCRIPTION OF THE INVENTION

[0099] Targeted immunostimulatory antibodies and/or fusion proteins for prevention or treatment of cancer: Chemotherapy is a cornerstone of systemic treatment of patients with most common types of advanced cancers. The vast majority of human cancers harbor genetic alterations and signaling mechanisms that impair the direct death signaling pathways entrained by chemotherapeutic agents. Although chemotherapeutic agents employ diverse mechanisms to directly kill tumor cells, the present invention provides that these agents have immuno-adjuvant effects which activate innate and adaptive antitumor immune responses that are crucial for their antitumor efficacy *in vivo*. The present invention also provides that antitumor $CD8^+$ T cells play an instrumental role in the *in vivo* response of tumors to diverse cytotoxic chemotherapeutic agents. Although chemotherapeutic agents can induce "immunogenic" tumor cell death and facilitate cross-presentation of antigens by dendritic cells, tumors create a tolerogenic environment that allows them to suppress the activation of innate and adaptive immune responses and evade immunologic attack by immune effector cells. The present invention provides that

Bicara Ex. 1006, Page 109 of 498
Bicara v. JHU - PGR2026-00025

strategies to counteract tumor-induced immune tolerance in the tumor microenvironment can enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against disseminated cancer cells.

[0100] The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counteract or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment.

[0101] The present invention provides compositions and methods for targeted immunostimulatory antibodies and fusion proteins that counteract immune tolerance in the tumor microenvironment and promote T cell-mediated adaptive antitumor immunity for maintenance of durable long-term protection against recurrent or disseminated cancers. These tumor-targeted immunostimulatory molecules are designed to facilitate effective long term T cell-mediated immune responses against tumor cells by at least one of the following:

(i) promoting death of tumor cells via enhancement of antibody-dependent cellular cytotoxicity (ADCC);

(ii) facilitating effective cross-presentation of tumor antigen(s) from dying tumor cells by augmenting maturation of dendritic cells (DCs); and

(iii) increasing activation and proliferation of antitumor CD8+ T cells by negating immune suppression mediated by regulatory T cells and myeloid suppressor cells. These antitumor immune responses may be activated in tandem with the sensitization of tumor cells to immune effector-mediated cytotoxicity, thereby establishing a positive feedback loop that augments tumor cytoreduction and reinforces adaptive antitumor immunity. The tumor-targeted immunostimulatory monoclonal antibodies (mAbs) of the present invention provides the ability to generate and boost antitumor immunity to multiple cross-presented tumor antigens obtained from endogenous tumor

Bicara Ex. 1006, Page 110 of 498
Bicara v. JHU - PGR2026-00025

cells during the course of therapy (as an *in situ* tumor vaccine), while simultaneously leveraging the antitumor immune response to eliminate disseminated cancer cells. Accordingly, the targeted immunostimulatory antibodies and fusion proteins of the invention can integrate the hitherto distinct fields of passive and active immunotherapy and provide a novel platform for simultaneously leveraging the synergistic benefits of these strategies to entrain effective innate and adaptive immune responses against targeted cancers.

[0102] While passive immunotherapy of cancer with tumor-targeted monoclonal antibodies has demonstrated clinical efficacy, the goal of active therapeutic vaccination to induce T cell-mediated immunity and establish immunological memory against tumor cells has remained challenging. Several tumor-specific and tumor-associated antigens have been identified, yet tumors employ diverse mechanisms to create a tolerogenic environment that allows them to suppress the activation of a T cell-mediated antitumor immune response. The tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention are designed to overcome such immune tolerance in the tumor microenvironment and activate robust levels of T cell responses for effective cancer immunotherapy or chemo-immunotherapy. Accordingly, the tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention have broad clinical relevance for advancing the treatment of many types of human cancers.

[0103] The tumor-targeted immunostimulatory mAbs and/or fusion proteins of the invention provide their ability to generate and boost antitumor immunity to multiple cross-presented tumor antigens obtained from endogenous tumor cells during the course of therapy (as an *in situ* tumor vaccine), while simultaneously leveraging the antitumor immune response to eliminate disseminated cancer cells. Accordingly, the tumor-targeted immunostimulatory antibodies and/or fusion proteins of the invention can integrate the hitherto distinct fields of passive and active immunotherapy and provide a novel platform for simultaneously leveraging the synergistic benefits of these strategies to entrain effective innate and adaptive immune responses against targeted cancers. This approach of the present invention is distinguished from and superior to conventional tumor antigen-, allogeneic tumor cell- or DC-based vaccines in at least one of the following aspects: (i)

Bicara Ex. 1006, Page 111 of 498
Bicara v. JHU - PGR2026-00025

There is no *a priori* requirement to define, clone and purify individual tumor antigens, since the patient's tumor itself is the *in vivo* source of antigens; (ii) Multivalent antitumor immune responses that are naturally tailored against antigens from the patient's own tumor are less likely to allow immune escape than a pre-selected tumor antigen; (iii) The activation of antitumor immune responses by the immuno-adjuvant effects of tumor-targeted immunostimulatory antibodies or fusion proteins occurs in tandem with the sensitization of tumor cells to immune effector-mediated cytotoxicity, thereby establishing a positive feedback loop that augments tumor cytoreduction and reinforces adaptive antitumor immunity; and (iv) The molecules of the invention have broad clinical relevance for advancing the treatment of many types of human cancers.

[0104] In addition, the targeted immunostimulatory antibodies and/or fusion proteins of the invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) to counteract immune tolerance in the tumor microenvironment and promote T cell-mediated adaptive antitumor immunity for maintenance of long-term protection against recurrent or disseminated cancers (for prevention or treatment of diverse cancers); (ii) to produce immune cell compositions for adoptive cellular therapy of diverse cancers; and (iii) to serve as immune adjuvants or vaccines for prophylaxis of diverse cancers or infectious diseases.

[0105] The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to disrupt immunosuppressive networks in the tumor microenvironment. Tumors employ a wide array of regulatory mechanisms to avoid or suppress the immune response. Cancer cells actively promote immune tolerance in the tumor microenvironment via the expression of cytokines and molecules that inhibit the differentiation and maturation of antigen-presenting dendritic cells. The immunosuppressive cytokines and ligands produced by tumor cells include the following: (i) Transforming growth factor-beta (TGF-β); (ii) Programmed death-1 ligand 1 (PD-L1; B7-H1); (iii) Vascular endothelial growth factor (VEGF); and (iv) Interleukin-10 (IL-10). In addition to blocking dendritic cell (DC) maturation, these molecules promote the development of specialized subsets of immunosuppressive $CD4^+$ T cells (regulatory T cells; Treg cells) and myeloid-derived suppressor cells (MDSC). Tregs are a minority

Bicara Ex. 1006, Page 112 of 498
Bicara v. JHU - PGR2026-00025

sub-population of $CD4^+$ T cells that constitutively express CD25 [the interleukin-2 (IL-2) receptor α-chain] and the forkhead box P3 (FOXP3) transcription factor. Tregs (CD4+CD25+FoxP3+ cells) maintain immune tolerance by restraining the activation, proliferation, and effector functions of a wide range of immune cells, including $CD4^+$ and $CD8^+$ T cells, natural killer (NK) and NKT cells, B cells and antigen presenting cells (APCs) *in vitro* and *in vivo*. The accumulation of Treg cells in the tumor microenvironment re-inforces tumor immune tolerance and facilitates tumor progression and metastases. The increased expression of immunosuppressive cytokines (TGF-β; PD-L1) and tumor-infiltrating Tregs is correlated with a reduction of survival of patients with diverse types of cancers. The present invention provides that tumor-induced immune tolerance mediated via Tregs is a crucial determinant of the resistance of cancers to cytotoxic chemotherapeutic agents and tumor-targeted antibodies. The targeted immunostimulatory antibodies and/or fusion proteins of the invention inhibit key immunosuppressive molecules expressed by the targeted tumor cell or tumor-infiltrating Treg cells and myeloid suppressor cells (DCs or MDSC). As such, they provide the targeted ability to inhibit the development or function of Tregs within the tumor microenvironment. In another aspect, they provide the ability to counteract Treg-induced immune suppression in the tumor microenvironment.

[0106] The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to inhibit the development or function of Tregs and myeloid suppressor cells (DCs or MDSC) within the tumor microenvironment. Tregs (CD4+CD25+FoxP3+ cells) express an array of immunosuppressive cytokines and molecules which act in concert to induce immune tolerance and promote tumor progression and metastases. These include: (i) Cytotoxic T-lymphocyte associated protein 4 (CTLA-4; CD152), a co-inhibitory receptor that binds to the ligands CD80 (B7-1) or CD86 (B7-2) on the antigen presenting cell (APC) and inhibits co-stimulation of T cells; (ii) Programmed death-1 ligand 1 (PD-L1; B7-H1), a ligand which engages the co-inhibitory receptor Programmed death-1 (PD-1) and inhibits T cell activation and proliferation. (iii) Transforming growth factor-beta (TGF-β), a cytokine which regulates immune responses by restricting the maturation and antigen-presenting function of

dendritic cells, inhibiting the proliferation and activation of naïve T cells, suppressing the expression of cytotoxic molecules (Granzyme A/B, FasL, Apo2L/TRAIL, IFN-γ) in immune effector cells, and promoting the development and function of Tregs; (iv) Receptor activator of nuclear factor-κB ligand (RANKL), a ligand which engages Receptor activator of nuclear factor-κB (RANK) and promotes osteoclast differentiation, Treg development, and tumor metastases. In addition, Tregs express other surface molecules; (v) LAG-3, a CD4-related molecule that binds MHC class II; (vi) glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); and (vii) IL-10. The targeted immunostimulatory antibodies and/or fusion proteins of the invention provide the ability to bind a targeted molecule expressed by Tregs or myeloid suppressor cells while concurrently sequestering and inhibiting one or more immunosuppressive molecule that promotes their development, survival or function. In one aspect, the targeted immunostimulatory antibodies and/or fusion proteins directly deplete the number of Tregs.

[0107] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule on the tumor cell or tumor microenvironment (tumor stroma, tumor vasculature, or tumor infiltrating immune cell), and the immunomodulatory moiety specifically binds an immunosuppressive molecule expressed by the targeted tumor cell or tumor-infiltrating Treg cells and myeloid suppressor cells (DC or MDSC).

[0108] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule expressed by Treg cells, myeloid suppressor cells (MDSC), or dendritic cells (DC), and the immunomodulatory moiety specifically binds an immunosuppressive molecule that promotes their development, survival or function.

[0109] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety. The targeting moiety specifically binds a target molecule, and the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF-β); (ii)

Bicara Ex. 1006, Page 114 of 498
Bicara v. JHU - PGR2026-00025

Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2); (iii) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); (iv) Vascular endothelial growth factor (VEGF); (v) Transforming growth factor-beta receptor (TGF-βR); (vi) Programmed death-1 (PD-1); and (vii) Receptor activator of nuclear factor-κB (RANK).

[0110] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, or CD40.

[0111] In one aspect, the targeting moiety specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: (i) CD4; (ii) CD25 (IL-2α receptor; IL-2αR); (iii) cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); (iv) Interleukin-10 (IL-10); (v) Transforming growth factor-beta receptor (TGF-βR); (vi) Transforming growth factor-beta (TGF-β); (vii) Programmed Death-1 (PD-1); (viii) Programmed death-1 ligand (PD-L1 or PD-L2); (ix) Receptor activator of nuclear factor-κB (RANK); (x) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); (xi) LAG-3; or (xii) glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18).

[0112] In one aspect, the immunomodulatory moiety specifically binds one of the following molecules: (i) Transforming growth factor-beta (TGF-β); (ii) Programmed death-1 ligand (PD-L1 or PD-L2); (iii) Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); or (iv) vascular endothelial growth factor (VEGF).

Bicara Ex. 1006, Page 115 of 498
Bicara v. JHU - PGR2026-00025

[0113] In one aspect, the immunomodulatory moiety includes a molecule that binds TGF-β. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Transforming growth factor-beta receptor TGF-βRII, TGF-βRIIb, or TGF-βRIII. In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes a TGF-β-binding amino acid sequence corresponding to SEQ ID NOs: 79-91. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of TGF-β.

[0114] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

[0115] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Programmed Death-1 (PD-1), Programmed death-1 ligand 1 (PD-L1), or Programmed death-1 ligand 2 (PD-L2). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect, the molecule includes PD-1 ectodomain, immunoglobulin Fc region, and TGFβRII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 11 or 12.

[0116] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of TGF-βRII. In another aspect,

Bicara Ex. 1006, Page 116 of 498
Bicara v. JHU - PGR2026-00025

the molecule includes RANK ectodomain, immunoglobulin Fc region, and TGFβRII ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 13 or 14.

[0117] In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes a PD-L1-binding amino acid sequence corresponding to SEQ ID NO: 92, 93, or 94. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Programmed death-1 ligand 1 (PD-L1).

[0118] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Programmed Death-1 (PD-1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24.

[0119] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Receptor activator of nuclear factor-κB (RANK) or Receptor activator of nuclear factor-κB ligand (RANKL). In another aspect, the targeting moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain of Programmed Death-1 (PD-1). In another aspect, the molecule includes RANK ectodomain, immunoglobulin Fc region, and PD-1 ectodomain. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 25 or 26.

[0120] In one aspect, the immunomodulatory moiety includes a molecule that specifically binds to Receptor activator of nuclear factor-κB ligand (RANKL). In another

aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes a RANKL-binding amino acid sequence corresponding to SEQ ID NO: 95, 96, 97, or 98. In an additional aspect, the immunomodulatory moiety inhibits the activity or function of Receptor activator of nuclear factor-κB ligand (RANKL).

[0121] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to HER2/neu, EGFR1, CD20, vascular endothelial growth factor (VEGF), cytotoxic T-lymphocyte antigen-4 (CTLA-4), CD25 (IL-2α receptor; IL-2αR), or CD4. In an additional aspect, the immunomodulatory moiety includes an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36.

[0122] The present invention provides novel targeted immunosuppressive antibodies and fusion proteins that induce or promote immune tolerance by at least one of the following:

(i) inhibiting the activation of dendritic cells, T cells, and/or B cells; and

(ii) promoting the development and/or suppressor function of regulatory T cells and immunosuppressive myeloid DCs. These targeted immunosuppressive molecules of the invention are designed to suppress unwanted or excessive immune or inflammatory responses in order to treat autoimmune or inflammatory diseases or prevent the rejection of a transplanted cell, tissue, or organ.

[0123] Targeted immunosuppressive antibodies and/or fusion proteins: The aberrant activation of self-reactive T cells and/or breakdown of the mechanisms of immune tolerance promotes the development of autoimmunity that results in various diseases including type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis. The targeted immunosuppressive antibodies and/or fusion proteins of the invention are designed to suppress unwanted or excessive immune or inflammatory responses and restore or promote immune tolerance.

Bicara Ex. 1006, Page 118 of 498
Bicara v. JHU - PGR2026-00025

Accordingly, the compositions and methods of the invention have broad clinical relevance for the treatment of diverse autoimmune or inflammatory diseases and preventing the rejection of a transplanted cell, tissue, or organ grafts.

[0124] The targeted immunosuppressive antibodies and/or fusion proteins of the invention provides their ability to inhibit the activity of targeted pro-inflammatory cytokines or immune cells while simultaneously promoting immune tolerance via the targeted delivery of immunosuppressive molecules that facilitate the development and/or function of regulatory T cells. These molecules of the present invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) The molecules of the invention enable targeted delivery of immunosuppressive molecules to immune cells or pro-inflammatory molecules in the milieu of the affected cell, tissue or organ; (ii) The molecules of the invention can couple the inhibition of the targeted pro-inflammatory molecule or immune cell with the simultaneous delivery of an immunosuppressive molecule that promotes immune tolerance, thereby improving the suppression of immune effector cells; and (iii) The molecules of the invention can provide a mechanism of simultaneously engaging two independent or synergistic mechanisms of immune tolerance or immune suppression.

[0125] Further, the targeted immunosuppressive antibodies and/or fusion proteins of the invention are distinguished from and superior to existing therapeutic molecules in at least one of the following aspects: (i) To suppress unwanted or excessive immune or inflammatory responses in order to treat autoimmune or inflammatory diseases; and (ii) To prevent the rejection of a transplanted cell, tissue, or organ grafts.

[0126] In one aspect, the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes a PD-1-binding amino acid sequence corresponding to SEQ ID NO: 99, 100, or 101. In an additional aspect, the immunomodulatory moiety increases the function of PD-1.

Bicara Ex. 1006, Page 119 of 498
Bicara v. JHU - PGR2026-00025

[0127] In one aspect, the targeting moiety specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 37. In another aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2), and the immunomodulatory moiety includes a sequence from PD-1 ligand 1 (PD-L1 or B7-H1). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from PD-L1. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 38 or 39.

[0128] In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25, or CD4, and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 40, 41, 42, 43, 44, or 45.

[0129] In one aspect, the targeting moiety includes the extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 46 or 47.

[0130] In one aspect, the targeting moiety includes transforming growth factor-β (TGF-β) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) or Programmed death-1 ligand 2 (PD-L2). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 48 or 49.

Bicara Ex. 1006, Page 120 of 498
Bicara v. JHU - PGR2026-00025

[0131] In one aspect, the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 99, 100, or 101. In an additional aspect, the immunomodulatory moiety activates the signaling function of transforming growth factor-β (TGF-β) receptor.

[0132] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from TGF-β. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 50. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from transforming growth factor-β (TGF-β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 51 or 52.

[0133] In one aspect, the targeting moiety includes an antibody or antibody fragment that specifically binds to CD20, CD25 (IL-2α receptor; IL-2αR), or CD4, and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In an additional aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 53, 54, 55, 56, 57 or 58.

[0134] In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes a sequence from transforming growth factor-β (TGF-β). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 59 or 60.

[0135] In one aspect, the targeting moiety includes an antibody, antibody fragment, or polypeptide that specifically binds to Tumor Necrosis Factor-α (TNF-α), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or

ectodomain of Receptor activator of nuclear factor-κB (RANK) or Osteoprotegerin (OPG). In an additional aspect, the targeting moiety includes an antibody that binds TNF-α, and the immunomodulatory moiety includes a sequence from an extracellular RANKL-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 61. In one aspect, the targeting moiety includes an extracellular ligand-binding domain of tumor necrosis factor receptor 2 (TNFR2). In another aspect, the molecule includes TNFR2 Extracellular ligand binding domain, immunoglobulin Fc region, and a sequence from an extracellular RANK-binding domain or ectodomain of RANK. In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 62 or 63.

[0136] In one aspect, the targeting moiety includes an extracellular domain of CTLA-4 and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK) or Osteoprotegerin (OPG). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 64 or 65.

[0137] In one aspect, the targeting moiety includes a sequence from transforming growth factor-β (TGF-β) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 66 or 67.

[0138] In one aspect, the targeting moiety includes a sequence from Programmed death-1 ligand 1 (PD-L1) and immunoglobulin Fc region (IgG Cγ1), and the immunomodulatory moiety includes an extracellular RANKL-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK). In another aspect, the molecule includes an amino acid sequence corresponding to SEQ ID NO: 68 or 69.

[0139] In various aspects, the molecule is fused or directly linked to one or more antigen, antigenic determinant, or epitope.

Bicara Ex. 1006, Page 122 of 498
Bicara v. JHU - PGR2026-00025

[0140] In another embodiment, the present invention provides a composition including the molecule of the invention and a cell, wherein the cell is a tumor cell, immune cell, or dendritic cell.

[0141] In another embodiment, the present invention provides a method of counteracting or overcoming immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

[0142] In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. In one aspect, the neoplastic disease is a non-T cell malignancy which does not express CD4 on the tumor cell. In one embodiment, the method includes administration to a subject in need thereof an antibody that targets and depletes CD4+ regulatory T cells (Tregs) in combination with a cytotoxic anticancer therapy. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In various aspects, the cytotoxic anticancer therapy includes a chemotherapeutic molecule, tumor-targeted antibody, small molecule kinase inhibitor, hormonal agent, or tumor-targeted cytotoxic agent, anti-angiogenic agent or any combination thereof. In another aspect, the cytotoxic anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation.

[0143] In another embodiment, the method includes administration to a subject in need thereof an antibody or molecule that targets and depletes CD4+ regulatory T cells (Tregs) in combination with an immunostimulatory antibody, fusion protein, peptide or ligand that targets CTLA-4, PD1, PD-1L, RANKL, TGF- β, GITR, 4-1BB, OX-40, or Toll-like receptors (TLR 1-10). In one aspect, the TLR-agonist comprises an activator of TLR-8 or TLR-9. In one aspect, the TLR agonist comprises an immunostimulatory nucleic acid sequence containing CpG nucleotides. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody.

[0144] In another embodiment, the present invention provides a method of preventing or treating a neoplastic disease. The method includes administration to a subject in need thereof one or more molecule of the invention. In various aspects, the subject is

Bicara Ex. 1006, Page 123 of 498
Bicara v. JHU - PGR2026-00025

administered one or more molecule of the invention in combination with another anticancer therapy. In one aspect, the anticancer therapy includes a chemotherapeutic molecule, antibody, small molecule kinase inhibitor, hormonal agent, cytotoxic agent, targeted therapeutic agent, or anti-angiogenic agent. In another aspect, the anticancer therapy includes ionizing radiation, ultraviolet radiation, cryoablation, thermal ablation, or radiofrequency ablation. In another aspect, the subject is administered one or more molecule of the invention in combination with an antibody or molecule that inhibits the production or function of regulatory T cells (Tregs) or depletes the number of Tregs. In one aspect, the antibody that targets and depletes Tregs is an anti-CD4 antibody. In another aspect, the molecule that counteracts the function of Tregs is an antibody, fusion protein, peptide or ligand that targets CTLA-4, PD1, PD-1L, RANKL, TGF- β, GITR. In another aspect, the molecule that counteracts the function of Tregs is an antibody or fusion protein or ligand that targets 4-1BB or OX-40. In another aspect, the molecule that counteracts the function of Tregs is an agonist of Toll-like receptors (TLR 1-10). In one aspect, the TLR-agonist comprises an activator of TLR-8 or TLR-9. In one aspect, the TLR agonist is an immunostimulatory nucleic acid sequence containing CpG nucleotides.

[0145] In one aspect the chemotherapeutic agent is a topoisomerase-interacting agent, anthracycline, doxorubicin, mitoxantrone, camptothecin, camptothecin analogue, irinotecan, epipodophyilotoxin, etoposide, alkylating agent, cyclophosphamide, cisplatin, cisplatin analogue, oxaliplatin, antimetabolite, fluoropyrimidine analogue, 5-fluorouracil, gemcitabine, azacytidine, antimicrotubule agent, taxane, paclitaxel, or docetaxel.

[0146] In another embodiment, the subject is administered one or more molecule of the invention in combination with any vaccine. In another aspect, the vaccine includes a tumor antigen, tumor-associated antigen, tumor epitope, tumor antigen-containing fusion protein, tumor cell, or dendritic cell. In another aspect, the vaccine includes a pathogen antigen, pathogen-associated antigen, pathogen epitope, or pathogen antigen-containing fusion protein. In one aspect, the vaccine includes a surrogate CD4+ T cell helper epitope from tetanus toxin. In one aspect, the CD4+ T helper sequence contains a domain of tetanus toxin fragment C (pDOM1). In one aspect, the pDOM sequence is fused to a cell-

Bicara Ex. 1006, Page 124 of 498
Bicara v. JHU - PGR2026-00025

permeabilizing cationic polypeptide (*e.g.,* Arginine-9). In another aspect, the Arg9-pDOM sequence is fused to a specific antigen comprising the vaccine.

[0147] In another embodiment, the present invention provides a method for treating immune cells wherein the cells are contacted *ex vivo* or *in vitro* with a molecule of the invention. In another embodiment, the present invention provides a method of treatment of a neoplastic disease. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

[0148] In another embodiment, the present invention provides a method of inducing or promoting immune tolerance. The method includes administering to a subject in need thereof one or more molecule of the invention.

[0149] In another embodiment, the present invention provides a method of preventing or treating an autoimmune or inflammatory disease including administering to a subject in need thereof one or more molecule of the invention. In one aspect, the subject is administered one or more molecule of the invention in combination with another anti-inflammatory or immunosuppressive therapy. In another embodiment, the present invention provides a method of treatment of immune cells wherein the cells are contacted *ex vivo* or *in vitro* with a molecule of the invention. In another embodiment, the present invention provides a method of treating an autoimmune or inflammatory disease or preventing rejection of grafted cells or tissue. The method includes administering to a subject in need thereof a composition of immune cells contacted with a molecule of the invention.

[0150] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0151] As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, references to "the method" includes one or more methods, and/or steps

Bicara Ex. 1006, Page 125 of 498
Bicara v. JHU - PGR2026-00025

of the type described herein which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0152] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described.

[0153] As used herein "immune cells" or "immune effector cells" include T lymphocytes, B lymphocytes, natural killer (NK) cells, NKT cells, monocytes, macrophages, dendritic cells (DC), antigen presenting cells (APC).

[0154] As used herein, "neoplasm" or "tumor" including grammatical variations thereof, means new and abnormal growth of tissue, which may be benign or cancerous. In a related aspect, the neoplasm is indicative of a neoplastic disease or disorder, including but not limited, to various cancers. For example, such cancers can include prostate, pancreatic, biliary, colon, rectal, liver, kidney, lung, testicular, breast, ovarian, pancreatic, brain, and head and neck cancers, melanoma, sarcoma, multiple myeloma, leukemia, lymphoma, and the like.

[0155] A used herein, "subject," including grammatical variations thereof, means a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse.

[0156] As used herein, "targeting moiety" refers to a molecule that has the ability to localize and bind to a specific molecule or cellular component. The targeting moiety can be an antibody, antibody fragment, scFv, Fc-containing polypeptide, fusion antibody, polypeptide, peptide, aptamer, ligand, nucleic acid, or any combination thereof. In one embodiment, a targeting moiety can bind to a molecule present in a cell or tissue. In one aspect, the targeting moiety can bind a molecule in a diseased cell or tissue, such as a cancer cell or tumor. In, another aspect, the targeting molecule can bind a normal cell or tissue, such as an immune cell. In another aspect, the targeting moiety can bind a cellular

Bicara Ex. 1006, Page 126 of 498
Bicara v. JHU - PGR2026-00025

or extracellular molecule that modulates the immune response. In another aspect, the targeting moiety binds a growth factor receptor, growth factor, cytokine receptor, cytokine, or cell surface molecule.

[0157] In another embodiment, the targeting moiety is a tumor-targeting moiety. The tumor-targeting moiety can bind a component of a tumor cell or bind in the vicinity of a tumor cell (*e.g.*, tumor vasculature or tumor microenvironment). In one embodiment, the tumor targeting moiety binds to a component of a tumor cell, tumor microenvironment, tumor vasculature, tumor-associated lymphocyte, tumor antigen, tumor-associated antigen, tumor cell surface molecule, tumor antigenic determinant, tumor antigen-containing fusion protein, tumor-associated cell, tumor-associated immune cell, or tumor vaccine.

[0158] For example, in various embodiments, a targeting moiety is specific for or binds to a molecule or component, which includes but is not limited to, epidermal growth factor receptor (EGFR, EGFR1, ErbB-1, HER1), ErbB-2 (HER2/neu), ErbB-3/HER3, ErbB-4/HER4, EGFR ligand family; insulin-like growth factor receptor (IGFR) family, IGF-binding proteins (IGFBPs), IGFR ligand family (IGF-1R); platelet derived growth factor receptor (PDGFR) family, PDGFR ligand family; fibroblast growth factor receptor (FGFR) family, FGFR ligand family, vascular endothelial growth factor receptor (VEGFR) family, VEGF family; HGF receptor family: TRK receptor family; ephrin (EPH) receptor family; AXL receptor family; leukocyte tyrosine kinase (LTK) receptor family; TIE receptor family, angiopoietin 1, 2; receptor tyrosine kinase-like orphan receptor (ROR) receptor family; discoidin domain receptor (DDR) family; RET receptor family; KLG receptor family; RYK receptor family; MuSK receptor family; Transforming growth factor alpha (TGF-α), TGF-α receptor; Transforming growth factor-beta (TGF-β), TGF-β receptor; Interleukin 13 receptor alpha2 chain (lL13Ralpha2), Interleukin-6 (IL-6), 1L-6 receptor, Interleukin-4, IL-4 receptor, Cytokine receptors, Class I (hematopoietin family) and Class II (interferon/lL-10 family) receptors, tumor necrosis factor (TNF) family, TNF-α, tumor necrosis factor (TNF) receptor superfamily (TNTRSF), death receptor family, TRAIL-receptor; cancer-testis (CT) antigens, lineage-specific antigens, differentiation antigens, alpha-actinin-4, ARTC1, breakpoint cluster region-Abelson (Bcr-

Bicara Ex. 1006, Page 127 of 498
Bicara v. JHU - PGR2026-00025

abl) fusion products, B-RAF, caspase-5 (CASP-5), caspase-8 (CASP-8), beta-catenin (CTNNB1), cell division cycle 27 (CDC27), cyclin-dependent kinase 4 (CDK4), CDKN2A, COA-1, dek-can fusion protein, EFTUD-2, Elongation factor 2 (ELF2), Ets variant gene 6/acute myeloid leukemia 1 gene ETS (ETC6-AML1) fusion protein, fibronectin (FN), GPNMB, low density lipid receptor/GDP-L fucose: beta-Dgalactose 2-alpha-Lfucosyltraosferase (LDLR/FUT) fusion protein, HLA-A2, arginine to isoleucine exchange at residue 170 of the alpha-helix of the alpha2-domain in the HLA-A2 gene (HLA-A*201-R170I), MLA-A11, heat shock protein 70-2 mutated (HSP70-2M), KIAA0205, MART2, melanoma ubiquitous mutated 1,2, 3 (MUM-1, 2,3), prostatic acid phosphatase (PAP), neo-PAP, Myosin class 1, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, K-ras (KRAS2), N-ras (NRAS), HRAS, RBAF600, SIRT2, SNRPD1, SYT-SSX1 or -SSX2 fusion protein, Triosephosphate Isomerase, BAGE, BAGE-1, BAGE-2,3,4,5, GAGE-1,2,3,4,5,6,7,8, GnT-V (aberrant N-acetyl giucosaminyl transferase V, MGAT5), HERV-K-MEL, KK-LC, KM-HN-1, LAGE, LAGE-1, CTL-recognized antigen on melanoma (CAMEL), MAGE-Al (MAGE-1), MAGE-A2, MAGE-A3, MAGE-A4, MAGE-AS, MAGE-A6, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-3, MAGE-B1, MAGE-B2, MAGE-B5, MAGE-B6, MAGE-C1, MAGE-C2, mucin 1 (MUCl), MART-1/Melan-A (MLANA), gp100, gp100/Pme117 (S1LV), tyrosinase (TYR), TRP-1, HAGE, NA-88, NY-ESO-1, NY-ESO-l/LAGE-2, SAGE, Sp17, SSX-1,2,3,4, TRP2-1NT2, carcino-embryonic antigen (CEA), Kallikfein 4, mammaglobm-A, OA1, prostate specific antigen (PSA), prostate specific membrane antigen, TRP-l/gp75, TRP-2, adipophilin, interferon inducible protein absent in nielanorna 2 (AIM-2), BING-4, CPSF, cyclin D1, epithelial cell adhesion molecule (Ep-CAM), EpbA3, fibroblast growth factor-5 (FGF-5), glycoprotein 250 (gp250intestinal carboxyl esterase (iCE), alpha-feto protein (AFP), M-CSF, mdm-2, MUCI, p53 (TP53), PBF, FRAME, PSMA, RAGE-1, RNF43, RU2AS, SOX10, STEAP1, survivin (BIRCS), human telomerase reverse transcriptase (hTERT), telomerase, Wilms' tumor gene (WT1), SYCP1, BRDT, SPANX, XAGE, ADAM2, PAGE-5, LIP1, CTAGE-1, CSAGE, MMA1, CAGE, BORIS, HOM-TES-85, AF15q14, HCA66I, LDHC, MORC, SGY-1, SPO11, TPX1, NY-SAR-35, FTHLI7, NXF2 TDRD1, TEX 15, FATE, TPTE, immunoglobulin idiotypes, Bence-Jones protein, estrogen receptors (ER), androgen receptors (AR), CD40,

CD30, CD20, CD19, CD33, CD4, CD25, CD3, cancer antigen 72-4 (CA 72-4), cancer antigen 15-3 (CA 15-3), cancer antigen 27-29 (CA 27-29), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), beta-human chorionic gonadotropin, 1-2 microglobulin, squamous cell carcinoma antigen, neuron-specific enoJase, heat shock protein gp96, GM2, sargramostim, CTLA-4, 707 alanine proline (707-AP), adenocarcinoma antigen recognized by T cells 4 (ART-4), carcinoembryogenic antigen peptide-1 (CAP-1), calcium-activated chloride channel-2 (CLCA2), cyclophilin B (Cyp-B), human signet ring tumor-2 (HST-2), Human papilloma virus (HPV) proteins (HPV-E6, HPV-E7, major or minor capsid antigens, others), Epstein-Barr vims (EBV) proteins (EBV latent membrane proteins—LMP1, LMP2; others), Hepatitis B or C virus proteins, and HIV proteins. A composition of the invention can further include the foregoing as a peptide/polypeptide and/or encoding the same.

[0159] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell. In one aspect, the targeting moiety specifically binds epidermal growth factor receptor (EGFR1, Erb-B1), HER2/neu (Erb-B2), CD20, Vascular endothelial growth factor (VEGF), insulin-like growth factor receptor (IGF-1R), TRAIL-receptor, epithelial cell adhesion molecule, carcino-embryonic antigen, Prostate-specific membrane antigen, Mucin-1, CD30, CD33, CD40, or a combination thereof.

[0160] Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as trastuzumab (anti-HER2/neu antibody); Pertuzumab (anti-HER2 mAb); cetuximab (chimeric monoclonal antibody to epidermal growth factor receptor EGFR); panitumumab (anti-EGFR antibody); nimotuzumab (anti-EGFR antibody); Zalutumumab (anti-EGFR mAb); Necitumumab (anti-EGFR mAb); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-447 (humanized anti-EGF receptor bispecific antibody); Rituximab (chimeric murine/human anti-CD20 mAb); Obinutuzumab (anti-CD20 mAb); Ofatumumab (anti-CD20 mAb); Tositumumab-I131 (anti-CD20 mAb); Ibritumomab tiuxetan (anti-CD20 mAb); Bevacizumab (anti-VEGF

mAb); Ramucirumab (anti-VEGFR2 mAb); Ranibizumab (anti-VEGF mAb); Aflibercept (extracellular domains of VEGFR1 and VEGFR2 fused to IgG1 Fc); AMG386 (angiopoietin-1 and -2 binding peptide fused to IgG1 Fc); Dalotuzumab (anti-IGF-1R mAb); Gemtuzumab ozogamicin (anti-CD33 mAb); Alemtuzumab (anti-Campath-1/CD52 mAb); Brentuximab vedotin (anti-CD30 mAb); Catumaxomab (bispecific mAb that targets epithelial cell adhesion molecule and CD3); Naptumomab (anti-5T4 mAb); Girentuximab (anti-Carbonic anhydrase ix); or Farletuzumab (anti-folate receptor). Other examples include antibodies such as Panorex™ (17-1A) (murine monoclonal antibody); Panorex (@ (17-1A) (chimeric murine monoclonal antibody); BEC2 (ami-idiotypic mAb, mimics the GD epitope) (with BCG); Oncolym (Lym-1 monoclonal antibody); SMART M195 Ab, humanized 13' 1 LYM-1 (Oncolym), Ovarex (B43.13, anti-idiotypic mouse mAb); 3622W94 mAb that binds to EGP40 (17-1A) pancarcinoma antigen on adenocarcinomas; Zenapax (SMART Anti-Tac (IL-2 receptor); SMART M195 Ab, humanized Ab, humanized); NovoMAb-G2 (pancarcinoma specific Ab); TNT (chimeric mAb to histone antigens); TNT (chimeric mAb to histone antigens); Gliomab-H (Monoclonals—Humanized Abs); GNI-250 Mab; EMD-72000 (chimeric-EGF antagonist); LymphoCide (humanized IL.L.2 antibody); and MDX-260 bispecific, targets GD-2, ANA Ab, SMART IDIO Ab, SMART ABL 364 Ab or ImmuRAIT-CEA. Examples of antibodies include those disclosed in US5736167, US7060808, and US5821337.

[0161] In one embodiment, the targeting moiety specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: CD4; CD25 (IL-2α receptor; IL-2αR); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta receptor (TGF-βR); Transforming growth factor-beta (TGF-β); Programmed Death-1 (PD-1); Programmed death-1 ligand (PD-L1 or PD-L2); Receptor activator of nuclear factor-κB (RANK); Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); or Interleukin-4 receptor (IL-4R). In one aspect, the targeting moiety is an agonist that increases the function of the targeted

Bicara Ex. 1006, Page 130 of 498
Bicara v. JHU - PGR2026-00025

molecule. In another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

[0162] In one aspect, the targeting moiety binds a specific cytokine, cytokine receptor, co-stimulatory molecule, co-inhibitory molecule, or immunomodulatory receptor that modulates the immune system. In another aspect, the targeting moiety specifically binds one of the following molecules: tumor necrosis factor (TNF) superfamily; tumor necrosis factor-α (TNF-α); tumor necrosis factor receptor (TNFR) superfamily; Interleukin-12 (IL-12); IL-12 receptor; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L; CD40; CD40 ligand (CD40L); CTLA-4; Programmed death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); or PD-1 ligand 2 (PD-L2; B7-DC); B7 family; B7-1 (CD80); B7-2 (CD86); B7-H3; B7-H4; GITR/AITR; GITRL/AITRL; BTLA; CD70; CD27; LIGHT; HVEM; Toll-like receptor (TLR)(TLR 1,2,3,4,5,6,7,8,9, 10). In one aspect, the targeting moiety is an agonist that increases the function of the targeted molecule. In another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

[0163] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide, or peptide that specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a cytokine, cytokine receptor, co-stimulatory molecule, or co-inhibitory molecule that modulates the immune system. In another aspect, the targeting moiety specifically binds one of the following molecules: CD4; CD25 (IL-2α receptor; IL-2αR); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta receptor (TGF-βR); Transforming growth factor-beta (TGF-β); Programmed Death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); PD-1 ligand 2 (PD-L2; B7-DC); Receptor activator of nuclear factor-κB (RANK); Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); Interleukin-4 receptor (IL-4R); tumor necrosis factor (TNF) superfamily; tumor necrosis factor-α (TNF-

Bicara Ex. 1006, Page 131 of 498
Bicara v. JHU - PGR2026-00025

α); tumor necrosis factor receptor (TNFR) superfamily; Interleukin-12 (IL-12); IL-12 receptor; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L; CD40; CD40 ligand (CD40L); CTLA-4; B7 family; B7-1 (CD80); B7-2 (CD86); B7-H3; B7-H4; GITR/AITR; GITRL/AITRL; BTLA; CD70; CD27; LIGHT; or HVEM. In one aspect, the targeting moiety is an agonist that increases the function of the targeted molecule. In another aspect, the targeting moiety is an antagonist that inhibits the function of the targeted molecule.

[0164] Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as Zanulimumab (anti-CD4 mAb), Keliximab (anti-CD4 mAb); Ipilimumab (MDX-101; anti-CTLA-4 mAb); Tremilimumab (anti-CTLA-4 mAb); (Daclizumab (anti-CD25/IL-2R mAb); Basiliximab (anti-CD25/IL-2R mAb); MDX-1106 (anti-PD1 mAb); antibody to GITR; GC1008 (anti-TGF-β antibody); metelimumab/CAT-192 (anti- TGF-β antibody); lerdelimumab/CAT-152 (anti- TGF-β antibody); ID11 (anti- TGF-β antibody); Denosumab (anti-RANKL mAb); BMS-663513 (humanized anti-4-1BB mAb); SGN-40 (humanized anti-CD40 mAb); CP870,893 (human anti-CD40 mAb); Infliximab (chimeric anti-TNF mAb; Adalimumab (human anti-TNF mAb); Certolizumab (humanized Fab anti-TNF); Golimumab (anti-TNF); Etanercept (Extracellular domain of TNFR fused to IgG1 Fc); Belatacept (Extracellular domain of CTLA-4 fused to Fc); Abatacept (Extracellular domain of CTLA-4 fused to Fc); Belimumab (anti-B Lymphocyte stimulator); Muromonab-CD3 (anti-CD3 mAb); Otelixizumab (anti-CD3 mAb); Teplizumab (anti-CD3 mAb); Tocilizumab (anti-IL6R mAb); REGN88 (anti-IL6R mAb); Ustekinumab (anti-IL-12/23 mAb); Briakinumab (anti-IL-12/23 mAb); Natalizumab (anti-α4 integrin); Vedolizumab (anti-α4 β7 integrin mAb); T1h (anti-CD6 mAb); Epratuzumab (anti-CD22 mAb); Efalizumab (anti-CD11a mAb); and Atacicept (extracellular domain of transmembrane activator and calcium-modulating ligand interactor fused with Fc).

[0165] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an "immunomodulatory moiety". As used herein, "immunomodulatory moiety" refers to a ligand, peptide, polypeptide, or Fc-containing

Bicara Ex. 1006, Page 132 of 498
Bicara v. JHU - PGR2026-00025

polypeptide that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell and modulates the number or function of Tregs or myeloid suppressor cells. In an additional aspect, the "immunomodulatory moiety" specifically binds a cytokine, cytokine receptor, co-stimulatory molecule, or co-inhibitory molecule that modulates the immune system. In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: Transforming growth factor-beta receptor (TGF-βR); Transforming growth factor-beta (TGF-β); Programmed Death-1 (PD-1); PD-1 ligand 1 (PD-L1; B7-H1); PD-1 ligand 2 (PD-L2; B7-DC); Receptor activator of nuclear factor-κB (RANK); or Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); or vascular endothelial growth factor (VEGF). In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18); GITRL/AITRL; 4-1BB (CD137); 4-1BB ligand (4-1BBL; CD137L); OX40 (CD134; TNR4); OX40 ligand (OX40L); B7-H3; B7-H4; BTLA; CD40; CD40 ligand (CD40L); CD70; CD27; LIGHT; or HVEM. In another aspect, the immunomodulatory moiety specifically binds one of the following molecules: tumor necrosis factor-α (TNF-α); Interleukin-12 (IL-12); IL-12R; Interleukin-10 (IL-10); IL-10R. In another aspect, the immunoodulatory moiety comprises an extracellular domain of CTLA-4. In one aspect, the immunomodulatory moiety is an agonist that increases the function of the bound molecule. In another aspect, the immunomodulatory moiety is an antagonist that inhibits the function of the targeted molecule.

[0166] In another aspect, the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF-βRII, TGF-βRIIb, or TGF-βRIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor-κB (RANK); vascular endothelial growth factor receptor (VEGFR1 or VEGFR2); or IL-10R. In another aspect, the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: tumor necrosis factor receptor 2 (TNFR2); 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18). In an additional

aspect, the extracellular domain of the specific receptor binds the cognate ligand and inhibits the interaction of the ligand with its native receptor.

[0167] In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: Transforming growth factor-beta (TGF-β); PD-1 ligand 1 (PD-L1); PD-1 ligand 2 (PD-L2); or IL-10. In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL.

[0168] In another aspect, the immunomodulatory moiety is fused to the C-terminus of the targeting moiety. In another aspect, the immunomodulatory moiety is fused to the N-terminus of the targeting moiety. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is the targeting moiety, Fc is an immunoglobulin Fc region, and Y is the immunomodulatory moiety. In another aspect, the fusion molecule is represented by Y-Fc-X, wherein X is the targeting moiety, and Y is the immunomodulatory moiety. In one aspect, the targeting moiety may additionally be an immunomodulatory moiety.

[0169] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell, and the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF-βRII, TGF-βRIIb, or TGF-βRIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor-κB (RANK); vascular endothelial growth factor receptor (VEGFR1 or VEGFR2); or IL-10R.

[0170] In one aspect, the targeting moiety includes an antibody, antibody fragment, scFv, or Fc-containing polypeptide that specifically binds a component of a tumor cell, tumor antigen, tumor vasculature, tumor microenvironment, or tumor-infiltrating immune cell, and the immunomodulatory moiety comprises one or more of the following ligands or

Bicara Ex. 1006, Page 134 of 498
Bicara v. JHU - PGR2026-00025

active ligand fragments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL.

[0171] In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds a specific component of a regulatory T cell, myeloid suppressor cell, or dendritic cell, and the immunomodulatory moiety comprises an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF-βRII, TGF-βRIIb, or TGF-βRIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor-κB (RANK); or IL-10R. In another aspect, the immunomodulatory moiety comprises one or more of the following ligands or active ligand fragments: 4-1BB ligand (4-1BBL; CD137L); OX40 ligand (OX40L); IL-12; CD40L; or GITRL/AITRL. In another aspect, the specific targeted component of a regulatory T cell, myeloid suppressor cell, or dendritic cell is one of the following molecules: CD4; CD25 (IL-2α receptor; IL-2αR); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta (TGF-β); Programmed Death-1 (PD-1); Programmed death-1 ligand (PD-L1 or PD-L2); Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); or Interleukin-4 receptor (IL-4R).

[0172] In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds one of the following: CTLA-4; 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; AITR; TNFRSF18); and the immunomodulatory moiety comprises a different molecule selected from the following: (i) an extracellular domain or ligand-binding sequence of one of the following receptors: Transforming growth factor-beta receptor (TGF-βRII, TGF-βRIIb, or TGF-βRIII); Programmed Death-1 (PD-1); Receptor activator of nuclear factor-κB (RANK); or IL-10R; or (ii) Fc-containing polypeptide or ligand that binds one of the following: CTLA-4; 4-1BB (CD137); OX40 (CD134; TNR4); CD40; IL-12R; or GITR (AITR; TNFRSF18).

Bicara Ex. 1006, Page 135 of 498
Bicara v. JHU - PGR2026-00025

[0173] In another aspect, the targeting moiety and immunomodulatory moiety are two different molecules selected from any of the following: an antibody, antibody fragment, scFv, Fc-containing polypeptide or ligand that binds TGF-β, CTLA-4, PD-1, 4-1BB (CD137), OX40 (CD134; TNR4), CD40; IL-12R, or GITR/AITR (TNFRSF18), or Toll-like receptor (TLR); an extracellular domain or ligand-binding sequence of Transforming growth factor-beta receptor (TGF-βRII, TGF-βRIIb, or TGF-βRIII), Programmed Death-1 (PD-1), Receptor activator of nuclear factor-κB (RANK), or IL-10R. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is an immunomodulatory targeting moiety and Y is a different immunomodulatory moiety.

[0174] In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds one of the following molecules: CD4; CD25 (IL-2α receptor; IL-2αR); or CD20; and the immunomodulatory moiety comprises one of the following ligands or active ligand fragments: Transforming growth factor-beta (TGF-β); PD-1 ligand 1 (PD-L1); PD-1 ligand 2 (PD-L2); or IL-10.

[0175] In another aspect, the targeting moiety includes an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds tumor necrosis factor-α (TNF-α), Interleukin-12 (IL-12), IL-6R, B-lymphocyte stimulator, CD11a, CD6, or CD22; and the immunomodulatory moiety comprises one of the following: (i) ligands or active ligand fragments of Transforming growth factor-beta (TGF-β), PD-1 ligand 1 (PD-L1), or IL-10; or (ii) an extracellular domain or ligand-binding fragment of RANK, 4-1BB (CD137), OX40 (CD134; TNR4), CD40, IL-12R or GITR/AITR (TNFRSF18).

[0176] In another aspect, the targeting moiety comprises the extracellular domain of CTLA-4 fused to immunoglobulin Fc, and the immunomodulatory moiety comprises one of the following: (i) ligands or active ligand fragments of Transforming growth factor-beta (TGF-β), PD-1 ligand 1 (PD-L1), or IL-10; or (ii) ligand-binding fragment of TNFR2, RANK, 4-1BB (CD137), OX40 (CD134; TNR4), CD40, IL-12R or GITR/AITR (TNFRSF18).

Bicara Ex. 1006, Page 136 of 498
Bicara v. JHU - PGR2026-00025

[0177] In another aspect, the targeting moiety and immunomodulatory moiety are two different molecules selected from any of the following: an antibody, antibody fragment, scFv, Fc-containing polypeptide that binds tumor necrosis factor-α (TNF-α), Interleukin-12 (IL-12), IL-6R, B-lymphocyte stimulator, CD11a, CD6, or CD22; a ligand-binding fragment of TNFR2, RANK, 4-1BB (CD137), OX40 (CD134; TNR4), CD40, IL-12R or GITR/AITR (TNFRSF18); ligands or active ligand fragments of Transforming growth factor-beta (TGF-β), PD-1 ligand 1 (PD-L1), or IL-10; or CTLA-4-Fc. In one aspect, the fusion molecule is represented by X-Fc-Y, wherein X is the immunomodulatory targeting moiety and Y is a different immunomodulatory moiety.

[0178] Antibodies: In one embodiment, the targeting moiety or fusion protein is an immunoglobulin. As used herein, the term "immunoglobulin" includes natural or artificial mono- or polyvalent antibodies including, but not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments. F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin ion can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA, and IgY), class (*e.g.*, IgGl, IgG2, IgG3, IgG4, IgAl, and IgA2) or subclass of immunoglobulin molecule.

[0179] An antibody as disclosed herein includes an antibody fragment, such as, but not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdfv) and fragments including either a VL or VH domain. In one embodiment, the targeting moiety is an antibody or scFv.

[0180] An antigen-binding antibody fragment, including single-chain antibody, may include the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. An antigen-binding fragment can also include any combination of variable region(s) with a hinge region, CHI, CH2, and

Bicara Ex. 1006, Page 137 of 498
Bicara v. JHU - PGR2026-00025

CH3 domains. Also includes is a Fc fragment, antigen-Fc fusion proteins, and Fc-targeting moiety. The antibody may be from any animal origin including birds and mammals. In one aspect, the antibody is, or derived from, a human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken. Further, such antibody may be a humanized version of an antibody. The antibody may be monospecific, bispecific, trispecific, or of greater multispecificity.

[0181] The antibody herein specifically include a "chimeric" antibody in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al. (1984) Proc. Natl. Acad. Sci. USA. 81:6851-6855). A chimeric antibody of interest herein includes "primatized" antibodies including variable domain antigen-binding sequences derived from a non-human primate (*e.g.*, Old World Monkey, Ape etc.) and human constant region sequences.

[0182] Various methods have been employed to produce antibodies. Hybridoma technology, which refers to a cloned cell line that produces a single type of antibody, uses the cells of various species, including mice (murine), hamsters, rats, and humans. Another method to prepare an antibody uses genetic engineering including recombinant DNA techniques. For example, antibodies made from these techniques include, among others, chimeric antibodies and humanized antibodies. A chimeric antibody combines DNA encoding regions from more than one type of species. For example, a chimeric antibody may derive the variable region from a mouse and the constant region from a human. A humanized antibody comes predominantly from a human, even though it contains nonhuman portions. Like a chimeric antibody, a humanized antibody may contain a completely human constant region. But unlike a chimeric antibody, the variable region may be partially derived from a human. The nonhuman, synthetic portions of a

Bicara Ex. 1006, Page 138 of 498
Bicara v. JHU - PGR2026-00025

humanized antibody often come from CDRs in murine antibodies. In any event, these regions are crucial to allow the antibody to recognize and bind to a specific antigen.

[0183] In one embodiment, a hybridoma can produce a targeted fusion protein comprising a targeting moiety and an immunomodulatory moiety. In one embodiment, a targeting moiety comprising an antibody, antibody fragment, or polypeptide is linked or fused to an immunomodulatory moiety consisting of a polypeptide, with a linker or without a linker. The linker can be an amino acid linker. In one embodiment, a linker is (GGGGS)n (SEQ ID NO: 123) wherein n is 1, 2, 3, 4, 5, 6, 7, or 8. For example, GGGGSGGGGSGGGGS (SEQ ID NO: 104). In another embodiment, a linker is EPKSCDK (SEQ ID NO: 105). In another embodiment, a linker is IEGRDMD (SEQ. ID. NO: 106). In various aspects, the length of the linker may be modified to optimize binding of the target moiety or the function of the immunomodulatory moiety. In various aspects, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the Fc region of the heavy chain of a targeting antibody or Fc-containing fusion protein. In another aspect, the immunomodulatory moiety is a polypeptide that is fused to the C-terminus of the light chain of a targeting antibody. In another aspect, the fusion protein comprises an X-Fc-Y sequence, wherein X is a targeting polypeptide and Y is an immunomodulatory polypeptide.

[0184] For example, a hybridoma can produce the polypeptides corresponding to SEQ. ID. NO: 1-69.

[0185] An antibody fragment can include a portion of an intact, antibody, *e.g.*, including the antigen-binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')2, and Fv fragments; Fc fragments or Fc-fusion products; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s).

[0186] An intact antibody is one which includes an antigen-binding variable region as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (*e.g.*, human

Bicara Ex. 1006, Page 139 of 498
Bicara v. JHU - PGR2026-00025

native sequence constant domains) or amino acid sequence variant thereof tor any other modified Fc (*e.g.,* glycosylation or other engineered Fc).

[0187] The intact antibody may have one or more "effector functions" which refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region or any other modified Fc region) of an antibody. Examples of antibody effector functions include Clq binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.*, B cell receptor (BCR); and cross-presentation of antigens by antigen presenting cells or dendritic cells. In one embodiment, the targeting antibody or Fc-containing fusion protein facilitates focused or preferential delivery of a immunomodulatory moiety to a target cell. In another aspect, a targeting antibody can induce death of the targeted cell or sensitize it to immune cell-mediated cytotoxicity. In another aspect, the Fc-fusion protein or antibody can facilitate delivery of the immunomodulatory moiety or immunogenic apoptotic material from antibody-bound tumor targets, or both, to an antigen presenting cells (APC) via interactions between their Fc and Fc receptors (on APC).

[0188] Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes." There arc five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), *e.g.*, IgG1, IgG2, IgC3, IgG4, IgA, and IgA2. The heavy-chain constant domains (hat correspond to the different classes of antibodies are called alpha (α), delta (δ), epsilon (ε), gamma (γ), and mu (μ) respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0189] Peptides: In some aspects of the invention the targeting moiety or immunomodulatory moiety is a peptide or polypeptide. A peptide includes any analog, fragment or chemical derivative of a peptide whose amino acid residue sequence is shown herein. Therefore, a present peptide can be subject to various changes, substitutions, insertions, and deletions where such changes provide for certain advantages in its use. In

Bicara Ex. 1006, Page 140 of 498
Bicara v. JHU - PGR2026-00025

this regard, a peptide of this invention corresponds to, rather than is identical to, the sequence of a recited peptide where one or more changes are made and it retains the ability to function as the unmodified peptide in one or more of the assays.

[0190] The term "analog" includes any peptide having an amino acid residue sequence substantially identical to a sequence specifically shown herein in which one or more residues have been conservatively substituted with a functionally similar residue and which displays the activity as described herein. Examples of conservative substitutions include the substitution of one non-polar (hydrophobic) residue such as isoleucine, valine, leucine or methionine for another, the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, between glycine and serine, the substitution of one basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue, such as aspartic acid or glutamic acid for another.

[0191] The term "fragment" refers to any subject polypeptide having an amino acid residue sequence shorter than that of a polypeptide whose amino acid residue sequence is disclosed herein.

[0192] As used herein "a tumor targeting peptide" includes polymers containing fewer than 100 amino acids, where the polymer specifically binds to a cellular component of a tumor cell, tumor vasculature, and/or a component of a tumor microenvironment.

[0193] A peptide of the present invention can be synthesized by any of the techniques that are known to those skilled in "the polypeptide art, including recombinant DNA techniques. Synthetic chemistry techniques, such as a solid-phase Merrifield-type synthesis, are preferred for reasons of purity, antigenic specificity, freedom from undesired side products, ease of production and the like. An excellent summary of the many techniques available can be found in Steward et al., "Solid Phase Peptide Synthesis"* W.H. Freeman Co., San Francisco, 1969; Bodanszky, et al., "Peptide Synthesis", John Wiley & Sons, Second Edition, 1976; J. Meienhofer, "Hormonal Proteins and Peptides". Vol. 2. p. 46, Academic Press (New York), 1983; Merrifield, Adv.

Bicara Ex. 1006, Page 141 of 498
Bicara v. JHU - PGR2026-00025

Enzymol., 32:221-96, 1969; Fields et al.. Int. J. Peptide Protein Res., 35:161-214, 1990; and U.S. Pat. No. 4,244,946 for solid phase peptide synthesis, and Schroder et al., "The Peptides", Vol. 1, Academic Press (New York), 1965 for classical solution synthesis. Appropriate protective groups usable in such synthesis are described in the above texts and in J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, New York, 1973.

[0194] Aptamers: In one aspect of the invention, the targeting moiety is an aptamer. In various embodiments, an aptamer is specific for a molecule on a tumor cell, tumor vasculature, and/or a tumor microenvironment. The term "aptamer" includes DNA, RNA or peptides that are selected based on specific binding properties to a particular molecule. For example, an aptamer(s) can be selected for binding a particular gene product in a tumor cell, tumor vasculature, tumor microenvironment, and/or an immune cell, as disclosed herein, where selection is made by methods known in the art and familiar to one of skill in the art. Subsequently, said aptamer(s) can be administered to a subject to modulate or regulate an immune response.

[0195] Some aptamers having affinity to a specific protein, DNA, amino acid and nucleotides have been described (*e.g.*, K. Y. Wang, et al., Biochemistry 32:1899-1904 (1993); Pitner et al., U.S. Pat. No. 5,691,145: Gold, et al., Ann. Rev. Biochem. 64:763-797 (1995); Szostak et al., U.S. Pat. No. 5,631,146). High affinity and high specificity binding aptamers have been derived from combinatorial libraries (supra, Gold, et al.). Aptamers may have high affinities, with equilibrium dissociation constants ranging from micromolar to sub-nanomolar depending on the selection used, aptamers may also exhibit high selectivity, for example, showing a thousand fold, discrimination between 7-methyl G and G (Haller and Sarnow, Proc. Natl. Acad. Sci. USA 94:8521-8526 (1997)) or between D and L-tryptophan (supra, Gold et al.). An aptamer can be selected based on the particular molecule targeted (*e.g.*, aptamer targeting EGFR or other cancer markers). Standard procedures for in vitro selection are known, such as SELEX experiments, described at Science 249 (4968) 505-510 (1990), and Nature (London), 346 (6287) 818-822 (1990) which can be followed throughout, or with modifications and improvements known in the art.

Bicara Ex. 1006, Page 142 of 498
Bicara v. JHU - PGR2026-00025

[0196] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

[0197] By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0198] The terms "administration of" and or "administering" should be understood to mean providing a composition in a therapeutically effective amount to the individual in need of treatment. Administration can be intratumoral or systemic (intravenous) administration. Furthermore, in conjunction with vaccination of recipient with pathogen antigen vaccine (*e.g.,* tetanus toxoid). In addition, in conjunction with agent to deplete or inactivate regulatory T cells (*e.g.,* cyclophosphamide) or myeloid suppressor cells (*e.g.,* gemcitabine). In a further example, *ex vivo* treatment of immune cells and tumor cells for generation of tumor reactive or pathogen antigen reactive immune cells—for adoptive cellular immunotherapy. Administration can be intradermal or subcutaneous.

[0199] Furthermore, administration can be in combination with one or more additional therapeutic agents deplete or inactivate regulatory T cells (cyclophosphamide) or myeloid suppressor cells (*e.g.,* gemcitabine). The pharmaceutical compositions of the invention identified herein are useful for parenteral, topical, oral, nasal (or otherwise inhaled), rectal, or local administration, such as by aerosol or transdermally, for prophylactic and/or therapeutic treatment of one or more of the pathologies/indications described herein (*e.g.*, cancer, pathogenic infectious agents, associated conditions thereof). The pharmaceutical compositions can be administered in a variety of unit dosage forms depending upon the method of administration. Suitable unit dosage forms, include, but are not limited to powders, tablets, pills, capsules, lozenges, suppositories, patches, nasal sprays, injectables, implantable sustained-release formulations, lipid complexes, etc.

Bicara Ex. 1006, Page 143 of 498
Bicara v. JHU - PGR2026-00025

[0200] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, as it will be understood that modifications and variations are encompassed within the spirit and scope of the instant disclosure.

[0201] The following examples are provided to further illustrate the embodiments of the present invention, but are not intended to limit the scope of the invention. While they are typical of those that might be used, other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

EXAMPLE 1

[0202] Counteracting Tumor Immune Tolerance via Antibody-mediated Depletion of $CD4^+$ Regulatory T Cells Facilitates the Activation of Tumor-Reactive $CD8^+$ T Cells and Enhances the *In Vivo* Antitumor Efficacy of Cytotoxic Anticancer Agents.

[0203] Immunogenic death of tumor cells by chemotherapeutic agents can induce $CD8^+$ T cell-mediated antitumor immunity. In response to specific chemotherapeutic agents, tumor cells exhibit the rapid translocation of intracellular calreticulin (CRT) to the cell surface where its aggregation provides a signal for the recognition and engulfment of dying tumor cells by antigen presenting dendritic cells (DCs). Treatment of mouse MB49 or human SW780 bladder cancer cells with doxorubicin, an anthracycline chemotherapeutic agent, induced rapid surface exposure of CRT that was detected by immunofluorescence cytometry of cells stained with Dylight 488-labeled anti-CRT antibody (FIG. 53A). To determine whether *ex vivo* treatment with doxorubicin induced an immunogenic death of tumor cells, either untreated live MB49 cells or an equivalent number of MB49 cells that were pre-treated *in vitro* with doxorubicin were injected into one flank of syngeneic immunocompetent C57BL/6 mice. Unlike mice injected with live tumor cells, mice injected with doxorubicin-treated tumor cells exhibited increased production of IFN-γ by draining lymph node (DLN) cells in response to *in vitro* re-challenge with MB49 cell lysates (FIG. 53B). Vaccination with doxorubicin-killed MB49

Bicara Ex. 1006, Page 144 of 498
Bicara v. JHU - PGR2026-00025

cells generated a tumor-specific immune response since no corresponding increase in IFN-γ secretion by DLN cells was observed following *in vitro* exposure to an irrelevant peptide (Hemagglutinin-HA). Injection of doxorubicin-treated MB49 tumor cells protected mice against tumor growth upon challenge with untreated live MB49 tumor cells injected into the opposite flank. (FIG. 1C). The protection against tumor growth by vaccination with doxorubicin-treated tumor cells was not observed in mice that were depleted of $CD8^+$ T cells with an anti-CD8 antibody before challenge with live tumor cells (FIG. 53C). These observations indicate that *ex vivo* treatment with chemotherapeutic agents can induce an immunogenic death of tumor cells that generates $CD8^+$ T cell-mediated adaptive antitumor immunity.

[0204] Tumor-induced immune tolerance inhibits activation of $CD8^+$ T cells in response to chemotherapy. To examine whether *in vivo* treatment with chemotherapeutic agents can activate $CD8^+$ T cell-mediated immune responses in mice with pre-established tumors, C57BL/6 mice were injected with live syngeneic MB49 tumor cells and then administered intratumoral doxorubicin at various time points following tumor inoculation. In contrast to vaccination of naïve mice with doxorubicin-killed MB49 cells, *in vivo* treatment of mice with established MB49 tumors at d10 following tumor inoculation failed to induce a corresponding increase in IFN-γ secretion by DLN cells in response to *in vitro* re-challenge with MB49 cell lysates (FIG. 53B). Whereas treatment with doxorubicin on d3 following tumor inoculation was able to arrest tumor growth, delayed administration of the same dose of doxorubicin on d10 failed to inhibit the progressive growth of established MB49 tumors (FIG. 53D). These results indicate that tumor-induced immune tolerance in the microenvironment of established cancers counteracts the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death.

[0205] Regulatory T cells (Treg) accumulate in the tumor microenvironment and counteract the ability of chemotherapy to activate $CD8^+$ T cell mediated antitumor immunity. To investigate whether $FoxP3^+$ Tregs are involved in enforcing immune tolerance in the tumor microenvironment, we examined the percentage of $CD4^+CD25^+FoxP3^+$ cells (Tregs) among $CD4^+$ T lymphocytes in the spleen, draining

Bicara Ex. 1006, Page 145 of 498
Bicara v. JHU - PGR2026-00025

lymph nodes (DLN), and tumors of immunocompetent C57BL/6 mice at d0 and d14 after tumor inoculation. Whereas tumor-bearing mice exhibited only a minor increase in the percentage of Tregs among $CD4^+$ T cells in the spleen and DLN at d14 following tumor inoculation, a majority of tumor-infiltrating $CD4^+$ T cells at this time were $CD4^+CD25^+FoxP3^+$ cells (FIG. 53E). To investigate whether Tregs infiltrating the tumor microenvironment can suppress the activation of adaptive antitumor immunity in response to chemotherapy-induced tumor cell death, $CD4^+CD25^+$ cells isolated from tumors and DLN of tumor-bearing mice were adoptively transferred into syngeneic C57BL/6 naïve mice before vaccination with doxorubicin-killed MB49 cells. The adoptive transfer of tumor-infiltrating $CD4^+CD25^+$ cells into naïve mice inhibited the ability of subsequent *in vivo* vaccination with doxorubicin-treated MB49 tumor cells to increase production of IFN-γ by draining lymph node (DLN) cells in response to *in vitro* re-challenge with MB49 cell lysates (FIG. 53F). Consistent with the ability of tumor-infiltrating $CD4^+CD25^+$ cells to suppress the tumor-specific immune response, the adoptive transfer of these cells counteracted the protection conferred by vaccination with doxorubicin-treated MB49 cells against tumor growth upon challenge with untreated live MB49 tumor cells (FIG. 53G). These results indicate that the tumor microenvironment fosters the accumulation of $FoxP3^+$ Tregs which counteract the activation of $CD8^+$ T cell mediated antitumor immunity in response to chemotherapy-induced tumor cell death.

[0206] Inhibition of TGF-β in the tumor microenvironment reduces tumor-infiltrating $FoxP3^+$ regulatory T cells and enhances the antitumor efficacy chemotherapy. TGF-β induces FoxP3 expression in naïve peripheral $CD4^+CD25^-FoxP3^-$ T cells and facilitates their conversion into 'adaptive' $FoxP3^+$ Tregs that share the immunosuppressive ability of natural $FoxP3^+$ Tregs generated in the thymus. Since human cancers frequently become refractory to the growth-inhibitory effect of TGF-β and acquire an ability to increase expression and secretion of TGF-β, we investigated whether this switch enables tumor cells to increase the number of adaptive Tregs in the tumor microenvironment. Examination of serum levels of TGF-β in mice at d0, d14, and d28 following inoculation of live MB49 tumor cells demonstrated that tumor growth resulted in a progressive increase in the level of serum TGF-β (FIG. 54A). To assess the precise source of TGF-β

Bicara Ex. 1006, Page 146 of 498
Bicara v. JHU - PGR2026-00025

in tumor-bearing mice, the total amount of TGF-β in supernatants of tumor cells or draining lymph node cells isolated from tumor-bearing mice were measured following *ex vivo* culture in serum-free medium for 24h. Measurement of the level of TGF-β/10^6 cells showed that tumor cells were the dominant source of the increased level of TGF-β in tumor-bearing mice (FIG. 54B). In addition to tumor cell-autonomous expression of TGF-β, T cells from tumor-bearing mice also expressed higher levels of TGF-β compared to their counterparts from tumor-free mice (FIG. 54B). To determine whether the elevation of TGF-β is responsible for the upregulation of Tregs in the tumor microenvironment, tumor-bearing mice were treated with a soluble chimeric protein comprising the extracellular domain of TGFβRII and the Fc portion of the murine IgG1 heavy chain (TGFβRII:Fc). This fusion protein interferes with the binding of TGF-β to endogenous TGFβRII and functions as a stable TGF-β antagonist. ELISA assays confirmed the ability of TGFβRII:Fc to sequester TGF-β in supernatants of MB49 tumor cells in a concentration-dependent manner (FIG. 54C). At 5d following inoculation of MB49 tumor cells, mice were either left untreated or treated with TGFβRII:Fc (1μg intratumoral; twice weekly) for 3 weeks followed by flow cytometric analyses of intracellular FoxP3 expression in $CD4^+CD25^+$ T cells infiltrating the tumors. *In vivo* treatment of tumors with TGFβRII:Fc resulted in a significant decline in FoxP3 expression in tumor-infiltrating $CD4^+$ T cells (FIG. 54D) and a dramatic reduction of $CD4^+CD25^+FoxP3^+$ Tregs in tumor tissue (FIG. 54E). To determine whether inhibition of TGF-β in the tumor microenvironment can improve the antitumor efficacy of chemotherapy, MB49 tumor-bearing mice were administered doxorubicin (5mg/kg i.p. weekly x 3) with or without twice weekly treatment with TGFβRII:Fc (1μg intratumoral). In contrast to treatment with either doxorubicin or TGFβRII:Fc alone, combined treatment with both agents was able to arrest the growth of MB49 tumors. These results indicate that tumor cell autonomous expression of TGF-β in the tumor microenvironment induces 'adaptive' $FoxP3^+$ Tregs and that counteracting tumor-induced TGF-β-mediated immune tolerance enhances the antitumor efficacy of chemotherapy.

[0207] Anti-CD4 antibody-mediated depletion of $CD4^+$ regulatory T cells facilitates chemotherapy-induced activation of tumor-reactive $CD8^+$ T cells and enhances the

antitumor efficacy of chemotherapy. To determine whether depletion of $CD4^+$ regulatory T cells can improve the antitumor efficacy of chemotherapy by enhancing the activity of $CD8^+$ T cells in the tumor microenvironment, immunocompetent mice bearing syngeneic tumors were administered an anti-CD4 antibody (Clone GK1.5) to deplete $CD4^+$ T cells or an anti-CD8 antibody (Clone GK2.43) to deplete $CD8^+$ T cells and then treated with specific chemotherapeutic agents. Flow cytometric analyses of peripheral blood mononuclear cells from MB49 tumor-bearing mice at d7 following administration of anti-CD4 antibody or anti-CD8 antibody confirmed the target-specific depletion of either $CD4^+$ T cells or $CD8^+$ T cells, respectively (FIG. 55A). Mice treated with anti-CD4 antibody showed loss of $CD4^+CD25^+FoxP3^+$ T cells in the peripheral blood as well as among tumor-infiltrating cells (FIGS. 55A, 55B). To determine whether antibody-mediated depletion of $CD4^+CD25^+FoxP3^+$ cells facilitates chemotherapy-induced activation of tumor-reactive $CD8^+$ T cells in the tumor microenvironment, we evaluated the expression of IFN-γ in $CD8^+$ T cells extracted from the tumor and draining lymph node of MB49 tumor-bearing mice that were left untreated or treated with doxorubicin (with or without anti-CD4 antibody). Flow cytometric analyses showed that $CD8^+$ T cells from untreated mice did not express IFN-γ in response to *in vitro* re-challenge with MB49 cell lysates (FIG. 55C). Whereas IFN-γ^+CD8^+ T cells became evident in mice treated with doxorubicin alone, antibody-mediated depletion of $CD4^+$ T cells further enhanced the percentage of tumor-reactive $CD8^+$ T cells that expressed IFN-γ in doxorubicin-treated animals (FIG. 55C). To directly evaluate whether the activation of tumor-reactive $CD8^+$ T cells determines the *in vivo* antitumor efficacy of chemotherapy, we examined the effect of antibody-mediated depletion of $CD8^+$ T cells or $CD4^+$ T cells on the response of MB49 tumor-bearing mice to systemic treatment with doxorubicin (5mg/kg). Treatment with doxorubicin alone inhibited the growth of MB49 tumors but failed to arrest tumor progression. Whereas depletion of $CD8^+$ T cells completely impaired the *in vivo* antitumor efficacy of doxorubicin, depletion of $CD4^+$ T cells enhanced the response to doxorubicin and resulted in tumor regression (FIG. 55D).

[0208] Anti-CD4 antibody-mediated depletion of $CD4^+$ regulatory T cells augments and sustains the antitumor effect of chemotherapy by enabling activation of adaptive

Bicara Ex. 1006, Page 148 of 498
Bicara v. JHU - PGR2026-00025

antitumor immunity. Whereas tumor cells treated with anthracyclins, such as doxorubicin, are particularly effective in eliciting an antitumor immune response, other chemotherapeutic agents are less effective in inducing immunogenic tumor cell death. The surface exposure of calreticulin is a key determinant of the immunogenicity of tumor cell death in response to chemotherapeutic agents. Compared to the efficient translocation of CRT to the cell surface in response to treatment with doxorubicin (FIG. 1A), treatment of MB49 tumor cells with equitoxic doses of either cisplatin or the combination of cisplatin and gemcitabine was less effective in increasing CRT exposure (FIG. 56A). Whereas tumor-reactive IFN-γ^+CD8^+ T cells were evident in tumors of MB49 tumor-bearing mice treated with doxorubicin (FIG. 55C), treatment with cisplatin was unable to induce a corresponding elevation of IFN-γ expression in $CD8^+$ T cells in response to *in vitro* re-challenge with MB49 cell lysates (FIG. 56B). To examine whether counteraction of Treg-mediated immune tolerance enables the activation of antitumor immunity by cisplatin, immunocompetent tumor-bearing mice were treated with cisplatin following depletion of Tregs with anti-CD4 antibody. Antibody-mediated depletion of $CD4^+$ T cells enhanced the percentage of tumor-reactive IFN-γ^+CD8^+ T cells as well as $CD8^+CD62L^-$ T cells in cisplatin-treated animals (FIGS. 56B, 56C). Treatment of MB49 tumor-bearing mice with cisplatin partially inhibited tumor growth but failed to arrest tumor progression. Whereas depletion of $CD8^+$ T cells completely negated the *in vivo* antitumor effect of cisplatin, depletion of $CD4^+$ T cells enhanced the response to cisplatin and arrested tumor growth (FIG. 56D). Although treatment of tumor-bearing mice with the combination of cisplatin and gemcitabine was also able to arrest tumor growth, tumor growth rapidly resumed following termination of therapy with none of the animals (0/8) being tumor-free at d50 following tumor inoculation (FIG. 56E). In contrast, mice depleted of $CD4^+$ T cells exhibited a more sustained response to either single agent or combination chemotherapy, with 7/16 mice exhibiting complete tumor regression. The complete regression of tumors was attended with establishment of adaptive antitumor immunity since none of the cured mice (7/7) developed tumors when re-challenged with live MB49 tumor cells in the opposite flank.

Bicara Ex. 1006, Page 149 of 498
Bicara v. JHU - PGR2026-00025

[0209] Chemotherapy-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD^{4+} regulatory T cells to stimulate CD^{8+} T cell-mediated tumor regression. NKG2D (NK group 2, member D) is a lectin-like type II transmembrane stimulatory receptor used by NK cells, $\gamma\delta$-TC^{R+} T cells and $\alpha\beta$-TC^{R+} T cells for immune surveillance of tumors. Expression of mouse and human ligands for NKG2D is upregulated in transformed epithelial cell lines in response to genotoxic stress or stalled DNA replication, via activation of a DNA damage checkpoint pathway initiated by ATM (ataxia telengiectasia, mutated) or ATR (ATM- and Rad3-related) protein kinases. Treatment of CT26 mouse colon cancer cells with genotoxic chemotherapeutic agents resulted in upregulation of mouse NKG2D ligands of the retinoic acid inducible gene family (Rae1) (FIG. 57A). RT-PCR showed that Rae1 mRNA was induced in CT26 cells by 2-4h, reached a plateau after 16-24h, and began to decline after 48h of treatment with either the irinotecan or oxaliplatin (FIG. 57A). Flow cytometric analysis demonstrated that cell surface expression of human NKG2D ligands (MHC-I-related A and B molecules – MICA, MICB) was also upregulated on human colorectal cancer cells (HCT116) in response to treatment with irinotecan (FIG. 53B). Isogenic HCT116 cells that differ only in their p53 status demonstrated that p53 is not required for irinotecan-induced upregulation of MICA/B (FIG. 53B). To examine whether the induction of NKG2D ligands contributes to the antitumor effect of chemotherapy *in vivo*, immunocompetent Balb/C mice inoculated with syngeneic CT26 tumor cells were treated with irinotecan (50 mg/kg i.p) with or without pre-treatment with an NKG2D blocking antibody (200 μg i.p.). Whereas treatment with irinotecan alone inhibited the growth of CT26 tumors, the antitumor effect of irinotecan was negated by pre-treatment with the NKG2D blocking antibody (FIG. 1C). Since engagement of NKG2D by its ligands provides a costimulatory signal for the activation of CD^{8+} T cells, we investigated whether DNA damage-induced expression of NKG2D ligands on tumor cells cooperates with depletion of CD^{4+} regulatory T cells to stimulate CD^{8+} T cell-mediated tumor regression. Balb/C mice bearing CT26 tumors were administered an anti-CD4 antibody (Clone GK1.5) to deplete CD^{4+} T cells and/or an anti-CD8 antibody (Clone GK2.43) to deplete CD^{8+} T cells and then treated with irinotecan. Flow cytometric analyses confirmed the loss of $CD^{4+}CD2^{5+}FoxP^{3+}$ T cells in the spleen and draining lymph node of mice treated

Bicara Ex. 1006, Page 150 of 498
Bicara v. JHU - PGR2026-00025

with anti-CD4 antibody (FIG. 57D). Antibody-mediated depletion of CD^{4+} T cells enhanced the percentage of tumor-reactive IFN-$\gamma^{+}CD^{8+}$ T cells in irinotecan-treated animals (FIG. 57E). Whereas treatment of CT26 tumor-bearing mice with irinotecan only slowed tumor growth, depletion of CD^{4+} T cells enhanced the response to irinotecan and arrested tumor growth (FIG. 57F). The ability of CD^{4+} T cell depletion to augment the antitumor efficacy of irinotecan was mediated by CD^{8+} T cells since antibody-mediated depletion of CD^{8+} T cells completely negated the *in vivo* antitumor effect of chemotherapy in CD^{4+} T cell-depleted mice (FIG. 57F).

[0210] These data provide the following insights: (i) activation of tumor-reactive $CD8^{+}$ T cells in response to immunogenic tumor cell death is a crucial determinant of the antitumor efficacy of chemotherapy *in vivo;* (ii) tumor-induced Tregs impair the antitumor efficacy of chemotherapy by inhibiting the activation of $CD8^{+}$ T cells in the tumor microenvironment; and (iii) Counteracting tumor-induced immune tolerance via antibody-mediated depletion of $CD4^{+}$ regulatory T cells facilitates chemotherapy-induced activation of antitumor immunity with memory, thereby enhancing the antitumor efficacy of chemotherapy; (iv) Strategies to decrease the number or function of CD4+ regulatory T cells in the tumor microenvironment can increase the activation of CD8+ T cells and improve the response of tumors to cytotoxic anticancer agents (chemotherapy, tumor-targeted antibodies, targeted therapeutics, kinase inhibitors) or chemoimmunotherapy (combination of chemotherapeutic agent with immunotherapeutic agents).

EXAMPLE 2

[0211] Exemplary Targeted Immunomodulatory Antibodies and Fusion Proteins

[0212] A targeting moiety, including an antibody, can be coupled to an immunomodulatory moiety including a polypeptide derived from the extracellular domain of TGFBR2. Crosslinkers or activating agents for such coupling or conjugation are well known in the art. Alternatively, the fusion proteins of the invention can be synthesized using recombination DNA technology well known in the art where the coding sequences of various portions of the fusion proteins can be linked together at the nucleic acid level. Subsequently the fusion proteins of the invention can be produced using a host cell well

Bicara Ex. 1006, Page 151 of 498
Bicara v. JHU - PGR2026-00025

known in the art. Examples of targeted immunomodulatory antibodies and fusion proteins are shown in Figures 1-33 and briefly described below.

[0213] In one embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety specifically binds to Transforming growth factor-beta (TGF-β). SEQ ID NO: 1 provides a fusion protein including anti-HER2/neu antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 2). SEQ ID NO: 2 provides a fusion protein including anti-EGFR1 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 3). SEQ ID NO: 3 provides a fusion protein including anti-CD20 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 4). SEQ ID NO: 4 provides a fusion protein including anti-VEGF antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 5). SEQ ID NO: 5 provides a fusion protein including anti-human CTLA-4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 6). SEQ ID NO: 6 provides a fusion protein including IL-2, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 7). SEQ ID NO: 7 provides a fusion protein including Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD), Fc, and IL-2 (FIG. 7). SEQ ID NO: 8 provides a fusion protein including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 8A). SEQ ID NO: 9 provides a fusion protein including anti-CD25 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 8B). SEQ ID NO: 10 provides a fusion protein including anti-CD4 antibody and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ECD) (FIG. 9). SEQ ID NO: 11 provides a fusion protein including PD-1 Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain) (PD-1 ectodomain + Fc + TGFβRII ectodomain; FIG. 10). SEQ ID NO: 12 provides a fusion protein including Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain), Fc, and PD-1

Bicara Ex. 1006, Page 152 of 498
Bicara v. JHU - PGR2026-00025

Ectodomain (TGFβRII ectodomain + Fc + PD-1 ectodomain; FIG. 10). SEQ ID NO: 13 provides a fusion protein including RANK Ectodomain, Fc, and Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain) (RANK ectodomain + Fc + TGFβRII ectodomain; FIG. 11). SEQ ID NO: 14 provides a fusion protein including Transforming growth factor-beta receptor II (TGFβ-RII) Extracellular domain (ectodomain), Fc, and RANK Ectodomain (TGFβRII ectodomain + Fc + RANK ectodomain; FIG. 11).

[0214] In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Programmed Death-1 ligand 1 (PD-L1 or B7-H1) or Programmed Death-1 ligand 2 (PD-L2 or B7-DC). SEQ ID NO: 15 provides a fusion protein including anti-HER2/neu antibody and PD-1 Ectodomain (FIG. 13). SEQ ID NO: 16 provides a fusion protein including anti-EGFR1 antibody and PD-1 Ectodomain (FIG. 14). SEQ ID NO: 17 provides a fusion protein including anti-CD20 antibody and PD-1 Ectodomain (FIG. 15). SEQ ID NO: 18 provides a fusion protein including anti-VEGF antibody and PD-1 Ectodomain (FIG. 16). SEQ ID NO: 19 provides a fusion protein including anti-human CTLA-4 antibody and PD-1 Ectodomain (FIG. 17). SEQ ID NO: 20 provides a fusion protein including anti-CD25 antibody and PD-1 Ectodomain (FIG. 18A). SEQ ID NO: 21 provides a fusion protein including anti-CD25 antibody and PD-1 Ectodomain (FIG. 18B). SEQ ID NO: 22 provides a fusion protein including IL-2, Fc, and PD-1 ectodomain (IL-2 + Fc + PD-1 ectodomain; FIG. 19). SEQ ID NO: 23 provides a fusion protein including PD-1 ectodomain, Fc, and IL-2 (PD-1 ectodomain + Fc + IL-2; FIG. 19). SEQ ID NO: 24 provides a fusion protein including anti-CD4 antibody and PD-1 Ectodomain (FIG. 20). SEQ ID NO: 25 provides a fusion protein including RANK Ectodomain, Fc, and PD-1 ectodomain (RANK ectodomain + Fc + PD-1 ectodomain; FIG. 21). SEQ ID NO: 26 provides a fusion protein including PD-1 ectodomain, Fc, and RANK Ectodomain (PD-1 ectodomain + Fc + RANK ectodomain; FIG. 21).

[0215] In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety

Bicara Ex. 1006, Page 153 of 498
Bicara v. JHU - PGR2026-00025

specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Receptor activator of NF-kB ligand (RANKL). SEQ ID NO: 27 provides a fusion protein including anti-HER2/neu antibody and RANK Ectodomain (FIG. 23). SEQ ID NO: 28 provides a fusion protein including anti-EGFR1 antibody and RANK Ectodomain (FIG. 24). SEQ ID NO: 29 provides a fusion protein including anti-CD20 antibody and RANK Ectodomain (FIG. 25). SEQ ID NO: 30 provides a fusion protein including anti-VEGF antibody and RANK Ectodomain (FIG. 26). SEQ ID NO: 31 provides a fusion protein including anti-human CTLA-4 antibody and RANK Ectodomain (FIG. 27). SEQ ID NO: 32 provides a fusion protein including anti-CD25 antibody and RANK Ectodomain (FIG. 28A). SEQ ID NO: 33 provides a fusion protein including anti-CD25 antibody and RANK Ectodomain (FIG. 28B). SEQ ID NO: 34 provides a fusion protein including IL-2, Fc, and RANK ectodomain (IL-2 + Fc + RANK ectodomain; FIG. 29). SEQ ID NO: 35 provides a fusion protein including RANK ectodomain, Fc, and IL-2 (RANK ectodomain + Fc + IL-2; FIG. 29). SEQ ID NO: 36 provides a fusion protein including anti-CD4 antibody and RANK Ectodomain (FIG. 30).

[0216] In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety includes a molecule that specifically binds to Programmed death-1 (PD-1). SEQ ID NO: 37 provides a fusion protein including anti-tumor necrosis factor (TNFα) antibody and PD-1 ligand 1 (FIG. 32). SEQ ID NO: 38 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and PD-1 ligand: (TNFR2 ECD + IgG Cγ1 + PD-L1; FIG. 33). SEQ ID NO: 39 provides a fusion protein including PD-1 ligand, Fc, and TNFR2 Extracellular ligand binding domain: (PD-L1 + IgG Cγ1 -TNFR2 ECD; FIG. 33). SEQ ID NO: 40 provides a fusion protein including anti-CD20 antibody and PD-1 ligand 1 (PD-L1) (FIG. 34). SEQ ID NO: 41 provides a fusion protein including anti-CD25 antibody and PD-1 ligand 1 (PD-L1) (FIG. 35A). SEQ ID NO: 42 provides a fusion protein including anti-CD25 antibody and PD-1 ligand 1 (PD-L1) (FIG. 35B). SEQ ID NO: 43 provides a fusion protein including PD-1 ligand 1 (PD-L1), Fc, and IL-2 (PD-L1 – Fc – IL2; FIG. 36). SEQ ID NO: 44 provides a fusion protein including IL-2, Fc, and PD-1

Bicara Ex. 1006, Page 154 of 498
Bicara v. JHU - PGR2026-00025

ligand 1 (PD-L1) (IL-2 – Fc – PD-L1; FIG. 36). SEQ ID NO: 45 provides a fusion protein including anti-CD4 antibody and PD-1 ligand 1 (PD-L1) (FIG. 37). SEQ ID NO: 46 provides a fusion protein including the extracellular domain of CTLA-4, Immunoglobulin Fc (IgG Cγ1), and a sequence from PD-1 ligand (PD-L1) (Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + PD-L1; FIG. 38). SEQ ID NO: 47 provides a fusion protein including the extracellular domain of PD-1 ligand (PD-L1), immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4: (PD-L1 + IgG Cγ1 + CTLA-4 ECD; FIG. 38). SEQ ID NO: 48 provides a fusion protein including Transforming growth factor-β (TGF-β), immunoglobulin Fc (IgG Cγ1), and a sequence from PD-1 ligand 1 (PD-L1) (TGFβ-1 + Fc + PD-L1; FIG. 39). SEQ ID NO: 49 provides a fusion protein including a sequence from PD-1 ligand 1 (PD-L1), immunoglobulin Fc (IgG Cγ1), and Transforming growth factor beta (TGF-□β) (PD-L1 + Fc + TGFβ-1; FIG. 39).

[0217] In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety includes a molecule that specifically binds to Transforming growth factor-beta receptor (TGF-βR). SEQ ID NO: 50 provides a fusion protein including an antibody that binds TNF-α, and a sequence from Transforming growth factor-β (TGF-β) (FIG. 41). SEQ ID NO: 51 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and a sequence from Transforming growth factor-β (TGF-β) (TNFR2 ECD + IgG Cγ1 + TGF-β; FIG. 42). SEQ ID NO: 52 provides a fusion protein including a sequence from Transforming growth factor-β (TGF-β), Fc, and TNFR2 Extracellular ligand binding domain: (TGF-β + IgG Cγ1 + TNFR2 ECD; FIG. 42). SEQ ID NO: 53 provides a fusion protein including anti-CD20 antibody and a sequence from Transforming growth factor-β (TGF-β) (FIG. 43). SEQ ID NO: 54 provides a fusion protein including anti-CD25 antibody and a sequence from transforming growth factor-β (TGF-β) (FIG. 44A). SEQ ID NO: 55 provides a fusion protein including anti-CD25 antibody and a sequence from transforming growth factor-β (TGF-β) (FIG. 44B). SEQ ID NO: 56 provides a fusion protein including a sequence from Transforming growth factor-β (TGF-β), Fc, and IL-2

Bicara Ex. 1006, Page 155 of 498
Bicara v. JHU - PGR2026-00025

(TGF-β + Fc + IL-2; FIG. 45). SEQ ID NO: 57 provides a fusion protein including IL-2, Fc, and Transforming growth factor-β (TGF-β)(IL-2 + Fc + TGF-β; FIG. 45). SEQ ID NO: 58 provides a fusion protein including anti-CD4 antibody and a sequence from transforming growth factor-β (TGF-β) (FIG. 46). SEQ ID NO: 59 provides a fusion protein including the extracellular domain of CTLA-4, immunoglobulin Fc (IgG Cγ1), and a sequence from a sequence from transforming growth factor-β (TGF-β) (Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + TGF-β1; FIG. 47). SEQ ID NO: 60 provides a fusion protein including a sequence from Transforming growth factor-β (TGF-β), immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4: (TGF-β1 + IgG Cγ1 + CTLA-4 ECD) (FIG. 47).

[0218] In another embodiment, the present invention provides a molecule including a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety specifically binds to a target molecule, and the immunomodulatory moiety is a molecule that specifically binds to Receptor activator of NF-kB ligand (RANKL). SEQ ID NO: 61 provides a fusion protein including an antibody that binds TNF-α, and a sequence from RANK Ectodomain (FIG. 48). SEQ ID NO: 62 provides a fusion protein including TNFR2 Extracellular ligand binding domain, Fc, and a sequence from RANK Ectodomain (TNFR2 ECD + IgG Cγ1 + RANK Ectodomain; FIG. 49). SEQ ID NO: 63 provides a fusion protein including a sequence from RANK Ectodomain, Fc, and TNFR2 Extracellular ligand binding domain: (RANK Ectodomain + IgG Cγ1 + TNFR2 ECD; FIG. 49). SEQ ID NO: 64 provides a fusion protein including the extracellular domain of CTLA-4, immunoglobulin Fc (IgG Cγ1), and a sequence from a sequence from RANK Ectodomain (Oncostatin M signal peptide + CTLA-4 ECD + IgG Cγ1 + RANK Ectodomain; FIG. 50). SEQ ID NO: 65 provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG Cγ1), and a sequence from the extracellular domain of CTLA-4: (RANK Ectodomain + IgG Cγ1 + CTLA-4 ECD) (FIG. 50). SEQ ID NO: 66 provides a fusion protein including a sequence from transforming growth factor-β (TGF-β), immunoglobulin Fc region (IgG Cγ1), and an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK) (TGF-β + IgG Cγ1 + RANK Ectodomain; FIG. 51). SEQ ID NO: 67

Bicara Ex. 1006, Page 156 of 498
Bicara v. JHU - PGR2026-00025

provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG Cγ1), and a sequence from transforming growth factor-β (TGF-β): (RANK Ectodomain + IgG Cγ1 + TGF-β) (FIG. 51). SEQ ID NO: 68 provides a fusion protein including a sequence from Programmed death-1 ligand 1 (PD-L1), immunoglobulin Fc region (IgG Cγ1), and an extracellular ligand-binding domain or ectodomain of Receptor activator of nuclear factor-κB (RANK) (PD-L1 + IgG Cγ1 + RANK Ectodomain; FIG. 52). SEQ ID NO: 69 provides a fusion protein including a sequence from RANK Ectodomain, immunoglobulin Fc (IgG Cγ1), and a sequence from Programmed death-1 ligand 1 (PD-L1): (RANK Ectodomain + IgG Cγ1 + PD-L1) (FIG. 52).

[0219] Although the invention has been described with reference to the above example, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

Bicara Ex. 1006, Page 157 of 498
Bicara v. JHU - PGR2026-00025

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/362,632

filed on November 28, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Atul Bedi Date (Optional) : _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/362,632

filed on November 28, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Rajani Ravi Date (Optional) : _____

Signature: Rajani Ravi

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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EFS ID:	37451141
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Aldon Griffis
Filer Authorized By:	
Attorney Docket Number:	JHU3260-8
Receipt Date:	14-OCT-2019
Filing Date:	
Time Stamp:	18:32:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	JHU3260-8ADS_EFS.pdf	1894450 9b45d86af1b148175aba69302398598fe1d7dacb	no	9

Warnings:

Information:					
2	Transmittal of New Application	JHU3260-8ContinuationTxEFS.pdf	206850 9c2ada749423a9991b279c878355235223b6cad3	no	3
Warnings:					
Information:					
3		JHU3260-8ContinuationEFS.pdf	4673120 cc1db1d101097ec9264b977796c98116 4dd6b46f	yes	153

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Drawings-only black and white line drawings	79	153
Abstract	78	78
Claims	75	77
Specification	1	74

Warnings:					
Information:					
4		JHU3260-8ParentInventorDeclsEFS.pdf	209025 96561942be608a357a430da40086ddc79a0e6d72	yes	2

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Oath or Declaration filed	2	2
Oath or Declaration filed	1	1

Warnings:					
Information:					
5	Sequence Listing (Text File)	JHU3260-8_ST25.txt	470010	no	-
Warnings:					
Information:					
			Total Files Size (in bytes):	7453455	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Atul		Bedi	

Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Timonium	MD	US

Mailing Address of Inventor:

Address 1	2211 Dalewood Road
Address 2	
City	Timonium
State/Province	MD
Postal Code	21093
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Rajani		Ravi	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	State/Province	Country of Residence
Ruxton	MD	US

Mailing Address of Inventor:

Address 1	7810 Ballston Road
Address 2	
City	Ruxton
State/Province	MD
Postal Code	21204
Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	100899		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		
Attorney Docket Number	JHU3260-8	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	75	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	100899		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
	Continuation of	15/362632	2016-11-28	
Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/362632	Division of	15/231309	2016-08-08	9850306	2017-12-26

Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/231309	Continuation of	14/645282	2015-03-11	9441044	2016-09-13

Prior Application Status	Patented			Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/645282	Continuation of	13/582717	2012-10-17	8993524	2015-03-31

Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
13/582717	a 371 of international	PCT/US2011/027317	2011-03-04	
Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
PCT/US2011/027317	Claims benefit of provisional	61/435671	2011-01-24	
Prior Application Status	Expired			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
PCT/US2011/027317	Claims benefit of provisional	61/311255	2010-03-05	

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Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	The Johns Hopkins University		
Mailing Address Information For Applicant:			
Address 1	3400 N. Charles Street		
Address 2			
City	Baltimore	**State/Province**	MD
Country	US	Postal Code	21218
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Lisa A. Haile/			Date (YYYY-MM-DD)	2019-10-14
First Name	Lisa	Last Name	Haile	Registration Number	38,347

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	JHU3260-8
	Application Number	
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anjum, Durreshwar
Timestamp: [year=2019; month=10; day=16; hr=13; min=4; sec=12; ms=523; ]
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BEDI, Atul
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Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
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Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
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Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
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Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
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Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
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Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
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Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
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Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
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Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                405                 410                 415

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
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Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
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Gly Ser Thr Ile Pro Pro His Val Gln Lys Ser Val Asn Asn Asp Met
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Ile Val Thr Asp Asn Asn Gly Ala Val Lys Phe Pro Gln Leu Cys Lys
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Val Ala Val Trp Arg Lys Asn Asp Glu Asn Ile Thr Leu Glu Thr Val
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Gly Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Ala Asp Phe
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Lys Arg Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
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Asn
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/601,347

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/601,347	10/14/2019		0.00	JHU3260-8	20	1

CONFIRMATION NO. 9807

100899
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

FILING RECEIPT

OC000000112170863

Date Mailed: 10/28/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Atul Bedi, Timonium, MD;
Rajani Ravi, Ruxton, MD;

Applicant(s)

The Johns Hopkins University, Baltimore, MD;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/362,632 11/28/2016 PAT 10442860
which is a DIV of 15/231,309 08/08/2016 PAT 9850306
which is a CON of 14/645,282 03/11/2015 PAT 9441044
which is a CON of 13/582,717 10/17/2012 PAT 8993524
which is a 371 of PCT/US2011/027317 03/04/2011
which claims benefit of 61/435,671 01/24/2011
and claims benefit of 61/311,255 03/05/2010

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/25/2019
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/601,347**
Projected Publication Date: To Be Determined - pending completion of Missing Parts
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative,

this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/601,347	10/14/2019	Atul Bedi	JHU3260-8

CONFIRMATION NO. 9807

100899
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

FORMALITIES LETTER

OC000000112170664

Date Mailed: 10/28/2019

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **75** basic filing fee.
- $ **80** surcharge.
- $ **330** search fee.
- $ **380** examination fee.
- $(**0**) previous unapplied payment amount.
- $ **865** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/afessehaye/

Bicara Ex. 1006, Page 191 of 498
Bicara v. JHU - PGR2026-00025

PATENT
ATTORNEY DOCKET NO.: JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	Not Yet Assigned
Application No.:	16/601,347	Examiner:	Not Yet Assigned
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY BY ASSIGNEE

As the below-named assignee of the above-identified application ("Application"), **THE JOHNS HOPKINS UNIVERSITY**, through its duly-delegated representative, hereby appoints the practitioners of **USPTO CUSTOMER NO. 100899** at DLA Piper LLP (US) to represent and transact all business for the undersigned as attorneys or agents before the United States Patent and Trademark Office (USPTO) in connection with the above-identified patent application according to USPTO assignment records.

Statement under 37 C.F.R. §3.73(c):

THE JOHNS HOPKINS UNIVERSITY is the assignee of the entire right, title and interest in the above-identified application by virtue of an assignment recorded in the U.S. Patent and Trademark Office at Reel 041196, Frame 0155.

287948162.1
331323-001301

Direct all telephone calls to:

LISA A. HAILE, J.D., Ph.D.
Telephone: (858) 677-1456
Facsimile: (858) 638-5040

Address all correspondence to: **USPTO CUSTOMER NO. 100899**

The Johns Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

THE JOHNS HOPKINS UNIVERSITY

By : _____
(Signature)

Name : Steven Kousouris
(Typed or Printed Name)

Title : Executive Director, Johns Hopkins Technology Ventures

Date : 17 October, 2019

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331323-001301

Electronic Acknowledgement Receipt

EFS ID:	37706342
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Aldon Griffis
Filer Authorized By:	
Attorney Docket Number:	JHU3260-8
Receipt Date:	08-NOV-2019
Filing Date:	14-OCT-2019
Time Stamp:	22:06:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	C11123-P11123-37_20191014_APP_DLAP_PowerAttyEFS.pdf	926832 38b48556ceda253d96fd3077ed14e67d8670311d	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	926832

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
16/601,347	10/14/2019	The Johns Hopkins University	JHU3260-8	102379

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 12/27/2019 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Aldon Griffis/
Name:	Aldon Griffis
Registration Number:	55949

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Aldon Griffis
Attorney Docket Number:	JHU3260-8

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1880

Electronic Acknowledgement Receipt

EFS ID:	38162651
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Aldon Griffis
Filer Authorized By:	
Attorney Docket Number:	JHU3260-8
Receipt Date:	30-DEC-2019
Filing Date:	14-OCT-2019
Time Stamp:	14:22:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1880
RAM confirmation Number	E2019BTE24409925
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		C11123-P11123-37_20191230_OTH_DLAP_MissingPartsResponseEFS.pdf	481888 3d82e2b935512266eca481a9ad4b19299b54ce02	yes	7
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Preliminary Amendment		3	7	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	36956 b9d6f5fc17920a768891320aa131d03db2d62b3f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	518844		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Attorney Docket No.: JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	Not Yet Assigned
Application No.:	16/601,347	Examiner:	Not Yet Assigned
Filed:	October 14, 2019	Conf. No.	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop MISSING PARTS
Commissioner for Patents
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Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS

Sir:

In response to the Notice to File Missing Parts of Nonprovisional Application mailed October 28, 2019, attached is:

1. Preliminary Amendment (5 pages).

Applicant claims **LARGE ENTITY** status in the above-identified application.

The filing fee has been calculated as follows:

	Number Filed		Number Extra		Rate			Fee	
					Large Entity	Small Entity		Large Entity	Small Entity
Total Claims	**20**-20	=	**0**	X	$100		=	$ 0.00	
Independent Claims	**2**-3	=	**0**	X	$460		=	$ 0.00	
Multiple Dependent Claims Present: ____ Yes __x__ No					$820			N/A	
Fee for Each Additional 67 Sheets in Excess of 133 Pages					$400			N/A	
					FILING FEE			$ 300.00	
					SEARCH FEE			$ 660.00	
					EXAM FEE			$ 760.00	
					SURCHARGE FEE			$ 160.00	
					TOTAL FEE			**$1,880.00**	

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The fees for this filing total $1,880.00, which consist of $300.00 for the filing fee, $660.00 for the search fee, $760.00 for the exam fee and $160.00 for the late filing fee surcharge. The Commissioner is hereby authorized to charge any additional fees associated with the filing submitted herewith, or credit any overpayment, to Deposit Account 07-1896.

Respectfully submitted,

Date: December 30, 2019

/Pamela E. Hwang/
Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
Facsimile: (858) 638-5040

USPTO Customer No. 100899
DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

288765519.1
331323-001301

PATENT
Attorney Docket No.: JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	Not Yet Assigned
Application No.:	16/601,347	Examiner:	Not Yet Assigned
Filed:	October 14, 2019	Conf. No.	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

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P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

In connection with the above-identified patent application, entry of the amendment and reconsideration of the application in view of the amendments and following remarks are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

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331323-001301

I. AMENDMENTS

A. In the Claims

Please cancel claims 1-20 and add new claims 21-40 without prejudice. Upon entry of the present amendment, the status of the claims will be as follows:

1-20. (canceled).

21. (new) An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

a) the targeting moiety comprises a polypeptide that specifically binds a tumor cell surface molecule; and

b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of a receptor selected from the group consisting of: Transforming growth factor-beta receptor (TGFbR), Programmed death-1 (PD-1), and Vascular endothelial growth factor receptor (VEGFR1, VEGFR2).

22. (new) The molecule of claim 21 wherein the targeting moiety specifically binds a tumor growth factor receptor.

23. (new) The molecule of claim 21 wherein the targeting moiety comprises an antigen-binding domain of an immunoglobulin, antibody, bispecific or multispecific antibody, antibody fragment, single chain variable fragment (scFv), or bivalent or multivalent scFv.

24. (new) The molecule of claim 21, wherein said immunomodulatory moiety is fused to the C-terminus or N-terminus of said targeting moiety.

25. (new) The molecule of claim 21, wherein the targeting moiety is fused to the immunomodulatory moiety via a linker.

26. (new) The molecule of claim 25, wherein the linker is (GGGGS)n and wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

27. (new) The molecule of claim 21, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFbRII) or a binding fragment thereof.

28. (new) The molecule of claim 27, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87, or a binding fragment thereof.

29. (new) The molecule of claim 21, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Programmed Death-1 (PD-1) or a binding fragment thereof.

30. (new) The molecule of claim 29, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 93, or a binding fragment thereof.

31. (new) An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

a) the targeting moiety comprises a polypeptide that specifically binds a T cell co-inhibitory molecule and is an antagonist that inhibits the function of the targeted molecule; and

b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of a receptor selected from the group consisting of: Transforming growth factor-beta receptor (TGFbR), Programmed death-1 (PD-1), and Vascular endothelial growth factor receptor (VEGFR1, VEGFR2).

32. (new) The molecule of claim 31 wherein the targeting moiety comprises an antigen-binding domain of an immunoglobulin, antibody, bispecific or multispecific antibody, antibody fragment, single chain variable fragment (scFv), or bivalent or multivalent scFv.

33. (new) The molecule of claim 31, wherein said immunomodulatory moiety is fused to the C-terminus or N-terminus of said targeting moiety.

34. (new) The molecule of claim 31, wherein the targeting moiety is fused to the immunomodulatory moiety via a linker.

35. (new) The molecule of claim 34, wherein the targeting moiety is an Fc-containing polypeptide comprising a linker at the CH3 region of the Fc.

36. (new) The molecule of claim 34, wherein the linker is (GGGGS)n and wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

37. (new) The molecule of claim 31, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFbRII) or a binding fragment thereof.

38. (new) The molecule of claim 37, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87, or a binding fragment thereof.

39. (new) The molecule of claim 31, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Programmed Death-1 (PD-1) or a binding fragment thereof.

40. (new) The molecule of claim 39, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 93, or a binding fragment thereof.

II. REMARKS

Claims 1-20 have been canceled and, therefore, do not add new matter. New claims 21-40 have been added and are supported by the specification as originally filed. As such, claims 21-40 do not add new matter. As a result, claims 21-40 remain pending in this application. Accordingly, entry of the amendments is respectfully requested.

The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The fees for this filing total $1,880.00, which consist of $300.00 for the filing fee, $660.00 for the search fee, $760.00 for the exam fee and $160.00 for the late filing fee surcharge. The Commissioner is hereby authorized to charge any additional fees associated with the filing submitted herewith, or credit any overpayment, to Deposit Account 07-1896.

Respectfully submitted,

Date: December 30, 2019

/Pamela E. Hwang/

Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
Facsimile: (858) 638-5040

USPTO Customer No. 100899
DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/601,347	10/14/2019		1880	JHU3260-8	20	2

CONFIRMATION NO. 9807

UPDATED FILING RECEIPT

100899
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

OC000000113705879

Date Mailed: 01/06/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Atul Bedi, Timonium, MD;
Rajani Ravi, Ruxton, MD;

Applicant(s)

The Johns Hopkins University, Baltimore, MD;

Power of Attorney: The patent practitioners associated with Customer Number 100899

Domestic Priority data as claimed by applicant

This application is a CON of 15/362,632 11/28/2016 PAT 10442860
which is a DIV of 15/231,309 08/08/2016 PAT 9850306
which is a CON of 14/645,282 03/11/2015 PAT 9441044
which is a CON of 13/582,717 10/17/2012 PAT 8993524
which is a 371 of PCT/US2011/027317 03/04/2011
which claims benefit of 61/435,671 01/24/2011
and claims benefit of 61/311,255 03/05/2010

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/25/2019
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/601,347**
Projected Publication Date: 04/16/2020
Non-Publication Request: No
Early Publication Request: No
Title

COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Title 35, United States Code, Section 184

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Bicara Ex. 1006, Page 211 of 498
Bicara v. JHU - PGR2026-00025

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/601,347

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1720

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/601,347	10/14/2019	Atul Bedi	JHU3260-8

CONFIRMATION NO. 9807

100899
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

POA ACCEPTANCE LETTER

OC000000113705611

Date Mailed: 01/06/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/08/2019.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cnguyen/

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16601347
Filing Date	2019-10-14
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	HAMA, JOANNE
Attorney Docket Number	JHU3260-8

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7317091	B2	2008-01-08	LAZAR et al.	
	2	7527791	B2	2009-05-05	ADAMS et al.	
	3	7795389	B2	2010-09-14	SUN et al.	
	4	7803378	B2	2010-09-28	TRANCHAND-BUNEL DENIS	
	5	7820165	B2	2010-10-26	MCKENNA et al.	
	6	8101720	B2	2012-01-24	LAZAR et al.	
	7	8114845	B2	2012-02-14	LANGERMANN et al.	
	8	8399618	B2	2013-03-19	LAZAR et al.	

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	Attorney Docket Number	JHU3260-8

	9	8815247	B2	2014-08-26	GOVINDAPPA et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050054832	A1	2005-03-10	LAZAR et al.	
	2	20060135459	A1	2006-06-22	EPSTEIN et al.	
	3	20060193849	A1	2006-08-31	KRAUSS et al.	
	4	20060263368	A1	2006-11-23	ROSENBLUM et al.	
	5	20070212337	A1	2007-09-13	BEDI et al.	
	6	20070244042	A1	2007-10-18	SUN et al.	
	7	20080075717	A1	2008-03-27	TRANCHAND-BUNEL DENIS	
	8	20090053240	A1	2009-02-26	LAZAR et al.	

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	9	20090226435	A1	2009-09-10	KHARE SANJAY	
	10	20110052585	A1	2011-03-03	SCARIA et al.	
	11	20130017199	A1	2013-01-17	LANGERMANN SOLOMON	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2542590	EP	B1	2017-05-03	UNIV JOHNS HOPKINS	English Abstract Submitted	☐
	2	2009/152610	WO	A1	2009-12-23	UNIV MCGILL		☐
	3	2010/003118	WO	A1	2010-01-07	TRUBION PHARMACEUTICALS INC		☐
	4	2011/109789	WO	A2	2011-09-09	UNIV JOHNS HOPKINS		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	HAMA, JOANNE
	Attorney Docket Number	JHU3260-8

	1	Alignment of SEQ ID No. 10 of D3 with SEQ ID No. 87 of B1.	☐
	2	Alignment of SEQ ID No. 744 of D2 with SEQ ID No. 87 of B1.	☐
	3	Canadian Office Action dated Mar. 28, 2018, regarding CA 2,791,383.	☐
	4	Coffelt et al.: "Angiopoietin 2 Stimulates TIE2-Expressing Monocytes to Suppress T Cell Activation and to Promote Regulatory T Cell Expression"; The Journal of Immunology 2011, 186 (7), p. 4183-4190.	☐
	5	EP Communication dated Sep. 5, 2018, pursuant to Rule 114(2) EPC regarding EP 2542590.	☐
	6	European Search Report and Search Opinion Received for EP Application No. 17168491.3, mailed on November 24, 2017, 5 pages.	☐
	7	Fernandez-Botran et al.: "Soluble cytokine receptors in biological therapy"; Expert Opinion on Biological Therapy, 2002, vol. 2, Issue 6, p. 585-605.	☐
	8	Fonseca et al.: "Capitalizing on the immunogenicity of Dying Tumor Cells"; Clinical Cancer Research 2008, 14 (6), p. 1603-1608.	☐
	9	International Preliminary Report on Patentability received for PCT Patent Application No. PCT/US2011/027317, mailed on September 20, 2012, 9 pages.	☐
	10	International Search Report and Written Opinion received for PCT Patent Application No. PCT/US2011/027317, mailed on February 08, 2012, 11 pages.	☐
	11	Jones et al.: "Degree of CD25 expression in T-Cell lymphoma is dependent on tissue site: implications for targeted therapy"; Clinical Cancer Research, 2004, vol. 10, p. 5587-5594.	☐

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	Filing Date	2019-10-14
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	Attorney Docket Number	JHU3260-8

	12	Jung et al.: "Double anti-angiogenic and anti-inflammatory protein valpha targeting VEGF-A and TNF-.alpha. in retinopathy and psoriasis"; JBC, vol. 286, No. 16, Feb. 23, 2011, pp. 14410-14418.	☐
	13	Koh et al.: "Double anti-angiogenic protein, DAAP, targeting VEGF-A and angiopoietins in tumor angiogenesis, metastasis, and vascular leakage"; Cancer Cell, vol. 18, Issue 2, Aug. 16, 2010, p. 171-184. Supplementary data, 28 pages.	☐
	14	Kwiatkowska et al.: "Expression of soluble recombinant TGF-.beta. type II receptor fused with the Fc portion of human IgG1 (sT.beta.II-Fc) in NSO cells"; Acta Biochimica Polonica, 2006, 53(2), pp. 361-369.	☐
	15	Letourneau et al.: "IL-2- and CD25-dependent immunoregulatory mechanisms in the homeostasis of T-cell subsets"; J Allergy Clin Immunol. 2009, 123(4), pp. 758-762.	☐
	16	Malek et al.: "Interleukin-2 receptor signaling: at the interface between tolerance and immunity"; Immunity 2010, vol. 33, Issue 2, p. 153-165.	☐
	17	Office Action received for European Application No. 11751481.0, mailed on January 22, 2016, 3 pages.	☐
	18	Podar et al.: "Inhibition of the TGF-.beta. signaling pathway in tumor cells"; Recent Results in Cancer Research, 2007, vol. 172, p. 77-97.	☐
	19	Regnault et al.: "Fc.gamma. Receptor-mediated Induction of Dendritic Cell Maturation and Major Histocompatibility Complex Class I-restricted Antigen Presentation after Immune Complex Internalization"; J. Exp. Med., 1999, vol. 189, No. 2, p. 371-380.	☐
	20	Rose-John et al. 2007. Expert Opinion in Therapeutic Targets. 11:613-624	☐
	21	Schrama et al.: "Antibody targeted drugs as cancer therapeutics"; Nature Reviews Drug Discovery, Jan. 20, 2006, vol. 5, p. 147-159.	☐
	22	Supplementary European Search Report received for EP Patent Application No. 11751481.0, mailed on June 27, 2013, 16 pages.	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	HAMA, JOANNE
	Attorney Docket Number	JHU3260-8

	23	Trail et al.: "Monoclonal antibody drug conjugates in the treatment of cancer"; Current Opinion in Immunology, 1999, vol. 11, Issue 5, p. 584-588.	☐
	24	U.S. Appl. No. 61/311,255, Mar. 5, 2010, Atul Bedi.	☐
	25	U.S. Appl. No. 61/435,671, Jan. 24, 2011, Atul Bedi.	☐
	26	Wang et al.: "Tumor necrosis factor and cancer, buddies or foes?"; Acta Pharmacologica Sinica, 2008, 29 (11), p. 1275-1288.	☐
	27	Yang et al.: "The role of T.sub.reg in the cancer immunological response"; American Journal of Immunology, 2009, 5 (1), p. 17-28.	☐
	28	Yao and Chen: "Contribution of B7-H1/PD-1 Co-inhibitory Pathway to T-Ce11 Dysfunction in Cancer"; D.I. Gabrilovich, A.A. Hurwitz (eds.), Tumor-Induced Immune Suppression. pp. 29-40 .COPYRGT. Springer 2008.	☐
	29	Zhang et al., "Design and Optimization of a Linker for Fusion Protein Construction," Prog. Natural Sci. (2009), 19:1197-1200, Elsevier.	☐
	30	Zhang et al: "Expression of a Soluble TGF-.beta. Receptor by Tumor Cells Enhances Dendritic Cell/Tumor Fusion Vaccine Efficacy.sup.1"; J. Immunology, 2008, 181, pp. 3690-3697.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	Joanne Hama
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Dear Madam:

In accordance with 37 C.F.R. § 1.97, enclosed is a Form PTO/SB/08 relating to the above-identified application. Since the present application is a continuation application of a prior application under 37 CFR § 1.98(d), the listed references are not required to be filed with the attached Form PTO/SB/08.

The Applicants respectfully submit that the Information was previously submitted to the Office in a prior application number 15/362,632, filed November 28, 2016, (now U.S. patent 10,442,860), and is relied on earlier filing date under 35 U.S.C. § 120. The Prosecution history documents for the application number 15/362,632, are of record with the U.S. Patent and Trademark Office and are stored in IFW. In addition, the IDS submitted in the earlier application complies with 37 CFR § 1.98(a)-(c). As such, in accordance with 37 CFR § 1.98(d) the references listed in Form PTO/SB/08 are not provided.

This Information Disclosure Statement is being submitted before the mailing date of a First Office Action on the merits for the above-identified application.

No fee is believed to be due in connection with this submission. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: January 14, 2020

/Pamela E. Hwang/
Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
Facsimile: (858) 638-5040

DLA PIPER LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No.: 100899

Electronic Acknowledgement Receipt

EFS ID:	38290480
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Pamela Elaine Bechtel/Tia de Langen
Filer Authorized By:	Pamela Elaine Bechtel
Attorney Docket Number:	JHU3260-8
Receipt Date:	14-JAN-2020
Filing Date:	14-OCT-2019
Time Stamp:	14:24:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		JHU3260-8_IDS.pdf	822634 c5702d4797f317f5e0d627dd41b87ffae1898cd9	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Information Disclosure Statement (IDS) Form (SB08)	3	9
	Transmittal Letter	1	2
Warnings:			
Information:			
	Total Files Size (in bytes):	822634	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/601,347	10/14/2019	Atul Bedi	JHU3260-8

CONFIRMATION NO. 9807

100899
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

PUBLICATION NOTICE

OC00000116286136

Title:COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

Publication No.US-2020-0115455-A1
Publication Date:04/16/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

100899 7590 05/27/2020

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/27/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gtdocket@dlapiper.com

Office Action Summary	Application No. 16/601,347	Applicant(s) Bedi et al.	
	Examiner SHULAMITH H SHAFER	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-40 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 21-40 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 21-30, drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a tumor cell surface molecule, classified in A61K 2039/505, for example.

II. Claims 31-40, drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a T cell co-inhibitory molecule and is an antagonist that inhibits the function of the targeted molecule, classified in C07K 2319/00.

The inventions are distinct, each from the other because of the following reasons:

Although both Inventions I and II are directed to isolated molecules comprising fusion proteins, Invention I recites a targeting moiety comprising a polypeptide that specifically binds a tumor cell surface molecule, whereas Invention II recites a targeting moiety comprising a polypeptide that specifically binds a T cell co-inhibitory molecule and is an antagonist that inhibits the function of the targeted molecule. Thus, the search for the two molecules would not be co-extensive and would present a search burden. Furthermore, there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Species Election

This application contains claims directed to the following patentably distinct species: amino acid sequence of the extracellular domain of a receptor (immunomodulatory moiety):

1)Transforming growth factor-beta receptor (TGFβR),

2) Programmed death-1 (PD-1),

3) Vascular endothelial growth factor receptor 1 (VEGFR1) and

4) Vascular endothelial growth factor receptor 2 (VEGFR2)

The species are independent or distinct because each amino acid sequence of the extracellular domain of a receptor comprises a sequence of unique and distinct amino acid residues and functionality. In addition, these species are not obvious variants of each other based on the current record.

If either of Groups I or II is elected, Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, chosen from species 1-4, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: each amino acid sequence of the extracellular domain of a receptor comprises a sequence of unique and distinct amino acid residues and functionality. A search for a fusion protein comprising the extracellular domain of TGFβR for example, would not reveal art reading on a fusion protein comprising the extracellular domain of PD-1, for example.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on M-F 8AM-5PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JOANNE HAMA can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHULAMITH H SHAFER/
Primary Examiner, Art Unit 1647

PTO/SB/08a (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	16/601,347
Filing Date	October 14, 2019
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	Joanne Hama
Attorney Docket Number	JHU3260-8

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US 2009/0214533	08-27-2009	Ralph Clynes	

FOREIGN PATENT DOCUMENTS

		Foreign Patent Document Country Code[3] "Number[4] "Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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PTO/SB/08b (07-09)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	16/601,347
Filing Date	October 14, 2019
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	Joanne Hama
Attorney Docket Number	JHU3260-8

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	AB	Japanese Office Action issued on May 27, 2020, regarding JP 2018-140050.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

291357517.1
331323-001301

Electronic Acknowledgement Receipt

EFS ID:	40091132
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Pamela Elaine Bechtel/Tia de Langen
Filer Authorized By:	Pamela Elaine Bechtel
Attorney Docket Number:	JHU3260-8
Receipt Date:	23-JUL-2020
Filing Date:	14-OCT-2019
Time Stamp:	17:49:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		JHU3260-8_IDS2.pdf	265639 c428784b20b0def45ba26b5e29440797f822ad07	yes	4

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	4	
Warnings:					
Information:					
2	Other Reference-Patent/App/Search documents	JP201814005_AB.pdf	155445 22c335f9ed6e947ed0817ee8b4af93837d17eaf6	no	3
Warnings:					
Information:					
		Total Files Size (in bytes):	421084		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	Joanne Hama
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Dear Madam:

In accordance with 37 C.F.R. § 1.97, enclosed are references relating to the above-identified application. For the convenience of the Examiner, the cited references are listed on the attached Form PTO/SB/08.

It is respectfully requested that these references be considered in the examination of this application and their consideration be made of written record in the application file.

This Information Disclosure Statement is being submitted before the mailing date of a First Office Action on the merits for the above-identified application.

No fee is believed to be due in connection with this submission. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: July 23, 2020

/Pamela E. Hwang/
Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
Facsimile: (858) 638-5040

DLA PIPER LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No.: 100899

291357584.1
331323-001301

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Lisa Haile/Karen LePari
Attorney Docket Number:	JHU3260-8

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
		Total in USD ($)		**100**

Electronic Acknowledgement Receipt

EFS ID:	40405729
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Lisa Haile/Karen LePari
Filer Authorized By:	Lisa Haile
Attorney Docket Number:	JHU3260-8
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Deposit Account	071896
Authorized User	Karen LePari
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37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	JHU3260-8_RspToResReq_27AUG2020.pdf	121256 10f3380db98ed5c8b112021e9992aa3d12c6ea88	no	5
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30801 6e36d07118416736cb8e583a8f86d4675fde25b9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	152057		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	Joanne Hama
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Sir:

In response to the Restriction Requirement mailed May 27, 2020, please enter the following amendment and remarks in the above-identified application.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **4** of this paper.

Amendments to the Claims:

Please amend claims 21-24 and 27-28 as shown in the listing of claims.

Please cancel claims 29-40 without prejudice or disclaimer.

Please add new claims 41-42.

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1-20. (Canceled)

21. (Currently amended) An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and

b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain ~~of a receptor selected from the group consisting of:~~ Transforming growth factor-beta receptor (TGFbR)~~, Programmed death-1 (PD-1), and Vascular endothelial growth factor receptor (VEGFR1, VEGFR2)~~.

22. (Currently amended) The molecule of claim 21 wherein the targeting moiety specifically binds a cell surface molecule that is a tumor antigen, tumor growth factor receptor, or cytokine receptor.

23. (Currently amended) The molecule of claim 21 wherein the targeting moiety comprises an antigen-binding domain of an immunoglobulin, antibody, bispecific or multispecific antibody, antibody fragment, single chain variable fragment (scFv), ~~or~~ bivalent or multivalent scFv or Fc-containing polypeptide.

24. (Currently Amended) The molecule of claim 21, wherein the ~~said~~ immunomodulatory moiety is fused to the C-terminus or N-terminus of said targeting moiety.

25. (Previously presented) The molecule of claim 21, wherein the targeting moiety is fused to the immunomodulatory moiety via a linker.

26. (Previously presented) The molecule of claim 25, wherein the linker is (GGGGS)n and wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

27. (Currently amended) The molecule of claim 21, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFbRII) or a ligand-binding fragment thereof.

28. (Currently amended) The molecule of claim 27, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87, or a ligand-binding fragment thereof.

29-40. (Canceled)

41. (New) The molecule of claim 25, wherein the targeting moiety is an Fc-containing polypeptide comprising a linker at the CH3 region of the Fc.

42. (New) The molecule of claim 21, wherein the targeting moiety specifically binds HVEM, CEA, PSMA, PD-L1, or EGFR.

REMARKS

Prior to this Communication, claims 21-40 were pending and under consideration. With the present communication, claims 21-24 and 27-28 have been amended, claims 29-40 have been canceled without prejudice or disclaimer and new claims 41-42 have been added. Support for the claim amendments may be find generally throughout the application and claims as originally filed. No new matter is added. After entry of the amendments, claims 21-28 and 41-42 will be pending and under consideration.

As set forth in the Office Action issued on May 27, 2020 ("the Office Action") in the above-identified patent application, Applicants are required under 35 U.S.C. 121 to restrict the application to a patentably distinct species.

In response to the Requirement for Restriction, Applicants elects the following invention, without traverse: Group I, claims 21-30 drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a tumor cell surface.

Applicants reserve the right to pursue prosecution of non-elected subject matter and/or species upon an indication of allowance of any generic claims and to request rejoinder in the present application or in a later filed application claiming the benefit of priority of the above-identified application. The following claims are encompassed by the elected invention: Claims 21-28 and 41-42.

CONCLUSION

In view of the amendments and above remarks, reconsideration and withdrawal of the restriction requirement is respectfully requested. Applicant provides that the claims are ready for examination. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of $100.00 to cover the One-Month Extension of Time fee, for small entity, to Deposit Account No. 07-1896. No other fee is deemed necessary in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees that are required or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: August 27, 2020

/Lisa A. Haile/
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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/601,347	Filing Date 10/14/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/27/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

100899 7590 12/10/2020

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
12/10/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gtdocket@dlapiper.com

Office Action Summary	Application No. 16/601,347	Applicant(s) Bedi et al.	
	Examiner FOZIA M HAMUD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 08/27/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 21-28 and 41-42 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 21-28 and 41-42 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☑ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 10/14/2019 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 01/14/2020; 07/23/2020.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☑ Other: PTO-2301.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1a. The present application is being examined under the pre-AIA first to invent provisions.

1b. The drawings filed on 14 October 2019 are acceptable.

Restriction/Election:

1c. Applicant's election without traverse of Group I (claims 21-30), filed on 27 August 2020 is acknowledged. All of the pending claims are drawn to the elected invention.

Claim Status:

1d. Claims 21-28 and 41-42 are pending and under consideration.

Information Disclosure Statement:

2. The information disclosure statements filed on 14 January 2020 and 23 July 2020 have been received and comply with the provisions of 37 CFR §1.97 and §1.98. The attached references and reference in parent application 15/362,632 have been considered as to the merits.

Sequence Compliance:

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR

1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Specifically, the sequence recited in claim 26 is not accompanied by the required reference to the relevant sequence identifiers. See the attached sequence compliance form. APPLICANT IS GIVEN THREE MONTHS FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLYWITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821- 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response. Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Web

(https://www.uspto.gov/patents-application-process/applying-online/about-efs-web)

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3. Hand Carry, Federal Express, United Parcel Service or other delivery service to:
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Randolph Building 401 Dulany Street
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Claim Objections:

4. Claims 21 and 42 are objected to because of the following informalities:

4a. In claim 21, line 6, after the phrase "extracellular domain", there is a word missing. Please note that this issue could be overcome by amending the claim to recite, for example, "extracellular domain of".

4b. Claim 42 recites the acronyms "HVEM, CEA, PSMA, PD-L1, EGFR". It is suggested to spell the acronym first. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

5a. Claims 21-27 and 41-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of US. Patent 9,850,306.

Although the conflicting claims are not identical, they are not patentably distinct from each other because, the instant claims are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein; (a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain Transforming growth factor-beta receptor (TGFbR). Meanwhile, the claims of '306 are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein: (a) the targeting moiety is a polypeptide that specifically binds Programmed Death-1 ligand (PD-1 ligand); and (b) the immunomodulatory moiety comprises an

amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFbR).

Thus, the instant claims and the patented claims encompass an isolated molecule that comprises a targeting moiety fused with an immunomodulatory moiety (an amino acid sequence of the extracellular domain of TGFbR). Instant claim 42 recites that the targeting moiety binds PD-L1.

Accordingly, the patented claims anticipate the instant claims, since species will anticipate a claim to a genus, (see MPEP 2131.02 [R-6]).

5b. Claims 21-27 and 41-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of US. Patent 9,441,044.

Although the conflicting claims are not identical, they are not patentably distinct from each other because, the instant claims are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein; (a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain Transforming growth factor-beta receptor (TGFbRII).

Meanwhile, the claims of ‘044 are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein: (a) the targeting moiety specifically binds Epidermal Growth Factor Receptor (EGFR); and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFbRII).

Thus, the instant claims and the patented claims encompass the same isolated molecule that comprise the targeting moiety is a polypeptide that specifically binds Epidermal Growth Factor Receptor (EGFR); and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFbRII), (see instant claims 27, 42).

Accordingly, the patented claims anticipate the instant claims, since species will anticipate a claim to a genus, (see MPEP 2131.02 [R-6]).

5c. Claims 21-27 and 41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of US. Patent 8,993,524 in view of Contardi et al, (Int. J. Cancer: 117, 538–550; 2005).

Although the conflicting claims are not identical, they are not patentably distinct from each other because, the instant claims are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein; (a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain Transforming growth factor-beta receptor (TGFbRII).

Meanwhile, the claims of ‘524 are drawn to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein: (a) the targeting moiety specifically binds Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4); and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFbR).

The Contardi et al reference teaches that CTL-4 is constitutively expressed on tumor cells, (see abstract and page 539). The reference teaches antibodies that bind CTLA-4, (see page 539, column 1). Therefore, it would be obvious to one skilled in the art to fuse the recited extracellular domain transforming growth factor-beta receptor (TGFbRII) with antibodies that bind CTLA-4 to target tumor cells, (see Contardi et al at page 549, column 1). One would be motivated to make these modifications and have a reasonable expectation of success since making fusion proteins is routine in the art and the '524 patent teaches making numerus such fusion proteins.

Accordingly, the patented claims anticipate the instant claims, since species will anticipate a claim to a genus, (see MPEP 2131.02 [R-6]).

Claim Rejections - 35 USC § 103:

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

6a. Claims 21-28 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mckenna et al. (US 7,820,165; cited on IDS of 01/14/2020, reference #5) and Sun et al. (US 7,795,389, cited on IDS of 01/14/2020, reference #3).

The instant claims encompass an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain transforming growth factor-beta receptor (TGFbRII); wherein the targeting moiety specifically binds EGFR.

Mckenna et al. teaches that hybrid antigen binding molecules have superior properties relative to their non-hybrid counterparts (column 1, lines 47-50). The reference discloses hybrid proteins comprising an antigen binding moiety (targeting moiety, antibody) binding specifically to the EGFR, wherein the hybrid protein has EGFR antagonist activity (column 2, lines 1-3). Such proteins may be used to treat cancer and other cell proliferative disorders (Column 4, lines 65-67). The antigen binding moiety may be linked to the other protein via a peptide linker (column 2, lines 35-39). The McKenna et al. reference also teaches peptide linkers comprising $(GGGGS)_4$, and peptide linker to 15 amino acids comprising glycine and serine (column 11, lines 34-53). The reference also teaches that the engineered binding moieties are linked scFv-CH3-scFv-Fc, (see column 15, lines 25-30).

However, McKenna et al does not teach an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGF- βRII), wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO:87.

Sun et al. teach TGF-beta antagonists comprising soluble cell surface type II TGF-beta receptors and fusion proteins comprising said soluble cell surface type II TGF-beta receptors (column 3, lines 26-28, 31-33). These soluble type II receptors comprise the extracellular domain of the TGFβ-RII (see claim 1, for example). Said antagonists may be used to treat cancers (abstract). The reference teaches a sequence, SEQ ID NO:8, which comprises an amino acid sequence which is 100% identical to SEQ ID NO:87 of the instantly claimed invention (see results in SCORE SEQ ID NO:8 of Sun et al).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art teachings of McKenna et al and Sun et al. to construct the isolated molecule comprising a targeting moiety which specifically binds to EGFR (as disclosed by McKenna et al) and an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of TGFβ-RII of SEQ ID NO:87, as taught by Sun et al. It would also be obvious to fuse the two with a linker as taught by McKenna et al. wherein said linker comprises the specific amino acid sequence of $(GGGGS)_{1-8}$. One would be motivated to make these modifications and

have a reasonable expectation of success as both references disclose fusion proteins comprising said polypeptides as therapeutic agents to treat cancers.

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (MPEP 2144.06)

One of ordinary skill would be motivated to combine the two therapeutic proteins as a fusion protein, as one would recognize that administration of one therapeutic protein composition would be advantageous as a treatment protocol. The person of ordinary skill in the art would have been motivated to make that modification and reasonably would have expected success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007)).

Accordingly, the invention, taken as a whole, is prima facie obvious over the cited prior art.

6b. Claims 21-28 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mckenna et al. and Sun et al. in view of Scaria et al. (US 2011/0052585, priority claimed to SN 60/974,892, filed 25 Sept. 2007; cited on IDS of 01/14/2020, reference #12).

The teachings of Mckenna et al. and Sun et al. are set forth above.

However, the Mckenna et al. and Sun et al. references, singularly or in combination, do not teach a molecule comprising a linker at the CH3 region of the Fc.

Scaria et al teaches fusion proteins comprising a cytokine cell surface receptor and Fc (paragraph 0017). The Fc component comprises the CH3 domain of an IgG (paragraph 0021). The fusion construct may comprise a soluble cytokine receptor fragment linked to the CH3 domain of the Fc via a linker (paragraph 0034 and 0035). Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art teachings of McKenna et al and Sun et al. to construct the isolated molecule comprising a targeting moiety which specifically binds to EGFR (as disclosed by McKenna et al) and an immunomodulatory moiety comprising an amino acid sequence of the extracellular domain of TGFβ-RII of SEQ ID NO:87, as taught by Sun et al. and include a linker at the CH3 region of the Fc, as taught by Scaria et al. wherein said linker comprises the specific amino acid sequence of $(GGGGS)_{1-8}$, an obvious design variant of the linkers taught by McKenna et al. and Scaria et al. teach fusion proteins comprising linkers and one of ordinary skill is aware of the advantages of utilizing a linker in a fusion protein such as correct folding and corresponding biological activities of the different domains of the fusion protein.

One of ordinary skill would be motivated to combine the two therapeutic proteins as a fusion protein, as one would recognize that administration of one therapeutic protein composition would be advantageous as a treatment protocol. The person of ordinary skill in the art would have been motivated to make that modification and reasonably would have expected success because a person of ordinary skill has good

reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007)).

Accordingly, the invention, taken as a whole, is prima facie obvious over the cited prior art.

Conclusion:

7. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday 8AM-4:30Pm.

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Fozia Hamud
Patent Examiner
Art Unit 1647
01 December 2020

/BRIDGET E BUNNER/
Primary Examiner, Art Unit 1647

Notice of References Cited	Application/Control No. 16/601,347	Applicant(s)/Patent Under Reexamination Bedi et al.	
	Examiner FOZIA M HAMUD	Art Unit 1647	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9850306-B2	12-2017	Bedi; Atul	A61P37/04	1/1
*	B	US-9441044-B2	09-2016	Bedi; Atul	A61K47/6803	1/1
*	C	US-8993524-B2	03-2015	Bedi; Atul	A61K31/704	514/19.2
	D					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Contardi et al, Int. J. Cancer: 117, 538–550; 2005.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi et al.
	Examiner	Art Unit
	FOZIA M HAMUD	1647

CPC - Searched*		
Symbol	**Date**	**Examiner**
(C07K14/71|C07K16/2863|A61P35/00|A61K45/06|A61K38/179| C07K14/495|C07K16/30|C07K7/08|C12N2500/22|A61K31/704| A61K47/6803|A61P37/00|C07K2317/70).CPC.); See WEST Search History Printout	12/01/2020	FH

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Search Notes		
Search Notes	**Date**	**Examiner**
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WEST, (US Patent Full, Derwent, JPO, EPO, PG-Pub), see Search Print out. STN, via (Medline, Caplus, Biosis, Embase). Inventor name searched on Palm, West and STN, See Search Print out.	12/01/2020	FH

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Bicara Ex. 1006, Page 265 of 498
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Sheet 1 of 2

Complete if Known	
Application Number	16/601,347
Filing Date	October 14, 2019
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	Joanne Hama
Attorney Docket Number	JHU3260-8

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US 2009/0214533	08-27-2009	Ralph Clynes	

FOREIGN PATENT DOCUMENTS

		Foreign Patent Document Country Code[3] "Number[4] "Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

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Sheet 2 of 2

Complete if Known	
Application Number	16/601,347
Filing Date	October 14, 2019
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	Joanne Hama
Attorney Docket Number	JHU3260-8

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	AB	Japanese Office Action issued on May 27, 2020, regarding JP 2018-140050.	

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Application Number	16601347
Filing Date	2019-10-14
First Named Inventor	Atul Bedi
Art Unit	1647
Examiner Name	HAMA, JOANNE
Attorney Docket Number	JHU3260-8

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7317091	B2	2008-01-08	LAZAR et al.	
	2	7527791	B2	2009-05-05	ADAMS et al.	
	3	7795389	B2	2010-09-14	SUN et al.	
	4	7803378	B2	2010-09-28	TRANCHAND-BUNEL DENIS	
	5	7820165	B2	2010-10-26	MCKENNA et al.	
	6	8101720	B2	2012-01-24	LAZAR et al.	
	7	8114845	B2	2012-02-14	LANGERMANN et al.	
	8	8399618	B2	2013-03-19	LAZAR et al.	

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	Examiner Name	HAMA, JOANNE
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	9	8815247	B2	2014-08-26	GOVINDAPPA et al.	

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	1	20050054832	A1	2005-03-10	LAZAR et al.	
	2	20060135459	A1	2006-06-22	EPSTEIN et al.	
	3	20060193849	A1	2006-08-31	KRAUSS et al.	
	4	20060263368	A1	2006-11-23	ROSENBLUM et al.	
	5	20070212337	A1	2007-09-13	BEDI et al.	
	6	20070244042	A1	2007-10-18	SUN et al.	
	7	20080075717	A1	2008-03-27	TRANCHAND-BUNEL DENIS	
	8	20090053240	A1	2009-02-26	LAZAR et al.	

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	Examiner Name	HAMA, JOANNE
	Attorney Docket Number	JHU3260-8

	9	20090226435	A1	2009-09-10	KHARE SANJAY	
	10	20110052585	A1	2011-03-03	SCARIA et al.	
	11	20130017199	A1	2013-01-17	LANGERMANN SOLOMON	

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	1	2542590	EP	B1	2017-05-03	UNIV JOHNS HOPKINS	English Abstract Submitted	☐
	2	2009/152610	WO	A1	2009-12-23	UNIV MCGILL		☐
	3	2010/003118	WO	A1	2010-01-07	TRUBION PHARMACEUTICALS INC		☐
	4	2011/109789	WO	A2	2011-09-09	UNIV JOHNS HOPKINS		☐

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	Attorney Docket Number	JHU3260-8

	1	Alignment of SEQ ID No. 10 of D3 with SEQ ID No. 87 of B1. 05-2018	☐
	2	Alignment of SEQ ID No. 744 of D2 with SEQ ID No. 87 of B1. 05-2018	☐
	3	Canadian Office Action dated Mar. 28, 2018, regarding CA 2,791,383.	☐
	4	Coffelt et al.: "Angiopoietin 2 Stimulates TIE2-Expressing Monocytes to Suppress T Cell Activation and to Promote Regulatory T Cell Expression"; The Journal of Immunology 2011, 186 (7), p. 4183-4190.	☐
	5	EP Communication dated Sep. 5, 2018, pursuant to Rule 114(2) EPC regarding EP 2542590.	☐
	6	European Search Report and Search Opinion Received for EP Application No. 17168491.3, mailed on November 24, 2017, 5 pages.	☐
	7	Fernandez-Botran et al.: "Soluble cytokine receptors in biological therapy"; Expert Opinion on Biological Therapy, 2002, vol. 2, Issue 6, p. 585-605.	☐
	8	Fonseca et al.: "Capitalizing on the immunogenicity of Dying Tumor Cells"; Clinical Cancer Research 2008, 14 (6), p. 1603-1608.	☐
	9	International Preliminary Report on Patentability received for PCT Patent Application No. PCT/US2011/027317, mailed on September 20, 2012, 9 pages.	☐
	10	International Search Report and Written Opinion received for PCT Patent Application No. PCT/US2011/027317, mailed on February 08, 2012, 11 pages.	☐
	11	Jones et al.: "Degree of CD25 expression in T-Cell lymphoma is dependent on tissue site: implications for targeted therapy"; Clinical Cancer Research, 2004, vol. 10, p. 5587-5594.	☐

EFS Web 2.1.18

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /F.M.H/

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	Attorney Docket Number	JHU3260-8

	12	Jung et al.: "Double anti-angiogenic and anti-inflammatory protein valpha targeting VEGF-A and TNF-.alpha. in retinopathy and psoriasis"; JBC, vol. 286, No. 16, Feb. 23, 2011, pp. 14410-14418.	☐
	13	Koh et al.: "Double anti-angiogenic protein, DAAP, targeting VEGF-A and angiopoietins in tumor angiogenesis, metastasis, and vascular leakage"; Cancer Cell, vol. 18, Issue 2, Aug. 16, 2010, p. 171-184. Supplementary data, 28 pages.	☐
	14	Kwiatkowska et al.: "Expression of soluble recombinant TGF-.beta. type II receptor fused with the Fc portion of human IgG1 (sT.beta.II-Fc) in NSO cells"; Acta Biochimica Polonica, 2006, 53(2), pp. 361-369.	☐
	15	Letourneau et al.: "IL-2- and CD25-dependent immunoregulatory mechanisms in the homeostasis of T-cell subsets"; J Allergy Clin Immunol. 2009, 123(4), pp. 758-762.	☐
	16	Malek et al.: "Interleukin-2 receptor signaling: at the interface between tolerance and immunity"; Immunity 2010, vol. 33, Issue 2, p. 153-165.	☐
	17	Office Action received for European Application No. 11751481.0, mailed on January 22, 2016, 3 pages.	☐
	18	Podar et al.: "Inhibition of the TGF-.beta. signaling pathway in tumor cells"; Recent Results in Cancer Research, 2007, vol. 172, p. 77-97.	☐
	19	Regnault et al.: "Fc.gamma. Receptor-mediated Induction of Dendritic Cell Maturation and Major Histocompatibility Complex Class I-restricted Antigen Presentation after Immune Complex Internalization"; J. Exp. Med., 1999, vol. 189, No. 2, p. 371-380.	☐
	20	Rose-John et al. 2007. Expert Opinion in Therapeutic Targets. 11:613-624	☐
	21	Schrama et al.: "Antibody targeted drugs as cancer therapeutics"; Nature Reviews Drug Discovery, Jan. 20, 2006, vol. 5, p. 147-159.	☐
	22	Supplementary European Search Report received for EP Patent Application No. 11751481.0, mailed on June 27, 2013, 16 pages.	☐

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	Attorney Docket Number	JHU3260-8

	23	Trail et al.: "Monoclonal antibody drug conjugates in the treatment of cancer"; Current Opinion in Immunology, 1999, vol. 11, Issue 5, p. 584-588.	☐
	24	U.S. Appl. No. 61/311,255, Mar. 5, 2010, Atul Bedi.	☐
	25	U.S. Appl. No. 61/435,671, Jan. 24, 2011, Atul Bedi.	☐
	26	Wang et al.: "Tumor necrosis factor and cancer, buddies or foes?"; Acta Pharmacologica Sinica, 2008, 29 (11), p. 1275-1288.	☐
	27	Yang et al.: "The role of T.sub.reg in the cancer immunological response"; American Journal of Immunology, 2009, 5 (1), p. 17-28.	☐
	28	Yao and Chen: "Contribution of B7-H1/PD-1 Co-inhibitory Pathway to T-Ce11 Dysfunction in Cancer"; D.I. Gabrilovich, A.A. Hurwitz (eds.), Tumor-Induced Immune Suppression. pp. 29-40 .COPYRGT. Springer 2008.	☐
	29	Zhang et al., "Design and Optimization of a Linker for Fusion Protein Construction," Prog. Natural Sci. (2009), 19:1197-1200, Elsevier.	☐
	30	Zhang et al: "Expression of a Soluble TGF-.beta. Receptor by Tumor Cells Enhances Dendritic Cell/Tumor Fusion Vaccine Efficacy.sup.1"; J. Immunology, 2008, 181, pp. 3690-3697.	☐

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EFS Web 2.1.18

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WEST Search History for Application 16601347

Creation Date: 2020120115:49

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
10442860.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
9850306.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	5	ADJ	YES		12-01-2020
16601347	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	1	ADJ	YES		12-01-2020
9441011.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
9441044.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
8993524.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(8993524.pn.) and (TGF)		2	ADJ	YES		12-01-2020

	PGPB, USPT, EPAB, JPAB, DWPI, FPRS					
7795389.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(7795389.pn.) and TGF-beta	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(bedi atul or ravi rajani).in.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	45	ADJ	YES		12-01-2020
(targeting moiety fused with immunomodulatory moiety)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety)) and (polypeptide and binds and tumor cell)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell)) and ((targeting moiety fused with immunomodulatory moiety))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety)) and	PGPB, USPT, EPAB, JPAB,	28	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 276 of 498
Bicara v. JHU - PGR2026-00025

(Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)	DWPI, FPRS					
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)) and (TGFbRII or type 2 or type II or extracellular domain)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain)) and (linker or glycine linker)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-(10442860.pn.))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type	PGPB, USPT, EPAB, JPAB, DWPI,	10	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 277 of 498
Bicara v. JHU - PGR2026-00025

or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-L1)) and ((bedi atul or ravi rajani).in.)	FPRS					
(Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	66911	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)) with (TGFbRII or type 2 or type II or extracellular domain)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	3014	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain)) and (linker or glycine linker)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	1384	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	586	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-(10442860.pn.))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	388	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (carcinoembryonic antigen or CEA or	PGPB, USPT, EPAB, JPAB, DWPI,	1	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 278 of 498
Bicara v. JHU - PGR2026-00025

prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-L1)) and (10442860.pn.)	FPRS					
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety)) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/00 | C07K16/32 | C07K7/08 | C07K19/00 | C07K1/00 | C07K14/475 | C07K14/715 | C07K16/18 | C07K16/22 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/16 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 | A61B18/18 | C12P21/08).IPCR.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/00 | C07K16/32 | C07K7/08 | C07K19/00 | C07K1/00 | C07K14/475 | C07K14/715 | C07K16/18 | C07K16/22 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/16 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 | A61B18/18 | C12P21/08).IPCR.)) and ((bedi atul or ravi rajani).in.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	10	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 279 of 498
Bicara v. JHU - PGR2026-00025

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file hcaplus

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.18       0.18

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FILE LAST UPDATED: 30 Nov 2020 (20201130/ED)

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=> e bedi atul/au

E1            1     BEDI ASHISH AKSHAY/AU
E2            1     BEDI ASHWANI/AU
E3           39 --> BEDI ATUL/AU
E4            2     BEDI B/AU
E5            1     BEDI B R/AU
E6            8     BEDI B S/AU
E7            1     BEDI BALWINDER S/AU
E8            4     BEDI BANSHI LAL/AU
E9            3     BEDI BHARAT VEER/AU
E10           1     BEDI BHUPINDER S/AU
E11          18     BEDI BRAHMCHETNA/AU
E12           4     BEDI BRENDA/AU

=> s e3

L1           39 "BEDI ATUL"/AU

=> e ravi rajani/au

E1            5     RAVI RAJAGOPALAN P T/AU
E2            1     RAVI RAJAMANICKAM/AU
E3           37 --> RAVI RAJANI/AU
E4            7     RAVI RAJANI K/AU
E5            4     RAVI RAJASHREE/AU
E6            4     RAVI RAJESH/AU
E7            2     RAVI RAJI/AU
E8            3     RAVI RAJIV/AU
E9            1     RAVI RAJKUMAR/AU
E10           1     RAVI RAJPUT/AU
E11           7     RAVI RAJU/AU
E12           7     RAVI RAM K/AU

=> s e3-e4

             37 "RAVI RAJANI"/AU
              7 "RAVI RAJANI K"/AU
L2           44 ("RAVI RAJANI"/AU OR "RAVI RAJANI K"/AU)
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=> s l1-l2

L3          55 (L1 OR L2)

=> file .medline

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      14.04      14.22

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=> s (targeting moiety fused with immunomodulatory moiety)

L4           0 (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)

=> s (polypeptide and binds and tumor cell)

L5         439 (POLYPEPTIDE AND BINDS AND TUMOR CELL)

=> s (targeting moiety fused or  immunomodulatory moiety)

L6          35 (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)

=> s l5 and l6

L7           0 L5 AND L6

=> s (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)

L8      374372 (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TGF-B
               ETA OR TGFBR)

=> s l8 and (TGFbRII or type 2 or type II or extracellular domain)

L9       35612 L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN)

=> s l9 and (fusion or chimeric or heterodimer)

L10       1487 L9 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> s l10 and  (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry media
tor or HVEM)

L11        162 L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES VIRU
               S ENTRY MEDIATOR OR HVEM)

=> d bib ab


L11  ANSWER 1 OF 162     MEDLINE ®  on STN
AN   1990203065     MEDLINE Full-text
DN   PubMed ID: 1969420
TI   Regulation by EGF is maintained in an overexpressed chimeric EGFR/neu
     receptor tyrosine kinase.
AU   Lehvaslaiho H
CS   Department of Virology, University of Helsinki, Finland.
AU   Sistonen L; diRenzo F; Partanen J; Comoglio P; Holtta E; Alitalo K
SO   Journal of cellular biochemistry, (1990 Mar) Vol. 42, No. 3, pp. 123-33.
     Journal code: 8205768. ISSN: 0730-2312. L-ISSN: 0730-2312.
DOI  http://dx.doi.org/10.1002/jcb.240420303
```

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 199004
ED Entered STN: 1 Jun 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Apr 1990
OSC.G 2 There are 2 MEDLINE records that cite this record
AB The effects of a ligand regulated neu tyrosine kinase were examined in NIH 3T3 cells. A chimeric construct encoding the human EGF receptor extracellular domain fused to the tyrosine kinase domain of the rat neu cDNA was expressed under the transcriptional control of the Moloney murine leukemia virus LTR promoter. This resulted in higher levels of expression of the chimeric receptor than were previously obtained from the SV40 virus early promoter in the same cells. The chimeric receptor showed strict ligand-dependent tyrosine kinase and signal transducing activities for the induction of growth-regulated biochemical activities and DNA synthesis in resting cells. The ligand-activated cells became morphologically transformed and grew in agar in the presence of EGF and TGF beta as efficiently as did the ligand-independent neu oncogene-transformed cells. Our results establish similarities between the signal pathways of the EGF receptor and the neu tyrosine kinase.

=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES

=> s l11 and py<=2010

L12 44 L11 AND PY<=2010

=> d bib ab

L12 ANSWER 1 OF 44 MEDLINE ® on STN
AN 1990203065 MEDLINE Full-text
DN PubMed ID: 1969420
TI Regulation by EGF is maintained in an overexpressed chimeric EGFR/neu receptor tyrosine kinase.
AU Lehvaslaiho H
CS Department of Virology, University of Helsinki, Finland.
AU Sistonen L; diRenzo F; Partanen J; Comoglio P; Holtta E; Alitalo K
SO Journal of cellular biochemistry, (1990 Mar) Vol. 42, No. 3, pp. 123-33.
Journal code: 8205768. ISSN: 0730-2312. L-ISSN: 0730-2312.
DOI http://dx.doi.org/10.1002/jcb.240420303
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LA English
FS MEDLINE; Priority Journals
FS Print
EM 199004
ED Entered STN: 1 Jun 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Apr 1990
OSC.G 2 There are 2 MEDLINE records that cite this record
AB The effects of a ligand regulated neu tyrosine kinase were examined in NIH 3T3 cells. A chimeric construct encoding the human EGF receptor extracellular domain fused to the tyrosine kinase domain of the rat neu cDNA was expressed under the transcriptional control of the Moloney murine leukemia virus LTR promoter. This resulted in higher levels of expression of the chimeric receptor than were previously obtained from the SV40 virus early promoter in the same cells. The chimeric receptor showed strict ligand-dependent tyrosine kinase and signal transducing activities for the induction of growth-regulated biochemical activities and DNA synthesis in resting cells. The ligand-activated cells became morphologically transformed and grew in agar in the presence of EGF and TGF beta as efficiently as did the ligand-independent neu oncogene-transformed cells. Our results establish similarities between the signal pathways of the EGF receptor and the neu tyrosine kinase.

=> d 10 ab

L12 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2020 ACS on STN
AB Methods of inducing the presentation of tumor antigens and co-stimulatory mols. to immune cells using aptamers binding the antigen and the costimulatory mol. are described. Presentation of the antigen in a preferred stoichiometry with a costimulatory mol. improves the immune response to the tumor. Use of an aptamer binding prostate-specific membrane antigen and two mols. of 4-1BB receptors is demonstrated. The aptamer was as effective as anti-4-1BB antibody in costimulating CD8-pos. T cells presented with prostate-specific membrane antigen.

=> d 40

L12 ANSWER 40 OF 44 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2002:754431 CAPLUS Full-text
DN 137:274074
TI Recombinant production of polyanionic polymers, and uses thereof as drug carriers for improvement of bioactivity and water-solubility
IN Leung, David W.; Bergman, Philip A.; Lofquist, Alan; Pietz, Gregory E.; Tompkins, Christopher K.; Waggoner, David W., Jr.
PA Cell Therapeutics Inc, USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002077036	A2	20021003	WO 2002-US8614	20020321
WO 2002077036	A3	20040129		
US 20020169125	A1	20021114	US 2002-101487	20020320
AU 2002252429	A1	20021008	AU 2002-252429	20020321
US 20050118136	A1	20050602	US 2004-939988	20040914
US 20080176288	A1	20080724	US 2007-928737	20071030

```
PRAI US 2001-60277705     P    20010321
     US 2002-101487       A3   20020320
     WO 2002-US8614       W    20020321
     US 2004-939988       A1   20040914
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G   8     THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
RE.CNT  1     THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT



=> d his


     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1             39 S E3
                E RAVI RAJANI/AU
L2             44 S E3-E4
L3             55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5            439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6             35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7              0 S L5 AND L6
L8         374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9          35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10          1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11           162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12            44 S L11 AND PY<=2010

=> s l8 (5n)  (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry media
tor or HVEM)

L13         1466 L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
                 VIRUS ENTRY MEDIATOR OR HVEM)

=> s l13 and (fusion or chimeric or heterodimer)

L14           23 L13 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> dup rem l14

PROCESSING COMPLETED FOR L14
L15            15 DUP REM L14 (8 DUPLICATES REMOVED)
                  ANSWERS '1-2' FROM FILE MEDLINE
                  ANSWER '3' FROM FILE BIOSIS
                  ANSWERS '4-11' FROM FILE CAPLUS
                  ANSWERS '12-15' FROM FILE EMBASE

=> d bib ab


L15  ANSWER 1 OF 15     MEDLINE ®  on STN           DUPLICATE 1
AN   2016797565     MEDLINE Full-text
DN   PubMed ID: 26971374
TI   TCDD promoted EMT of hFPECs via AhR, which involved the activation of
     EGFR/ERK signaling.
AU   Gao Zhan
CS   School of Public Health, Xinxiang Medical University, 453003, China, The
     Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU   Bu Yongjun; Wang Xugang; Zhang Guofu; Wang Erhui; Ding Shibin; Liu
     Yongfeng; Shi Ruling
CS   School of Public Health, Xinxiang Medical University, 453003, China.
AU   Liu Xiaozhuan
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AU Yu Zengli
CS School of Public Health, Xinxiang Medical University, 453003, China, School of Public Health, Zhengzhou University, 450001, China. zly@zzu.edu.cn
SO Toxicology and applied pharmacology, (2016 May 01) Vol. 298, pp. 48-55. Electronic Publication Date: 10 Mar 2016 Journal code: 0416575. E-ISSN: 1096-0333. L-ISSN: 0041-008X.
DOI http://dx.doi.org/10.1016/j.taap.2016.03.005
CY United States
DT Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201608
ED Entered STN: 15 Mar 2016 Last Updated on STN: 16 Aug 2016 Indexing Added: 16 Aug 2016 Entered Medline: 15 Aug 2016
OSC.G 4 There are 4 MEDLINE records that cite this record
AB One critical step of second palatal fusion is the newly formed medial epithelia seam (MES) disintegration, which involves apoptosis, epithelial to mesenchymal transition (EMT), and cell migration. Although the environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) produces cleft palate at high rates, little is known about the effects of TCDD exposure on the fate of palatal epithelial cells. By using primary epithelial cells isolated from human fetal palatal shelves (hFPECs), we show that TCDD increased cell proliferation and EMT, as demonstrated by increased the epithelial markers (E-cadherin and cytokeratin14) and enhanced the mesenchymal markers (vimentin and fibronectin), but had no effect on cell migration and apoptosis. TCDD exposure led to a dose-dependent increase in Slug protein expression. Coimmunoprecipitation revealed that TCDD promoted AhR to form a protein complex with Slug. ChIP assay confirmed that TCDD exposure recruited AhR to the xenobiotic responsive element of Slug promoter. Knockdown of AhR by siRNA remarkably weakened TCDD-induced binding of AhR to the XRE promoter of slug, thereby suppressed TCDD-induced vimentin. Further experiment showed that TCDD stimulated EGFR phosphorylation did not influence the TGFβ3/Smad signaling; whereas TCDD increased phosphorylation of ERK1/2 and p38 with no effect on activation of JNK. By using varieties of inhibitors, we confirmed that TCDD promoted proliferation and EMT of hFPECs via activation of EGFR/ERK pathway. These data make a novel contribution to the molecular mechanism of cleft palate by TCDD.
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=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12 44 S L11 AND PY<=2010
L13 1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14 23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)

L15 15 DUP REM L14 (8 DUPLICATES REMOVED)

=> d 1-15 bib ab

L15 ANSWER 1 OF 15 MEDLINE ® on STN DUPLICATE 1
AN 2016797565 MEDLINE Full-text
DN PubMed ID: 26971374
TI TCDD promoted EMT of hFPECs via AhR, which involved the activation of EGFR/ERK signaling.
AU Gao Zhan
CS School of Public Health, Xinxiang Medical University, 453003, China, The Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU Bu Yongjun; Wang Xugang; Zhang Guofu; Wang Erhui; Ding Shibin; Liu Yongfeng; Shi Ruling
CS School of Public Health, Xinxiang Medical University, 453003, China.
AU Liu Xiaozhuan
CS Medical College, Henan University of Science & Technology, 471023, China.
AU Li Qiaoyun; Fu Jianhong
CS The Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU Yu Zengli
CS School of Public Health, Xinxiang Medical University, 453003, China, School of Public Health, Zhengzhou University, 450001, China. zly@zzu.edu.cn
SO Toxicology and applied pharmacology, (2016 May 01) Vol. 298, pp. 48-55. Electronic Publication Date: 10 Mar 2016
Journal code: 0416575. E-ISSN: 1096-0333. L-ISSN: 0041-008X.
DOI http://dx.doi.org/10.1016/j.taap.2016.03.005
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201608
ED Entered STN: 15 Mar 2016
Last Updated on STN: 16 Aug 2016
Indexing Added: 16 Aug 2016
Entered Medline: 15 Aug 2016
OSC.G 4 There are 4 MEDLINE records that cite this record
AB One critical step of second palatal fusion is the newly formed medial epithelia seam (MES) disintegration, which involves apoptosis, epithelial to mesenchymal transition (EMT), and cell migration. Although the environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) produces cleft palate at high rates, little is known about the effects of TCDD exposure on the fate of palatal epithelial cells. By using primary epithelial cells isolated from human fetal palatal shelves (hFPECs), we show that TCDD increased cell proliferation and EMT, as demonstrated by increased the epithelial markers (E-cadherin and cytokeratin14) and enhanced the mesenchymal markers (vimentin and fibronectin), but had no effect on cell migration and apoptosis. TCDD exposure led to a dose-dependent increase in Slug protein expression. Coimmunoprecipitation revealed that TCDD promoted AhR to form a protein complex with Slug. ChIP assay confirmed that TCDD exposure recruited AhR to the xenobiotic responsive element of Slug promoter. Knockdown of AhR by siRNA remarkably weakened TCDD-induced binding of AhR to the XRE promoter of slug, thereby suppressed TCDD-induced vimentin. Further experiment showed that TCDD stimulated EGFR phosphorylation did not influence the TGFβ3/Smad signaling; whereas TCDD increased phosphorylation of ERK1/2 and p38 with no effect on activation of JNK. By using varieties of inhibitors, we confirmed that TCDD promoted proliferation and EMT of hFPECs via activation of EGFR/ERK pathway. These data make a novel contribution to the molecular mechanism of cleft palate by TCDD.
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L15 ANSWER 2 OF 15 MEDLINE ® on STN DUPLICATE 3
AN 2001689821 MEDLINE Full-text
DN PubMed ID: 11737589
TI Angiotensin II signaling and HB-EGF shedding via metalloproteinase in glomerular mesangial cells.
AU Uchiyama-Tanaka Y

CS Department of Medicine II, Kansai Medical University, Osaka, Japan.
AU Matsubara H; Nozawa Y; Murasawa S; Mori Y; Kosaki A; Maruyama K; Masaki H; Shibasaki Y; Fujiyama S; Nose A; Iba O; Hasagawa T; Tateishi E; Higashiyama S; Iwasaka T
SO Kidney international, (2001 Dec) Vol. 60, No. 6, pp. 2153-63.
Journal code: 0323470. ISSN: 0085-2538. L-ISSN: 0085-2538.
DOI http://dx.doi.org/10.1046/j.1523-1755.2001.00067.x
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 200201
ED Entered STN: 13 Dec 2001
Last Updated on STN: 30 Jan 2002
Entered Medline: 29 Jan 2002
OSC.G 20 There are 20 MEDLINE records that cite this record
AB BACKGROUND: Angiotensin II (Ang II) has been implicated in the development of glomerulosclerosis by stimulating fibronectin (FN) synthesis. The processing and release of heparin binding-endothelin growth factor (HB-EGF) are activated by protein kinase C (PKC) and Ca2+ signaling. We studied the roles of HB-EGF and endothelial growth factor (EGF) receptor (EGFR) in Ang II-induced FN expression using mesangial cells.

METHODS: Mesangial cells were prepared from mouse kidneys by the explant method and cells were used at passages 4 and 5.

RESULTS: Ang II stimulated FN mRNA levels dose-dependently with a maximal increase (3.4-fold) after 12 hours of incubation. This action was completely inhibited by PKC inhibitors and slightly blocked by Ca2+ chelating agents. FN mRNA accumulation by Ang II was abolished by tyrosine kinase inhibitors, a specific inhibitor for EGFR (AG1478) and extracellular signal-regulated kinase (ERK) inactivation. Addition of neutralizing anti-HB-EGF antibody, as well as pretreatment with heparin or the metalloproteinase inhibitor batimastat abolished induction of FN expression by Ang II. In mesangial cells stably transfected with a chimeric construct containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by Ang II (1.7-fold at 0.5 min) and reached a 4.1-fold increase at two minutes. Ang II phosphorylated EGFR (maximal at 2 min) and ERK (maximal at 8 min) in a PKC- and metalloproteinase-dependent manner. Ang II stimulated the expression and release of transforming growth factor-beta (TGF-beta) via EGFR-mediated signaling, and the released TGF-beta also contributed to Ang II-mediated FN expression via EGFR transactivation.

CONCLUSIONS: Ang II-mediated FN expression was regulated by autocrine effects of HB-EGF and TGF-beta, suggesting a novel paradigm for cross-talk between Ang II and growth factor receptor signaling pathways.

L15 ANSWER 3 OF 15 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 2
AN 2005:233362 BIOSIS Full-text
DN PREV200510021990
TI Bikunin down-regulates heterodimerization between CD44 and growth factor receptors and subsequently suppresses agonist-mediated signaling.
AU Wakahara, Kiyoshi; Kobayashi, Hiroshi [Reprint Author]; Yagyu, Tatsuo; Matsuzaki, Hidenori; Kondo, Toshiharu; Kurita, Noriyuki; Sekino, Hideo; Inagaki, Kiyokazu; Suzuki, Mika; Kanayama, Naohiro; Terao, Toshihiko
CS Hamamatsu Univ Sch Med, Dept Obstet and Gynecol, Handayama 1-20-1, Hamamatsu, Shizuoka 4313192, Japan
hirokoba@hama.med.ac.jp
SO Journal of Cellular Biochemistry, (APR 1 2005) Vol. 94, No. 5, pp. 995-1009.
CODEN: JCEBD5. ISSN: 0730-2312.
DOI 10.1002/jcb.20364
DT Article
LA English
ED Entered STN: 23 Jun 2005
Last Updated on STN: 11 Jun 2008

AB We provided evidence previously that bikunin, a Kunitz-type protease inhibitor, can disrupt dimerization of CD44 proteins, which may result in suppression of receptor-mediated MAP kinase signaling. However, to what extent dimerization may alter ligand-induced signaling has not been documented. Given the recent recognition that some growth factor receptors can form heterodimers with CD44, the present study was undertaken to determine whether the CD44 and growth factor receptors (e.g., EGFR, FGFR, HGFR, VEGFR, TGF-beta RI, or TGF-beta RII) can form heterodimers in cancer cells and, if so, to investigate the potential functional consequences of such heterodimerization. We also examined whether bikunin can abrogate these heterodimerizations and inhibit CD44/growth factor-dependent signaling. Here, we show direct evidence for heterodimerization of CD44-FGFR and CD44-TGF-beta RI in human chondrosarcoma HCS-2/8 cells, CD44-EGFR complex in human glioma U87MG cells, and CD44-TGF-beta RI heterodimer in human ovarian cancer HRA cells. Coupling of CD44 and growth factor receptor maybe selective, depending on a cell type. Bikunin does not alter the ligand binding, whereas functionally reduces heterodimerization between CD44 and growth factor receptors. The disruption of heterodimerization substantially reduces receptor-induced tyrosine phosphorylation and ERK1/2 activation. Taken together, our data suggest that bikunin-mediated suppression of heterodimerization between CD44 and growth factors may inhibit the agonist-promoted activation of the signaling pathway. (c) 2004 Wiley-Liss, Inc.

L15 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2019:1144025 CAPLUS Full-text
DN 171:71535
TI Multispecific molecules comprising TGF-β inhibitor, anti-CSF1R or CCR2 antibody and tumor-targeting moiety for cancer therapy
IN Loew, Andreas; Vash, Brian Edward; Maiocco, Stephanie J.
PA Elstar Therapeutics, Inc., USA
SO PCT Int. Appl., 207pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2019113464	A1	20190613	WO 2018-US64506	20181207
EP 3720881	A1	20201014	EP 2018-830572	20181207
PRAI US 2017-62596173	P	20171208		
WO 2018-US64506	W	20181207		

AB Multispecific mols. comprising (i) a TGF-beta inhibitor and (ii) a binding moiety that binds to CSF1R or CCR2, and methods of using the same, are disclosed.

L15 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2018:999364 CAPLUS Full-text
DN 169:4235
TI TGFβ signal convertor and engineered DARIC receptor, antigen receptor, TCR, chimeric antigen receptor or chimeric cytokine receptor for adoptive T cell therapy
IN Boyerinas, Benjamin
PA Bluebird Bio, Inc., USA
SO PCT Int. Appl., 203pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2018094244	A1	20180524	WO 2017-US62358	20171117
CA 3043888	A1	20180524	CA 2017-3043888	20171117
AU 2017362484	A1	20190530	AU 2017-362484	20171117
IL 266628	A	20190630	IL 2017-266628	20171117
KR 2019077562	A	20190703	KR 2019-7017172	20171117
MX 2019005724	A	20190708	MX 2019-5724	20171117

	CN 110072885	A	20190730	CN 2017-80077533	20171117
	BR 112019009904	A2	20190813	BR 2019-112019009904	20171117
	EP 3541833	A1	20190925	EP 2017-872043	20171117
	JP 2019535275	T	20191212	JP 2019-526305	20171117
	US 20190350974	A1	20191121	US 2019-16348450	20190508
	IN 201917022415	A	20190726	IN 2019-17022415	20190606
PRAI	US 2016-62423565	P	20161117		
	US 2017-62467496	P	20170306		
	WO 2017-US62358	W	20171117		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2018:999364

AB The present disclosure provides improved compns. for adoptive T cell therapies for treating, preventing, or ameliorating at least one symptom of a cancer, infectious disease, autoimmune disease, inflammatory disease, and immunodeficiency, or condition assocd. therewith.

L15 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2018:2419881 CAPLUS Full-text

DN 170:120475

TI Lentiviral vector for expressing TGF-β antibody and construction method of CAR-T cell and application in treatment of solid tumor

IN Li, Jie; Han, Jiangmeng; Liu, Zhenyun; Wang, Wei; Cheng, Fengwei

PA Anhui Guyi Biotechnology Co., Ltd., Peop. Rep. China

SO Faming Zhuanli Shenqing, 33pp.
CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 108949828	A	20181207	CN 2018-10812789	20180723
PRAI CN 2018-10812789		20180723		

AB The title lentiviral vector for expressing TGF-β antibody is pCDH lentiviral vector of CAR gene, and contains solid tumor-specific antigen target. The invention also provides a construction method of the lentiviral vector for expressing TGF-β antibody, a CAR-T cell for expressing TGF-β antibody and prepd. from the lentiviral vector, and a construction method and application of the CAR-T cell in reparation of drug for treatment of solid tumor. The invention can realize targeting of tumor cell, reduce the inhibitive mol. in tumor microenvironment, kill solid tumor in max. extent, and achieve solid tumor immunotherapy new breakthrough.

L15 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2017:698315 CAPLUS Full-text

DN 166:489022

TI Preparation of TGF-β-targeting chimeric antigen receptor for T cell activation, immunostimulatory cytokine increase and autoimmune disease or caner therapy

IN Chen, Yvonne Yu-Hsuan; Chang, Zenan Li

PA The Regents of the University of California, USA

SO PCT Int. Appl., 89pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2017075433	A1	20170504	WO 2016-US59444	20161028
KR 2018092947	A	20180820	KR 2018-7015353	20161028
EP 3368571	A1	20180905	EP 2016-860930	20161028
CN 108884155	A	20181123	CN 2016-80077053	20161028
JP 2019500012	T	20190110	JP 2018-522004	20161028
US 20180312580	A1	20181101	US 2018-15772403	20180430
PRAI US 2015-62248685	P	20151030		
WO 2016-US59444	W	20161028		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2017:698315

AB Aspects of the disclosure relate to polypeptides comprising a signal peptide, an antigen-binding domain that specifically binds TGF-β, a peptide spacer, a transmembrane domain, and an endodomain. When expressed in a cell, the polypeptides are capable of not only neutralizing the TGF-β but also specifically triggering T-cell activation in the presence of TGF-β. T-cell activation spurs the immune cell to produce immunostimulatory cytokines and proliferate, thus turning TGF-β from an immunosuppressive signal to an activating stimulus.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2017:389707 CAPLUS Full-text
DN 166:319538
TI Engineering TGF-β receptor ectodomain fusion proteins with antibodies for neutralizing TGFβ ligands and treatment of cancer and fibrotic diseases
IN Zwaagstra, John C.; Sulea, Traian; Jaramillo, Maria; O'Connor, Maureen D.; Lenferink, Anne E. G.
PA National Research Council of Canada, Can.
SO PCT Int. Appl., 101pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2017037634	A1	20170309	WO 2016-IB55204	20160831
CA 2996996	A1	20170309	CA 2016-2996996	20160831
EP 3344660	A1	20180711	EP 2016-840942	20160831
US 20200231652	A1	20200723	US 2018-15755595	20180227
PRAI US 2015-62212058	P	20150831		
WO 2016-IB55204	W	20160831		

OS CASFORMULTNS 2017:389707
AB The present invention relates, in general, to polypeptides capable of binding and neutralizing transforming growth factor β (TGF-β) ligands, and uses of these polypeptides for treating disorders related to TGF-beta expression or activation (e.g. cancer and fibrotic diseases), and methods of making such mols.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2016:587936 CAPLUS Full-text
DN 164:456408
TI Peptides having anti-inflammatory properties
IN Jaynes, Jesse M.; Lopez, Henry W.; Martin, George R.; Yates, Clayton; Garvin, Charles E.
PA Riptide Bioscience, Inc., USA
SO U.S. Pat. Appl. Publ., 180pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160101150	A1	20160414	US 2015-14882293	20151013
US 9492499	B2	20161115		
CA 2963478	A1	20160421	CA 2015-2963478	20151013
WO 2016061133	A1	20160421	WO 2015-US55380	20151013
AU 2015333678	A1	20170427	AU 2015-333678	20151013
AU 2015333678	B2	20200514		
KR 2017070152	A	20170621	KR 2017-7012890	20151013
EP 3206704	A1	20170823	EP 2015-851584	20151013
CN 107106638	A	20170829	CN 2015-80067933	20151013
JP 2017537141	T	20171214	JP 2017-540551	20151013
BR 112017007543	A2	20171219	BR 2017-112017007543	20151013
US 20170020956	A1	20170126	US 2016-15286491	20161005
US 10149886	B2	20181211		
IN 201747012819	A	20170421	IN 2017-47012819	20170411

	ZA 2017002537	A	20201028	ZA 2017-2537	20171004
	US 20190046601	A1	20190214	US 2018-16169819	20181024
	JP 2020180149	A	20201105	JP 2020-118752	20200709
PRAI	US 2014-62063909	P	20141014		
	JP 2017-540551	A3	20151013		
	US 2015-14882293	A1	20151013		
	WO 2015-US55380	W	20151013		
	US 2016-15286491	A1	20161005		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2016:587936

AB Aspects of the present invention relate to peptides having anti-inflammatory activity, compns. contg. one or more of the peptides, and use of the peptides to treat conditions assocd. with excessive inflammation in animals, particularly humans and other mammals. In particular embodiments, peptides bind to an NF-kB Class II protein, specifically RelB,TGFβ, Notch1, Wnt8R, TRAIL, IL6R, IL10R, EGFR, CDK6, CD206, CD47, SIRP-α, HMT, and TGM2, and other signaling proteins that functions as a pro-inflammatory cytokine, an inhibitor of macrophage activity, or a regulator of histone function including TGFβ, Notch1, Wnt8R, TRAIL, IL6R, IL10R, EGFR, CDK6, CD206, CD47, SIRP-α, HMT, TGM2. etc. are provided. These peptides contain a striapathic region consisting of alternating hydrophobic and hydrophilic modules and demonstrate strong inhibitions of pro-inflammatory cytokines, an macrophage activity, and suppression of tumor growth.

OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2013:1911217 CAPLUS Full-text

DN 161:642856

TI Impact of TGF-b on breast cancer from a quantitative proteomic analysis

AU Ahn, Jaegyoon; Yoon, Youngmi; Yeu, Yunku; Lee, Hookuen; Park, Sanghyun

CS Department of Computer Science, Yonsei University, Seoul, 120-749, S. Korea

SO Computers in Biology and Medicine (2013), 43(12), 2096-2102
CODEN: CBMDAW; ISSN: 0010-4825

DOI 10.1016/j.compbiomed.2013.09.022

PB Elsevier Ltd.

DT Journal; (online computer file)

LA English

AB There has been much active research in bioinformatics to support our understanding of oncogenesis and tumor progression. Most research relies on mRNA gene expression data to identify marker genes or cancer specific gene networks. However, considering that proteins are functional mols. that carry out the biol. tasks of genes, they can be direct markers of biol. functions. Protein abundance data on a genome scale have not been investigated in depth due to the limited availability of high throughput protein assays. This hindrance is chiefly caused by a lack of robust techniques such as RT-PCR (real-time polymerase chain reaction). In this study, we quantified phospho-proteomes of breast cancer cell lines treated with TGF-beta (transforming growth factor beta). To discover biomarkers and observe changes in the signaling pathways related to breast cancer, we applied a protein network-based approach to generate a classifier of subnet markers. The accuracy of that classifier outperformed other network-based classification algorithms, and current feature selection and classification algorithms. Moreover, many cancer-related proteins were identified in those sub-networks. Each sub-network provides functional insights and can serve as a potential marker for TGF-beta treatments. After interpreting the roles of proteins in sub-networks with various signaling pathways, we found strong candidate proteins and various related interactions that are expected to affect breast cancer outcomes. These results demonstrate the high quality of the quantified phospho-proteomes data and show that our network construction and classification method is appropriate for an anal. of this type of data.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2008:1102620 CAPLUS Full-text

DN 149:324137

TI Meroduplex gapped or nicked double-stranded RNAs specific for inhibiting

transforming growth factor β receptor gene expression and their therapeutic use

IN Quay, Steven C.; McSwiggen, James; Vaish, Narendra K.; Ahmadian, Mohammad

PA MDRNA, Inc., USA

SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 80

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2008109546	A2	20080912	WO 2008-US55695	20080303
	WO 2008109546	A3	20081030		
	EP 2468864	A1	20120627	EP 2012-153919	20080228
	EP 2471920	A2	20120704	EP 2012-153915	20080303
	EP 2471920	A3	20121010		
	US 20100105134	A1	20100429	US 2009-552082	20090901
	US 20130011922	A1	20130110	US 2011-13327545	20111215
PRAI	US 2007-60934940	P	20070302		
	US 2007-60934930	P	20070316		
	US 2007-61016343	P	20071221		
	US 2007-60934931	P	20070420		
	US 2007-60934928	P	20070424		
	US 2007-60934934	P	20070424		
	US 2007-60934942	P	20070425		
	US 2007-60934943	P	20070425		
	US 2007-60932949	P	20070503		
	US 2007-61015611	P	20071220		
	EP 2008-731034	A3	20080228		
	WO 2008-US55353	A2	20080228		
	WO 2008-US55505	A2	20080229		
	WO 2008-US55511	A2	20080229		
	WO 2008-US55515	A2	20080229		
	WO 2008-US55516	A2	20080229		
	WO 2008-US55519	A2	20080229		
	WO 2008-US55524	A2	20080229		
	WO 2008-US55526	A2	20080229		
	WO 2008-US55527	A2	20080229		
	WO 2008-US55532	A2	20080229		
	WO 2008-US55533	A2	20080229		
	WO 2008-US55542	A2	20080229		
	WO 2008-US55548	A2	20080229		
	WO 2008-US55550	A2	20080229		
	WO 2008-US55551	A2	20080229		
	WO 2008-US55554	A2	20080229		
	WO 2008-US55556	A2	20080229		
	WO 2008-US55560	A2	20080229		
	WO 2008-US55563	A2	20080229		
	EP 2008-731244	A3	20080303		
	WO 2008-US55597	A2	20080303		
	WO 2008-US55599	A2	20080303		
	WO 2008-US55601	A2	20080303		
	WO 2008-US55603	A2	20080303		
	WO 2008-US55604	A2	20080303		
	WO 2008-US55606	A2	20080303		
	WO 2008-US55608	A2	20080303		
	WO 2008-US55611	A2	20080303		
	WO 2008-US55612	A2	20080303		
	WO 2008-US55615	A2	20080303		
	WO 2008-US55618	A2	20080303		
	WO 2008-US55622	A2	20080303		
	WO 2008-US55625	A2	20080303		
	WO 2008-US55627	A2	20080303		
	WO 2008-US55631	A2	20080303		
	WO 2008-US55635	A2	20080303		
	WO 2008-US55644	A2	20080303		
	WO 2008-US55649	A2	20080303		
	WO 2008-US55651	A2	20080303		
	WO 2008-US55662	A2	20080303		
	WO 2008-US55676	A2	20080303		
	WO 2008-US55678	A2	20080303		

WO 2008-US55693 A2 20080303
WO 2008-US55695 A2 20080303
WO 2008-US55697 A2 20080303
WO 2008-US55698 A2 20080303
WO 2008-US55701 A2 20080303
WO 2008-US55704 A2 20080303
WO 2008-US55708 A2 20080303
WO 2008-US55709 A2 20080303
WO 2008-US55711 A2 20080303
US 2009-552082 A1 20090901
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 149:324137
AB The present disclosure is based on the discovery that a nicked or gapped double-stranded RNA comprising at least three strands (termed meroduplex RNA or mdRNA) is a suitable substrate for Dicer or RISC and, therefore may be advantageously employed for gene silencing via, for example, the RNA interference pathway. An mdRNA comprises at least three strands that combine to form at least two non-overlapping double-stranded regions sepd. by a nick or gap wherein one strand is complementary to a mRNA. Partially duplexed dsRNA mols. (mdRNAs) are thus capable of initiating an RNA interference cascade that reduces expression of a target mRNA, such as a human transforming growth factor β receptor (TGFBR) mRNA. The introduction of substituted and modified nucleotides into mdRNA provides a powerful tool in overcoming potential limitations of in vivo stability and bioavailability inherent to nature RNA mols. The mean inhibitory concn. (IC50) of RISC and Dicer mdRNAs specific for influenza range from about 200 pM to about 15 nM; inclusion of a single locked nucleic acid reduced the IC50 of Dicer mdRNAs by up to 4-fold. In addn., the mdRNAs induce cytokines to a lesser extent than intact (i.e., not nicked) parent mols. Meroduplex RNAs are designed with the first strand complementary to a TGFBR mRNA, including TGFBR I, TGFBR II, and TGFBR III. Also provided are methods of decreasing expression of a TGFBR gene in a cell or in a subject to treat a TGFBR-related disease.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 12 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051974617 EMBASE Full-text
DN 72002361
TI ERG onc oprotein evaluation and its correlation with other molecular biomarkers in prostate cancer.
AU Liatkouskaya, T.; Cherstvoy, E.; Zakharava, V.; Masansky, I.; Sagalchik, L.; Ivanovskaya, M.; Dedik, S.
AU Rogov, Y. (correspondence)
CS Belarusian Medical Academy, Dept. of Pathology, Minsk, Belarus.
SO Virchows Archiv, (September 2015) Vol. 467, No. 1, Supp. SUPPL. 1, pp. S276. Abstract Number: PS-24-067.
Meeting Info: 27th European Congress of Pathology, ECP 2015. Belgrade, Serbia. 05 Sep 2015-09 Sep 2015
ISSN: 0945-6317
DOI 10.1007/s00428-015-1805-9
PB Springer Verlag.
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 9 Sep 2015
Last Updated on Embase: 9 Sep 2015
AB Objective: The aim of this study was to assess the frequency of expression of the ERG oncoprotein, a product of the chimeric gene TMPRSS2: ERG, in cancer containing prostate biopsy material, to evaluate its prognostic significance and correlation with other molecular biomarkers. Method: Expression of the markers such as ERG oncoprotein, Ki-67, cycline D1 (CycD1), topoisomerase IIα (TopoIIα), chromogranin A (ChrA), androgen receptors (AR) and estrogens α and β receptors in epithelium (ERα, ERβ) and stroma (SRα, SRβ), p53, BCL2, BAX, VEGF, TGFβ, EGFR was assessed immunohistochemically in the biopsy material from 238 cases of prostate cancer. Results: ERG expression was found in 47 % of the patients. It was demonstrated that ERG-positive cancer if compared to ERG-negative type is characterized by

enhanced ($p < 0.05$) expression of Ki-67, CycD1, TopoIIα, AR, ERα, p53, TGFβ and EGFR and decreased expression of BAX, ERβ, SRα and SRβ, whereas no difference in expression of ChrA, BCL2 and VEGF was revealed. It was shown that marked ERG expression in biopsy samples is associated with poor prognosis: higher risk of biochemical recurrence and clinically significant disease progression after radical prostatectomy. Conclusion: ERG-positive cancer was found in biopsy material from 47 % of patients and is characterized by enhanced proliferative activity, increased expression of AR, ERα, p53, TGFβ and EGFR, and decreased expression of BAX, ERβ, SRα and SRβ; it is associated with higher risk of unfavorable outcome.

L15 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052156602 EMBASE Full-text
DN 72194680
TI Targeting NANOG: Genes, proteins and response to viral RNAi in preclinical models.
AU Jessup, J. Milburn (correspondence); Mattoo, Abid R.; Korokhov, Nikolay
CS National Cancer Institute, Bethesda, MD, United States.
SO Cancer Research, (1 Aug 2015) Vol. 75, No. 15, Supp. SUPPL. 1. Abstract Number: 4216.
Meeting Info: 106th Annual Meeting of the American Association for Cancer Research, AACR 2015. Philadelphia, PA, United States. 18 Apr 2015-22 Apr 2015
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2015-4216
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 21 Mar 2016
Last Updated on Embase: 21 Mar 2016
AB Purpose: Since the NANOG family controls stemness and neoplastic progression in human colorectal carcinoma (CRC), our postulate is that targeting the dominant NANOG and NANOGP8 members with viral vector delivered shRNA will inhibit CRC progression in preclinical models and that replicating viral vectors are more active than non-replicating vectors. Methods: Cells were human CRC lines (Clone A, CX-1 and LS174T) and mouse fibroblasts (3T3). shRNA specific to NANOG (shNG-1), NANOGP8 (shNp8-1) or a control (shNEG) were created in lentivirus (LV) and chimeric adenovirus 5/3 (Ad5/3). CRC and 3T3 were cultured in monolayer with serum-containing medium or in suspension in ultra low attachment plates without serum. Nanostring 770 gene cancer panel was analyzed in 72 hr cultures with NMF clustering and GSEA analysis. Annexin V expression and caspase-3, 8 or 9 activation in suspension culture assessed Apoptosis. LV or Ad5/3 shRNAs were added to spheroids in 3-D suspension cultures to test therapy in vitro. Intratumoral injection of LV or Ad5/3 shRNA into 5-10 mm sub cutis nodules in groups of 5-10 NOD/SCID mice measured activity in vivo. Results: LV shNp8-1 in both Clone A and CX-1 caused significant inhibition of TGF-beta, EGFR, NRF2, E2F3 and the Cyclin D1 pathways by NMF and GSEA analysis in monolayer culture. LV shNp8-1 inhibited growth of LS174T, Clone A and CX-1 by 50% in 3 days in 3-D suspension cultures without further decrease. Apoptosis was due to Caspase 9 activation. In contrast, Ad5/3-shNp8-1 decreased spheroid growth by up to 94% at 9 -14 days while Ad5/3 decreases spheroid growth by 80%. Ad5/3-shNp8-1 but nit Ad5/3 was active in co-cultures with 3T3 to a 2:1 CRC:3T3 ratio. Transduction level was ~50% in LV treated cells but ~90% in Ad5/3 treated cells. Intratumoral injection of LVshNG-1 or LVshNp8-1, decreased tumor size by 50% compared to LVshNEG or untreated CX-1 tumors for 11 days after which tumor growth rebounded to match controls. Ad5/3-shNp8-1 injection into 5-9 mm nodules inhibited CX-1 and LS14T growth by ~50% until euthanized. Conclusions: Targeting NANOGP8 more than NANOG inhibits proliferation and activates apoptosis through multiple pathways. Nonreplicating LV delivered shRNA inhibited tumor growth in in vitro and in vivo preclinical models but replicating oncolytic Ad5/3 infects more cells and promotes shRNA efficacy. Replicating vectors targeting NANOG are important for further development.

L15 ANSWER 14 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051695487 EMBASE Full-text
DN 71723238
TI Insights into mechanisms of breast cancer metastasis.
AU Hynes, Nancy E. (correspondence)
CS Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland.
SO Cancer Research, (1 Oct 2014) Vol. 74, No. 19, Supp. SUPPL. 1. Abstract Number: SY20-02.
Meeting Info: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014. San Diego, CA, United States. 05 Apr 2014-09 Apr 2014
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2014-SY20-02
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 3 Feb 2015
Last Updated on Embase: 3 Feb 2015
AB Breast carcinoma is the most frequent cancer in women, affecting one million yearly. In the past decades there have been great improvements in surgery, screening and therapy. These have led to dramatic changes in the 5-year overall survival rates, which have gone from 40% in the 1950's up to 86% in the past decade (Maxmen 2012). However, many patients who present with early stage disease die from metastases, despite complete surgical removal of primary breast tumors. Indeed, if a tumor has spread to distant organs at the time of presentation, the 5-year overall survival is only 23% compared to 90% or higher for patients with localized tumors. Today, primary tumors are efficiently removed by surgical intervention, but there are essentially no successful therapeutic options for metastatic disease. Metastasis is a complex process whereby tumor cells detach from the primary site, acquire migratory properties, enter and survive in the circulation, and colonize and grow at distant sites (Gupta and Massague 2006). Metastatic relapse can occur years after surgery, suggesting that tumor cells have the ability to survive in a dormant state in metastatic niches (Karrison, Ferguson et al. 1999). Typical sites of relapse of breast cancer are the bone, lungs, liver and brain (Weigelt, Peterse et al. 2005; Nguyen, Bos et al. 2009). Thus, the most relevant clinical and experimental questions in the breast cancer field revolve around metastasis. Important research areas are: the identification of specific molecules and pathways contributing to metastatic spread, tumor cell survival and growth in distant sites, as well as uncovering metastatic therapies. My presentation will cover our recent work on: 1-targeting receptor tyrosine kinases (RTKs) in metastatic breast cancer models; 2-Memo, a novel enzyme that affects intracellular ROS production, and is essential for in vivo metastasis; 3- analyses aimed at uncovering molecular mechanisms involved in crosstalk between tumor cells and the bone marrow (BM) environment. 1-Targeting RTKs with antibodies or small molecular inhibitors is a clinically validated approach for cancer therapy. In breast cancer, the ErbB2/HER2 specific antibody trastuzumab is routinely given in combination with chemotherapy to ErbB2/HER2-positive breast cancer patients and has had a significant impact on patient mortality (Gianni, Dafni et al., 2011). Only a sub-set of patients, however, are eligible for this treatment, making it essential to uncover additional RTKs that could be useful in for therapy; the Ret kinase might be an interesting new target. Ret was discovered as an outlier kinase in breast cancer, with unexpectedly high expression levels detected in many breast tumors (Esseghir, Todd et al. 2007; Boulay, Breuleux et al. 2008; Kothari, Wei et al. 2013). Unlike thyroid or lung tumors that carry oncogenic Ret, as fusion proteins or with activating mutations, Ret appears to be wild type in breast cancer. We have shown that elevated Ret levels are found in different sub-types of human breast cancers and that high Ret correlates with decreased metastasis-free survival. Using a metastatic breast cancer model, we showed that in vivo blockade of Ret inhibits tumor outgrowth and metastatic potential (Gattelli, Nalvarte et al. 2013). Our results suggest that Ret has an important role in tumor growth and metastasis. Multiple RTKs are often active in cancer cells and combining RTK inhibitors has been shown to have strong anti-tumor activity

(e.g., Stommel, Kimmelman et al. 2007). Considering that breast tumors often co-express ErbB and FGFRs (Cancer Genome Atlas Network, 2012), we have tested the impact of blocking both in metastatic breast cancer models. We have recently shown that only when both RTKs are blocked do we observe: blockade of the ERK and PI3K pathways, prolonged tumor-stasis and a significant decrease in metastasis (Dey, Bianchi et al. 2010; Issa, Gill et al. 2013). 2-Our group originally identified Memo as being essential for breast cancer cell motility in response to several RTKs (Marone, Hess et al. 2004; Meira, Masson et al. 2009). The 2.1 A crystal structure of Memo revealed its structural homology with bacterial enzymes (Qiu, Lienhard et al. 2008); we have recently discovered that Memo is a metal-binding enzyme that requires Cu(II) for its oxidase-like activity. Memo knock-down (KD) in breast cancer models affects localized intracellular ROS production, cell migration and invasion, as well as in vivo spontaneous lung metastasis from xenografts. To investigate if Memo plays a role in human breast disease, immunohistochemistry (IHC) was carried out on breast cancer tissue microarrays (TMAs). Memo expression is low in non-neoplastic breast tissue and exhibits significantly higher expression in > 40% of tumors. Memo is diffusely localized to the cytoplasm and the nucleus and accumulates at the membrane upon growth factor stimulation (Schlatter, Meira et al. 2012). To examine if the sub-cellular localization of Memo correlates with clinical or histopathological parameters, we categorized the breast tumor samples according to expression and localization of Memo. We found that elevated Memo was prognostic of poor outcome; elevated levels of cytoplasmic Memo, but not nuclear Memo, significantly predicted early metastasis and death at 5 years in a multivariable Cox model. These data suggest that Memo has distinct roles in different cellular compartments and that its cytoplasmic function regulates pathways that promote tumor dissemination. 3- Bone marrow is particularly permissive for disseminated tumor cells since structural and environmental features needed to allow trafficking of hematopoietic stem cells and their progeny can also be employed by the tumor cells. The fenestration of bone sinusoidal capillaries facilitates the entrance of tumor cells. Moreover, bone stroma is a potent source of CXCL12 that attracts tumor cells expressing its receptor CXCR4, making BM a perfect soil for circulating tumor cells (Morrison and Spradling 2008). Metastatic tumors show different molecular features compared to primary tumors, which could reflect tumor-cell selection for particular conditions in the distant site and/or the influence of the surrounding stroma on a disseminated tumor cells (Kang, Siegel et al. 2003; Minn, Gupta et al. 2005). The BM niche is a complex, multicellular structure composed of osteoblasts, osteoclasts, stromal fibroblasts, endothelial cells, and mesenchymal progenitors, all of which contribute to general bone homeostasis (Mendez-Ferrer, Michurina et al. 2010; Ehninger and Trumpp 2011). Considering the strong interplay between these elements, it has been suggested that blocking the crosstalk between tumor and the bone environment would be a potential strategy to inhibit tumor expansion. To uncover molecular mechanisms involved in the crosstalk between tumor cells and the BM environment, we compared the transcriptome of different cell populations from the BM environment from tumor-bearing and tumor-free mice. For this, we used purified stromal cell subsets of: endothelial and osteoblastic cells, as well as mesenchymal and osteogenic progenitors. These analyses revealed that BM is strongly affected by breast cancer cell dissemination. Indeed, several components of key molecular pathways involved in tumor development, including TGFBR, PDGFRB, EGFR, HGFR, IGFR and JAK/Stat, are modulated in the BM of mice with tumor cells.

L15 ANSWER 15 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 2004223470 EMBASE Full-text
DN 38657721 PMID: 15144206
TI A mammalian genetic system to screen for small molecules capable of disrupting protein-protein interactions.
AU Zhao, Hui-Fen; Kiyota, Taira; Chowdhury, Shafinaz; Purisima, Enrico; Banville, Denis; Konishi, Yasuo; Shen, Shi-Hsiang (correspondence)
CS Health Sector, Biotechnology Research Institute, National Research Council of Canada, 6100 Royalmount Avenue, Montreal, Que. H4P 2R2, Canada. shi.shen@nrc.ca
AU Shen, Shi-Hsiang (correspondence)
CS Department of Medicine, McGill University, Montreal, Que. H3G 1A4, Canada. shi.shen@nrc.ca

SO Analytical Chemistry, (15 May 2004) Vol. 76, No. 10, pp. 2922-2927.
    Refs: 18
    ISSN: 0003-2700 CODEN: ANCHAM
DOI 10.1021/ac035396m
PB American Chemical Society, 2540 Olentangy River Road, P.O. Box 3337,
    Columbus, OH 43210-3337, United States.
CY United States
DT Journal; Article
FS Intellectual Indexing
    022   Human Genetics
    037   Drug Literature Index
LA English
SL English
ED Entered Embase: 10 Jun 2004
    Last Updated on Embase: 10 Jun 2004
AB A mammalian two-hybrid system was developed for high-throughput screening
    of compounds that disrupt specific protein-protein interactions. The
    existing mammalian systems are unsatisfactory for drug screening due to
    non-regulated expression of interacting proteins. To construct a tightly
    regulated system, the tetracycline repressor was fused with the inhibitory
    KRAB domain as a suppressor. The binding of the suppressor to the tet
    operator entirely blocked expression of two interacting proteins. When
    both the inducer doxycycline and drugs were added to the culture, the
    reporter gene was either activated by interaction of the paired proteins
    with ineffective drugs or remained silent due to disruption of the protein
    interactions by the effective drugs. We demonstrate that interactions of
    the type I receptor for TGFβ with FKBP12 and the epidermal
    growth factor receptor (EGFR) with p85 are effectively disrupted by
    FK506 and EGFR kinase inhibitor AG 1478, respectively. The power of this
    system for drug screening was further demonstrated by rapid identification
    of inhibitors from a druglike library for the receptor kinases.

=> d his

    (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

    FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1   39 S E3
                E RAVI RAJANI/AU
L2   44 S E3-E4
L3   55 S L1-L2

    FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4   0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5   439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6   35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7   0 S L5 AND L6
L8   374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9   35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10   1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11   162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12   44 S L11 AND PY<=2010
L13   1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14   23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15   15 DUP REM L14 (8 DUPLICATES REMOVED)

=> s l15 and py<=2010

L16   4 L15 AND PY<=2010

=> d 1-4 bib ab

L16 ANSWER 1 OF 4   MEDLINE ® on STN
AN   2001689821   MEDLINE Full-text
DN   PubMed ID: 11737589
TI   Angiotensin II signaling and HB-EGF shedding via metalloproteinase in

glomerular mesangial cells.
AU Uchiyama-Tanaka Y
CS Department of Medicine II, Kansai Medical University, Osaka, Japan.
AU Matsubara H; Nozawa Y; Murasawa S; Mori Y; Kosaki A; Maruyama K; Masaki H; Shibasaki Y; Fujiyama S; Nose A; Iba O; Hasagawa T; Tateishi E; Higashiyama S; Iwasaka T
SO Kidney international, (2001 Dec) Vol. 60, No. 6, pp. 2153-63.
Journal code: 0323470. ISSN: 0085-2538. L-ISSN: 0085-2538.
DOI http://dx.doi.org/10.1046/j.1523-1755.2001.00067.x
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 200201
ED Entered STN: 13 Dec 2001
Last Updated on STN: 30 Jan 2002
Entered Medline: 29 Jan 2002
OSC.G 20 There are 20 MEDLINE records that cite this record
AB BACKGROUND: Angiotensin II (Ang II) has been implicated in the development of glomerulosclerosis by stimulating fibronectin (FN) synthesis. The processing and release of heparin binding-endothelin growth factor (HB-EGF) are activated by protein kinase C (PKC) and Ca2+ signaling. We studied the roles of HB-EGF and endothelial growth factor (EGF) receptor (EGFR) in Ang II-induced FN expression using mesangial cells.

METHODS: Mesangial cells were prepared from mouse kidneys by the explant method and cells were used at passages 4 and 5.

RESULTS: Ang II stimulated FN mRNA levels dose-dependently with a maximal increase (3.4-fold) after 12 hours of incubation. This action was completely inhibited by PKC inhibitors and slightly blocked by Ca2+ chelating agents. FN mRNA accumulation by Ang II was abolished by tyrosine kinase inhibitors, a specific inhibitor for EGFR (AG1478) and extracellular signal-regulated kinase (ERK) inactivation. Addition of neutralizing anti-HB-EGF antibody, as well as pretreatment with heparin or the metalloproteinase inhibitor batimastat abolished induction of FN expression by Ang II. In mesangial cells stably transfected with a chimeric construct containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by Ang II (1.7-fold at 0.5 min) and reached a 4.1-fold increase at two minutes. Ang II phosphorylated EGFR (maximal at 2 min) and ERK (maximal at 8 min) in a PKC- and metalloproteinase-dependent manner. Ang II stimulated the expression and release of transforming growth factor-beta (TGF-beta) via EGFR-mediated signaling, and the released TGF-beta also contributed to Ang II-mediated FN expression via EGFR transactivation.

CONCLUSIONS: Ang II-mediated FN expression was regulated by autocrine effects of HB-EGF and TGF-beta, suggesting a novel paradigm for cross-talk between Ang II and growth factor receptor signaling pathways.

L16 ANSWER 2 OF 4 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2005:233362 BIOSIS Full-text
DN PREV200510021990
TI Bikunin down-regulates heterodimerization between CD44 and growth factor receptors and subsequently suppresses agonist-mediated signaling.
AU Wakahara, Kiyoshi; Kobayashi, Hiroshi [Reprint Author]; Yagyu, Tatsuo; Matsuzaki, Hidenori; Kondo, Toshiharu; Kurita, Noriyuki; Sekino, Hideo; Inagaki, Kiyokazu; Suzuki, Mika; Kanayama, Naohiro; Terao, Toshihiko
CS Hamamatsu Univ Sch Med, Dept Obstet and Gynecol, Handayama 1-20-1, Hamamatsu, Shizuoka 4313192, Japan
hirokoba@hama.med.ac.jp
SO Journal of Cellular Biochemistry, (APR 1 2005) Vol. 94, No. 5, pp. 995-1009.
CODEN: JCEBD5. ISSN: 0730-2312.
DOI 10.1002/jcb.20364
DT Article
LA English
ED Entered STN: 23 Jun 2005

Last Updated on STN: 11 Jun 2008

AB We provided evidence previously that bikunin, a Kunitz-type protease inhibitor, can disrupt dimerization of CD44 proteins, which may result in suppression of receptor-mediated MAP kinase signaling. However, to what extent dimerization may alter ligand-induced signaling has not been documented. Given the recent recognition that some growth factor receptors can form heterodimers with CD44, the present study was undertaken to determine whether the CD44 and growth factor receptors (e.g., EGFR, FGFR, HGFR, VEGFR, TGF-beta RI, or TGF-beta RII) can form heterodimers in cancer cells and, if so, to investigate the potential functional consequences of such heterodimerization. We also examined whether bikunin can abrogate these heterodimerizations and inhibit CD44/growth factor-dependent signaling. Here, we show direct evidence for heterodimerization of CD44-FGFR and CD44-TGF-beta RI in human chondrosarcoma HCS-2/8 cells, CD44-EGFR complex in human glioma U87MG cells, and CD44-TGF-beta RI heterodimer in human ovarian cancer HRA cells. Coupling of CD44 and growth factor receptor maybe selective, depending on a cell type. Bikunin does not alter the ligand binding, whereas functionally reduces heterodimerization between CD44 and growth factor receptors. The disruption of heterodimerization substantially reduces receptor-induced tyrosine phosphorylation and ERK1/2 activation. Taken together, our data suggest that bikunin-mediated suppression of heterodimerization between CD44 and growth factors may inhibit the agonist-promoted activation of the signaling pathway. (c) 2004 Wiley-Liss, Inc.

L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2008:1102620 CAPLUS Full-text
DN 149:324137
TI Meroduplex gapped or nicked double-stranded RNAs specific for inhibiting transforming growth factor β receptor gene expression and their therapeutic use
IN Quay, Steven C.; McSwiggen, James; Vaish, Narendra K.; Ahmadian, Mohammad
PA MDRNA, Inc., USA
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 80
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2008109546	A2	20080912	WO 2008-US55695	20080303
	WO 2008109546	A3	20081030		
	EP 2468864	A1	20120627	EP 2012-153919	20080228
	EP 2471920	A2	20120704	EP 2012-153915	20080303
	EP 2471920	A3	20121010		
	US 20100105134	A1	20100429	US 2009-552082	20090901
	US 20130011922	A1	20130110	US 2011-13327545	20111215
PRAI	US 2007-60934940	P	20070302		
	US 2007-60934930	P	20070316		
	US 2007-61016343	P	20071221		
	US 2007-60934931	P	20070420		
	US 2007-60934928	P	20070424		
	US 2007-60934934	P	20070424		
	US 2007-60934942	P	20070425		
	US 2007-60934943	P	20070425		
	US 2007-60932949	P	20070503		
	US 2007-61015611	P	20071220		
	EP 2008-731034	A3	20080228		
	WO 2008-US55353	A2	20080228		
	WO 2008-US55505	A2	20080229		
	WO 2008-US55511	A2	20080229		
	WO 2008-US55515	A2	20080229		
	WO 2008-US55516	A2	20080229		
	WO 2008-US55519	A2	20080229		
	WO 2008-US55524	A2	20080229		
	WO 2008-US55526	A2	20080229		
	WO 2008-US55527	A2	20080229		
	WO 2008-US55532	A2	20080229		
	WO 2008-US55533	A2	20080229		

WO 2008-US55542 A2 20080229
WO 2008-US55548 A2 20080229
WO 2008-US55550 A2 20080229
WO 2008-US55551 A2 20080229
WO 2008-US55554 A2 20080229
WO 2008-US55556 A2 20080229
WO 2008-US55560 A2 20080229
WO 2008-US55563 A2 20080229
EP 2008-731244 A3 20080303
WO 2008-US55597 A2 20080303
WO 2008-US55599 A2 20080303
WO 2008-US55601 A2 20080303
WO 2008-US55603 A2 20080303
WO 2008-US55604 A2 20080303
WO 2008-US55606 A2 20080303
WO 2008-US55608 A2 20080303
WO 2008-US55611 A2 20080303
WO 2008-US55612 A2 20080303
WO 2008-US55615 A2 20080303
WO 2008-US55618 A2 20080303
WO 2008-US55622 A2 20080303
WO 2008-US55625 A2 20080303
WO 2008-US55627 A2 20080303
WO 2008-US55631 A2 20080303
WO 2008-US55635 A2 20080303
WO 2008-US55644 A2 20080303
WO 2008-US55649 A2 20080303
WO 2008-US55651 A2 20080303
WO 2008-US55662 A2 20080303
WO 2008-US55676 A2 20080303
WO 2008-US55678 A2 20080303
WO 2008-US55693 A2 20080303
WO 2008-US55695 A2 20080303
WO 2008-US55697 A2 20080303
WO 2008-US55698 A2 20080303
WO 2008-US55701 A2 20080303
WO 2008-US55704 A2 20080303
WO 2008-US55708 A2 20080303
WO 2008-US55709 A2 20080303
WO 2008-US55711 A2 20080303
US 2009-552082 A1 20090901
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 149:324137
AB The present disclosure is based on the discovery that a nicked or gapped double-stranded RNA comprising at least three strands (termed meroduplex RNA or mdRNA) is a suitable substrate for Dicer or RISC and, therefore may be advantageously employed for gene silencing via, for example, the RNA interference pathway. An mdRNA comprises at least three strands that combine to form at least two non-overlapping double-stranded regions sepd. by a nick or gap wherein one strand is complementary to a mRNA. Partially duplexed dsRNA mols. (mdRNAs) are thus capable of initiating an RNA interference cascade that reduces expression of a target mRNA, such as a human transforming growth factor β receptor (TGFBR) mRNA. The introduction of substituted and modified nucleotides into mdRNA provides a powerful tool in overcoming potential limitations of in vivo stability and bioavailability inherent to nature RNA mols. The mean inhibitory concn. (IC50) of RISC and Dicer mdRNAs specific for influenza range from about 200 pM to about 15 nM; inclusion of a single locked nucleic acid reduced the IC50 of Dicer mdRNAs by up to 4-fold. In addn., the mdRNAs induce cytokines to a lesser extent than intact (i.e., not nicked) parent mols. Meroduplex RNAs are designed with the first strand complementary to a TGFBR mRNA, including TGFBR I, TGFBR II, and TGFBR III. Also provided are methods of decreasing expression of a TGFBR gene in a cell or in a subject to treat a TGFBR-related disease.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L16 ANSWER 4 OF 4 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 2004223470 EMBASE Full-text
DN 38657721 PMID: 15144206
TI A mammalian genetic system to screen for small molecules capable of

disrupting protein-protein interactions.
AU Zhao, Hui-Fen; Kiyota, Taira; Chowdhury, Shafinaz; Purisima, Enrico; Banville, Denis; Konishi, Yasuo; Shen, Shi-Hsiang (correspondence)
CS Health Sector, Biotechnology Research Institute, National Research Council of Canada, 6100 Royalmount Avenue, Montreal, Que. H4P 2R2, Canada. shi.shen@nrc.ca
AU Shen, Shi-Hsiang (correspondence)
CS Department of Medicine, McGill University, Montreal, Que. H3G 1A4, Canada. shi.shen@nrc.ca
SO Analytical Chemistry, (15 May 2004) Vol. 76, No. 10, pp. 2922-2927.
Refs: 18
ISSN: 0003-2700 CODEN: ANCHAM
DOI 10.1021/ac035396m
PB American Chemical Society, 2540 Olentangy River Road, P.O. Box 3337, Columbus, OH 43210-3337, United States.
CY United States
DT Journal; Article
FS Intellectual Indexing
022 Human Genetics
037 Drug Literature Index
LA English
SL English
ED Entered Embase: 10 Jun 2004
Last Updated on Embase: 10 Jun 2004
AB A mammalian two-hybrid system was developed for high-throughput screening of compounds that disrupt specific protein-protein interactions. The existing mammalian systems are unsatisfactory for drug screening due to non-regulated expression of interacting proteins. To construct a tightly regulated system, the tetracycline repressor was fused with the inhibitory KRAB domain as a suppressor. The binding of the suppressor to the tet operator entirely blocked expression of two interacting proteins. When both the inducer doxycycline and drugs were added to the culture, the reporter gene was either activated by interaction of the paired proteins with ineffective drugs or remained silent due to disruption of the protein interactions by the effective drugs. We demonstrate that interactions of the type I receptor for TGFβ with FKBP12 and the epidermal growth factor receptor (EGFR) with p85 are effectively disrupted by FK506 and EGFR kinase inhibitor AG 1478, respectively. The power of this system for drug screening was further demonstrated by rapid identification of inhibitors from a druglike library for the receptor kinases.

=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12 44 S L11 AND PY<=2010
L13 1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14 23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15 15 DUP REM L14 (8 DUPLICATES REMOVED)
L16 4 S L15 AND PY<=2010

=> s l8 (5n) (carcinoembryonic antigen or CEA or prostate-specific membrane antigen

```
 or PSMA or programmed death-ligand 1 or PD-L1)

L17        651 L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
               MEMBRANE ANTIGEN OR PSMA OR PROGRAMMED DEATH-LIGAND 1 OR PD-L1)

=> s l17 and (fusion or chimeric or heterodimer)

L18        133 L17 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> s l18 and py<=2010

L19          2 L18 AND PY<=2010

=> d 1-2 bib ab


L19  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2009:625581  CAPLUS Full-text
DN   151:377870
TI   Anaplastic lymphoma kinase (ALK)-induced malignancies: novel mechanisms of
     cell transformation and potential therapeutic approaches
AU   Wasik, Mariusz A.; Zhang, Qian; Marzec, Michal; Kasprzycka, Monika; Wang,
     Hong Yi; Liu, Xiaobin
CS   Department of Pathology and Laboratory Medicine, University of
     Pennsylvania, Philadelphia, PA, USA
SO   Seminars in Oncology (2009), 36(2, Suppl. 1), S27-S35
     CODEN: SOLGAV; ISSN: 0093-7754
DOI  10.1053/j.seminoncol.2009.02.007
PB   Elsevier Inc.
DT   Journal; General Review
LA   English
AB   A review.  Among the many oncogenic variants of the anaplastic lymphoma
     kinase (ALK), nucleophosmin 1 (NPM)/ALK fusion protein expressed in the
     subset of T-cell lymphoma (ALK+TCL) is currently the best characterized.
     NPM/ALK activates several signal transduction pathways, including
     PI3K/AKT, MEK/ERK, mTORC1, STAT3, and STAT5b.  In turn, the pathways
     modulate expression and function of many genes and proteins involved in
     the key cellular functions such as proliferation, growth, survival,
     metab., and angiogenesis.  Recent data indicate that NPM/ALK also promotes
     immune evasion of the ALK+TCL by inducing through STAT3 activation the
     expression of immunosuppressive cytokines interleukin-10 (IL-10) and
     transforming growth factor-beta (TGFβ) and cell surface protein
     CD274 (PD-L1, B7-H1).  In addn., NPM/ALK protects its own expression
     by mediating via STAT3 and at least one member of the DNA
     methyltransferase family DNMT1 epigenetic silencing of the SHP-1 and
     STAT5a genes.  In ALK+TCL cells, SHP-1 and STAT5a proteins act as potent
     tumor suppressors by promoting degrdn. of the NPM/ALK protein and
     inhibiting expression of the NPM/ALK gene, resp.  These findings provide
     further rationale to therapeutically target ALK and its effector proteins,
     foremost STAT3.  They also suggest that immunotherapeutic approaches to
     ALK+TCL and, possibly, other ALK-driven malignancies may require
     inhibition of ALK and STAT3 to achieve the optimal clin. efficacy.
OSC.G   8     THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
RE.CNT  78    THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT


L19  ANSWER 2 OF 2  EMBASE  COPYRIGHT (c) 2020 Elsevier B.V. All rights
     reserved on STN
AN   0050140648  EMBASE   Full-text
DN   70144356
TI   Adoptive transfer of PSMA-specific, TGF-β insensitive memory
     CD8+T cells: Suppression of human prostate cancer (CaP).
AU   Zhang, Qiang (correspondence); Helfand, Brian; Chen, Lin; Smith, Norm;
     Lee, Chung
CS   Chicago, IL, United States.
AU   Qin, Weijun
CS   Xian, China.
AU   Zhu, Julie
CS   Boston, MA, United States.
AU   Guo, Yinglu
CS   Beijing, China.
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SO Journal of Urology, (April 2010) Vol. 183, No. 4, Supp. SUPPL. 1, pp. e265-e266. Abstract Number: 680.
Meeting Info: 2010 Annual Meeting of the American Urological Association, AUA. San Francisco, CA, United States. 29 May 2010-03 Jun 2010
ISSN: 0022-5347
DOI 10.1016/j.juro.2010.02.1079
PB Elsevier Inc..
PUI S 0022-5347(10)01335-2
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: Sep 2012
Last Updated on Embase: Sep 2012
AB INTRODUCTION AND OBJECTIVES: Tumor derived TGF-β is a potent immunosuppressant molecule which promotes CaP progression. Here we report a new immunotherapeutic approach using the adoptive transfer of PSMA-specific, TGF-β insensitive human memory CD8+ T cells to inhibit solid xenograft CaP. METHODS: Whole blood was collected from men with CaP prior to prostatectomy and CD45RAhighCD27-CD28-CCR7-memory CD8+ T cells were isolated using the EasySep CD8+ T cells enrichment kit, and then cultured in the presence of both fresh PSMA and irradiated autologous CD4+ T cells. We developed an anti-PSMA-vβ12-ζ-IRES-TβRIIDN chimeric T cell receptor construct (PZ-1-TβRIIDN) using an anti-PSMA IgTCR(ζ) gene (provided by Dr. Sadelain at Sloan-Kettering Cancer Center) and a dominant negative TGF-β type II receptor (TβRIIDN). Infection with a retroviral vector encoding this construct could induce memory T cells to be PSMA reactive and insensitive to TGF-β. Subcutaneous injection (5×105 cells) of either PC-3 CaP cells (PSMA negative; ATCC) or PSMA positive PC-3-PSMA cells (gift from Dr. Heston; Cleveland Clinic) into the right flank region of 15 immunodeficient RAG-1 mice was performed. Three weeks later, each set of animals was randomly assigned to one of three adoptive transfer groups: Group 1: memory CD8+ T cells infected with PZ-1-TβRIIDN; Group 2: memory CD8+ T cells infected with TβRIIDN only and Group 3: no treatment control. The animals were sacrificed after a total of 2 adoptive transfer treatments. The size and the weight of tumor and spleen were recorded. RESULTS: In Group 1 of PC-3-PSMA injected mice, the average tumor weight and volume of these mice was 2.62 g and 384.67 mm2, respectively. This was almost significantly less (~2-5 x) than that of animals in Group 2 (6.20g and 646.56 mm2) and Group 3 (11.66g and 752.24 mm2; P<0.05). Also, there was a significant difference between Groups 2 and 3. Interestingly, spleen weight of Group 1 (48.8mg) and Group 2 (64.5mg) increased compared to Group 3 (35.3 mg). Apoptosis in tumor cells was detected (TUNEL assay) only in animals of Group 1. There was no significant difference between the tumor size and weight in any of the three PC-3 injected groups. CONCLUSIONS: Tumor derived TGF-β decreases the function of host memory CD8+ T cells. Our approach combines TGF-β-insensitive with PSMA selectivity, which significantly enhance the specificity and tumor killing ability of multi-clonal CD8+ memory T cells. Therefore, this construct may offer a novel therapeutic intervention for both primary CaP treatment as well as for recurrence after prostatectomy.

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(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)

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L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010

=> s l18 and (linker or glycine linker)

L20           5 L18 AND (LINKER OR GLYCINE LINKER)

=> d 1-5


L20  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2020:1876680  CAPLUS Full-text
DN   173:674244
TI   preparation of sPD-1-Fc-sTGFβRII fusion protein for increasing
     cytotoxicity of immune cells and treating tumor
IN   Wu, Song; Zhu, Shimao; Wang, Fei; Sun, Haiyan; Lei, Qifang
PA   Shenzhen Following Precision Medical Research Institute, Peop. Rep. China
SO   Faming Zhuanli Shenqing, 20pp.
     CODEN: CNXXEV
DT   Patent
LA   Chinese
FAN.CNT 1
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ---------------------    --------
     CN 111690070         A    20200922    CN 2020-10403144         20200513
PRAI CN 2020-10403144          20200513


L20  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2020:1423434  CAPLUS Full-text
DN   173:293160
TI   Engineering bispecific antitumor antagonists targeting TGFβ1 and
     PD-1 or PD-L1 for treatment of cancer, infections and immune disorders
IN   Karow, Margaret; Sheng, Jackie; Zhang, Wei
PA   Gensun Biopharma, Inc., USA
SO   U.S. Pat. Appl. Publ., 284 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ---------------------    --------
     US 20200231665       A1   20200723    US 2019-16706187         20191206
PRAI US 2019-62869111     P    20190701
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT


L20  ANSWER 3 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2018:1460154  CAPLUS Full-text
DN   169:281964
TI   TGFβ and/or ActRII antagonists for immunostimulation against immune
     exhaustion, for cancer immunotherapy and for potentiating vaccines
IN   Pearsall, Robert Scott; Kumar, Ravindra
PA   Acceleron Pharma Inc., USA
SO   PCT Int. Appl., 274pp.
     CODEN: PIXXD2
DT   Patent
```

LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2018144542	A1	20180809	WO 2018-US16148	20180131
	CA 3051696	A1	20180809	CA 2018-3051696	20180131
	AU 2018214979	A1	20190815	AU 2018-214979	20180131
	KR 2019115037	A	20191010	KR 2019-7025689	20180131
	CN 110494155	A	20191122	CN 2018-80023489	20180131
	EP 3576773	A1	20191211	EP 2018-747362	20180131
	JP 2020505475	T	20200220	JP 2019-562229	20180131
	US 20200306340	A1	20201001	US 2019-16482869	20190801
PRAI	US 2017-62453413	P	20170201		
	WO 2018-US16148	W	20180131		

OS CASFORMULTNS 2018:1460154
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L20 ANSWER 4 OF 5 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052792557 EMBASE Full-text
DN 619156187
TI Preclinical evaluation and mechanistic characterization of M7824 (MSB0011359C), a novel bifunctional fusion protein targeting the PD-L1 and TGFβ pathways.
AU Lan, Yan (correspondence); Zhang, Dong; Xu, Chunxiao; Marelli, Bo; Qi, Jin; Qi, Huakui; Qin, Guozhong; Xu, Xiaomei; Wang, Hong; Sircar, Aroop; Brunkhorst, Beatrice; Austin, Eric; Radvanyi, Laszlo; Lo, Kin-Ming
CS EMD Serono Research and Development Institute, Inc., Billerica, MA, United States.
SO Cancer Research, (July 2017) Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 2615.
Meeting Info: American Association for Cancer Research Annual Meeting 2017. Washington, DC, United States. 01 Apr 2017-05 Apr 2017
ISSN: 1538-7445
DOI 10.1158/1538-7445.AM2017-2615
PB American Association for Cancer Research Inc..
CY Netherlands
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 14 Nov 2017
Last Updated on Embase: 14 Nov 2017
Indexing Added: 14 Nov 2017
First Entered Embase or Embase Alert: 14 Nov 2017

L20 ANSWER 5 OF 5 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052750383 EMBASE Full-text
DN 618663162
TI Preclinical evaluation and mechanistic characterization of M7824 (MSB0011359C), a novel bifunctional fusion protein targeting the PD-L1 and TGFβ pathways.
AU Lan, Yan (correspondence); Zhang, Dong; Xu, Chunxiao; Marelli, Bo; Qi, Jin; Qi, Huakui; Qin, Guozhong; Xu, Xiaomei; Wang, Hong; Sircar, Aroop; Brunkhorst, Beatrice; Austin, Eric; Radvanyi, Laszlo; Lo, Kin-Ming
CS EMD Serono Research, Development Institute, Inc., Billerica, MA, United States.
SO Cancer Research, (July 2017) Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 2615.
Meeting Info: American Association for Cancer Research Annual Meeting 2017. Washington, DC, United States. 01 Apr 2017-05 Apr 2017
ISSN: 1538-7445
DOI 10.1158/1538-7445.AM2017-2615
PB American Association for Cancer Research Inc..
CY Netherlands
DT Journal; Conference; (Conference Abstract)
FS CONF

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FS   Intellectual Indexing
LA   English
SL   English
ED   Entered Embase: 13 Oct 2017
     Last Updated on Embase: 13 Oct 2017
     Indexing Added: 13 Oct 2017
     First Entered Embase or Embase Alert: 13 Oct 2017



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     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                 E BEDI ATUL/AU
L1             39 S E3
                 E RAVI RAJANI/AU
L2             44 S E3-E4
L3             55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5            439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6             35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7              0 S L5 AND L6
L8         374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9          35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10          1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11           162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12            44 S L11 AND PY<=2010
L13          1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14            23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15            15 DUP REM L14 (8 DUPLICATES REMOVED)
L16             4 S L15 AND PY<=2010
L17           651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18           133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19             2 S L18 AND PY<=2010
L20             5 S L18 AND (LINKER OR GLYCINE LINKER)

=> s l20 and py<=2010

L21             0 L20 AND PY<=2010

=> s l15 and l3

L22             0 L15 AND L3

=> s l12 and l3

L23             0 L12 AND L3

=> s l5 and l3

L24             0 L5 AND L3

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     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                 E BEDI ATUL/AU
L1             39 S E3
                 E RAVI RAJANI/AU
L2             44 S E3-E4
L3             55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
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L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010
L20           5 S L18 AND (LINKER OR GLYCINE LINKER)
L21           0 S L20 AND PY<=2010
L22           0 S L15 AND L3
L23           0 S L12 AND L3
L24           0 S L5 AND L3

=> s l3 and l8

L25          26 L3 AND L8

=> dup rem l25

PROCESSING COMPLETED FOR L25
L26           16 DUP REM L25 (10 DUPLICATES REMOVED)
                 ANSWERS '1-4' FROM FILE MEDLINE
                 ANSWERS '5-11' FROM FILE BIOSIS
                 ANSWERS '12-14' FROM FILE CAPLUS
                 ANSWERS '15-16' FROM FILE EMBASE

=> d 1-16 bib ab


L26  ANSWER 1 OF 16     MEDLINE ®  on STN           DUPLICATE 1
AN   2019540141     MEDLINE Full-text
DN   PubMed ID: 29467463
TI   Bifunctional immune checkpoint-targeted antibody-ligand traps that
     simultaneously disable TGFβ enhance the efficacy of cancer
     immunotherapy.
AU   Ravi Rajani; Pham Vui; Wysocki Piotr T; Sidransky David; Izumchenko
     Evgeny; Bedi Atul
CS   Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins
     University School of Medicine, Baltimore, MD, 21231, USA. abedil@jhmi.edu
AU   Noonan Kimberly A; Borrello Ivan M
CS   Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School
     of Medicine, Baltimore, MD, 21231, USA.
AU   Bedi Rishi
CS   Department of Computer Science, Stanford University, Palo Alto, CA, 94305,
     USA.
AU   Zhavoronkov Alex; Ozerov Ivan V; Makarev Eugene; V Artemov Artem
CS   Insilico Medicine, Inc., Emerging Technology Centers, Johns Hopkins
     University at Eastern, B301, 1101 33rd Street, Baltimore, MD, 21218, USA.
AU   Mehra Ranee
CS   Department of Oncology, Johns Hopkins University School of Medicine,
     Baltimore, MD, 21231, USA.
AU   Nimmagadda Sridhar
AUID ORCID: https://orcid.org/0000-0002-6413-7191
CS   Department of Radiology and Radiological Science, Johns Hopkins Medical
     Institutions, Baltimore, MD, 21287, USA.
AU   Marchionni Luigi
CS   Center for Computational Genomics, Johns Hopkins University School of
     Medicine, Baltimore, MD, 21231, USA.
SO   Nature communications, (20180221) Vol. 9, No. 1, pp. 741.  Electronic
     Publication Date: 21 Feb 2018
     Journal code: 101528555. E-ISSN: 2041-1723. L-ISSN: 2041-1723.
     Report No.: PMC-PMC5821872.
DOI  http://dx.doi.org/10.1038/s41467-017-03696-6
CY   England: United Kingdom
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DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Electronic
EM 201803
ED Entered STN: 22 Feb 2018
Last Updated on STN: 23 Mar 2018
Indexing Added: 23 Mar 2018
Entered Medline: 22 Mar 2018
GO United States NCI NIH HHS
GN R01 CA184199
GO United States NIDCR NIH HHS
GN P50 DE019032
OSC.G 41 There are 41 MEDLINE records that cite this record
REM.CNT 68 There are 68 cited references available in MEDLINE for this document.
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd). a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L26 ANSWER 2 OF 16 MEDLINE ® on STN DUPLICATE 2
AN 2015468037 MEDLINE Full-text
DN PubMed ID: 25593015
TI A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma.
AU Gilbert Jill; Murphy Barbara
CS Vanderbilt University, Nashville, TN, United States. jill.gilbert@vanderbilt.edu; barbara.murphy@Vanderbilt.Edu
AU Schell Michael J; Zhao Xiuhua; Tanvetyanon Tawee; Leon Marino E
CS H. Lee Moffitt Cancer Center, Tampa, FL, United States. Michael.Schell@moffitt.org; Xiuhua.Zhao@moffitt.org; Tawee.Tanvetyanon@moffitt.org; Marino.Leon@Moffitt.org
AU Neil Hayes D
CS UNC Lineberger Cancer Center, Chapel Hill, NC, United States. hayes@med.unc.edu
AU Haigentz Missak Jr
CS Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, United States. mhaigent@montefiore.org
AU Saba Nabil
CS Emory Winship Cancer Institute, Atlanta, GA, United States. NFSABA@emory.edu
AU Nieva Jorge
CS University of Southern California, Los Angeles, CA, United States. Jorge.Nieva@med.usc.edu
AU Bishop Justin; Sidransky David; Ravi Kajani; Bedi Atul; Chung Christine H
CS Johns Hopkins Medical Institutions, Baltimore, MD, United States. jbishop@jhmi.edu; dsidrans@jhmi.edu; ravira@jhmi.edu; abedi1@jhmi.edu; cchung11@jhmi.edu
SO Oral oncology, (2015 Apr) Vol. 51, No. 4, pp. 376-82. Electronic Publication Date: 13 Jan 2015
Journal code: 9709118. E-ISSN: 1879-0593. L-ISSN: 1368-8375.

Report No.: PMC-PMC4459134; MID-NIHMS651330.
DOI http://dx.doi.org/10.1016/j.oraloncology.2014.12.011
CY England: United Kingdom
DT (CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201512
ED Entered STN: 17 Jan 2015
Last Updated on STN: 16 Dec 2015
Indexing Added: 16 Dec 2015
Entered Medline: 7 Dec 2015
GO United States NCI NIH HHS
GN HHSN261201100100C; R25 CA174664; P30 CA076292
GO United States NIDCR NIH HHS
GN P50 DE019032; P50DE019032
GO United States PHS HHS
GN N01 261201100100C
OSC.G 11 There are 11 MEDLINE records that cite this record
REM.CNT 24 There are 24 cited references available in MEDLINE for this document.
AB INTRODUCTION: A combination of cetuximab and sorafenib in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) were assessed for potential benefit.

MATERIAL AND METHODS: In a randomized phase II study, R/M HNSCC patients were treated with cetuximab 400mg/m(2) IV on day 1 followed by 250mg/m(2) IV weekly (Arm A), or cetuximab at the same dose/schedule plus sorafenib 400mg PO twice-a-day (Arm B). Each cycle was 21days. Tumor p16 and HPV status, and plasma immunomodulatory cytokine levels were assessed.

RESULTS: Of 55 patients enrolled (Arm A-27, Arm B-28), 52 patients received assigned treatments and 43 were evaluable for response. Overall response rate was 8% for both arms. Median overall survival (OS) and progression-free survival (PFS) were 9.0 and 3.0months in Arm A, and 5.7 and 3.2months in Arm B, respectively. Forty-four patients had tumors available for p16 staining (35-negative, 9-positive). Three of nine p16-positive tumors were also HPV positive. The p16-negative patients had significantly better PFS compared to the p16-positive patients (3.7 vs. 1.6months; p-value: 0.03), regardless of study arms. Twenty-four plasma samples were tested for 12 cytokine levels and patients with higher TGFβ1 levels had inferior PFS compared to lower levels (1.9 vs. 4.7months; adjusted p-value: 0.015), regardless of study arms.

CONCLUSIONS: A subset of R/M patients with p16-negative tumors or lower plasma TGFβ1 levels had longer PFS given the cetuximab-based therapy. However, both arms showed only modest response and sorafenib given with cetuximab did not demonstrate clinical benefit.
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L26 ANSWER 3 OF 16 MEDLINE ® on STN DUPLICATE 3
AN 2014730904 MEDLINE Full-text
DN PubMed ID: 24830724
TI The TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors.
AU Izumchenko Evgeny; Chang Xiaofei; Michailidi Christina; Kagohara Luciane; Ravi Rajani; Brait Mariana; Hoque Mohammad O; Ling Shizhang; Bedi Atul; Sidransky David
CS Authors' Affiliations: Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, and. dsidrans@jhmi.edu
AU Paz Keren
CS Champions Oncology, Inc., Baltimore, Maryland.
SO Cancer research, (2014 Jul 15) Vol. 74, No. 14, pp. 3995-4005. Electronic Publication Date: 15 May 2014
Journal code: 2984705R. E-ISSN: 1538-7445. L-ISSN: 0008-5472.
Report No.: PMC-PMC4122100; MID-NIHMS597285.

DOI http://dx.doi.org/10.1158/0008-5472.CAN-14-0110
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201409
ED Entered STN: 17 May 2014
Last Updated on STN: 27 Sep 2014
Indexing Added: 27 Sep 2014
Entered Medline: 26 Sep 2014
GO United States NCI NIH HHS
GN P50 CA058184; U01CA084986; U01 CA084986
GO United States NIDCR NIH HHS
GN R37DE012588; P50 DE019032; R37 DE012588
OSC.G 46 There are 46 MEDLINE records that cite this record
REM.CNT 42 There are 42 cited references available in MEDLINE for this document.
AB Although specific mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) identify tumors that are responsive to EGFR tyrosine kinase inhibitors (TKI), these genetic alterations are present in only a minority of patients. Patients with tumors expressing wild-type EGFR lack reliable predictive markers of their clinical response to EGFR TKIs. Although epithelial-mesenchymal transition (EMT) has been inversely correlated with the response of cancers to EGFR-targeted therapy, the precise molecular mechanisms underlying this association have not been defined and no specific EMT-associated biomarker of clinical benefit has been identified. Here, we show that during transforming growth factor β (TGFβ)-mediated EMT, inhibition of the microRNAs 200 (miR200) family results in upregulated expression of the mitogen-inducible gene 6 (MIG6), a negative regulator of EGFR. The MIG6-mediated reduction of EGFR occurs concomitantly with a TGFβ-induced EMT-associated kinase switch of tumor cells to an AKT-activated EGFR-independent state. In a panel of 25 cancer cell lines of different tissue origins, we find that the ratio of the expression levels of MIG6 and miR200c is highly correlated with EMT and resistance to erlotinib. Analyses of primary tumor xenografts of patient-derived lung and pancreatic cancers carrying wild-type EGFR showed that the tumor MIG6(mRNA)/miR200 ratio was inversely correlated with response to erlotinib in vivo. Our data demonstrate that the TGFβ-miR200-MIG6 network orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors, and identify a low ratio of MIG6 to miR200 as a promising predictive biomarker of the response of tumors to EGFR TKIs.
©2014 American Association for Cancer Research.

L26 ANSWER 4 OF 16 MEDLINE ® on STN DUPLICATE 4
AN 2012918323 MEDLINE Full-text
DN PubMed ID: 22927667
TI Inhibition of TGF-β enhances the in vivo antitumor efficacy of EGF receptor-targeted therapy.
AU Bedi Atul
CS Head and Neck Cancer Research Division, Department of Otolaryngology-Head and Neck Surgery, 1550 Orleans Street, Johns Hopkins University School of Medicine, Cancer Research Building II, Baltimore, MD 21231, USA.
AU Chang Xiaofei; Noonan Kimberly; Pham Vui; Bedi Rishi; Fertig Elana J; Considine Michael; Califano Joseph A; Borrello Ivan; Chung Christine H; Sidransky David; Ravi Rajani
SO Molecular cancer therapeutics, (2012 Nov) Vol. 11, No. 11, pp. 2429-39.
Electronic Publication Date: 27 Aug 2012
Journal code: 101132535. E-ISSN: 1538-8514. L-ISSN: 1535-7163.
Report No.: PMC-PMC3640459; MID-NIHMS438147.
DOI http://dx.doi.org/10.1158/1535-7163.MCT-12-0101-T
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201304
ED Entered STN: 29 Aug 2012

Last Updated on STN: 24 Apr 2013
Entered Medline: 23 Apr 2013
GO United States NCI NIH HHS
GN K25CA141053; P30 CA006973; K25 CA141053; 5P50CA096784-05; P50 CA096784; R01 CA123277; R01CA123277; R01 CA184199
GO United States NIDCR NIH HHS
GN R01 DE017982; P50 DE019032
OSC.G 24 There are 24 MEDLINE records that cite this record
REM.CNT 46 There are 46 cited references available in MEDLINE for this document.
AB EGF receptor (EGFR)-targeted monoclonal antibodies (mAb), such as cetuximab, execute their antitumor effect in vivo via blockade of receptor-ligand interactions and engagement of Fcγ receptors on immune effector cells that trigger antibody-dependent cell-mediated cytotoxicity (ADCC). We show that tumors counteract the in vivo antitumor activity of anti-EGFR mAbs by increasing tumor cell-autonomous expression of TGF-β. We show that TGF-β suppresses the expression of key molecular effectors of immune cell-mediated cytotoxicity, including Apo2L/TRAIL, CD95L/FasL, granzyme B, and IFN-γ. In addition to exerting an extrinsic inhibition of the cytotoxic function of immune effectors, TGF-β-mediated activation of AKT provides an intrinsic EGFR-independent survival signal that protects tumor cells from immune cell-mediated apoptosis. Treatment of mice-bearing xenografts of human head and neck squamous cell carcinoma with cetuximab resulted in emergence of resistant tumor cells that expressed relatively higher levels of TGF-β compared with untreated tumor-bearing mice. Although treatment with cetuximab alone forced the natural selection of TGF-β-overexpressing tumor cells in nonregressing tumors, combinatorial treatment with cetuximab and a TGF-β-blocking antibody prevented the emergence of such resistant tumor cells and induced complete tumor regression. Therefore, elevated levels of TGF-β in the tumor microenvironment enable tumor cells to evade ADCC and resist the antitumor activity of cetuximab in vivo. Our results show that TGF-β is a key molecular determinant of the de novo and acquired resistance of cancers to EGFR-targeted mAbs, and provide a rationale for combinatorial targeting of TGF-β to improve anti-EGFR-specific antibody therapy of EGFR-expressing cancers.
©2012 AACR.

L26 ANSWER 5 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2019:842991 BIOSIS Full-text
DN PREV201900942198
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 10442860 20191015
SO Official Gazette of the United States Patent and Trademark Office Patents, (OCT 15 2019)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 6 Nov 2019
Last Updated on STN: 6 Nov 2019
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2018:318724 BIOSIS Full-text
DN PREV201800318724
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGF beta enhance the efficacy of cancer immunotherapy.
AU Ravi, Rajani; Noonan, Kimberly A.; Vui Pham; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; Artemov, Artem V.; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul [Reprint Author]
CS Johns Hopkins Univ, Sch Med, Dept Otolaryngol Head and Neck Canc Res, Baltimore, MD 21231 USA
abedi1@jhmi.edu
SO Nature Communications, (FEB 21 2018) Vol. 9, pp. Article No.: 741. http://www.nature.com/ncomms/index.html.
ISSN: 2041-1723.
DOI 10.1038/s41467-017-02696-6
DT Article
LA English
ED Entered STN: 28 Mar 2018
Last Updated on STN: 28 Mar 2018
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-beta (TGF beta), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and T(H)1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGF beta receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGF beta in the target cell microenvironment (alpha-CTLA4-TGF beta RIIecd and alpha-PDL1-TGF beta RIIecd). alpha-CTLA4-TGF beta RIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, alpha-PDL1-TGF beta RIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGF beta-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L26 ANSWER 7 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2018:123836 BIOSIS Full-text
DN PREV201800123836
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09850306 20171226
SO Official Gazette of the United States Patent and Trademark Office Patents, (DEC 26 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 17 Jan 2018
Last Updated on STN: 17 Jan 2018
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional

in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2016:751124 BIOSIS Full-text
DN PREV201600751124
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09441044 20160913
SO Official Gazette of the United States Patent and Trademark Office Patents, (SEP 13 2016)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 5 Oct 2016
Last Updated on STN: 5 Oct 2016
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By conteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 9 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2015:392017 BIOSIS Full-text
DN PREV201500392017
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 08993524 20150331
SO Official Gazette of the United States Patent and Trademark Office Patents, (MAR 31 2015)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 13 May 2015
Last Updated on STN: 13 May 2015
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immune suppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant

or disseminated cancer cells.

L26 ANSWER 10 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2014:713314 BIOSIS Full-text
DN PREV201400713314
TI The TGF beta-miR200-Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors (vol 74, pg 3995, 2014).
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hogue, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
SO Cancer Research, (SEP 1 2014) Vol. 74, No. 17, pp. 4950.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/0008-5472.CAN-14-2153
DT Article
Errata
LA English
ED Entered STN: 15 Oct 2014
Last Updated on STN: 15 Oct 2014

L26 ANSWER 11 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2015:430029 BIOSIS Full-text
DN PREV201500430029
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. [Reprint Author]; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins Univ, Baltimore, MD USA
SO Cancer Research, (OCT 1 2014) Vol. 74, No. 19, Suppl. S, pp. 4382.
Meeting Info.: 105th Annual Meeting of the American-Association-for-Cancer-Research (AACR). San Diego, CA, USA. April 05 -09, 2014. Amer Assoc Canc Res.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/1538-7445.AM2014-4382
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 27 May 2015
Last Updated on STN: 27 May 2015

L26 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2018:1128946 CAPLUS Full-text
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy
AU Ravi, Rajani; Noonan, Kimberly A.; Pham, Vui; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; V. Artemov, Artem; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul
CS Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SO Nature Communications (2018), 9(1), 1-14
CODEN: NCAOBW; ISSN: 2041-1723
DOI 10.1038/s41467-017-02696-6
PB Nature Research
DT Journal; (online computer file)
LA English
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8+ and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd).

a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). The study demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2014:1471342 CAPLUS Full-text
DN 161:625200
TI The TGFβ-miR200-MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors [Erratum to document cited in CA161:458236]
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hoque, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
CS Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SO Cancer Research (2014), 74(17), 4950
CODEN: CNREA8; ISSN: 0008-5472
DOI 10.1158/0008-5472.CAN-14-2153
PB American Association for Cancer Research
DT Journal
LA English
AB On page 3995, the authors list was published with typog. errors; the correct authors list is given.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2011:1138357 CAPLUS Full-text
DN 155:404869
TI Fusion proteins of targeting antibody and immunomodulatory moiety for targeted antitumor therapy
IN Bedi, Atul; Ravi, Rajani
PA The Johns Hopkins University, USA
SO PCT Int. Appl., 154pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011109789	A2	20110909	WO 2011-US27317	20110304
WO 2011109789	A3	20120405		
CA 2791383	A1	20110909	CA 2011-2791383	20110304
CA 3083324	A1	20110909	CA 2011-3083324	20110304
IL 221607	A	20121031	IL 2011-221607	20110304
EP 2542590	A2	20130109	EP 2011-751481	20110304
EP 2542590	B1	20170503		
EP 2542590	B2	20200401		
JP 2013521311	T	20130610	JP 2012-556279	20110304
JP 6066732	B2	20170125		
ES 2638521	T3	20171023	ES 2011-751481	20110304
EP 3260470	A1	20171227	EP 2017-168491	20110304
IL 266971	A	20190731	IL 2011-266971	20110304
IN 2012CN08417	A	20140214	IN 2012-CN8417	20121001
US 20130039911	A1	20130214	US 2012-13582717	20121017
US 8993524	B2	20150331		
US 20150183881	A1	20150702	US 2015-14645282	20150311
US 9441044	B2	20160913		
JP 2017043600	A	20170302	JP 2016-145162	20160725
JP 6378262	B2	20180822		

	US 20160340430	A1	20161124	US 2016-15231309	20160808
	US 9850306	B2	20171226		
	US 20170158770	A1	20170608	US 2016-15362632	20161128
	US 10442860	B2	20191015		
	JP 2018172439	A	20181108	JP 2018-140050	20180726
	IN 201948021756	A	20191018	IN 2019-48021756	20190531
	US 20200115455	A1	20200416	US 2019-16601347	20191014
PRAI	US 2010-61311255	P	20100305		
	US 2011-61435671	P	20110124		
	CA 2011-2791383	A3	20110304		
	EP 2011-751481	A3	20110304		
	IL 2011-221607	A3	20110304		
	JP 2012-556279	A3	20110304		
	WO 2011-US27317	W	20110304		
	IN 2012-CN8417	A3	20121001		
	US 2012-13582717	A1	20121017		
	US 2015-14645282	A1	20150311		
	JP 2016-145162	A3	20160725		
	US 2016-15231309	A3	20160808		
	US 2016-15362632	A1	20161128		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2011:1138357

AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-β)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compns. and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)

L26 ANSWER 15 OF 16 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN

AN 20170658529 EMBASE Full-text

DN 618271173 PMID: 28522603

TI SMAD4 loss is associated with cetuximab resistance and induction of MAPK/JNK activation in head and neck cancer cells.

AU Ozawa, Hiroyuki; Ranaweera, Ruchira S.; Fertig, Elana J.; Howard, Jason D.; Markovic, Ana; Perez, Jimena; Wang, Hao; Kang, Hyunseok; Chung, Christine H. (correspondence)

CS Department of Oncology, School of Medicine, Johns Hopkins University, Baltimore, MD, United States. Christine.Chung@Moffitt.Org

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CS Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, H.

Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL, 33612, United States. Christine.Chung@Moffitt.Org
SO Clinical Cancer Research, (1 Sep 2017) Vol. 23, No. 17, pp. 5162-5175.
Refs: 65
ISSN: 1078-0432; E-ISSN: 1557-3265 CODEN: CCREF4
DOI 10.1158/1078-0432.CCR-16-1686
PB American Association for Cancer Research Inc..
CY United States
DT Journal; Article
FS Intellectual Indexing
016 Cancer
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered Embase: 26 Sep 2017
Last Updated on Embase: 5 Jul 2018
Indexing Added: 26 Sep 2017
First Entered Embase or Embase Alert: 26 Sep 2017
AB Purpose: We previously demonstrated an association between decreased SMAD4 expression and cetuximab resistance in head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to further elucidate the clinical relevance of SMAD4 loss in HNSCC. Experimental Design: SMAD4 expression was assessed by IHC in 130 newly diagnosed and 43 patients with recurrent HNSCC. Correlative statistical analysis with clinicopathologic data was also performed. OncoFinder, a bioinformatics tool, was used to analyze molecular signaling in TCGA tumors with low or high SMAD4 mRNA levels. The role of SMAD4 was investigated by shRNA knockdown and gene reconstitution of HPV-negative HNSCC cell lines in vitro and in vivo. Results: Our analysis revealed that SMAD4 loss was associated with an aggressive, HPV-negative, cetuximab-resistant phenotype. We found a signature of prosurvival and antiapoptotic pathways that were commonly dysregulated in SMAD4-low cases derived from TCGA-HNSCC dataset and an independent oral cavity squamous cell carcinoma (OSCC) cohort obtained from GEO. We show that SMAD4 depletion in an HNSCC cell line induces cetuximab resistance and results in worse survival in an orthotopic mouse model in vivo. We implicate JNK and MAPK activation as mediators of cetuximab resistance and provide the foundation for the concomitant EGFR and JNK/MAPK inhibition as a potential strategy for overcoming cetuximab resistance in HNSCCs with SMAD4 loss. Conclusions: Our study demonstrates that loss of SMAD4 expression is a signature characterizing the cetuximab-resistant phenotype and suggests that SMAD4 expression may be a determinant of sensitivity/resistance to EGFR/MAPK or EGFR/JNK inhibition in HPV-negative HNSCC tumors.

L26 ANSWER 16 OF 16 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051693676 EMBASE Full-text
DN 71721427
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. (correspondence); Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins University, Baltimore, MD, United States.
SO Cancer Research, (1 Oct 2014) Vol. 74, No. 19, Supp. SUPPL. 1. Abstract Number: 4382.
Meeting Info: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014. San Diego, CA, United States. 05 Apr 2014-09 Apr 2014
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2014-4382
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 3 Feb 2015
Last Updated on Embase: 3 Feb 2015
AB While sensitizing mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) render tumors more sensitive to EGFR

tyrosine kinase inhibitors (TKIs), these genetic alterations are present in only a minority of patients who respond to treatment and are rare in tumors other than NSCLCs. Thus, clinical benefit of TKIs in a subset of patients with wild-type EGFR may be underestimated due to the lack of appropriate predictive markers to stratify them from larger number of patients who do not response. It has long been observed that the response of anti-EGFR agents is associated with epithelial and mesenchymal transition (EMT) in multiple types of tumors without known EGFR mutations. However, little is known about the molecular mechanisms underlying this association, and no EMT-associated biomarkers of clinical utility have been successfully developed. Here we show that during the TGFβ-induced EMT, upregulation of mitogen-inducible gene 6 (Mig6), a negative regulator of EGFR, by microRNAs 200 (miR200) family is leading to reduced EGFR dependence, initiation of kinase switch in mesenchymal cells and subsequent insensitivity of these cells to EGFR inhibition. Moreover, we found that the ratio between mRNA levels of Mig6 and miR200c highly correlated with erlotinib sensitivity and EMT status in panel of 25 cancer cell lines of different tissue origins. Furthermore, analysis of directly xenografted human lung and pancreatic tumors (tumorgrafts) bearing wtEGFR demonstrated a higher response to EGFR inhibitor erlotinib for models with low Mig6 (mRNA)/miR200 ratio. Collectively, our data demonstrates that during the EMT-associated evolution of resistance to EGFR inhibitors, Mig6 expression is highly correlated with EMT status and identifies the ratio of Mig6 mRNA to miR200 as a novel, reliable and cost-effective predictor of biologic and clinical response to TKIs.

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=> d his

     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1            39 S E3
                E RAVI RAJANI/AU
L2            44 S E3-E4
L3            55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4             0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5           439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6            35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7             0 S L5 AND L6
L8        374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9         35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10         1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11          162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12           44 S L11 AND PY<=2010
L13         1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14           23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15           15 DUP REM L14 (8 DUPLICATES REMOVED)
L16            4 S L15 AND PY<=2010
L17          651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18          133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19            2 S L18 AND PY<=2010
L20            5 S L18 AND (LINKER OR GLYCINE LINKER)
L21            0 S L20 AND PY<=2010
L22            0 S L15 AND L3
L23            0 S L12 AND L3
L24            0 S L5 AND L3
L25           26 S L3 AND L8
L26           16 DUP REM L25 (10 DUPLICATES REMOVED)

=> s l16 AND (LINKER OR GLYCINE LINKER)

L27            0 L16 AND (LINKER OR GLYCINE LINKER)

=> d his
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     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1           39 S E3
                E RAVI RAJANI/AU
L2           44 S E3-E4
L3           55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4            0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010
L20           5 S L18 AND (LINKER OR GLYCINE LINKER)
L21           0 S L20 AND PY<=2010
L22           0 S L15 AND L3
L23           0 S L12 AND L3
L24           0 S L5 AND L3
L25          26 S L3 AND L8
L26          16 DUP REM L25 (10 DUPLICATES REMOVED)
L27           0 S L16 AND (LINKER OR GLYCINE LINKER)

=>
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Notice to Comply	Application No. 16/604,347	Applicant(s) BEDI et al.	
	Examiner Fozia Hamud	Art Unit 1647	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other. Claim 26 recited a sequence. However, the sequence is not accompanied by the required reference to the relevant sequence identifiers.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
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BIB DATA SHEET

CONFIRMATION NO. 9807

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/601,347	10/14/2019 RULE	530	1647	JHU3260-8

APPLICANTS
The Johns Hopkins University, Baltimore, MD;

INVENTORS
Atul Bedi, Timonium, MD;
Rajani Ravi, Ruxton, MD;

**** CONTINUING DATA ***************************
This application is a CON of 15/362,632 11/28/2016 PAT 10442860
which is a DIV of 15/231,309 08/08/2016 PAT 9850306
which is a CON of 14/645,282 03/11/2015 PAT 9441044
which is a CON of 13/582,717 10/17/2012 PAT 8993524
which is a 371 of PCT/US2011/027317 03/04/2011
which claims benefit of 61/435,671 01/24/2011
and claims benefit of 61/311,255 03/05/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/25/2019

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /FOZIA M HAMUD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		MD	75	20	2

ADDRESS
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
UNITED STATES

TITLE
COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

FILING FEE RECEIVED		
1880	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/601,347	Filing Date 10/14/2019	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	06/09/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PATENT
Attorney Docket No. JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	Fozia M. Hamud
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-OFFICE ACTION

Sir:

In response to the Non-Final Office Action mailed December 10, 2020, please enter the following amendment and remarks in the above-identified application.

Amendments to the Claims are reflected in the listing of claims which begins on page **2** of this paper.

Remarks/Arguments begin on page **4** of this paper.

Amendments to the Claims:

Please amend claims 21, 26 and 42 as shown in the listing of claims.

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1-20. (Canceled)

21. (Currently Amended) An isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein:

a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and

b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFbR).

22. (Previously Presented) The molecule of claim 21 wherein the targeting moiety specifically binds a cell surface molecule that is a tumor antigen, tumor growth factor receptor, or cytokine receptor.

23. (Previously Presented) The molecule of claim 21 wherein the targeting moiety comprises an antigen-binding domain of an immunoglobulin, antibody, bispecific or multispecific antibody, antibody fragment, single chain variable fragment (scFv), bivalent or multivalent scFv or Fc-containing polypeptide.

24. (Previously Presented) The molecule of claim 21, wherein the immunomodulatory moiety is fused to the C-terminus or N-terminus of said targeting moiety.

25. (Previously presented) The molecule of claim 21, wherein the targeting moiety is fused to the immunomodulatory moiety via a linker.

26. (Previously presented) The molecule of claim 25, wherein the linker is (GGGGS)n (SEQ ID NO:123) and wherein n is 1, 2, 3, 4, 5, 6, 7, or 8.

27. (Previously Presented) The molecule of claim 21, wherein the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor II (TGFbRII) or a ligand-binding fragment thereof.

28. (Previously Presented) The molecule of claim 27, wherein the immunomodulatory moiety comprises the amino acid sequence corresponding to SEQ ID NO: 87, or a ligand-binding fragment thereof.

29-40. (Canceled)

41. (Previously Presented) The molecule of claim 25, wherein the targeting moiety is an Fc-containing polypeptide comprising a linker at the CH3 region of the Fc.

42. (Currently Amended) The molecule of claim 21, wherein the targeting moiety specifically binds Herpesvirus entry mediator (HVEM), Carcinoembryonic antigen (CEA), Prostate-specific membrane antigen (PSMA), Programmed death-ligand 1 (PD-L1), or Epidermal growth factor receptor (EGFR).

REMARKS

Prior to this Communication, claims 21-28 and 41-42 were pending and under consideration. With the present communication, claims 21, 26 and 42 have been amended. Support for the claim amendments may be found generally throughout the application and claims as originally filed. No new matter is added. After entry of the amendments, claims 21-28 and 41-42 will be pending and under consideration.

Sequence Listing

The Examiner has stated that the claims are not incompliance with the Sequence Listing requirements. The Examiner stated that claim 26 contains an amino acid sequence which is not accompanied by a sequence identifier.

Applicants have amended claim 26 to add a sequence identifier for the amino acid sequence. Applicants submit that this amendment renders the objection moot and respectfully request withdrawal of the objection.

Claim Objections

The Examiner objected to claim 21 stating that the phrase "extracellular domain" has a word missing. The Examiner states that the claim should be amended to recite "extracellular domain of".

Applicants have amended claim 21 as suggested by the Examiner. Applicants submit that these amendments render the objection moot and respectfully request withdrawal of the objection.

The Examiner objected to claim 42 for reciting acronyms without spelling out the acronym first.

Applicants have amended claim 42 to spell out the acronyms. Applicants submit that these amendments render the objection moot and respectfully request withdrawal of the objection.

Double Patenting Rejection

Claims 21-27 and 41-42 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-12 of U.S. Patent No. 9,850,306. Applicants respectfully traverse this rejection.

Without acquiescing to the Examiner's assertion and to expedite prosecution of the claimed invention, a terminal disclaimer is hereby submitted together with this paper to overcome the non-statutory obviousness-type double patenting rejections over U.S. Patent No. 9,850,306. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

Claims 21-27 and 41-42 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-12 of U.S. Patent No. 9,441,044. Applicants respectfully traverse this rejection.

Without acquiescing to the Examiner's assertion and to expedite prosecution of the claimed invention, a terminal disclaimer is hereby submitted together with this paper to overcome the non-statutory obviousness-type double patenting rejections over U.S. Patent No. 9,441,044. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

Claims 21-27 and 41 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1-12 of U.S. Patent No. 8,993,524 in view of Contardi et al. (Int. J. Cancer: 117, 538-550; 2005). Applicants respectfully traverse this rejection.

Without acquiescing to the Examiner's assertion and to expedite prosecution of the claimed invention, a terminal disclaimer is hereby submitted together with this paper to overcome the non-statutory obviousness-type double patenting rejections over U.S. Patent No. 8,993,524. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

Rejections under 35 USC § 103(a)

Claims 21-28 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over McKenna et al. (U.S. Patent No. 7,820,165; hereafter "McKenna") and Sun et al. (U.S. Patent No. 7,795,389; hereafter "Sun"). Applicants respectfully traverse this objection.

The Examiner states that McKenna discloses hybrid antigen binding molecules which have superior properties relative to non-hybrid counterparts. The Examiner states that McKenna discloses an antigen binding moiety that specifically binds EGFR and that the hybrid protein has EGFR antagonist activity. The Examiner further states that McKenna discloses that the binding moiety may be linked to another peptide via linker and that the molecule can be used to treat cancer. However, McKenna does not disclose an isolated molecule comprising a targeting moiety fused to an immunomodulatory moiety. The Examiner states that Sun discloses TGF-beta antagonists comprising the extracellular domain of TGFβRII and fusion proteins. The Examiner states that it would have been obvious to combine the targeting moiety that specifically binds EGFR disclosed in McKenna with the immunomodulatory molecule comprising the extracellular domain of TGFβRII disclosed in Sun.

Applicants respectfully disagree. The U.S. Supreme Court decision in KSR International v. Teleflex Inc. modified the standard for establishing a prima facie case of obviousness. KSR, 550 US 398, 82 USPQ 2d 1385 (2007). Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references.

The 2010 KSR Guidelines Update provides additional guidance in view of decisions by the United States Court of Appeals for the Federal Circuit (Federal Circuit) since KSR. However, familiar lines of argument still apply, including teaching away from the claimed invention by the prior art, lack of a reasonable expectation of success, and unexpected results. Indeed, such arguments may have even taken on added importance in view of the recognition in KSR of a variety of possible rationales. See Federal Register, Vol. 75, No. 169, September 1,

2010, page 53645. Applicants respectfully submit that the Office has not met the burden of establishing a prima facie case of obviousness for the reasons discussed below.

Applicants submit that McKenna discloses hybrid molecules comprising heterodimeric proteinaceous hormones that are fused to one or more antigen binding moieties (column 1, lines 41-44). Specifically, McKenna discloses that the antigen binding moieties can bind to EGFR, IGFR and VEGF column 1, line 65 to column 2, line 13). McKenna discloses a molecules comprising a binding moiety to EGFR, VEGF or IGFR; a linker which is either comprised of alanines or glycines and serines (gly/ser); and either hCGα or hCGβ (Examples 1-3). The application does not disclose any molecules where the antigen binding moiety is attached to TGFβRII via a gly/ser linker. The hCG hormone component of the molecules disclosed in McKenna functions completely differently from the TGFβRII component of the presently claimed molecules. The TGFβRII component counteracts tumor-induced immune tolerance and enhances antitumor immunity by binding and disabling TGFβ within the localized microenvironment of the targeted tumor cell. By disabling TGFβ in the localized microenvironment of the targeted tumor cell, the bifunctional molecule enables activation of innate and adaptive immune responses to tumor antigens during the course of therapy that can sustain antitumor activity after the cessation of therapy. The hCG components of the molecules disclosed have no relation to TGFβRII, are biologically inactive and are used to generate a hybrid antigen binding molecule.

Additionally, while the molecules in McKenna have shown increased activity for the antigen binding moiety compared to antibody alone, there is no showing that the molecules bind two separate proteins, that each component has activity independent of the other and that each component of the hybrid molecule has increased activity compared to individual antibodies alone or in combination. Submitted here with is a Declaration from Dr. Atul Bedi, an inventor on the present application, describing experiments in which α-IL-6R-TGFβRII, α-EGFR-TGFβRII and α-PDL1-TGFβRII molecules all exhibit increased anti-tumor efficacy compared to the individual components or their combinations, which would not be expected in light of the prior art.

In the Declaration, it is demonstrated that the α-IL-6R-TGFβRII molecule binds both IL-6R and TGFβ1 simultaneously (Appendix A Figure 2B). Further, the Declaration provides data

demonstrating that the α-IL-6R-TGFβRII molecule has increased antitumor efficacy compared to α-IL-6R and a TGFβ antagonist either alone or in combination in SCID mice injected with cells from a triple negative breast cancer cell line (MDA-MB-231-Luc(D3H2LN) (Appendix A Figure 3). In another experiment, it was demonstrated that the α-IL-6R-TGFβRII molecule suppresses TH17 cell differentiation and promotes the differentiation of IFNγ+ TH1 effector cells (Appendix A Figure 4A). Additionally, it was demonstrated that the α-IL6R-TGFβRII molecule prolongs the onset of osteolytic skeletal-related events from tumor bone metastases in vivo more effectively than α-IL6R antibody, TGFβ antagonist, or the combination of α-IL6R and α-TGFβ (Appendix A Figure 4C). These data demonstrate that the α-IL6R-TGFβRII molecule has superior anti-tumor efficacy via its unique ability to localize the TGFβRIIecd to the immediate microenvironment of IL6R expressing tumor cells.

Additionally, the Declaration presents data demonstrating that the α-EGFR-TGFβRII molecule simultaneously binds EGFR and TGFβ1 (Appendix A Figure 5A). The α-EGFR-TGFβRII molecule was shown to effectively counteract tumor-induced TGFβ-mediated immune tolerance and exhibits superior antitumor efficacy compared to anti-EGFR mAb. (Appendix A Figure 6D). In another experiment, it was demonstrated that the α-EGFR-TGFβRII molecule is more effective at inhibiting tumor growth compared with either anti-EGFR antibody or anti-TGF-β Ab, either alone or in combination in human colon cancer-bearing humanized NSG mice (Appendix A Figure 6E). Further, it was shown that the α-EGFR-TGFβRII molecule exhibits superior in vivo antitumor efficacy compared to α-EGFR antibody in human Triple-Negative Breast Cancer-bearing humanized NSG mice (Appendix A Figure 7A). In an additional experiment, it was demonstrated that the α-EGFR-TGFβRII molecule is more effective at inhibiting tumor growth compared with either anti-EGFR antibody or anti-TGF-β1 Ab or a combination of both in human Triple-Negative Breast Cancer-bearing NOD-SCID mice (Appendix A Figure 7D). These data demonstrate that the α-EGFR-TGFβRII molecule has superior anti-tumor efficacy via its unique ability to localize the TGFβRIIecd to the immediate microenvironment of EGFR expressing tumor cells.

The Declaration also provides data showing that the α-PDL1-TGFβRII molecule simultaneously binds TGF-β1 and PD-L1 (Appendix A Figure 9C). In an additional experiment,

the Declaration provides data demonstrating that in Triple-Negative Breast Cancer-bearing humanized NSG mice, the antitumor efficacy of the α-PD-L1-TGFβRII molecule exceeds that of the corresponding α-PD-L1 antibody, non-specific IgG-TGFβRII, and the combination of both (Appendix A, Figure 10). In another experiment it was shown that the TGFbRIIecd-Fc-PD1ecd molecule that simultaneously binds TGFb1 and PD-L1 exhibits superior antitumor efficacy compared to the non-specific IgG-PD1ecd, non-specific TGFβRIIecd-Fc, or the combination of both in Triple-Negative Breast Cancer-bearing humanized NSG mice (Appendix A Figure 12). These data demonstrate that the α-PD-L1-TGFβRII and TGFbRIIecd-Fc-PD1ecd molecules have superior anti-tumor efficacy via their unique ability to localize the TGFβRIIecd to the immediate microenvironment of PD-L1 expressing tumor cells.

As such, as shown in the declaration, the antitumor efficacy of the presently claimed molecules require the bifunctional properties of both the targeting moiety and the TGFbR-comprising immunomodulatory moiety. Applicants submit that McKenna does not disclose or suggest bifunctional molecules comprising a targeting moiety and immunomodulatory moiety; rather McKenna discloses monofunctional molecules that can bind one another to form a molecule with two antigen binding moieties. Further, the superior antitumor efficacy of the presently claimed molecules is crucially dependent on the physical linkage of the targeting moiety with the ligand-binding sequence of TGFβRIIecd which disables TGFβ in the localized microenvironment of the targeted tumor cell. Therefore, bifunctional molecules of the present invention enable activation of innate and adaptive immune responses to tumor antigens during the course of therapy that can sustain antitumor activity. McKenna does not disclose or suggest the presently claimed molecules.

The Examiner relies on Sun to cure the deficiencies of McKenna. Sun discloses TGF-β antagonists comprising soluble cell surface type II TGF-β receptors and fusion proteins comprising said soluble cell surface type II TGF-β receptors. However, Sun does not disclose an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor

(TGFbR) as is presently claimed. Sun does not describe fusion proteins capable of tumor cell-localized TGFb blockade or anticipate the antitumor effects of such fusion proteins. As such, Sun fails to cure the deficiencies of McKenna.

Applicants submit that neither McKenna nor Sun disclose or suggest the presently claimed invention and that one of skill in the art would not arrive at the presently claimed invention based on the disclosure of McKenna or Sun, either alone or in combination. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 21-28 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over McKenna and Sun in view of Scaria et al. (U.S. Patent Appl. Pub. No. 2011/0052585; hereafter Scaria"). Applicants respectfully traverse this objection.

The Examiner states that McKenna and Sun apply as described previously. The Examiner states that McKenna and Sun do not disclose a molecule comprising a linker at the CH3 region of the Fc. Scaria discloses fusion proteins comprising a cytokine cell surface receptor and an Fc where the Fc component comprises an CH2 domain.

As discussed above, neither McKenna nor Sun disclose or suggest the presently claimed invention. The Examiner relies on Scaria to cure the deficiencies of McKenna and Sun. Scaria discloses a delivery method for IL-17 and IL-23 receptor constructs or proteins expressed from such constructs and specifically that the interleukin domain can be linked to a multimerization domain via a linker comprised of glycine and serine. Scaria does not disclose or suggest an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of Transforming growth factor-beta receptor (TGFbR) as is presently claimed. Further, none of Scaria, McKenna, and Sun, alone or in combination, would predict the surprising and unexpected result that the fusion of a targeting moiety binding a tumor cell surface molecule and the TGFbR-comprising immunomodulatory moiety would be more effective than treatment with the targeting moiety and immunomodulatory moiety as separate agents. As such, Scaria fails to cure the deficiencies of McKenna and Sun.

Applicants submit that none of McKenna, Sun or Scaria disclose or suggest the presently claimed invention and that one of skill in the art would not arrive at the presently claimed invention based on the disclosure of McKenna, Sun or Scaria either alone or in combination. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the amendments and above remarks, reconsideration and withdrawal of the restriction requirement is respectfully requested. Applicant provides that the claims are ready for examination. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge the total amount of $1,650.00 to cover the Three-Month Extension of Time fee ($1,480.00) and Terminal Disclaimer fee ($170.00), for large entity, to Deposit Account No. 07-1896. No other fee is deemed necessary in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees that are required or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: June 9, 2021

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	Fozia M. Hamud
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Dr. Atul Bedi, declare and state that:

1. I am a named inventor of the subject matter described and claimed in U.S. Patent Application Serial No. 16/601,347, filed on October 14, 2019 entitled, "Compositions and Methods for Targeted Immunomodulatory Antibodies and Fusion Proteins." I am a physician-scientist and medical oncologist, and an Associate Professor of Otolaryngology/Head & Neck Surgery and Oncology at the Johns Hopkins University School of Medicine. My CV is attached (Appendix B).

2. I understand that claims 21-28 and 41-42 have been rejected as being obvious given the disclosures of McKenna et al. (U.S. Patent No. 7,820,165; hereafter "McKenna") and Sun et al. (U.S. Patent No. 7,795,389; hereafter "Sun"), in view of Scaria (U.S. Patent Appl. Serial No. 2011/0052585).

3. I disagree with the Examiner's assertion that McKenna, Sun, and Scaria render the present invention obvious. McKenna allegedly discloses hybrid proteins which comprise two polypeptide chains, with at least one chain further comprising one or more antigen binding moiety binding specifically to EGFR, IGF-1R, or VEGF, where the hybrid protein has EGFR, IGF-1R, or VEGF antagonistic activity. McKenna additionally discloses that the hybrid proteins can bind to growth factors such as transforming growth factors (TGFs). Further, the hybrid

proteins may be used to treat cancer. However, McKenna does not teach a molecule comprising a targeting moiety that binds a tumor cell surface molecule fused to an amino acid sequence of the extracellular domain of TGF-beta receptor (TGFβR).

4. Sun allegedly discloses TGFβ antagonists comprising TGFβ receptors and fusion proteins comprising sRII. The TGFβ antagonists may include a therapeutically effective amount of a mixture or combination of therapeutically active portions of sRII, E domain of sRIII, or U domain of sRIII. Further, the TGFβ antagonists may be used for the treatment of cancer. However, Sun does not teach a molecule comprising a targeting moiety that binds a tumor cell surface molecule fused to an amino acid sequence of the extracellular domain of TGF-beta receptor (TGFβR).

6. Scaria allegedly discloses a delivery method for IL-17 and IL-23 receptor constructs or proteins expressed from such constructs. Scaria additionally discloses that the interleukin receptor can be linked to a multimerization domain via a linker comprising glycine and serine. However, Scaria does not teach a molecule comprising a targeting moiety that binds a tumor cell surface molecule fused to an amino acid sequence of the extracellular domain of TGF-beta receptor (TGFβR).

7. My invention provides molecules which counteract tumor-induced immune tolerance and enhance antitumor immunity by binding and disabling TGFβ within the localized microenvironment of the targeted tumor cell. By disabling TGFβ in the localized microenvironment of the targeted tumor cell, the bifunctional molecule enables activation of innate and adaptive immune responses to tumor antigens during the course of therapy that can sustain antitumor activity after the cessation of therapy. The claimed invention is directed to a molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein: the targeting moiety specifically binds a component of a tumor cell that is a tumor cell surface molecule; and the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain (ECD) of TGFβR.

8. As illustrative examples, I show the following: (i) anti-IL6R-TGFβRII, a bifunctional antibody that targets and binds IL6R and simultaneously inactivates TGFβ by an extracellular domain sequence of TGFβRII fused to the C terminus of the heavy chain of an anti-IL6R antibody via a flexible linker sequence $(GGGGS)_3$, (ii) anti-EGFR-TGFβRII, a bifunctional antibody that targets and binds EGFR and simultaneously inactivates TGFβ by an extracellular domain sequence of TGFβRII fused to the C terminus of the heavy chain of an anti-EGFR antibody via a flexible linker sequence $(GGGGS)_3$, and (iii) anti-PDL1-TGFβRII, a bifunctional antibody that targets and binds PDL1 and simultaneously inactivates TGFβ by an extracellular domain sequence of TGFβRII fused to the C terminus of the heavy chain of an anti-PDL1 antibody via a flexible linker sequence $(GGGGS)_3$. In each of these three illustrative examples, the targeting moiety binds a tumor cell surface molecule (IL6R, EGFR, or PDL1, respectively) and the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain of TGFβ receptor.

9. The anti-IL6R-TGFβRII molecule is, as an illustrative example, a bifunctional antibody that targets and binds IL-6R and simultaneously inactivates TGF-β by an extracellular domain sequence of TGF-β Receptor II (TGF-βRIIecd) fused to the C-terminus of the heavy chain of an anti-IL-6R antibody via a flexible linker sequence, $(GGGGS)_3$ (see Appendix A Figure 1A). Appendix A Figure 1B is an SDS-PAGE comparison of an anti-IL-6R antibody and anti-IL6R-TGFβRII under reducing and non-reducing conditions showing the expected higher molecular weight of the heavy chain of anti-IL-6R-TGFβRII. In contrast to anti- IL-6R antibody, anti-IL6R-TGFβRII exhibited simultaneous binding to IL-6R and TGF-β1 (Appendix A Figure 2).

10. I show that anti-IL6R-TGFβRII binds TGF-β1 with efficiency equivalent to that of TGFβRII-Fc (Appendix A Figure 2A). The ability of anti-IL6R-TGFβRII to bind TGF-β was evaluated by ELISA, wherein recombinant human TGFβ (rhTGFβ1; 0-10000 pg/ml) was added to plates coated with anti-IL6R-TGFβRII or TGFβRII-Fc (positive control), which was detected by biotinylated anti-TGFβ1 antibody and HRP-Avidin (R&D systems). Plates coated with non-specific rhTGFβRII-Fc served as positive controls to analyze the binding ability of the test

samples to TGFβ. anti-IL6R-TGFβRII exhibited binding to TGFβ with an efficiency that was similar to the positive control TGFβRII-Fc (Appendix A Figure 2A). The data show the optical density (OD) values (mean of three replicate wells for each assay condition) from a representative of two independent experiments.

11. In another experiment, I show that anti-IL6R-TGFβRII simultaneously binds TGF-β1 and IL-6R (Appendix A Figure 2B). The ability of anti-IL6R-TGFβRII to simultaneously bind both IL-6R and TGF-β was evaluated by a bispecific ELISA, wherein anti- IL6R-TGFβRII or anti-IL-6R antibody (0-1000 μg/ml) was added to IL-6R-Fc coated plates (1 μg/ml), followed by rhTGFβ1 (100 ng/ml) that was detected by a biotinylated anti-human TGF- β1 antibody. In contrast to the a-IL-6R antibody, anti-IL6R-TGFβRII exhibited simultaneous binding to IL-6R and TGFβ (Appendix A Figure 2B). The data show the optical density (OD) values (mean of three replicate wells for each assay condition) from a representative of two independent experiments.

12. Most significantly, I have demonstrated that in conjunction with a-EGFR antibody, the antitumor efficacy of the a-IL6R-TGFβRII molecule of my invention exceeds that of a-IL6R antibody, or the combination of the a-IL6R antibody and TGFβ antagonist (a-TGFβ: non-specific IgG-TGFβRII; the same TGFβRII sequence linked to a non-specific IgG heavy chain) (Appendix A Figure 3). The comparative antitumor efficacy of a-IL6R-TGFβRII, a-IL-6R antibody, non-specific TGFβ antagonist, and the combination of a-IL-6R antibody and TGFβ antagonist, all in conjunction with a-EGFR antibody, against human cancers expressing TGFβ was evaluated in NOD-SCID mice. MDA-MB-231 is a metastatic human Triple-Negative Breast Cancer (TNBC) cell line with mesenchymal-like morphology (Basal B-like). MDA-MB-231-Luc (D3H2LN) is a TNBC subline with enhanced primary tumor growth and lung metastases that was derived from a metastatic deposit of bioluminescent MDA-MB-231 cells stably expressing firefly luciferase. MDA-MB-231-Luc express high TGF-β (531 pg/10^6 cells/48h). Mice were injected with TNBC cells (1.5 x10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 10 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week with the following (either alone or in combination, as indicated): (i) anti- EGFR Ab + anti-IL6R-

TGFβRII; (ii) anti-EGFR Ab + anti-IL-6R Ab; (iii) anti-EGFR Ab + non- specific TGFβ antagonist (IgG-TGFβRII); (iv) anti-EGFR Ab + anti-IL-6R Ab + IgG-TGFβRII; (v) anti-EGFR Ab; (vi) Vehicle alone (Control). Tumor size was evaluated weekly and tumor volume calculated [length × width x height]. In vivo tumor growth curves (mean + SEM) in both the experiments demonstrated that treatment of tumor-bearing mice with a-EGFR Ab + a-IL6R- TGFβRII was significantly more effective at inhibiting the progression of MDA-MB-231-luc tumors compared with a-EGFR Ab in combination with a-IL6R Ab, non-specific TGFβ antagonist, or a-IL6R Ab + non-specific TGFβ antagonist (Appendix A Figure 3).

13. In another experiment, I show that anti-IL6R-TGFβRII suppresses TH17 cell differentiation and instead promotes the differentiation of interferon expressing (IFNγ+) TH1 effector cells (Appendix A Figure 4A). Peripheral blood lymphocytes (PBL) were stimulated with anti-CD3/anti-CD28-beads and cultured alone, with IL17-skewing cytokines [10 ng/mL IL-6, 5 ng/mL TGFβ, 10 ng/mL anti–IFN-γ, and 10 ng/mL anti–IL-4], autologous myeloma bone marrow (BM) plasma, or autologous BM plasma and a-IL6R-TGFβRII (5 μg/ml) for 3 days. Following addition of Leukocyte Activation Cocktail (2 μL/mL for 4 hours), cells were analyzed by flow cytometry for intracellular expression of IL-17 and IFN-γ in CD4+ T cells. In the presence of either canonical IL-17 skewing conditions (IL-6 + TGFβ + a-IFN-γ mAb) or autologous myeloma bone marrow plasma, IFN-γ expression is strongly repressed while IL17 expression is induced, indicating TH17 dominance amongst CD4+ T cells. However, in the presence of a-IL6R-TGFβRII, autologous BM plasma is unable to promote TH17 skewing and instead, an IFN-γ + TH1-like phenotype dominates.

14. In another experiment, I show that anti-IL6R-TGFβRII suppresses osteoclast (OC) proliferation in vitro significantly more effectively than a-IL6R antibody ($p < 0.0001$) (Appendix A Figure 4B). Normal bone marrow was cultured in Dulbecco modified Eagle medium plus 20% horse serum in medium alone or with 10 μg/mL macrophage colony- stimulating factor plus 20 μg/mL RANKL (referred to as MR), MR plus a-IL6R antibody, or MR + anti-IL6R-TGFβRII for 21 days in 96-well, flat-bottom plates. 12 wells were plated for each condition. Fresh medium was exchanged every third day (with or without cytokines/antibodies according to each well). On

day 21, medium was removed and OCs were stained with 23C6 (antibody that binds an osteoclast-specific vitronectin receptor). Briefly, media was aspirated and the cells were fixed with 37% formaldehyde for 20 minutes at room temperature followed by methanol. All wells were then washed with PBS plus 1% horse serum (HS). 23C6 antibody was added for 30 minutes at room temperature. Cells were again washed 3 times with PBS plus 1% HS. Biotinylated anti–mouse IgG was added for 30 minutes at room temperature and wells were again washed with PBS plus 1% HS. ABC Complex was added for 30 minutes at room temperature, and then wells were then washed with PBS plus 1% HS. A total of 0.1M Tris-HCl buffer (pH 9.5) was added for 10 to 15 minutes until development was detected. OCs were scored as 23C6 positive cells possessing 3 or more nuclei. Data were compiled by averaging the total number of OCs in the 12 wells of each group.

15. In another experiment, I show that anti-IL6R-TGFβRII prolongs the onset of osteolytic skeletal-related events from tumor bone metastases in vivo more effectively than a-IL6R antibody, TGFβ antagonist (a-TGFβ: IgG-TGFβRII), or the combination of a-IL6R and a-TGFβ (Appendix A Figure 4C). NOD-SCID mice were injected with multiple myeloma cells (2 x 10^6 cells of U266 cell line). Mice were treated with the specified antibodies at a dose of 5 mg/kg weekly starting at week 5 until week 19. Mice were visually inspected for hind-limb paralysis and euthanized if hind-limb paralysis was observed. Only mice treated with a-IL6R-TGFβRII survived longer than 31 weeks and those mice remained healthy one year after tumor inoculation.

16. My data demonstrates that this exemplary bifunctional molecule of the invention (anti-IL6R-TGFβRII) has superior anti-tumor efficacy via its unique ability to localize the TGFβRIIecd to the immediate microenvironment of IL6R expressing tumor cells. Unlike a non-targeted TGF-β antagonist (a-TGFβ or IgG-TGFβRII), a-IL6R-TGFβRII is therefore able to efficiently interrupt autocrine and paracrine TGF-β signaling in the tumor immune microenvironment via its ability to efficiently compete with native cellular TGFβRII for TGF-β binding on the surface of IL6R-expressing cells. The superior anti-tumor efficacy of anti-IL6R-TGFβRII is crucially dependent on the physical linkage of the IL6R-targeting moiety with the

ligand-binding sequence of TGFβRIIecd, and cannot be achieved by the simultaneous administration of a IL6R-targeting antibody and a non-targeted TGFβRIIecd-Fc which is not preferentially localized to IL6R-expressing tumor cells.

17. These data demonstrate that anti-IL6R-TGFβRII has unexpected and surprising properties and demonstrates that the presence of both a IL-6R antagonist and the ligand-binding sequence of a TGF-β receptor on the same molecule is significantly more effective at inhibiting tumor growth and metastases than the simultaneous administration of a IL-6R antagonist and non-targeted TGF-β antagonist.

18. The anti-EGFR-TGFβRII molecule is, as an illustrative example, a bifunctional antibody that targets and binds EGFR and simultaneously inactivates TGF-β by an extracellular domain sequence of TGF-β Receptor II (TGF-βRIIecd) fused to the C-terminus of the heavy chain of an anti-IL-6R antibody via a flexible linker sequence, $(GGGGS)_3$ (see Appendix A Figure 5A). I have shown that the α-EGFR-TGFβRII molecule simultaneously binds EGFR and TGF-β1. Appendix A Figure 5b shows ELISA wherein anti-EGFR-TGFβRII or anti-EGFR mAb (Cetuximab) was added to EGFR-Fc coated plates, followed by rhTGF-β1 (1 ng/ml) that was detected by a biotinylated anti-huTGF-β1 antibody. In contrast to α-EGFR mAb, anti-EGFR-TGFβRII exhibited simultaneous binding to EGFR and TGF-β1. The ability of anti-EGFR-TGFβRII to bind TGF-β1 was also evaluated by competition immunoassays. The ELISA plate was coated with capture antibody 1 μg/ml), followed by rhTGF-β1 in the presence of either α-EGFR-TGFβRII or α-EGFR mAb (Appendix A Figure 5C). Unlike α-EGFR mAb, anti-EGFR-TGFβRII antibody exhibits the ability to compete for binding to TGF-β1.

19. I have shown that α-EGFR-TGFβRII molecule effectively counteracts tumor-induced TGFβ-mediated immune tolerance and exhibits superior antitumor efficacy compared to anti-EGFR mAb. Exposure of human PBMCs to TGF-β1 inhibited their ability to mediate ADCC of cetuximab-opsonized DLD1 K-ras wt/null (D-WT1) tumor cells (Appendix A Figure 6A). An isogenic K-ras mutant derivative of DLD-1 [K-ras mut/null (D-MUT1)] expressed higher levels of TGF-β in tumor cell supernatants compared to D-WT1 cells (Appendix A Figure 6B), and

mice bearing D-MUT1 tumor xenografts exhibited high levels of TGF-β. Consistent with the clinical resistance of KRAS mutant cancers to cetuximab, treatment of D-MUT1 tumor-bearing nude mice with cetuximab failed to inhibit tumor growth (Appendix A Figure 6D). Treatment with anti-EGFR-TGFβRII significantly inhibited TGF-β (140.6 ± 139 pg/ml compared to a-EGFR 98580 ± 4843 pg/ml)($p<0.00001$) (Appendix A Figure 6C), and resulted in significantly smaller tumors (mean ± SEM = 423.1 ± 84) compared to tumors in mice treated with cetuximab (930.8 ± 91.5)($p=0.004$) or untreated controls (1233.4 ± 123.5) ($p<0.00034$) (Appendix A Figure 6D).

20. Additionally, I have demonstrated that anti-EGFR-TGFβRII is more effective at inhibiting tumor growth compared with either anti-EGFR antibody or anti-TGF-β Ab or a combination of anti-EGFR mAb and anti-TGF-β Ab in human colon cancer-bearing NSG mice reconstituted with human CD34+ hematopoietic cells. The ability of α-EGFR-TGFβRII to reverse tumor-induced immune tolerance and enhance antitumor immune responses was examined in D-MUT1 tumor-bearing NSG mice reconstituted with human CD34+ cells. Mice with human tumor xenografts were randomized and treated with the following: (i) anti-EGFR-TGFβRII mAb (5mg/kg i.p. weekly); (ii) anti-EGFR mAb (Cetuximab; 5 mg/kg, i.p, weekly); (iii) anti-TGFβ Ab (5 mg/kg, i.p, weekly); (iv) α-EGFR mAb (5mg/kg i.p. weekly) + α-TGFβ Ab (5 mg/kg, i.p, weekly); (v) Vehicle (Untreated Control). Tumor volume was calculated [length × width x height]. Treatment of D-MUT1 tumor-bearing mice with either α-EGFR, α-TGFβ, or even the combination of both antagonists (α-EGFR and α-TGFβ) (5mg/kg i.p. weekly x 5) failed to inhibit tumor growth (Appendix A Figure 6E). In contrast, treatment with anti-EGFR-TGFβRII (5mg/kg i.p. weekly x 5) resulted in significantly smaller tumors compared to tumors in untreated controls, mice treated with non-tumor targeted α-TGFβ or α-EGFR alone ($p<0.0027$), or mice treated with the combination of α-EGFR and α-TGFβ ($p<0.03$)(Appendix A Figure 6E).

21. I have also shown that the anti-EGFR-TGFβRII molecule exhibits superior in vivo antitumor efficacy compared to α-EGFR antibody in human Triple-Negative Breast Cancer (TNBC)-bearing NSG mice reconstituted with human CD34+ cells. The ability of α-EGFR-

TGFβRII to reverse tumor-induced immune tolerance and enhance T cell-mediated antitumor responses was examined in TNBC-bearing NSG mice reconstituted with human CD34+ hematopoietic cells. Mice with the human tumor xenografts were randomized and treated for four weeks with the following: (i) α-EGFR-TGFβRII (5mg/kg i.p. weekly); (ii) α-EGFR mAb (Cetuximab; 5 mg/kg, i.p, weekly); (iii) α-TGFβ Ab (5mg/kg i.p. weekly); (iv) Vehicle (Untreated Control). Tumor volume was calculated [length × width x height]. Treatment with α-EGFR-TGFβRII resulted in significantly smaller tumors (257.6 ± 58.5) compared to tumors in mice treated with α-EGFR (766.3 ± 64) ($p=0.00004$) or untreated controls (839.4 ± 77.4)($p<0.0001$) (Appendix A Figure 7A). Tumor burden in mice bearing MDA-MB-231-Luc (D3H2LN) was assessed by visualization of in vivo luciferase activity using a Xenogen IVIS Spectrum system. Images were acquired at 10 min post injection of 50 mg/kg i.p. dose of luciferin. At day 35, luciferin injected animals were sacrificed, lungs harvested and imaged ex vivo to detect lung metastases. Photon flux was used to quantify the differences in tumor burden between treatment groups. α-EGFR-TGFβRII was more effective in inhibiting primary tumors and lung metastases compared to α-EGFR mAb (Appendix A Figures 7 B and C).

22. Additionally, I have demonstrated that anti-EGFR-TGFβRII is more effective at inhibiting tumor growth compared with either anti-EGFR antibody or anti-TGF-β1 Ab or a combination of anti-EGFR mAb and anti-TGF-β1 Ab in NOD-SCID mice. The in vivo effect of anti-EGFR-TGFβRII was compared with anti-EGFR mAb (cetuximab) or a combination of anti-EGFR mAb and anti-TGF-β Ab in human tumor-bearing NOD-SCID mice. Human tumor xenografts were generated by mammary fat pad implantation of the MDA-MB-231-Luc (D3H2LN) TNBC line in female NOD-SCID mice ($1x10^6$ cells in 50% PBS/50% matrigel). At day 7 following tumor cell inoculation, mice were randomized and treated with the following: (i) α-EGFR-TGFβRII (5mg/kg i.p. weekly); (ii) α-EGFR mAb (Cetuximab; 5 mg/kg, i.p, weekly); (iii) α-TGFβ Ab (5mg/kg i.p. weekly); (iv) anti-EGFR mAb (5 mg/kg, i.p, weekly) + α-TGFβ Ab (5mg/kg i.p. weekly); (v) Untreated Control. Treatment with α-EGFR-TGFβRII resulted in significantly greater inhibition of tumor growth with significantly reduced tumor volume (mean ± SEM = 438.8 ± 94.8 mm3) compared to untreated controls (1368.5 ± 124.9 mm3) ($p<0.0002$),

α-EGFR mAb (974.7 ± 192.6 mm3) (p=0.031), α-TGFβ Ab (1020.3 ± 214.4 mm3) (p=0.026), or combination of α-EGFR mAb and α-TGFβ Ab (869.8 ± 165.2 mm3) ($p<0.04$) (Appendix A Figure 7D).

23. My data demonstrates that this exemplary bifunctional molecule of the invention (anti-EGFR-TGFβRII) has superior anti-tumor efficacy via its unique ability to localize the TGFβRIIecd to the immediate microenvironment of EGFR expressing tumor cells. Unlike a non-targeted TGF-β antagonist (a-TGFβ or IgG-TGFβRII), a-EGFR-TGFβRII is therefore able to efficiently interrupt autocrine and paracrine TGF-β signaling in the tumor immune microenvironment via its ability to efficiently compete with native cellular TGFβRII for TGF-β binding on the surface of EGFR-expressing cells. The superior anti-tumor efficacy of anti-EGFR-TGFβRII is crucially dependent on the physical linkage of the EGFR-targeting moiety with the ligand-binding sequence of TGFβRIIecd, and cannot be achieved by the simultaneous administration of an EGFR-targeting antibody and a non-targeted TGFβRIIecd-Fc which is not preferentially localized to EGFR-expressing tumor cells.

24. This data demonstrates that the α-EGFR-TGFβRII molecule has unexpected and surprising properties and demonstrates that the presence of both an EGFR antagonist and the ECD of TGFβ receptor on the same molecule is critical for anti-tumor efficacy with a clinically relevant therapeutic index.

25. The anti-PD-L1-TGFβRII molecule is, as an illustrative example, a bifunctional antibody that targets and sequesters PD-L1 and simultaneously inactivates TGF-β by an extracellular domain sequence of TGF-β Receptor II (TGF-βRIIecd) fused to the C-terminus of the heavy chain of an anti-PD-L1 antibody via a flexible linker sequence, $(GGGGS)_3$ (see Appendix A Figure 8A). Appendix A Figure 8B is an SDS-PAGE comparison of two different anti-PD-L1 antibodies and their corresponding anti-PD-L1-TGFβRII products (I and II) under reducing and non-reducing conditions showing the expected higher molecular weight of the heavy chain of anti-PD-L1-TGFβRII. Appendix A Figure 8C shows SEC-HPLC analysis of

purified anti-PD-L1-TGFβRII. In contrast to anti-PD-L1 antibody, the anti-PD-L1-TGFβRII antibody exhibited simultaneous binding to PD-L1 and TGF-β1 (Appendix A Figure 9).

26. The present invention demonstrates that a fusion protein comprising the ligand-binding sequence of the extracellular domain of TGFβRII linked to the C-terminus of IgG1 Fc binds TGF-β1 (IgG-TGFβRII) with efficiency that is equivalent to that of a fusion protein of the same ligand-binding sequence of the extracellular domain of TGFβRII linked to the N-terminus of IgG1 Fc (TGFβRII-Fc) (Appendix A Figure 9A). This enabled the design of a bifunctional fusion protein comprising the same ligand-binding sequence of the extracellular domain of TGFβRII linked to the C-terminus of the heavy chain of an anti-PD-L1 antibody (anti-PD-L1-TGFβRII). Furthermore, I show that anti-PD-L1-TGFβRII binds TGF-β1 with efficiency equivalent to that of TGFβRII-Fc (Appendix A Figure 9A). The comparative ability of anti-PD-L1-TGFβRII and anti-PD-L1 antibody to bind TGF-β was evaluated by ELISA, wherein recombinant human TGFβ (rhTGFβ1; 0-2000 pg/ml) was added to plates coated with anti-PD-L1-TGFβRII or anti-PD-L1 antibody (1 μg/ml), which was detected by biotinylated anti-TGFβ1 and HRP-Avidin (R&D systems). Plates coated with non-specific IgG-TGFβRII and rhTGFβRII-Fc served as positive controls to analyze the binding ability of the test samples to TGFβ. In contrast to the respective a-PD-L1 antibody that failed to bind TGFβ, each of the corresponding anti-PD-L1-TGFβRII products (I and II) exhibited binding to TGFβ with an efficiency that was similar to the positive controls (IgG-TGFβRII and TGFβRII-Fc coated plates) (Appendix A Figure 9A). The data show the optical density (OD) values (mean of three replicate wells for each assay condition) from a representative of two independent experiments.

27. Additionally, I show that anti-PD-L1-TGFβRII also binds PD-L1, with efficiency equivalent to anti-PD-L1 antibody (Appendix A Figure 9B). The comparative ability of anti-PD-L1-TGFβRII and anti-PD-L1 antibody to bind PD-L1 was evaluated by ELISA, wherein biotinylated recombinant human PD-L1 (rh B7-H1-biotin; 0-100 ng/ml) was added to plates coated with anti-PD-L1-TGFβRII or anti-PD-L1 antibody (1 μg/ml), followed by detection with HRP-Avidin. Plates coated with non-specific IgG-TGFβRII showed no binding to PD-L1 and served as a negative control to analyze the binding ability of the test samples. Each of the

corresponding anti-PD-L1-TGFβRII products (I and II) exhibited specific binding to rhPD-L1 with an efficiency that was similar to the respective a-PD-L1 antibody (Appendix A Figure 9B). The data show the optical density (OD) values (mean of three replicate wells for each assay condition) from a representative of two independent experiments.

28. In another experiment, I show that anti-PD-L1-TGFβRII simultaneously binds TGF-β1 and PD-L1 (Appendix A Figure 9C). I show each of these results for two different anti-PD-L1-TGFβRII molecules (I and II), and their corresponding anti-PD-L1 antibodies. The ability of anti-PD-L1-TGFβRII to simultaneously bind both PD-L1 and TGF-β was evaluated by a bispecific ELISA, wherein anti-PD-L1-TGFβRII or anti-PD-L1 antibody (0-100 ng/ml) was added to PD-L1-Fc coated plates (1 μg/ml), followed by rhTGFβ1 (100 ng/ml) that was detected by a biotinylated anti-human TGF-β1 antibody (R&D systems). In contrast to the respective a-PD-L1 antibody, each of the corresponding anti-PD-L1-TGFβRII products (I and II) exhibited simultaneous binding to PD-L1 and TGFβ (Appendix A Figure 9C). The data show the optical density (OD) values (mean of three replicate wells for each assay condition) from a representative of two independent experiments.

29. Most significantly, I have demonstrated that the antitumor efficacy of the a-PD-L1-TGFβRII molecule of my invention exceeds that of either the corresponding anti-PD-L1 antibody, or the combination of the corresponding anti-PD-L1 antibody and non-specific IgG-TGFβRII (the same TGFβRII sequence linked to a non-specific IgG heavy chain) (Appendix A, Figure 10). The comparative antitumor efficacy of a-PD-L1-TGFβRII, a-PD-L1 antibody, non-specific IgG-TGFβRII, and the combination of a-PD-L1 antibody and IgG-TGFβRII against human cancers expressing both PD-L1 and TGFβ was evaluated in NSG (NOD/Shi-scid IL-2rgnull) mice reconstituted with human CD34+ hematopoietic stem cells (HSC). MDA-MB-231 is a metastatic human Triple-Negative Breast Cancer (TNBC) cell line with mesenchymal-like morphology (Basal B-like). MDA-MB-231-Luc (D3H2LN) is a TNBC subline with enhanced primary tumor growth and lung metastases that was derived from a metastatic deposit of bioluminescent MDA-MB-231 cells stably expressing firefly luciferase. MDA-MB-231-Luc express high TGF-β (531 pg/10^6 cells/48h) and Programmed death-1 ligand 1 (PD-L1)

(Appendix A Figure 10A). NSG mice (6-8 week old) were irradiated at 200 cGy, followed by adoptive transfer of CD34+ human hematopoietic cells (10^5/mouse) from a normal donor (HLA-A2 matched to the TNBC line). Mice were tested for engraftment of human CD3+ T cells in peripheral blood obtained via tail-bleed at 10 weeks following injection of CD34+ cells. Mice demonstrating evidence of human CD3+ cell engraftment were injected with TNBC cells (1.5 $x10^6$ cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 10 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week with the following (either alone or in combination, as indicated): (i) anti-PD-L1-TGFβRII; (ii) anti-PD-L1 antibody; (iii) Control non-specific IgG-TGFβRII (anti-gp120-TGFβRII); (iv) a-PD-L1 mAb + IgG-TGFβRII; (vi) Vehicle alone (Control). Independent experiments were conducted to compare two different anti-PD-L1-TGFβRII antibody-ligand traps with their respective a-PD-L1 antibodies (I and II). Tumor size was evaluated weekly and tumor volume calculated [length × width x height]. In vivo tumor growth curves (mean + SEM) in both the experiments (I and II) demonstrated that treatment of tumor-bearing mice with a-PD-L1-TGFβRII was significantly more effective at inhibiting the progression of MDA-MB-231-luc tumors compared with the respective α-PD-L1 alone (I, $p<0.001$ and II, $p<0.001$), IgG-TGFβRII alone, and the combination of α-PD-L1 and non-specific IgG-TGFβRII (I, $p=0.004$ and II, $p<0.002$) (Appendix A Figures 10 B and C).

30. The TGFβRIIecd-Fc-PD1ecd molecule is, as another illustrative example, a bifunctional fusion molecule that targets and sequesters PD-L1 via an extracellular domain sequence of PD-1 (PD1ecd) and simultaneously inactivates TGF-β by an extracellular domain sequence of TGF-β Receptor II (TGF-βRIIecd) fused to the IgG Fc sequence via a flexible linker sequence, $(GGGGS)_3$ (see Appendix A Figure 11A). Appendix A Figure 11B is an SDS-PAGE of TGFβRIIecd-Fc-PD1ecd under reducing and non-reducing conditions showing the expected molecular weight of the monomer and dimer (indicated). ELISA demonstrated that TGFβRIIecd-Fc-PD1ecd exhibited binding to TGF-β1, PD-L1 and PD-L2 (Appendix A Figure 11 C and D).

31. Most significantly, I have demonstrated that the TGFβRIIecd-Fc-PD1ecd molecule of the present invention exhibits superior antitumor efficacy compared to the non-specific IgG-

PD1ecd (the same PD1ecd sequence linked to a non-specific control IgG), non-specific TGFβRIIecd-Fc (the same TGFβRIIecd sequence linked to IgG Fc), or the combined administration of IgG-PD1ecd and TGFβRIIecd-Fc (Appendix A Figure 12). The comparative antitumor efficacy of TGFβRIIecd-Fc-PD1ecd, non-specific IgG-PD1ecd, non-specific TGFβRIIecd-Fc, and the combination of non-specific IgG-PD1ecd and TGFβRIIecd-Fc against human cancers expressing both PD-L1 and TGFβ was evaluated in NSG (NOD/Shi-scid IL-2rgnull) mice reconstituted with human CD34+ hematopoietic stem cells (HSC). MDA-MB-231-Luc (D3H2LN) is human Triple-Negative Breast Cancer (TNBC) sub-line with enhanced primary tumor growth and lung metastases that was derived from a metastatic deposit of bioluminescent MDA-MB-231 cells stably expressing firefly luciferase. MDA-MB-231-Luc express high TGF-β (531 pg/10^6 cells/48h) and Programmed death-1 ligand 1 (PD-L1) (Appendix A Figure 10A).

32. NSG mice (6-8 week old) were irradiated at 200 cGy, followed by adoptive transfer of CD34+ human hematopoietic cells (10^5/mouse) from a normal donor (HLA-A2 matched to the TNBC line). Mice were tested for engraftment of human CD3+ T cells in peripheral blood obtained via tail-bleed at 10 weeks following injection of CD34+ cells. Mice demonstrating evidence of human CD3+ cell engraftment were injected with TNBC cells (1.5 x10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 10 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week of the following (either alone or in combination, as indicated): (i) TGFβRIIecd-Fc-PD1ecd; (ii) non-specific IgG-PD1ecd (anti-gp120-PD1ecd) ; (iii) non-specific TGFβRIIecd-Fc; (iv) IgG-PD1ecd + TGFβRIIecd-Fc; (vi) Vehicle alone (Control). The following parameters were used to evaluate and compare the antitumor efficacy of treatment groups: (1) Tumor size was evaluated and tumor volume calculated [length × width x height]; (2) Bioluminescent Imaging of primary and metastatic tumors: Tumor burden in mice bearing MDA-MB-231-Luc was assessed by visualization of in vivo luciferase activity using a Xenogen IVIS Spectrum system. To detect metastases, the lower portion of each animal was shielded before re-imaging to minimize bioluminescence from the

primary tumor. Lungs were harvested and imaged ex vivo to confirm in vivo observations. Photon flux was used to quantify the differences in tumor burden between treatment groups.

33. In vivo bioluminescent imaging (Appendix A Figures 12 A and B) and tumor growth curves (mean + SEM) (Appendix A Figure 12C) of primary tumors demonstrated that treatment of tumor-bearing mice with TGFβRIIecd-Fc-PD1ecd was significantly more effective at inhibiting the progression of MDA-MB-231-luc tumors compared with IgG-PD1ecd alone ($p<0.0001$) or the combination of IgG-PD1ecd and TGFβRIIecd-Fc ($p<0.003$) (Appendix A Figure 12A,B,C). In vivo bioluminescent imaging of lung metastases demonstrated that treatment of MDA-MB-231-luc-bearing mice with treatment TGFβRIIecd-Fc-PD1ecd was effective at inhibiting lung metastases of MDA-MB-231-luc tumors, whereas either IgG-PD1ecd alone or the combination of IgG-PD1ecd and TGFβRIIecd-Fc failed to inhibit lung metastases compared to untreated animals (Appendix A Figure 12D).

34. The data demonstrate that these exemplary bifunctional molecules of my invention (anti-PD-L1-TGFβRII and TGFβRIIecd-Fc-PD1ecd) have superior anti-tumor efficacy via their unique ability to localize the TGFβRIIecd to the immediate microenvironment of PD-L1 expressing tumor cells. Unlike anti-TGF-β antibodies or non-targeted TGFβRIIecd-Fc, anti-PD-L1-TGFβRII and TGFβRIIecd-Fc-PD1ecd are therefore able to efficiently interrupt autocrine and paracrine TGF-β signaling in the tumor immune microenvironment via their ability to efficiently compete with native cellular TGFβRII for TGF-β binding on the surface of PD-L1-expressing cells. The superior anti-tumor efficacy of anti-PD-L1-TGFβRII and TGFβRIIecd-Fc-PD1ecd is crucially dependent on the physical linkage of the PD-L1-targeting moiety with the ligand-binding sequence of TGFβRIIecd, and cannot be achieved by the simultaneous administration of a PD-L1-targeting antibody and a non-targeted TGFβRIIecd-Fc which is not preferentially localized to PD-L1-expressing tumor cells.

35. This data demonstrates that anti-PD-L1-TGFβRII and TGFβRIIecd-Fc-PD1ecd have unexpected and surprising properties and demonstrates that the presence of both a PD-L1 antagonist and the ligand-binding sequence of a TGF-β receptor on the same molecule is

significantly more effective at inhibiting tumor growth and metastases than the simultaneous administration of a PD-L1 antagonist and non-targeted TGF-β antagonist.

36. In summary, I have shown the unexpected and surprising result that fusion proteins of the invention comprising a targeting moiety binding a tumor cell surface molecule and TGFβ receptor ECD are significantly more effective at inhibiting tumor growth than combination therapy of said targeting moiety and TGFβ receptor ECD as separate agents. These data demonstrate that the fusion proteins of my invention have unexpected and surprising properties, and demonstrate that the presence of the targeting moiety binding a tumor cell surface molecule and ECD of TGFβ receptor on the same molecule is critical for anti-tumor efficacy with a clinically relevant therapeutic index.

37. The superior antitumor efficacy of the fusion proteins of the invention is crucially dependent on the physical linkage of the targeting moiety with the ligand-binding sequence of TGFβRIIecd, and cannot be achieved by the simultaneous administration of a targeting antibody and a non-targeted TGFβRIIecd which is not preferentially localized to tumor cells expressing the tumor cell surface molecule bound by the targeting moiety.

38. In my opinion, one of skill in the art would have no motivation to combine a targeting moiety binding a tumor cell surface molecule and the extracellular domain of TGFβ receptor in a fusion protein since, prior to my invention, there was no reason to believe that the fusion protein would be more effective than the simultaneous administration of a targeting moiety binding a tumor cell surface molecule and non-targeted TGF-β antagonist, as separate agents. Moreover, it would not be obvious to one of skill in the art that the TGF-β binding properties of the ECD of TGFβRII would be preserved when linked to the C-terminus of a targeting polypeptide. Further, one of skill in the art would not have predicted the surprising and unexpected properties of the presently claimed molecules based on the disclosures in McKenna and Sun.

39. I declare that all statements made herein are of my own knowledge and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

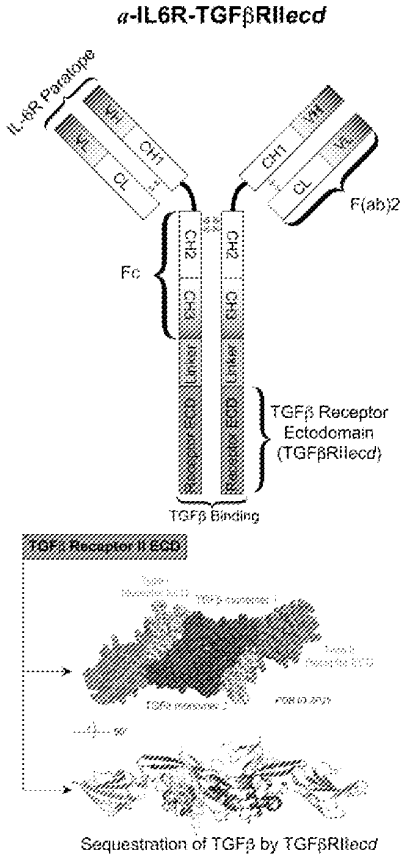
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Date Dr. Atul Bedi

Figure 1

APPENDIX A

a



b

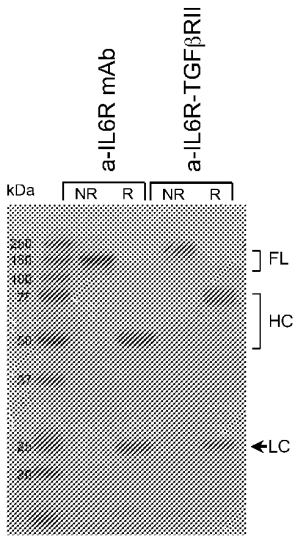
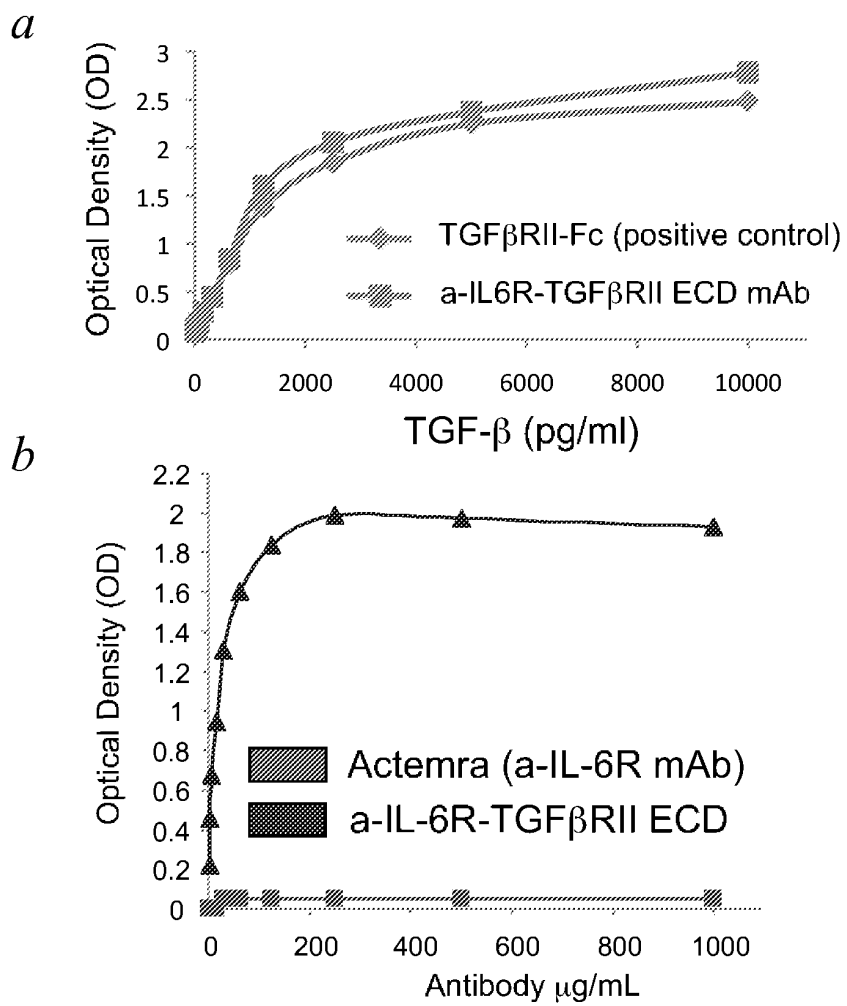


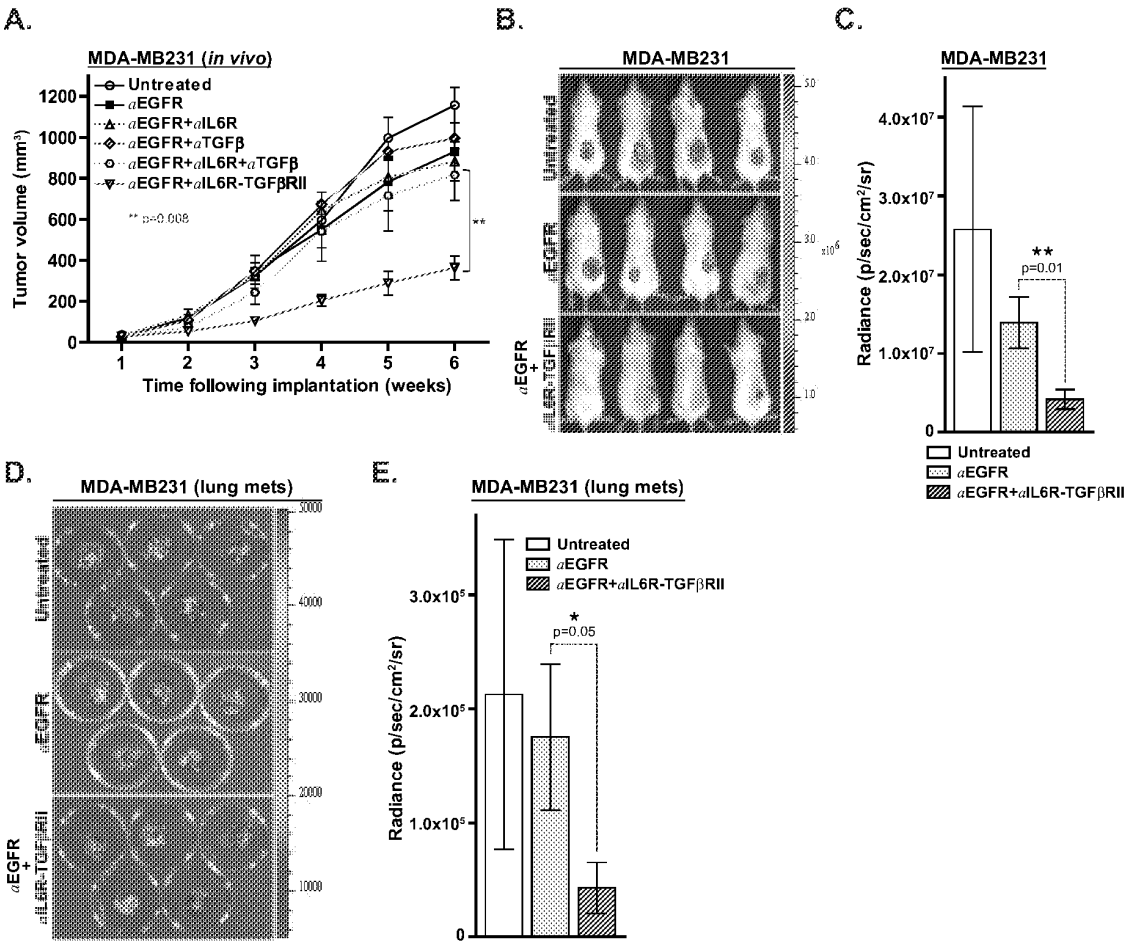
Figure 2



Bicara Ex. 1006, Page 353 of 498
Bicara v. JHU - PGR2026-00025

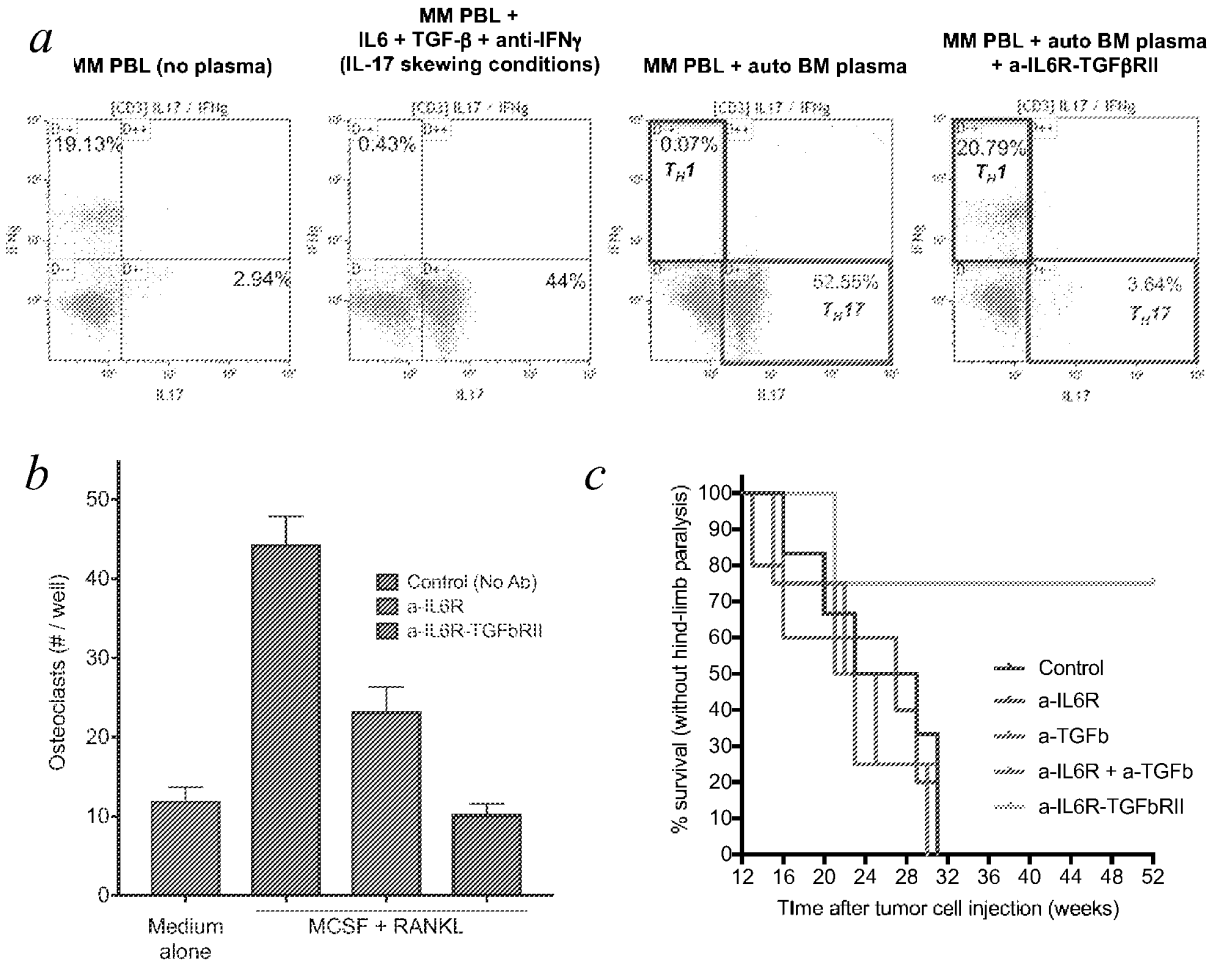
Figure 3

APPENDIX A



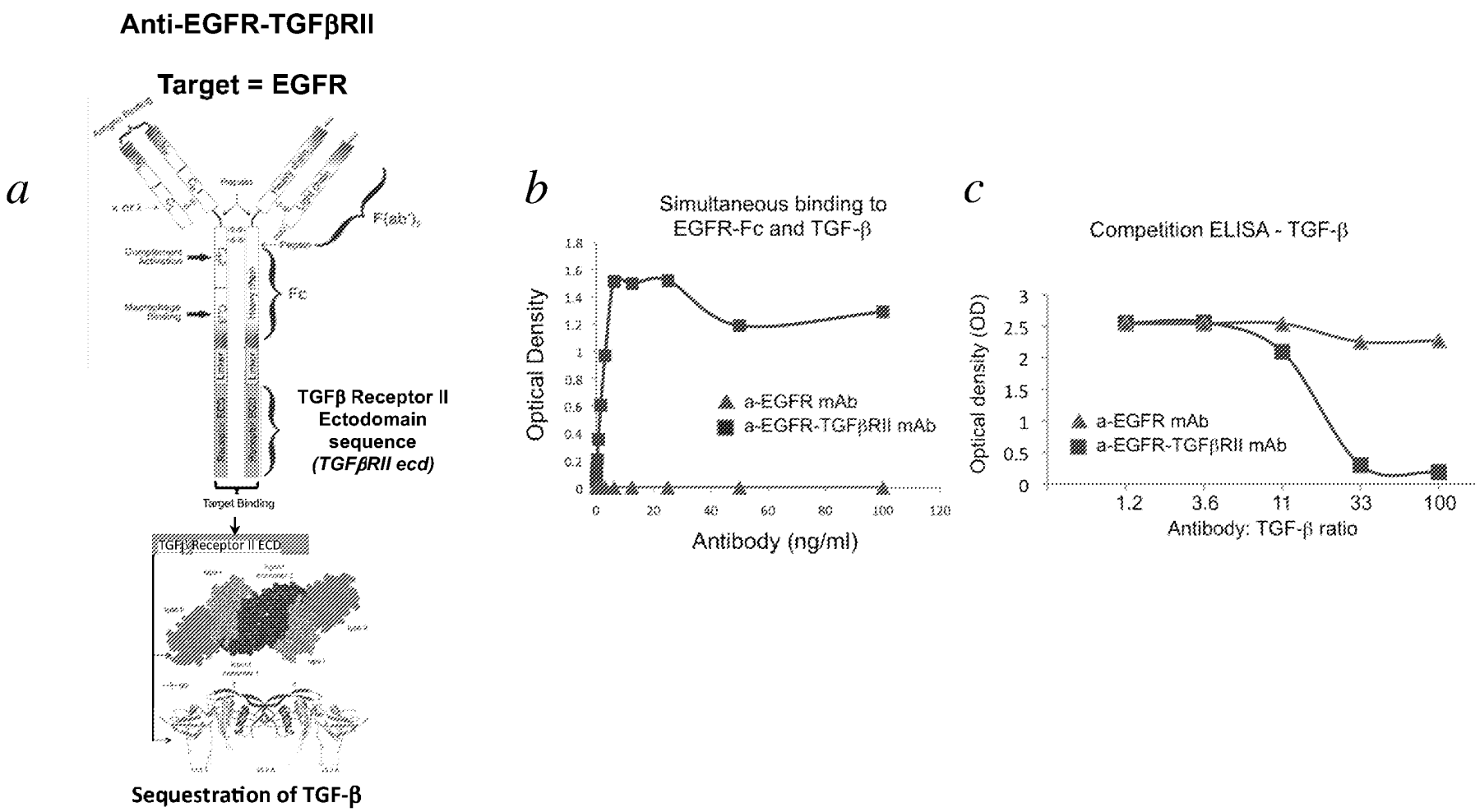
Bicara Ex. 1006, Page 354 of 498
Bicara v. JHU - PGR2026-00025

Figure 4



Bicara Ex. 1006, Page 355 of 498
Bicara v. JHU - PGR2026-00025

Figure 5



Bicara Ex. 1006, Page 356 of 498
Bicara v. JHU - PGR2026-00025

Figure 6

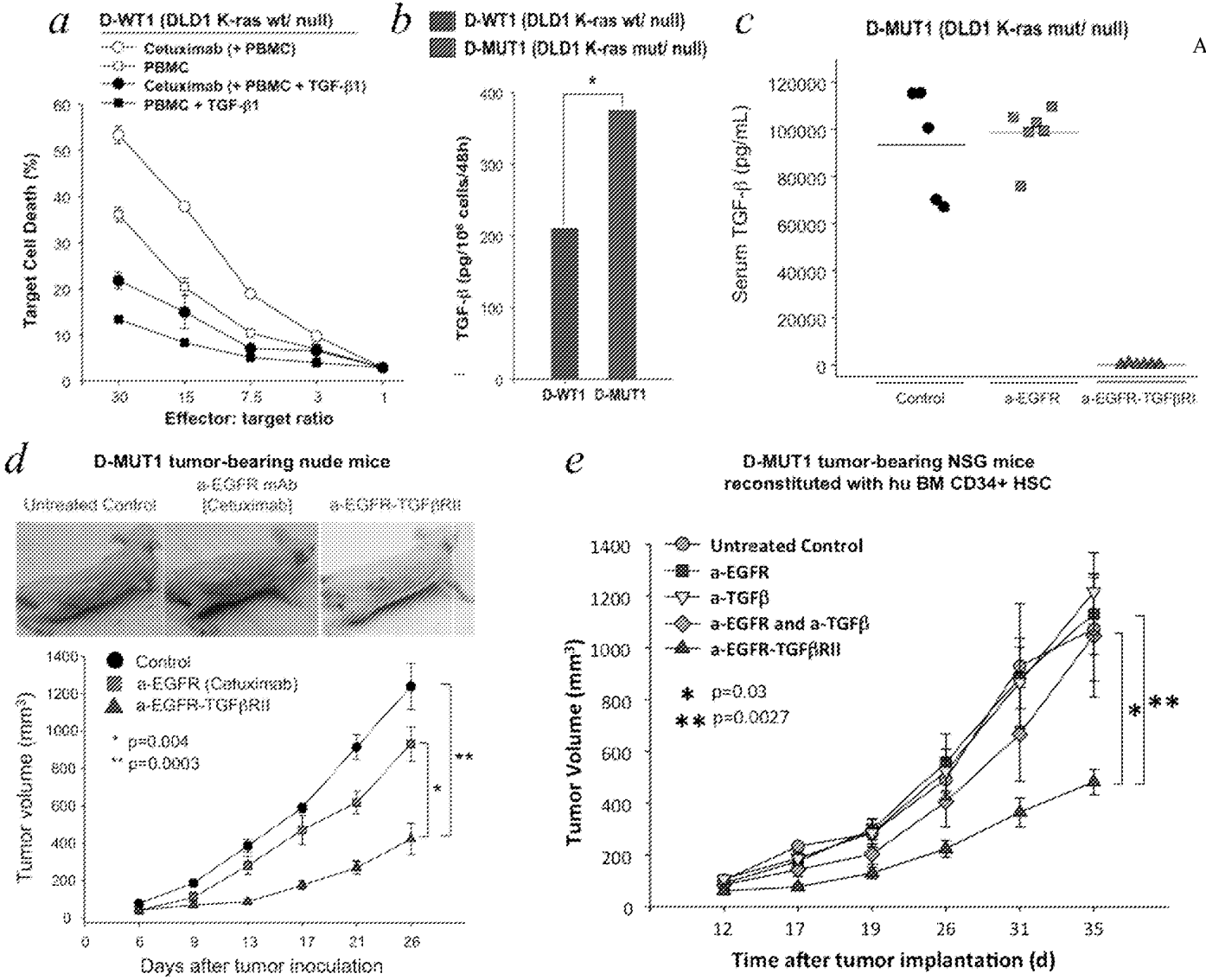
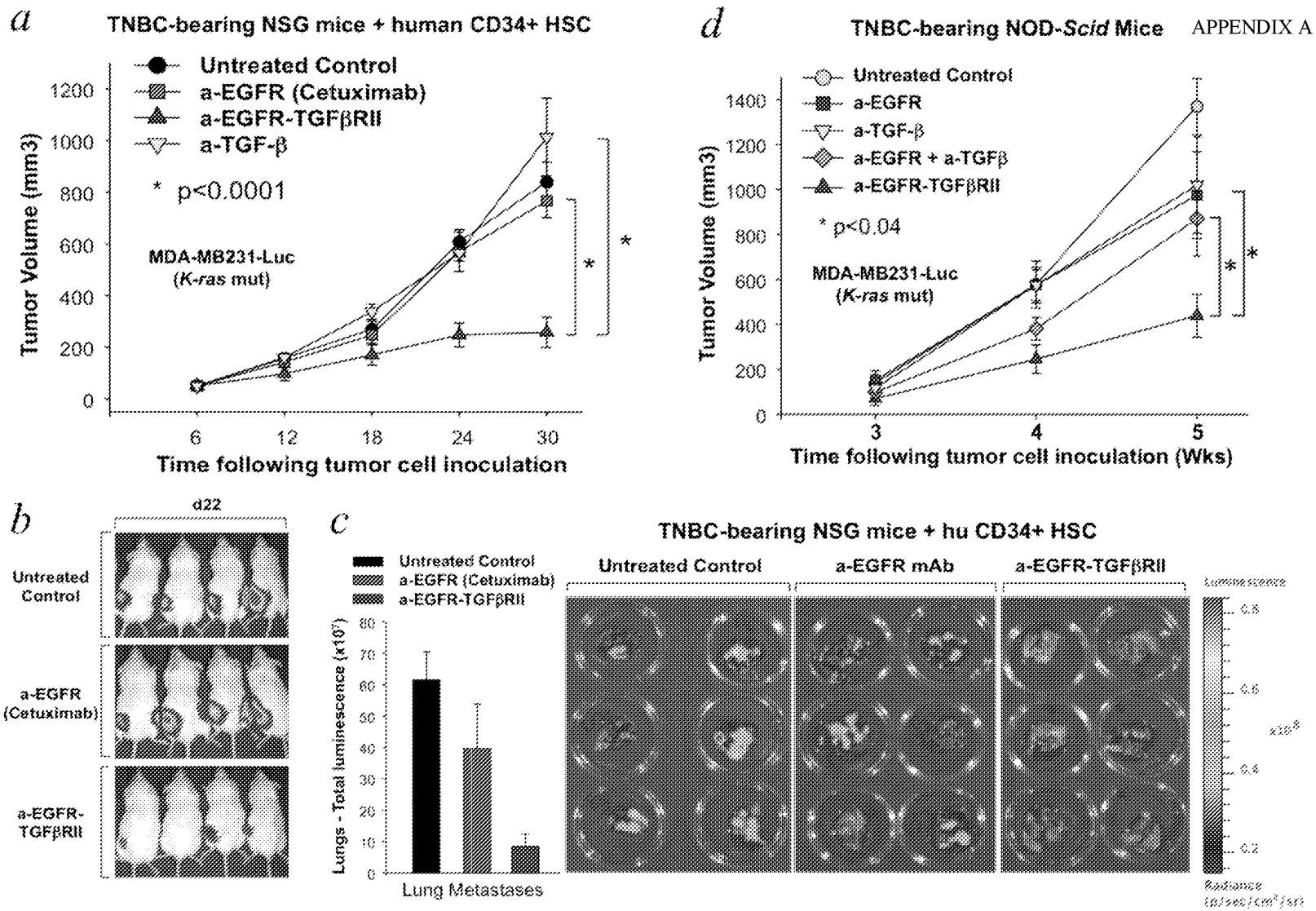
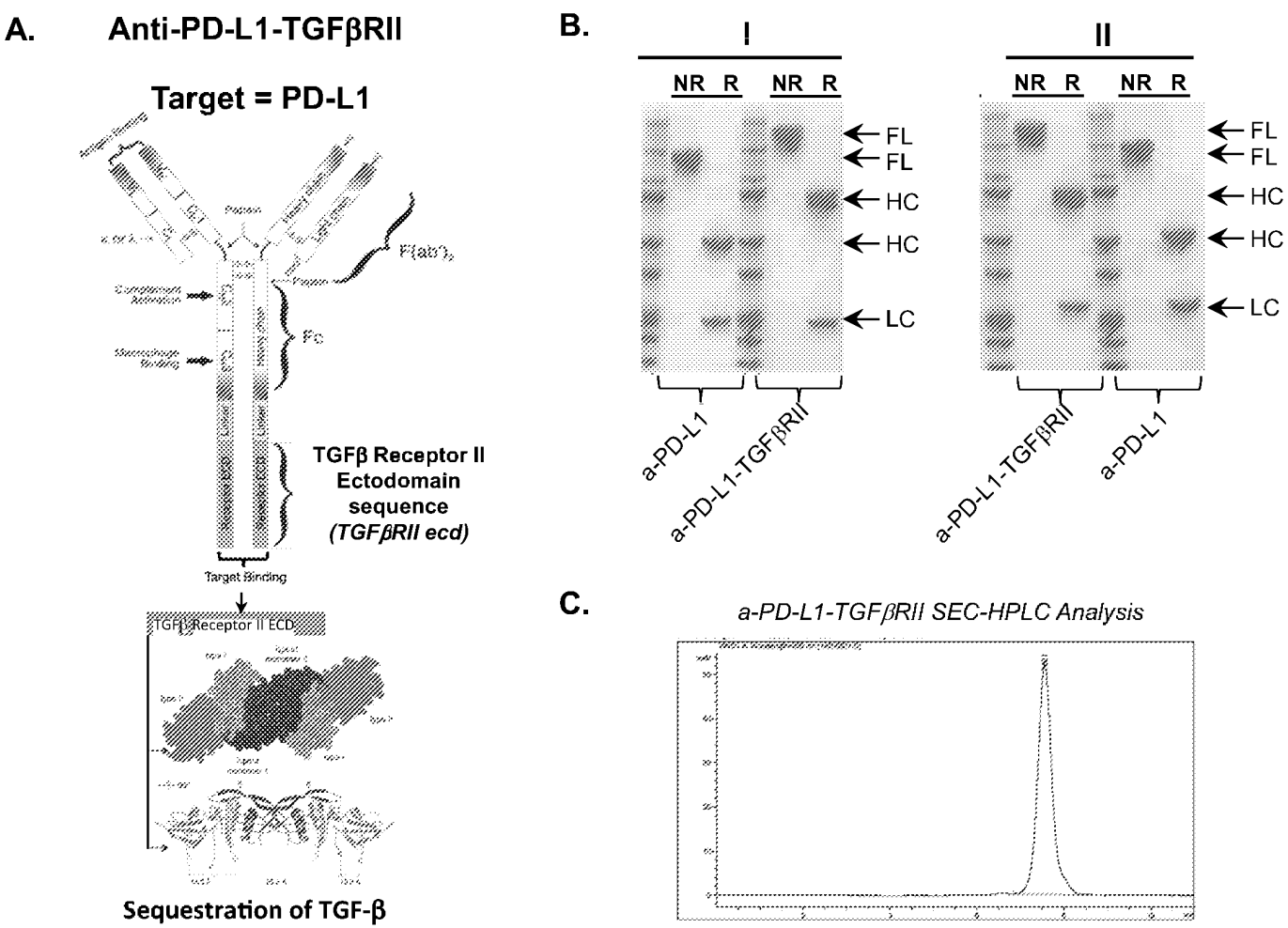

a
D-WT1 (DLD1 K-ras wt/ null)
Cetuximab (+ PBMC)
PBMC
Cetuximab (+ PBMC + TGF-β1)
PBMC + TGF-β1
Target Cell Death (%)
Effector: target ratio
b
D-WT1 (DLD1 K-ras wt/ null)
D-MUT1 (DLD1 K-ras mut/ null)
TGF-β (pg/10^6 cells/48h)
D-WT1
D-MUT1
c
D-MUT1 (DLD1 K-ras mut/ null)
Serum TGF-β (pg/mL)
Control
a-EGFR
a-EGFR-TGFβRII
d
D-MUT1 tumor-bearing nude mice
a-EGFR mAb
Untreated Control
(Cetuximab)
a-EGFR-TGFβRII
Control
a-EGFR (Cetuximab)
a-EGFR-TGFβRII
* p=0.004
** p=0.0003
Tumor volume (mm³)
Days after tumor inoculation
e
D-MUT1 tumor-bearing NSG mice
reconstituted with hu BM CD34+ HSC
Untreated Control
a-EGFR
a-TGFβ
a-EGFR and a-TGFβ
a-EGFR-TGFβRII
* p=0.03
** p=0.0027
Tumor Volume (mm³)
Time after tumor implantation (d)

Figure 7



Bicara Ex. 1006, Page 358 of 498
Bicara v. JHU - PGR2026-00025

FIGURE 8

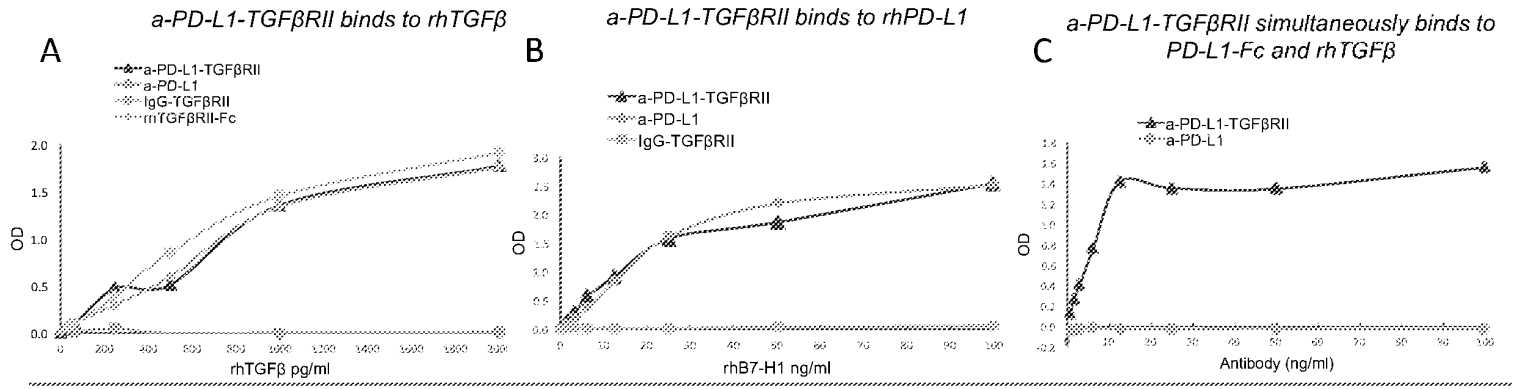


Bicara Ex. 1006, Page 359 of 498
Bicara v. JHU - PGR2026-00025

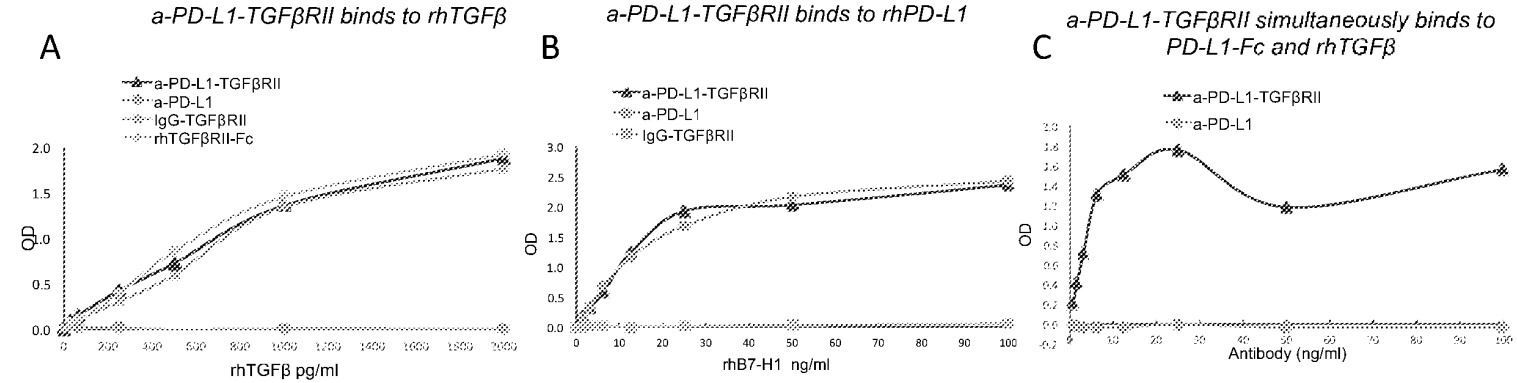
FIGURE 9

APPENDIX A

I. ***Anti-PDL1-TGFβRII***

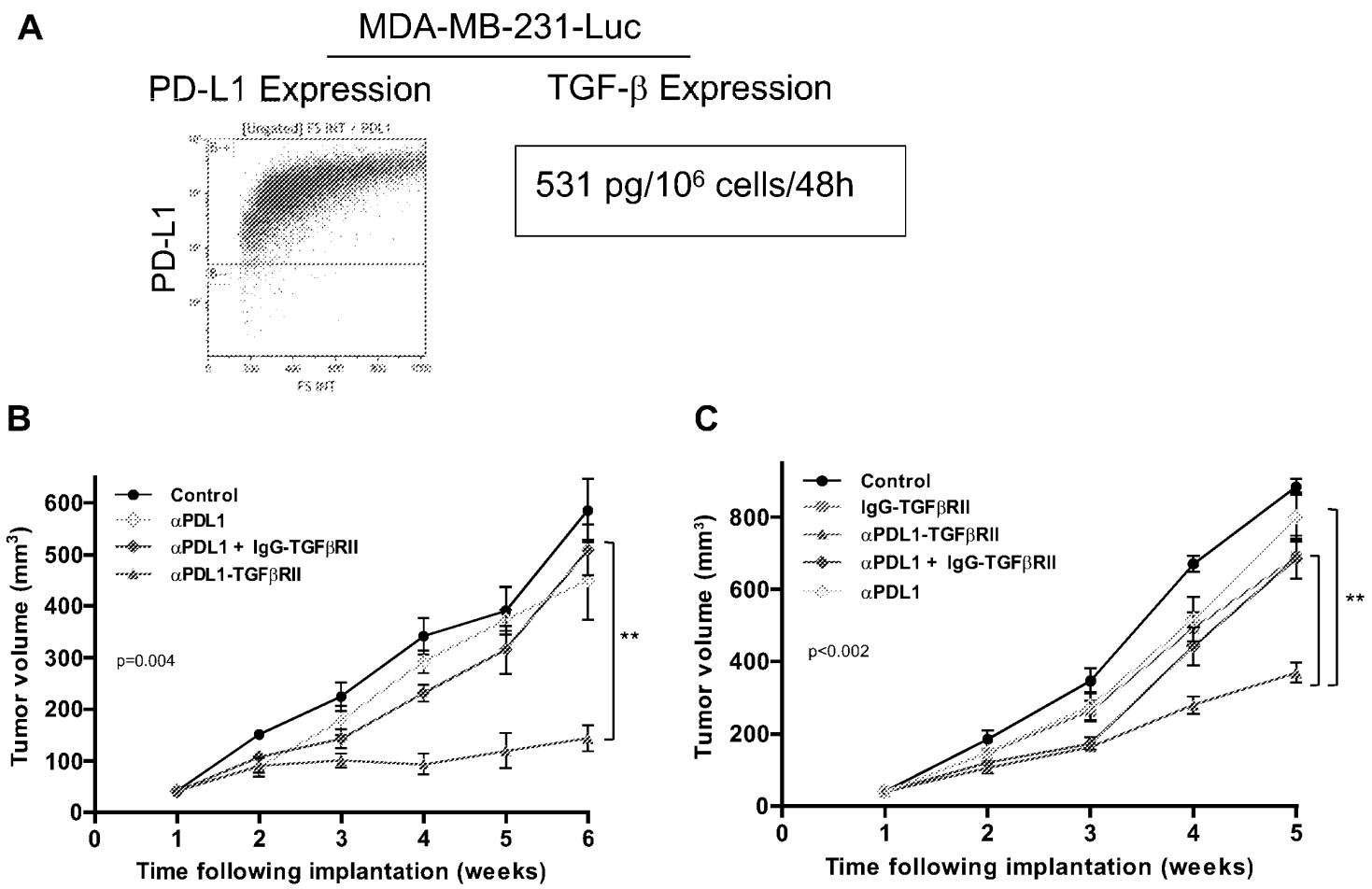


II. ***Anti-PDL1-TGFβRII***



Bicara Ex. 1006, Page 360 of 498
Bicara v. JHU - PGR2026-00025

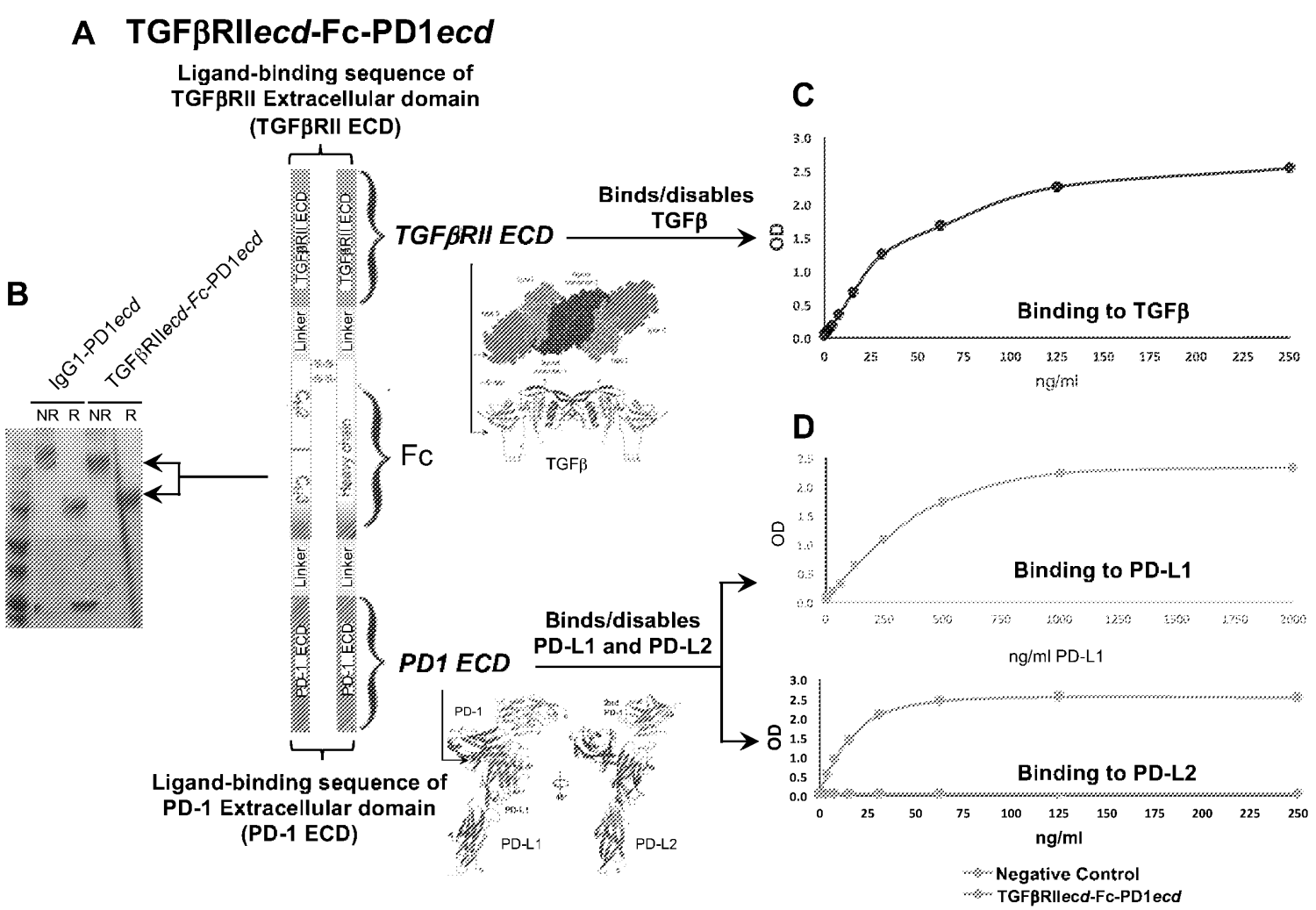
FIGURE 10 APPENDIX A



Bicara Ex. 1006, Page 361 of 498
Bicara v. JHU - PGR2026-00025

FIGURE 11

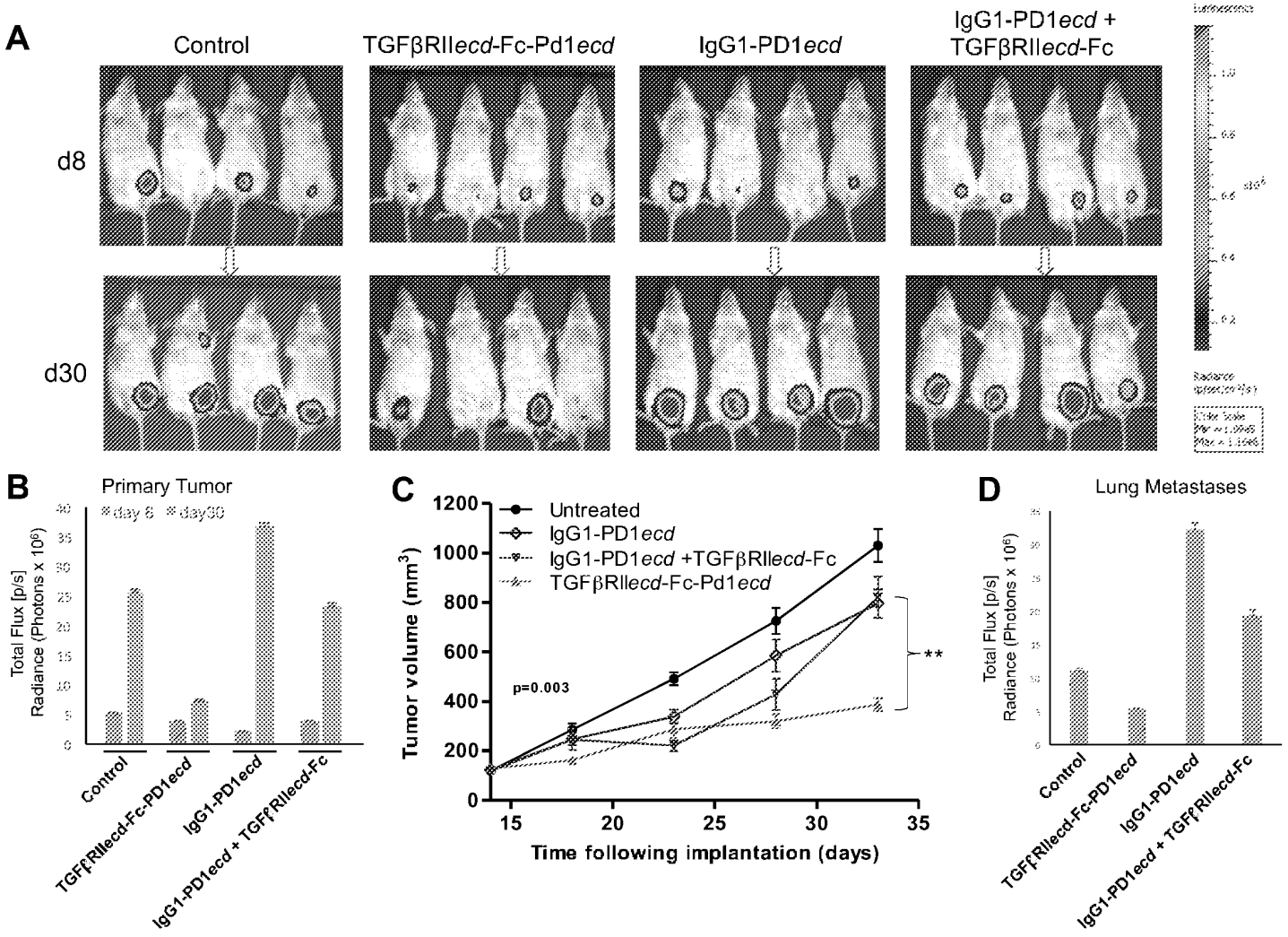
APPENDIX A



Bicara Ex. 1006, Page 362 of 498
Bicara v. JHU - PGR2026-00025

FIGURE 12

APPENDIX A



Bicara Ex. 1006, Page 363 of 498
Bicara v. JHU - PGR2026-00025

APPENDIX B

Atul Bedi

POSITION TITLE: Associate Professor – Oncology, Otolaryngology – Head and Neck Surgery;
Director, Developmental Immunotherapeutics Program (HNCR), Johns Hopkins Medicine
Member, Bloomberg-Kimmel Institute for Cancer Immunotherapy

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
All-India Institute of Medical Sciences, New Delhi, India	M.B.B.S. M.D.	12/1986	Medicine
University of Virginia School of Medicine, Charlottesville, VA	Internship	6/1987	Emergency Medicine
Wayne State University School of Medicine, Detroit, MI	Residency	6/1990	Internal Medicine
The Johns Hopkins University School of Medicine, Baltimore, MD	Clinical and Research Fellowship	6/1993	Medical Oncology
The Johns Hopkins University School of Medicine, Baltimore, MD	Clinical and Research Fellowship	6/1994	Transplantation Immunology - Bone Marrow Transplantation
The Johns Hopkins Carey Business School, Baltimore, MD	M.B.A.	6/2009	Management – Medical Services and Life Sciences

A. Personal Statement

As a physician-scientist in the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Dr. Bedi dovetails his research expertise in tumor immunobiology with his clinical experience as a medical oncologist. His translational cancer research program at JHU has provided fundamental insights into the molecular mechanisms by which tumor cells evade death signals entrained by anticancer agents and the immune system. His program has demonstrated an instrumental role of the immune system in the *in vivo* antitumor efficacy of cytotoxic chemotherapeutic agents and tumor-targeted antibodies, and has identified mechanisms by which these agents cooperate with immune effector cells to induce tumor cell death. His studies show that tumor-induced immune tolerance also limits the *in vivo* antitumor efficacy of tumor-targeted antibodies. To address this therapeutic challenge, Dr. Bedi invented and developed a novel platform of targeted multifunctional antibody-ligand traps ("Y-traps") that are being advanced for cancer immunotherapy. This platform has been leveraged to develop novel multifunctional antibody-ligand traps that are designed to counteract key molecular determinants of immune dysfunction in the tumor microenvironment. Dr. Bedi's work has been published in Science, Nature Medicine, Nature Cell Biology, Nature Communications, Genes & Development, Blood, and Cancer Research. He has served on advisory committees for the National Cancer Institute (National Institutes of Health), the U.S. Army Medical Research and Material Command, and the American Association for Cancer Research. He has been a member of the Experimental Therapeutics and Developmental Therapeutics Study Sections of the National Cancer Institute. Dr. Bedi also has an MBA in Life Sciences and medical services management.

B. Positions and Honors

Positions and Employment

1994-95	Instructor in Oncology, Johns Hopkins University School of Medicine, Baltimore, MD
1995-2001	Assistant Professor of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD
2002-	Associate Professor of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD
2008-	Associate Professor of Otolaryngology – Head & Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD
2011-	Director, Developmental Immunotherapeutics Program (HNCR), Johns Hopkins Medicine

2018- Member, Bloomberg-Kimmel Institute for Cancer Immunotherapy,
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Other Experience and Professional Memberships

2001-2003 Member (*Ad Hoc*), Study Section - Experimental Therapeutics-2 (ET-2),
National Cancer Institute (NCI) – National Institutes of Health (NIH)

2002-2003 Member, Specialized Program of Research Excellence (SPORE) Review Panel,
National Cancer Institute (NCI) – National Institutes of Health (NIH)

2003-2007 Member, Study Section - Developmental Therapeutics (DT),
Oncologic Sciences Integrated Review Group,
National Cancer Institute (NCI) – National Institutes of Health (NIH)

2015 Member (*Ad Hoc*), Study Section – Cancer Immunopathology and Immunotherapy (CII),
National Cancer Institute (NCI) – National Institutes of Health (NIH)

2016-17 Member (*Ad Hoc*), Special Emphasis Panel, [ZCA1 SRB-J M2 S, Omnibus SEP-5]
National Cancer Institute (NCI) – National Institutes of Health (NIH)

Member (*Ad Hoc*), Special Emphasis Panel,
P20 ("Renewal of Centers of Biomedical Research Excellence [COBRE]
National Institute of General Medical Sciences (NIGMS) - National Institutes of Health

Member (*Ad Hoc*), Special Emphasis Panel, NCI Program Project III (PO1) ZCA1 RPRB-F (01)
National Cancer Institute (NCI) – National Institutes of Health (NIH)

2018- Member (*Ad Hoc*), Special Emphasis Panel, ZCA1 SRB-C (A1)
Immuno-Oncology Translational Network, National Cancer Institute – NIH

1997-2003 Integration Panel Member; Breast Cancer Research Program, Department of Defense,
U.S. Army Medical Research and Material Command (USAMRMC).

2000 Member, Pancreatic Cancer Progress Review Group (PRG), NCI-NIH

2005 Member, Drug Resistance Section, Experimental and Molecular Therapeutics Subcommittee,
American Association for Cancer Research (AACR)

Honors

1985 Sorel Catherine Freyman Award, All-India Institute of Medical Sciences

1994 American Society of Hematology Scholar Award

1994 American Society of Clinical Oncology Young Investigator Award

1994 Catherine and Isaac Hecht Award for Cancer Research

1996 Wendy Will Case Cancer Research Award

1996 Passano Physician Scientist Award – The Passano Foundation

1996 Clinician-Scientist Award, Johns Hopkins University

1996 American Cancer Society Research Award

1998 Scholar Award from The Valvano Foundation of Cancer Research

1998 Scholar Award from the Arthur and Rochelle Belfer Foundation.

1999 USAMRMC-DOD Breast Cancer Research Program Award

2001 Mary Kay Ash Foundation Award for Cancer Research

2001 The Susan G. Komen Breast Cancer Foundation Award

2001 Virginia and D.K. Ludwig Cancer Research Award

2015 Maryland Innovation Institute Award, State of Maryland (TEDCO)

C. Contribution to Science/Selected Publications

1. Bifunctional Immune Checkpoint-targeted Antibody-Ligand Traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy. Ravi R, Noonan K, Pham V, Bedi R, Izumchenko E, Sidransky D, Borrello I, Bedi A. *Nature Communications 2018*; 9(1):741. PMCID:PMC5821872.

2. Engineering smart antibodies. Matsiko, A. *Nature Materials* **17**, 295 (2018) – (News and Views)

3. Compositions and methods for targeted immunomodulatory antibodies and fusion proteins. Johns Hopkins University. [PCT/US2011/027317; U.S. Patent No. 9,850,306; U.S. Patent 8,993,524; U.S. Patent 9,441,044; EPO Patent 2542590; Japan Patent No. 6066732B2]

   Multifunctional Antibody-Ligand Traps to Counteract Immune Tolerance. [PCT patent application serial number PCT/US2018/034755 (2018); Patent application 62872194 (2019)]

4. Izumchenko E, Chang X, Michailidi C, Kagohara L, Ravi R, Paz K, Brait M, Hoque MO, Ling S, Bedi A, **Sidransky D.** The **TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces** resistance to EGFR inhibitors. *Cancer Res*. 2014 Jul 15; 74(14):3995-4005.PMCID: PMC4122100.

   5. Bedi A, Chang X, Noonan K, Pham V, Bedi R, Fertig EJ, Considine M, Califano JA, Borrello I, Chung CH, **Sidransky D, Ravi R. Inhibition of TGF-β enhances the in vivo antitumor efficacy of EGF receptor-targeted** therapy. *Mol Cancer Ther*. 2012 Nov; 11(11):2429-39. PMCID: PMC3640459

6. Bedi A, Zehnbauer BA, Barber JP, Sharkis SJ, Jones RJ. Inhibition of apoptosis by BCR-ABL in chronic myeloid leukemia. *Blood*. 1994 Apr 15; 83(8):2038-44.

7. Bedi A, Pasricha PJ, Akhtar AJ, Barber JP, Bedi GC, Giardiello FM, Zehnbauer BA, Hamilton SR, Jones RJ. Inhibition of apoptosis during development of colorectal cancer. *Cancer Res*. 1995; 55(9): 1811-6.

8. Makarev E, Schubert AD, Kanherkar RR, London N, Teka M, Ozerov I, Lezhnina K, Bedi A, Ravi R, Mehra R, *et al.* In silico analysis of pathways activation landscape in oral squamous cell carcinoma and oral leukoplakia. *Cell Death Discov*. 2017 May 22;3:17022. PMCID: PMC5439156.

9. Fuchs EJ, Bedi A, Jones RJ, Hess AD. Cytotoxic T cells overcome BCR-ABL-mediated resistance to apoptosis. *Cancer Res*. 1995 Feb 1; 55(3):463-6.

10. Cheng EH, Kirsch DG, Clem RJ, Ravi R, Kastan MB, Bedi A, Ueno K, Hardwick JM. Conversion of Bcl-2 to a Bax-like death effector by caspases. *Science*. 1997 Dec 12; 278(5345):1966-8.

11. Fuchs EJ, McKenna KA, Bedi A. p53-dependent DNA damage-induced apoptosis requires Fas/APO-1-independent activation of CPP32beta. *Cancer Res*. 1997 1; 57(13):2550-4.

12. Ravi R, Jain AJ, Schulick RD, Pham V, Prouser TS, Allen H, Mayer EG, Yu H, Pardoll DM, Ashkenazi A, Bedi A. Elimination of hepatic metastases of colon cancer cells via p53-independent cross-talk between irinotecan and Apo2 ligand/TRAIL. *Cancer Res*. 2004 Dec 15; 64(24):9105-14.

13. Ravi R, Fuchs EJ, Jain A, Pham V, Yoshimura K, Prouser T, Jalla S, Zhou X, Garrett-Mayer E, Kaufmann SH, Schulick RD, Pardoll DM, Bedi A. Resistance of cancers to immunologic cytotoxicity and adoptive immunotherapy via X-linked inhibitor of apoptosis protein expression and coexisting defects in mitochondrial death signaling. *Cancer Res*. 2006 Feb 1; 66(3):1730-9.

14. Ravi R, Bedi A. Requirement of BAX for TRAIL/Apo2L-induced apoptosis of colorectal cancers: synergism with sulindac-mediated inhibition of Bcl-x (L). *Cancer Res*. 2002 Mar 15; 62(6):1583-7.

15. Ravi R, Bedi GC, Engstrom LW, Zeng Q, Mookerjee B, Gélinas C, Fuchs EJ, Bedi A. Regulation of death receptor expression and TRAIL/Apo2L-induced apoptosis by NF-kappaB. *Nature Cell Biol*. 2001 Apr; 3(4):409-16.

16. Ravi R, Mookerjee B, van Hensbergen Y, Bedi GC, Giordano A, El-Deiry WS, Fuchs EJ, Bedi A. p53-mediated repression of nuclear factor-kappaB RelA via the transcriptional integrator p300. *Cancer Res*. 1998 Oct 15; 58(20):4531-6.

17. Izumchenko E, Chang X, Brait M, Fertig E, Kagohara LT, Bedi A, Marchionni L, Agrawal N, Ravi R, Jones S, Hoque MO, Westra WH, Sidransky D. Targeted sequencing reveals clonal genetic changes in the progression of early lung neoplasms and paired circulating DNA. *Nature Commun*. 2015 Sep 16; 6:8258. PMCID: PMC4595648.

18. Ravi R, Mookerjee B, Bhujwalla ZM, Sutter CH, Artemov D, Zeng Q, Dillehay LE, Madan A, Semenza GL, Bedi A. Regulation of tumor angiogenesis by p53-induced degradation of hypoxia-inducible factor 1alpha. *Genes Dev*. 2000 Jan 1; 14(1):34-44. PMCID: PMC316350.

19. Yao SL, Akhtar AJ, McKenna KA, Bedi GC, Sidransky D, Mabry M, Ravi R, Collector MI, Jones RJ, Sharkis SJ, Fuchs EJ, Bedi A. Selective radiosensitization of p53-deficient cells by caffeine-mediated activation of p34cdc2 kinase. *Nature Med*. 1996 Oct; 2(10):1140-3.

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Lisa Haile/Karen LePari
Attorney Docket Number:	JHU3260-8

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
		Total in USD ($)		**1480**

Electronic Acknowledgement Receipt

EFS ID:	42946819
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Lisa Haile/Karen LePari
Filer Authorized By:	Lisa Haile
Attorney Docket Number:	JHU3260-8
Receipt Date:	09-JUN-2021
Filing Date:	14-OCT-2019
Time Stamp:	21:16:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1480
RAM confirmation Number	E202169L17232944
Deposit Account	071896
Authorized User	Karen LePari
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		JHU3260-8_RspToNFOA_09JUN2021.pdf	230060 241d77d1830606da5f6e830d55fef469de877277	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	12	
Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	JHU3260-8_132_DECLARATION_09JUN2021.pdf	4127705 46873dc85ba1a235161762761d75d5e229cdd67d	no	32
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31144 3fb344e4db40491a7f18a8b65e78d9d0c9377e0d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4388909		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	16601347
Filing Date	14-Oct-2019
First Named Inventor	Atul Bedi
Attorney Docket Number	JHU3260-8
Title of Invention	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
The Johns Hopkins University	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

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8993524

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request. ○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 38347 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request	
Signature	/Lisa A. Haile/
Name	Lisa A. Haile

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Lisa Haile/Karen LePari
Attorney Docket Number:	JHU3260-8

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**170**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16601347

Filing Date: 14-Oct-2019

Applicant/Patent under Reexamination: Bedi

Electronic Terminal Disclaimer filed on June 9, 2021

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	42945717
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Lisa Haile/Karen LePari
Filer Authorized By:	Lisa Haile
Attorney Docket Number:	JHU3260-8
Receipt Date:	09-JUN-2021
Filing Date:	14-OCT-2019
Time Stamp:	21:19:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$170
RAM confirmation Number	E202169L19072954
Deposit Account	071896
Authorized User	Karen LePari
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33797 64fe166a916a6a86c4ab77fd3b98a290b2ce8e26	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30197 97670747162e2e119b55fa18ee43e4fb68569ead	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	63994		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/26 (04-14)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) JHU3260-8

In re Application of: THE JOHNS HOPKINS UNIVERSITY

Application No.: 16/601,347

Filed: October 14, 2019

For: COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

The applicant, THE JOHNS HOPKINS UNIVERSITY, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 10,442,860 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 38,347

/Lisa A. Haile/ — Signature
September 30, 2021 — Date

Lisa A. Haile — Typed or printed name

Attorney for Applicant — Title
858.677.1456 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Lisa Haile/Karen LePari
Attorney Docket Number:	JHU3260-8

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
		Total in USD ($)		**170**

Electronic Acknowledgement Receipt

EFS ID:	43917628
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Lisa Haile/Karen LePari
Filer Authorized By:	Lisa Haile
Attorney Docket Number:	JHU3260-8
Receipt Date:	30-SEP-2021
Filing Date:	14-OCT-2019
Time Stamp:	18:10:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$170
RAM confirmation Number	E20219TI10452993
Deposit Account	071896
Authorized User	Karen LePari
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	JHU3260-8_TERMINAL_DISCLAIMER_PRIOR_PATENT_30SEP2021.PDF	163721 d4cff4062f47d5e750c48f28016fc9598febcae9	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	37722 9137ab22357dfc3839a89d4c7b99cce917e16aba	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	201443		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/601,347 *	16/601,347	Bedi et al.	
	Examiner	Art Unit	
	HAMUD, FOZIA M	1647	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 30 September 2021	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

/PAMELA A YOUNG/

Technology Center: OPLC

Telephone: (571)272-3622

_____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

100899 7590 11/02/2021

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/02/2021

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	02/02/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

100899 7590 11/02/2021

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	02/02/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
HAMUD, FOZIA M	1647	530-387100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Bicara Ex. 1006, Page 387 of 498
Bicara v. JHU - PGR2026-00025

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

100899 7590 11/02/2021

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER	
HAMUD, FOZIA M	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/02/2021

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/601,347	Applicant(s) Bedi, Atul	
	Examiner FOZIA M HAMUD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the response filed on 09 June 2021.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 21-28 and 41-42 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 20210913.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/BRIDGET E BUNNER/
Primary Examiner, Art Unit 1647

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1a. The present application is being examined under the pre-AIA first to invent provisions.

1b. The amendment filed on 09 June 2021 has been entered.

1c. Receipt of the declaration under 37 C.F.R. §1.132 is acknowledged.

Claim Status:

1c. Claims 21-28 and 41-42 are pending and under consideration.

Response to Applicants' amendment and arguments:

2. The following objection and rejections are withdrawn in light of Applicants' amendment and arguments:

2a. This application now complies with the requirements of 37 CFR 1.821 through 1.825. Specifically, the sequence recited in claim 26 is now accompanied by the required reference to the relevant sequence identifier.

2b. The amendment has overcome the objections to claims 21 and 42. Claim 21 now recites "extracellular domain of". The acronyms recited in claim 42 recites have been spelled out.

2c. The rejections of claims 21-27 and 41-42 made on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of US. Patent 9,850,306; 9,441,044; 8,993,524 are withdrawn. Applicants have timely filed the required terminal disclaimers.

2d. The rejection of claims 21-28 and 42 made 35 U.S.C. 103(a) as being unpatentable over Mckenna et al. (US 7,820,165) and Sun et al. (US 7,795,389), is withdrawn in view of Applicant's arguments and the declaration under 37 CFR 1.132 by Dr. Atul Bedi filed 09 June 2021. Applicant's argument that the combination of the targeting/binding moiety (such as an antibody) and TGFbetaRII molecule is unexpected as compared to the antibody and IGFβII alone, is found persuasive (in particular, see the Declaration, paragraphs 12, 14, 15, 17, 19-22, 24, and 34-36; Figures 3A, 4C, 6D, 6E, 7A-7D, 10B, 10C, 12C, 12D). Specifically, the activity of the combination of the targeting moiety and the TGFbetaRII molecule is a greater than additive effect.

2e. The rejection of claims 21-28 and 41-42 made 35 U.S.C. 103(a) as being unpatentable over Mckenna et al. (US 7,820,165), Sun et al. (US 7,795,389), and Scaria et al. (US 2011/0052585) is withdrawn for reasons set forth above in (2d).

Conclusion:

3. Claims 21-28 and 41-42 are allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday 8AM-4:30Pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on 571-272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/FOZIA M HAMUD/
Examiner, Art Unit 1647
13 September 2021

/BRIDGET E BUNNER/
Primary Examiner, Art Unit 1647

Examiner-Initiated Interview Summary	**Application No.** 16/601,347	**Applicant(s)** Bedi, Atul		
	Examiner FOZIA M HAMUD	**Art Unit** 1647	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FOZIA M HAMUD	Examiner	Telephonic
Lisa A. Haile	Attorney of Record	

Date of Interview: 28 September 2021

Issues Discussed:

Non-statutory Double Patenting

Upon review of an updated search, the Examiner determined that the instant claims would have a nonstatutory double patenting issue over claims 1-10 of U.S. Patent 10,442,860. Specifically, the claims of the instant application and the claims of the '860 patent are both directed to an isolated molecule comprising a targeting moiety fused with an immunomodulatory moiety, wherein; (a) the targeting moiety comprises a polypeptide that specifically binds a component of a tumor cell that is a tumor cell surface molecule; and (b) the immunomodulatory moiety comprises an amino acid sequence of the extracellular domain Transforming growth factor-beta receptor (TGFbR). The claims of the '860 patent recite that the targeting moiety is a polypeptide that specifically binds interleukin-6 Receptor (IL6R) and thus, are species claims that anticipate the genus claims of the instant application. In light of this finding, the Examiner requested Applicant's representative, Lisa A. Haile submit a terminal disclaimer to put the instant case in condition for allowance. Lisa A. Haile indicated that solely to expedite allowance and without acquiescing to the rejection, Applicant will submit a terminal disclaimer.

/FOZIA M HAMUD/ Examiner, Art Unit 1647	10/08/2021

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi, Atul
	Examiner	**Art Unit**
	FOZIA M HAMUD	1647

CPC						
Symbol					**Type**	**Version**
C07K	/	16	/	2827	F	2013-01-01
C07K	/	14	/	70532	I	2013-01-01
C07K	/	14	/	70575	I	2013-01-01
C07K	/	14	/	70578	I	2013-01-01
C07K	/	14	/	70596	I	2013-01-01
C07K	/	14	/	71	I	2013-01-01
C07K	/	16	/	28	I	2013-01-01
C07K	/	16	/	2812	I	2013-01-01
C07K	/	16	/	2815	I	2013-01-01
C07K	/	16	/	2851	I	2013-01-01
C07K	/	19	/	00	I	2013-01-01
C07K	/	14	/	495	I	2013-01-01
A61K	/	39	/	3955	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
C07K	/	16	/	2863	I	2013-01-01
C07K	/	16	/	30	I	2013-01-01
A61K	/	47	/	6803	I	2017-08-01
A61K	/	31	/	704	I	2013-01-01
A61K	/	38	/	179	I	2013-01-01
A61K	/	39	/	39558	I	2013-01-01
C07K	/	16	/	2866	I	2013-01-01
C07K	/	2319	/	00	A	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2317	/	73	A	2013-01-01
C07K	/	2317	/	76	A	2013-01-01
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C07K	/	2317	/	33	A	2013-01-01
C07K	/	2317	/	526	A	2013-01-01
C07K	/	2319	/	70	A	2013-01-01
A61K	/	2039	/	572	A	2013-01-01

/FOZIA M HAMUD/ Examiner, Art Unit 1647	06 October 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/BRIDGET E BUNNER/ Primary Examiner, Art Unit 1647	08 October 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20210913

Bicara Ex. 1006, Page 395 of 498
Bicara v. JHU - PGR2026-00025

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi, Atul
	Examiner	**Art Unit**
	FOZIA M HAMUD	1647

CPC Combination Sets					
Symbol		**Type**	**Set**	**Ranking**	**Version**
	/ /				

/FOZIA M HAMUD/ Examiner, Art Unit 1647	06 October 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/BRIDGET E BUNNER/ Primary Examiner, Art Unit 1647	08 October 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20210913

Bicara Ex. 1006, Page 396 of 498
Bicara v. JHU - PGR2026-00025

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi, Atul
	Examiner	**Art Unit**
	FOZIA M HAMUD	1647

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07K	/	16	/	28
C07K	/	14	/	71
C07K	/	19	/	00

NON-CLAIMED				
A61K	/	39	/	395

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/FOZIA M HAMUD/ Examiner, Art Unit 1647 (Assistant Examiner)	06 October 2021 (Date)	**Total Claims Allowed:** 10	
/BRIDGET E BUNNER/ Primary Examiner, Art Unit 1647 (Primary Examiner)	08 October 2021 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office — Part of Paper No.: 20210913

Bicara Ex. 1006, Page 397 of 498
Bicara v. JHU - PGR2026-00025

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi, Atul
	Examiner	**Art Unit**
	FOZIA M HAMUD	1647

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	21	10	42												
2	22														
3	23														
4	24														
5	25														
6	26														
8	27														
9	28														
7	41														

/FOZIA M HAMUD/ Examiner, Art Unit 1647	06 October 2021	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	10	
/BRIDGET E BUNNER/ Primary Examiner, Art Unit 1647	08 October 2021	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20210913

Bicara Ex. 1006, Page 398 of 498
Bicara v. JHU - PGR2026-00025

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi et al.
	Examiner	Art Unit
	FOZIA M HAMUD	1647

CPC - Searched*		
Symbol	**Date**	**Examiner**
(C07K14/71|C07K16/2863|A61P35/00|A61K45/06|A61K38/179| C07K14/495|C07K16/30|C07K7/08|C12N2500/22|A61K31/704| A61K47/6803|A61P37/00|C07K2317/70).CPC.); See WEST Search History Printout	12/01/2020	FH
(A61P35/00|C07K14/71|C07K16/2863|C07K2319/00|A61K2039/505| A61K45/06|C07K16/2866|A61K38/179|C07K14/70575|C07K2317/33| C07K14/70503|C07K2319/30).CPC.); See WEST Search History Printout	09/14/2021	FH

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Bicara Ex. 1006, Page 399 of 498
Bicara v. JHU - PGR2026-00025

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/601,347	Bedi et al.
	Examiner	Art Unit
	FOZIA M HAMUD	1647

Search Notes		
Search Notes	**Date**	**Examiner**
STIC: SEQ ID NO: 87 has been searched against commercial and interference data bases. See Score for Results.	10/10/2020	FH
WEST, (US Patent Full, Derwent, JPO, EPO, PG-Pub), see Search Print out. STN, via (Medline, Caplus, Biosis, Embase). Inventor name searched on Palm, West and STN, See Search Print out.	12/01/2020	FH
WEST, (US Patent Full, Derwent, JPO, EPO, PG-Pub), see Search Print out. STN, via (Medline, Caplus, Biosis, Embase). Inventor name searched on Dav, Palm, West and STN, See Search Print out.	09/14/2021	FH
STIC: SEQ ID NO: 87and 123 have been searched against commercial and interference data bases. See Score for Results.	10/06/2021	FH

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
See	Seach Notes	10/05/2021	FH

Bicara Ex. 1006, Page 400 of 498
Bicara v. JHU - PGR2026-00025

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file hcaplus

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.18       0.18

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FILE LAST UPDATED: 30 Nov 2020 (20201130/ED)

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E1            1     BEDI ASHISH AKSHAY/AU
E2            1     BEDI ASHWANI/AU
E3           39 --> BEDI ATUL/AU
E4            2     BEDI B/AU
E5            1     BEDI B R/AU
E6            8     BEDI B S/AU
E7            1     BEDI BALWINDER S/AU
E8            4     BEDI BANSHI LAL/AU
E9            3     BEDI BHARAT VEER/AU
E10           1     BEDI BHUPINDER S/AU
E11          18     BEDI BRAHMCHETNA/AU
E12           4     BEDI BRENDA/AU

=> s e3

L1           39 "BEDI ATUL"/AU

=> e ravi rajani/au

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E3           37 --> RAVI RAJANI/AU
E4            7     RAVI RAJANI K/AU
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E10           1     RAVI RAJPUT/AU
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E12           7     RAVI RAM K/AU

=> s e3-e4

             37 "RAVI RAJANI"/AU
              7 "RAVI RAJANI K"/AU
L2           44 ("RAVI RAJANI"/AU OR "RAVI RAJANI K"/AU)
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=> s l1-l2

L3          55 (L1 OR L2)

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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      14.04      14.22

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=> s (targeting moiety fused with immunomodulatory moiety)

L4           0 (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)

=> s (polypeptide and binds and tumor cell)

L5         439 (POLYPEPTIDE AND BINDS AND TUMOR CELL)

=> s (targeting moiety fused or  immunomodulatory moiety)

L6          35 (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)

=> s l5 and l6

L7           0 L5 AND L6

=> s (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)

L8      374372 (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TGF-B
               ETA OR TGFBR)

=> s l8 and (TGFbRII or type 2 or type II or extracellular domain)

L9       35612 L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN)

=> s l9 and (fusion or chimeric or heterodimer)

L10       1487 L9 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> s l10 and  (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry media
tor or HVEM)

L11        162 L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES VIRU
               S ENTRY MEDIATOR OR HVEM)

=> d bib ab


L11  ANSWER 1 OF 162     MEDLINE ®  on STN
AN   1990203065     MEDLINE Full-text
DN   PubMed ID: 1969420
TI   Regulation by EGF is maintained in an overexpressed chimeric EGFR/neu
     receptor tyrosine kinase.
AU   Lehvaslaiho H
CS   Department of Virology, University of Helsinki, Finland.
AU   Sistonen L; diRenzo F; Partanen J; Comoglio P; Holtta E; Alitalo K
SO   Journal of cellular biochemistry, (1990 Mar) Vol. 42, No. 3, pp. 123-33.
     Journal code: 8205768. ISSN: 0730-2312. L-ISSN: 0730-2312.
DOI  http://dx.doi.org/10.1002/jcb.240420303
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CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 199004
ED Entered STN: 1 Jun 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Apr 1990
OSC.G 2 There are 2 MEDLINE records that cite this record
AB The effects of a ligand regulated neu tyrosine kinase were examined in NIH 3T3 cells. A chimeric construct encoding the human EGF receptor extracellular domain fused to the tyrosine kinase domain of the rat neu cDNA was expressed under the transcriptional control of the Moloney murine leukemia virus LTR promoter. This resulted in higher levels of expression of the chimeric receptor than were previously obtained from the SV40 virus early promoter in the same cells. The chimeric receptor showed strict ligand-dependent tyrosine kinase and signal transducing activities for the induction of growth-regulated biochemical activities and DNA synthesis in resting cells. The ligand-activated cells became morphologically transformed and grew in agar in the presence of EGF and TGF beta as efficiently as did the ligand-independent neu oncogene-transformed cells. Our results establish similarities between the signal pathways of the EGF receptor and the neu tyrosine kinase.

=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES

=> s l11 and py<=2010

L12 44 L11 AND PY<=2010

=> d bib ab

L12 ANSWER 1 OF 44 MEDLINE ® on STN
AN 1990203065 MEDLINE Full-text
DN PubMed ID: 1969420
TI Regulation by EGF is maintained in an overexpressed chimeric EGFR/neu receptor tyrosine kinase.
AU Lehvaslaiho H
CS Department of Virology, University of Helsinki, Finland.
AU Sistonen L; diRenzo F; Partanen J; Comoglio P; Holtta E; Alitalo K
SO Journal of cellular biochemistry, (1990 Mar) Vol. 42, No. 3, pp. 123-33.
Journal code: 8205768. ISSN: 0730-2312. L-ISSN: 0730-2312.
DOI http://dx.doi.org/10.1002/jcb.240420303
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LA English
FS MEDLINE; Priority Journals
FS Print
EM 199004
ED Entered STN: 1 Jun 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Apr 1990
OSC.G 2 There are 2 MEDLINE records that cite this record
AB The effects of a ligand regulated neu tyrosine kinase were examined in NIH 3T3 cells. A chimeric construct encoding the human EGF receptor extracellular domain fused to the tyrosine kinase domain of the rat neu cDNA was expressed under the transcriptional control of the Moloney murine leukemia virus LTR promoter. This resulted in higher levels of expression of the chimeric receptor than were previously obtained from the SV40 virus early promoter in the same cells. The chimeric receptor showed strict ligand-dependent tyrosine kinase and signal transducing activities for the induction of growth-regulated biochemical activities and DNA synthesis in resting cells. The ligand-activated cells became morphologically transformed and grew in agar in the presence of EGF and TGF beta as efficiently as did the ligand-independent neu oncogene-transformed cells. Our results establish similarities between the signal pathways of the EGF receptor and the neu tyrosine kinase.

=> d 10 ab

L12 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2020 ACS on STN
AB Methods of inducing the presentation of tumor antigens and co-stimulatory mols. to immune cells using aptamers binding the antigen and the costimulatory mol. are described. Presentation of the antigen in a preferred stoichiometry with a costimulatory mol. improves the immune response to the tumor. Use of an aptamer binding prostate-specific membrane antigen and two mols. of 4-1BB receptors is demonstrated. The aptamer was as effective as anti-4-1BB antibody in costimulating CD8-pos. T cells presented with prostate-specific membrane antigen.

=> d 40

L12 ANSWER 40 OF 44 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2002:754431 CAPLUS Full-text
DN 137:274074
TI Recombinant production of polyanionic polymers, and uses thereof as drug carriers for improvement of bioactivity and water-solubility
IN Leung, David W.; Bergman, Philip A.; Lofquist, Alan; Pietz, Gregory E.; Tompkins, Christopher K.; Waggoner, David W., Jr.
PA Cell Therapeutics Inc, USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002077036	A2	20021003	WO 2002-US8614	20020321
WO 2002077036	A3	20040129		
US 20020169125	A1	20021114	US 2002-101487	20020320
AU 2002252429	A1	20021008	AU 2002-252429	20020321
US 20050118136	A1	20050602	US 2004-939988	20040914
US 20080176288	A1	20080724	US 2007-928737	20071030

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PRAI US 2001-60277705     P    20010321
     US 2002-101487       A3   20020320
     WO 2002-US8614       W    20020321
     US 2004-939988       A1   20040914
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G   8     THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
RE.CNT  1     THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT



=> d his


     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1             39 S E3
                E RAVI RAJANI/AU
L2             44 S E3-E4
L3             55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5            439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6             35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7              0 S L5 AND L6
L8         374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9          35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10          1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11           162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12            44 S L11 AND PY<=2010

=> s l8 (5n)  (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry media
tor or HVEM)

L13         1466 L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
                 VIRUS ENTRY MEDIATOR OR HVEM)

=> s l13 and (fusion or chimeric or heterodimer)

L14           23 L13 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> dup rem l14

PROCESSING COMPLETED FOR L14
L15            15 DUP REM L14 (8 DUPLICATES REMOVED)
                  ANSWERS '1-2' FROM FILE MEDLINE
                  ANSWER '3' FROM FILE BIOSIS
                  ANSWERS '4-11' FROM FILE CAPLUS
                  ANSWERS '12-15' FROM FILE EMBASE

=> d bib ab


L15  ANSWER 1 OF 15     MEDLINE ®  on STN           DUPLICATE 1
AN   2016797565     MEDLINE Full-text
DN   PubMed ID: 26971374
TI   TCDD promoted EMT of hFPECs via AhR, which involved the activation of
     EGFR/ERK signaling.
AU   Gao Zhan
CS   School of Public Health, Xinxiang Medical University, 453003, China, The
     Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU   Bu Yongjun; Wang Xugang; Zhang Guofu; Wang Erhui; Ding Shibin; Liu
     Yongfeng; Shi Ruling
CS   School of Public Health, Xinxiang Medical University, 453003, China.
AU   Liu Xiaozhuan
CS   Medical College, Henan University of Science & Technology, 471023, China.
AU   Li Qiaoyun; Fu Jianhong
CS   The Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
```

AU Yu Zengli
CS School of Public Health, Xinxiang Medical University, 453003, China, School of Public Health, Zhengzhou University, 450001, China. zly@zzu.edu.cn
SO Toxicology and applied pharmacology, (2016 May 01) Vol. 298, pp. 48-55. Electronic Publication Date: 10 Mar 2016 Journal code: 0416575. E-ISSN: 1096-0333. L-ISSN: 0041-008X.
DOI http://dx.doi.org/10.1016/j.taap.2016.03.005
CY United States
DT Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201608
ED Entered STN: 15 Mar 2016 Last Updated on STN: 16 Aug 2016 Indexing Added: 16 Aug 2016 Entered Medline: 15 Aug 2016
OSC.G 4 There are 4 MEDLINE records that cite this record
AB One critical step of second palatal fusion is the newly formed medial epithelia seam (MES) disintegration, which involves apoptosis, epithelial to mesenchymal transition (EMT), and cell migration. Although the environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) produces cleft palate at high rates, little is known about the effects of TCDD exposure on the fate of palatal epithelial cells. By using primary epithelial cells isolated from human fetal palatal shelves (hFPECs), we show that TCDD increased cell proliferation and EMT, as demonstrated by increased the epithelial markers (E-cadherin and cytokeratin14) and enhanced the mesenchymal markers (vimentin and fibronectin), but had no effect on cell migration and apoptosis. TCDD exposure led to a dose-dependent increase in Slug protein expression. Coimmunoprecipitation revealed that TCDD promoted AhR to form a protein complex with Slug. ChIP assay confirmed that TCDD exposure recruited AhR to the xenobiotic responsive element of Slug promoter. Knockdown of AhR by siRNA remarkably weakened TCDD-induced binding of AhR to the XRE promoter of slug, thereby suppressed TCDD-induced vimentin. Further experiment showed that TCDD stimulated EGFR phosphorylation did not influence the TGFβ3/Smad signaling; whereas TCDD increased phosphorylation of ERK1/2 and p38 with no effect on activation of JNK. By using varieties of inhibitors, we confirmed that TCDD promoted proliferation and EMT of hFPECs via activation of EGFR/ERK pathway. These data make a novel contribution to the molecular mechanism of cleft palate by TCDD.
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=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12 44 S L11 AND PY<=2010
L13 1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14 23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)

L15 15 DUP REM L14 (8 DUPLICATES REMOVED)

=> d 1-15 bib ab

L15 ANSWER 1 OF 15 MEDLINE ® on STN DUPLICATE 1
AN 2016797565 MEDLINE Full-text
DN PubMed ID: 26971374
TI TCDD promoted EMT of hFPECs via AhR, which involved the activation of EGFR/ERK signaling.
AU Gao Zhan
CS School of Public Health, Xinxiang Medical University, 453003, China, The Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU Bu Yongjun; Wang Xugang; Zhang Guofu; Wang Erhui; Ding Shibin; Liu Yongfeng; Shi Ruling
CS School of Public Health, Xinxiang Medical University, 453003, China.
AU Liu Xiaozhuan
CS Medical College, Henan University of Science & Technology, 471023, China.
AU Li Qiaoyun; Fu Jianhong
CS The Fifth Affiliated Hospital, Zhengzhou University, 450052, China.
AU Yu Zengli
CS School of Public Health, Xinxiang Medical University, 453003, China, School of Public Health, Zhengzhou University, 450001, China. zly@zzu.edu.cn
SO Toxicology and applied pharmacology, (2016 May 01) Vol. 298, pp. 48-55. Electronic Publication Date: 10 Mar 2016
Journal code: 0416575. E-ISSN: 1096-0333. L-ISSN: 0041-008X.
DOI http://dx.doi.org/10.1016/j.taap.2016.03.005
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201608
ED Entered STN: 15 Mar 2016
Last Updated on STN: 16 Aug 2016
Indexing Added: 16 Aug 2016
Entered Medline: 15 Aug 2016
OSC.G 4 There are 4 MEDLINE records that cite this record
AB One critical step of second palatal fusion is the newly formed medial epithelia seam (MES) disintegration, which involves apoptosis, epithelial to mesenchymal transition (EMT), and cell migration. Although the environmental toxicant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) produces cleft palate at high rates, little is known about the effects of TCDD exposure on the fate of palatal epithelial cells. By using primary epithelial cells isolated from human fetal palatal shelves (hFPECs), we show that TCDD increased cell proliferation and EMT, as demonstrated by increased the epithelial markers (E-cadherin and cytokeratin14) and enhanced the mesenchymal markers (vimentin and fibronectin), but had no effect on cell migration and apoptosis. TCDD exposure led to a dose-dependent increase in Slug protein expression. Coimmunoprecipitation revealed that TCDD promoted AhR to form a protein complex with Slug. ChIP assay confirmed that TCDD exposure recruited AhR to the xenobiotic responsive element of Slug promoter. Knockdown of AhR by siRNA remarkably weakened TCDD-induced binding of AhR to the XRE promoter of slug, thereby suppressed TCDD-induced vimentin. Further experiment showed that TCDD stimulated EGFR phosphorylation did not influence the TGFβ3/Smad signaling; whereas TCDD increased phosphorylation of ERK1/2 and p38 with no effect on activation of JNK. By using varieties of inhibitors, we confirmed that TCDD promoted proliferation and EMT of hFPECs via activation of EGFR/ERK pathway. These data make a novel contribution to the molecular mechanism of cleft palate by TCDD.
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L15 ANSWER 2 OF 15 MEDLINE ® on STN DUPLICATE 3
AN 2001689821 MEDLINE Full-text
DN PubMed ID: 11737589
TI Angiotensin II signaling and HB-EGF shedding via metalloproteinase in glomerular mesangial cells.
AU Uchiyama-Tanaka Y

CS Department of Medicine II, Kansai Medical University, Osaka, Japan.
AU Matsubara H; Nozawa Y; Murasawa S; Mori Y; Kosaki A; Maruyama K; Masaki H; Shibasaki Y; Fujiyama S; Nose A; Iba O; Hasagawa T; Tateishi E; Higashiyama S; Iwasaka T
SO Kidney international, (2001 Dec) Vol. 60, No. 6, pp. 2153-63.
Journal code: 0323470. ISSN: 0085-2538. L-ISSN: 0085-2538.
DOI http://dx.doi.org/10.1046/j.1523-1755.2001.00067.x
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 200201
ED Entered STN: 13 Dec 2001
Last Updated on STN: 30 Jan 2002
Entered Medline: 29 Jan 2002
OSC.G 20 There are 20 MEDLINE records that cite this record
AB BACKGROUND: Angiotensin II (Ang II) has been implicated in the development of glomerulosclerosis by stimulating fibronectin (FN) synthesis. The processing and release of heparin binding-endothelin growth factor (HB-EGF) are activated by protein kinase C (PKC) and Ca2+ signaling. We studied the roles of HB-EGF and endothelial growth factor (EGF) receptor (EGFR) in Ang II-induced FN expression using mesangial cells.

METHODS: Mesangial cells were prepared from mouse kidneys by the explant method and cells were used at passages 4 and 5.

RESULTS: Ang II stimulated FN mRNA levels dose-dependently with a maximal increase (3.4-fold) after 12 hours of incubation. This action was completely inhibited by PKC inhibitors and slightly blocked by Ca2+ chelating agents. FN mRNA accumulation by Ang II was abolished by tyrosine kinase inhibitors, a specific inhibitor for EGFR (AG1478) and extracellular signal-regulated kinase (ERK) inactivation. Addition of neutralizing anti-HB-EGF antibody, as well as pretreatment with heparin or the metalloproteinase inhibitor batimastat abolished induction of FN expression by Ang II. In mesangial cells stably transfected with a chimeric construct containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by Ang II (1.7-fold at 0.5 min) and reached a 4.1-fold increase at two minutes. Ang II phosphorylated EGFR (maximal at 2 min) and ERK (maximal at 8 min) in a PKC- and metalloproteinase-dependent manner. Ang II stimulated the expression and release of transforming growth factor-beta (TGF-beta) via EGFR-mediated signaling, and the released TGF-beta also contributed to Ang II-mediated FN expression via EGFR transactivation.

CONCLUSIONS: Ang II-mediated FN expression was regulated by autocrine effects of HB-EGF and TGF-beta, suggesting a novel paradigm for cross-talk between Ang II and growth factor receptor signaling pathways.

L15 ANSWER 3 OF 15 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
DUPLICATE 2
AN 2005:233362 BIOSIS Full-text
DN PREV200510021990
TI Bikunin down-regulates heterodimerization between CD44 and growth factor receptors and subsequently suppresses agonist-mediated signaling.
AU Wakahara, Kiyoshi; Kobayashi, Hiroshi [Reprint Author]; Yagyu, Tatsuo; Matsuzaki, Hidenori; Kondo, Toshiharu; Kurita, Noriyuki; Sekino, Hideo; Inagaki, Kiyokazu; Suzuki, Mika; Kanayama, Naohiro; Terao, Toshihiko
CS Hamamatsu Univ Sch Med, Dept Obstet and Gynecol, Handayama 1-20-1, Hamamatsu, Shizuoka 4313192, Japan
hirokoba@hama.med.ac.jp
SO Journal of Cellular Biochemistry, (APR 1 2005) Vol. 94, No. 5, pp. 995-1009.
CODEN: JCEBD5. ISSN: 0730-2312.
DOI 10.1002/jcb.20364
DT Article
LA English
ED Entered STN: 23 Jun 2005
Last Updated on STN: 11 Jun 2008

AB We provided evidence previously that bikunin, a Kunitz-type protease inhibitor, can disrupt dimerization of CD44 proteins, which may result in suppression of receptor-mediated MAP kinase signaling. However, to what extent dimerization may alter ligand-induced signaling has not been documented. Given the recent recognition that some growth factor receptors can form heterodimers with CD44, the present study was undertaken to determine whether the CD44 and growth factor receptors (e.g., EGFR, FGFR, HGFR, VEGFR, TGF-beta RI, or TGF-beta RII) can form heterodimers in cancer cells and, if so, to investigate the potential functional consequences of such heterodimerization. We also examined whether bikunin can abrogate these heterodimerizations and inhibit CD44/growth factor-dependent signaling. Here, we show direct evidence for heterodimerization of CD44-FGFR and CD44-TGF-beta RI in human chondrosarcoma HCS-2/8 cells, CD44-EGFR complex in human glioma U87MG cells, and CD44-TGF-beta RI heterodimer in human ovarian cancer HRA cells. Coupling of CD44 and growth factor receptor maybe selective, depending on a cell type. Bikunin does not alter the ligand binding, whereas functionally reduces heterodimerization between CD44 and growth factor receptors. The disruption of heterodimerization substantially reduces receptor-induced tyrosine phosphorylation and ERK1/2 activation. Taken together, our data suggest that bikunin-mediated suppression of heterodimerization between CD44 and growth factors may inhibit the agonist-promoted activation of the signaling pathway. (c) 2004 Wiley-Liss, Inc.

L15 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2019:1144025 CAPLUS Full-text
DN 171:71535
TI Multispecific molecules comprising TGF-β inhibitor, anti-CSF1R or CCR2 antibody and tumor-targeting moiety for cancer therapy
IN Loew, Andreas; Vash, Brian Edward; Maiocco, Stephanie J.
PA Elstar Therapeutics, Inc., USA
SO PCT Int. Appl., 207pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2019113464	A1	20190613	WO 2018-US64506	20181207
EP 3720881	A1	20201014	EP 2018-830572	20181207
PRAI US 2017-62596173	P	20171208		
WO 2018-US64506	W	20181207		

AB Multispecific mols. comprising (i) a TGF-beta inhibitor and (ii) a binding moiety that binds to CSF1R or CCR2, and methods of using the same, are disclosed.

L15 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2018:999364 CAPLUS Full-text
DN 169:4235
TI TGFβ signal convertor and engineered DARIC receptor, antigen receptor, TCR, chimeric antigen receptor or chimeric cytokine receptor for adoptive T cell therapy
IN Boyerinas, Benjamin
PA Bluebird Bio, Inc., USA
SO PCT Int. Appl., 203pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2018094244	A1	20180524	WO 2017-US62358	20171117
CA 3043888	A1	20180524	CA 2017-3043888	20171117
AU 2017362484	A1	20190530	AU 2017-362484	20171117
IL 266628	A	20190630	IL 2017-266628	20171117
KR 2019077562	A	20190703	KR 2019-7017172	20171117
MX 2019005724	A	20190708	MX 2019-5724	20171117

	CN 110072885	A	20190730	CN 2017-80077533	20171117
	BR 112019009904	A2	20190813	BR 2019-112019009904	20171117
	EP 3541833	A1	20190925	EP 2017-872043	20171117
	JP 2019535275	T	20191212	JP 2019-526305	20171117
	US 20190350974	A1	20191121	US 2019-16348450	20190508
	IN 201917022415	A	20190726	IN 2019-17022415	20190606
PRAI	US 2016-62423565	P	20161117		
	US 2017-62467496	P	20170306		
	WO 2017-US62358	W	20171117		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS CASFORMULTNS 2018:999364
AB The present disclosure provides improved compns. for adoptive T cell therapies for treating, preventing, or ameliorating at least one symptom of a cancer, infectious disease, autoimmune disease, inflammatory disease, and immunodeficiency, or condition assocd. therewith.

L15 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2018:2419881 CAPLUS Full-text
DN 170:120475
TI Lentiviral vector for expressing TGF-β antibody and construction method of CAR-T cell and application in treatment of solid tumor
IN Li, Jie; Han, Jiangmeng; Liu, Zhenyun; Wang, Wei; Cheng, Fengwei
PA Anhui Guyi Biotechnology Co., Ltd., Peop. Rep. China
SO Faming Zhuanli Shenqing, 33pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 108949828	A	20181207	CN 2018-10812789	20180723
PRAI CN 2018-10812789		20180723		

AB The title lentiviral vector for expressing TGF-β antibody is pCDH lentiviral vector of CAR gene, and contains solid tumor-specific antigen target. The invention also provides a construction method of the lentiviral vector for expressing TGF-β antibody, a CAR-T cell for expressing TGF-β antibody and prepd. from the lentiviral vector, and a construction method and application of the CAR-T cell in reparation of drug for treatment of solid tumor. The invention can realize targeting of tumor cell, reduce the inhibitive mol. in tumor microenvironment, kill solid tumor in max. extent, and achieve solid tumor immunotherapy new breakthrough.

L15 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2017:698315 CAPLUS Full-text
DN 166:489022
TI Preparation of TGF-β-targeting chimeric antigen receptor for T cell activation, immunostimulatory cytokine increase and autoimmune disease or caner therapy
IN Chen, Yvonne Yu-Hsuan; Chang, Zenan Li
PA The Regents of the University of California, USA
SO PCT Int. Appl., 89pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2017075433	A1	20170504	WO 2016-US59444	20161028
KR 2018092947	A	20180820	KR 2018-7015353	20161028
EP 3368571	A1	20180905	EP 2016-860930	20161028
CN 108884155	A	20181123	CN 2016-80077053	20161028
JP 2019500012	T	20190110	JP 2018-522004	20161028
US 20180312580	A1	20181101	US 2018-15772403	20180430
PRAI US 2015-62248685	P	20151030		
WO 2016-US59444	W	20161028		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS CASFORMULTNS 2017:698315

AB Aspects of the disclosure relate to polypeptides comprising a signal peptide, an antigen-binding domain that specifically binds TGF-β, a peptide spacer, a transmembrane domain, and an endodomain. When expressed in a cell, the polypeptides are capable of not only neutralizing the TGF-β but also specifically triggering T-cell activation in the presence of TGF-β. T-cell activation spurs the immune cell to produce immunostimulatory cytokines and proliferate, thus turning TGF-β from an immunosuppressive signal to an activating stimulus.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2017:389707 CAPLUS Full-text
DN 166:319538
TI Engineering TGF-β receptor ectodomain fusion proteins with antibodies for neutralizing TGFβ ligands and treatment of cancer and fibrotic diseases
IN Zwaagstra, John C.; Sulea, Traian; Jaramillo, Maria; O'Connor, Maureen D.; Lenferink, Anne E. G.
PA National Research Council of Canada, Can.
SO PCT Int. Appl., 101pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2017037634	A1	20170309	WO 2016-IB55204	20160831
CA 2996996	A1	20170309	CA 2016-2996996	20160831
EP 3344660	A1	20180711	EP 2016-840942	20160831
US 20200231652	A1	20200723	US 2018-15755595	20180227
PRAI US 2015-62212058	P	20150831		
WO 2016-IB55204	W	20160831		

OS CASFORMULTNS 2017:389707
AB The present invention relates, in general, to polypeptides capable of binding and neutralizing transforming growth factor β (TGF-β) ligands, and uses of these polypeptides for treating disorders related to TGF-beta expression or activation (e.g. cancer and fibrotic diseases), and methods of making such mols.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2016:587936 CAPLUS Full-text
DN 164:456408
TI Peptides having anti-inflammatory properties
IN Jaynes, Jesse M.; Lopez, Henry W.; Martin, George R.; Yates, Clayton; Garvin, Charles E.
PA Riptide Bioscience, Inc., USA
SO U.S. Pat. Appl. Publ., 180pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20160101150	A1	20160414	US 2015-14882293	20151013
US 9492499	B2	20161115		
CA 2963478	A1	20160421	CA 2015-2963478	20151013
WO 2016061133	A1	20160421	WO 2015-US55380	20151013
AU 2015333678	A1	20170427	AU 2015-333678	20151013
AU 2015333678	B2	20200514		
KR 2017070152	A	20170621	KR 2017-7012890	20151013
EP 3206704	A1	20170823	EP 2015-851584	20151013
CN 107106638	A	20170829	CN 2015-80067933	20151013
JP 2017537141	T	20171214	JP 2017-540551	20151013
BR 112017007543	A2	20171219	BR 2017-112017007543	20151013
US 20170020956	A1	20170126	US 2016-15286491	20161005
US 10149886	B2	20181211		
IN 201747012819	A	20170421	IN 2017-47012819	20170411

	ZA 2017002537	A	20201028	ZA 2017-2537	20171004
	US 20190046601	A1	20190214	US 2018-16169819	20181024
	JP 2020180149	A	20201105	JP 2020-118752	20200709
PRAI	US 2014-62063909	P	20141014		
	JP 2017-540551	A3	20151013		
	US 2015-14882293	A1	20151013		
	WO 2015-US55380	W	20151013		
	US 2016-15286491	A1	20161005		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2016:587936

AB Aspects of the present invention relate to peptides having anti-inflammatory activity, compns. contg. one or more of the peptides, and use of the peptides to treat conditions assocd. with excessive inflammation in animals, particularly humans and other mammals. In particular embodiments, peptides bind to an NF-kB Class II protein, specifically RelB,TGF .beta ., Notch1, Wnt8R, TRAIL, IL6R, IL10R, EGFR , CDK6, CD206, CD47, SIRP-α, HMT, and TGM2, and other signaling proteins that functions as a pro-inflammatory cytokine, an inhibitor of macrophage activity, or a regulator of histone function including TGF .beta ., Notch1, Wnt8R, TRAIL, IL6R, IL10R, EGFR , CDK6, CD206, CD47, SIRP-α, HMT, TGM2. etc. are provided. These peptides contain a striapathic region consisting of alternating hydrophobic and hydrophilic modules and demonstrate strong inhibitions of pro-inflammatory cytokines, an macrophage activity, and suppression of tumor growth.

OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L15 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2013:1911217 CAPLUS Full-text

DN 161:642856

TI Impact of TGF-b on breast cancer from a quantitative proteomic analysis

AU Ahn, Jaegyoon; Yoon, Youngmi; Yeu, Yunku; Lee, Hookuen; Park, Sanghyun

CS Department of Computer Science, Yonsei University, Seoul, 120-749, S. Korea

SO Computers in Biology and Medicine (2013), 43(12), 2096-2102
CODEN: CBMDAW; ISSN: 0010-4825

DOI 10.1016/j.compbiomed.2013.09.022

PB Elsevier Ltd.

DT Journal; (online computer file)

LA English

AB There has been much active research in bioinformatics to support our understanding of oncogenesis and tumor progression. Most research relies on mRNA gene expression data to identify marker genes or cancer specific gene networks. However, considering that proteins are functional mols. that carry out the biol. tasks of genes, they can be direct markers of biol. functions. Protein abundance data on a genome scale have not been investigated in depth due to the limited availability of high throughput protein assays. This hindrance is chiefly caused by a lack of robust techniques such as RT-PCR (real-time polymerase chain reaction). In this study, we quantified phospho-proteomes of breast cancer cell lines treated with TGF-beta (transforming growth factor beta). To discover biomarkers and observe changes in the signaling pathways related to breast cancer, we applied a protein network-based approach to generate a classifier of subnet markers. The accuracy of that classifier outperformed other network-based classification algorithms, and current feature selection and classification algorithms. Moreover, many cancer-related proteins were identified in those sub-networks. Each sub-network provides functional insights and can serve as a potential marker for TGF-beta treatments. After interpreting the roles of proteins in sub-networks with various signaling pathways, we found strong candidate proteins and various related interactions that are expected to affect breast cancer outcomes. These results demonstrate the high quality of the quantified phospho-proteomes data and show that our network construction and classification method is appropriate for an anal. of this type of data.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2008:1102620 CAPLUS Full-text

DN 149:324137

TI Meroduplex gapped or nicked double-stranded RNAs specific for inhibiting

transforming growth factor β receptor gene expression and their therapeutic use

IN Quay, Steven C.; McSwiggen, James; Vaish, Narendra K.; Ahmadian, Mohammad

PA MDRNA, Inc., USA

SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 80

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2008109546	A2	20080912	WO 2008-US55695	20080303
	WO 2008109546	A3	20081030		
	EP 2468864	A1	20120627	EP 2012-153919	20080228
	EP 2471920	A2	20120704	EP 2012-153915	20080303
	EP 2471920	A3	20121010		
	US 20100105134	A1	20100429	US 2009-552082	20090901
	US 20130011922	A1	20130110	US 2011-13327545	20111215
PRAI	US 2007-60934940	P	20070302		
	US 2007-60934930	P	20070316		
	US 2007-61016343	P	20071221		
	US 2007-60934931	P	20070420		
	US 2007-60934928	P	20070424		
	US 2007-60934934	P	20070424		
	US 2007-60934942	P	20070425		
	US 2007-60934943	P	20070425		
	US 2007-60932949	P	20070503		
	US 2007-61015611	P	20071220		
	EP 2008-731034	A3	20080228		
	WO 2008-US55353	A2	20080228		
	WO 2008-US55505	A2	20080229		
	WO 2008-US55511	A2	20080229		
	WO 2008-US55515	A2	20080229		
	WO 2008-US55516	A2	20080229		
	WO 2008-US55519	A2	20080229		
	WO 2008-US55524	A2	20080229		
	WO 2008-US55526	A2	20080229		
	WO 2008-US55527	A2	20080229		
	WO 2008-US55532	A2	20080229		
	WO 2008-US55533	A2	20080229		
	WO 2008-US55542	A2	20080229		
	WO 2008-US55548	A2	20080229		
	WO 2008-US55550	A2	20080229		
	WO 2008-US55551	A2	20080229		
	WO 2008-US55554	A2	20080229		
	WO 2008-US55556	A2	20080229		
	WO 2008-US55560	A2	20080229		
	WO 2008-US55563	A2	20080229		
	EP 2008-731244	A3	20080303		
	WO 2008-US55597	A2	20080303		
	WO 2008-US55599	A2	20080303		
	WO 2008-US55601	A2	20080303		
	WO 2008-US55603	A2	20080303		
	WO 2008-US55604	A2	20080303		
	WO 2008-US55606	A2	20080303		
	WO 2008-US55608	A2	20080303		
	WO 2008-US55611	A2	20080303		
	WO 2008-US55612	A2	20080303		
	WO 2008-US55615	A2	20080303		
	WO 2008-US55618	A2	20080303		
	WO 2008-US55622	A2	20080303		
	WO 2008-US55625	A2	20080303		
	WO 2008-US55627	A2	20080303		
	WO 2008-US55631	A2	20080303		
	WO 2008-US55635	A2	20080303		
	WO 2008-US55644	A2	20080303		
	WO 2008-US55649	A2	20080303		
	WO 2008-US55651	A2	20080303		
	WO 2008-US55662	A2	20080303		
	WO 2008-US55676	A2	20080303		
	WO 2008-US55678	A2	20080303		

WO 2008-US55693 A2 20080303
WO 2008-US55695 A2 20080303
WO 2008-US55697 A2 20080303
WO 2008-US55698 A2 20080303
WO 2008-US55701 A2 20080303
WO 2008-US55704 A2 20080303
WO 2008-US55708 A2 20080303
WO 2008-US55709 A2 20080303
WO 2008-US55711 A2 20080303
US 2009-552082 A1 20090901
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 149:324137
AB The present disclosure is based on the discovery that a nicked or gapped double-stranded RNA comprising at least three strands (termed meroduplex RNA or mdRNA) is a suitable substrate for Dicer or RISC and, therefore may be advantageously employed for gene silencing via, for example, the RNA interference pathway. An mdRNA comprises at least three strands that combine to form at least two non-overlapping double-stranded regions sepd. by a nick or gap wherein one strand is complementary to a mRNA. Partially duplexed dsRNA mols. (mdRNAs) are thus capable of initiating an RNA interference cascade that reduces expression of a target mRNA, such as a human transforming growth factor β receptor (TGFBR) mRNA. The introduction of substituted and modified nucleotides into mdRNA provides a powerful tool in overcoming potential limitations of in vivo stability and bioavailability inherent to nature RNA mols. The mean inhibitory concn. (IC50) of RISC and Dicer mdRNAs specific for influenza range from about 200 pM to about 15 nM; inclusion of a single locked nucleic acid reduced the IC50 of Dicer mdRNAs by up to 4-fold. In addn., the mdRNAs induce cytokines to a lesser extent than intact (i.e., not nicked) parent mols. Meroduplex RNAs are designed with the first strand complementary to a TGFBR mRNA, including TGFBR I, TGFBR II, and TGFBR III. Also provided are methods of decreasing expression of a TGFBR gene in a cell or in a subject to treat a TGFBR-related disease.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L15 ANSWER 12 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051974617 EMBASE Full-text
DN 72002361
TI ERG onc oprotein evaluation and its correlation with other molecular biomarkers in prostate cancer.
AU Liatkouskaya, T.; Cherstvoy, E.; Zakharava, V.; Masansky, I.; Sagalchik, L.; Ivanovskaya, M.; Dedik, S.
AU Rogov, Y. (correspondence)
CS Belarusian Medical Academy, Dept. of Pathology, Minsk, Belarus.
SO Virchows Archiv, (September 2015) Vol. 467, No. 1, Supp. SUPPL. 1, pp. S276. Abstract Number: PS-24-067.
Meeting Info: 27th European Congress of Pathology, ECP 2015. Belgrade, Serbia. 05 Sep 2015-09 Sep 2015
ISSN: 0945-6317
DOI 10.1007/s00428-015-1805-9
PB Springer Verlag.
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 9 Sep 2015
Last Updated on Embase: 9 Sep 2015
AB Objective: The aim of this study was to assess the frequency of expression of the ERG oncoprotein, a product of the chimeric gene TMPRSS2: ERG, in cancer containing prostate biopsy material, to evaluate its prognostic significance and correlation with other molecular biomarkers. Method: Expression of the markers such as ERG oncoprotein, Ki-67, cycline D1 (CycD1), topoisomerase IIα (TopoIIα), chromogranin A (ChrA), androgen receptors (AR) and estrogens α and β receptors in epithelium (ERα, ERβ) and stroma (SRα, SRβ), p53, BCL2, BAX, VEGF, TGFβ, EGFR was assessed immunohistochemically in the biopsy material from 238 cases of prostate cancer. Results: ERG expression was found in 47 % of the patients. It was demonstrated that ERG-positive cancer if compared to ERG-negative type is characterized by

enhanced ($p < 0.05$) expression of Ki-67, CycD1, TopoIIα, AR, ERα, p53, TGFβ and EGFR and decreased expression of BAX, ERβ, SRα and SRβ, whereas no difference in expression of ChrA, BCL2 and VEGF was revealed. It was shown that marked ERG expression in biopsy samples is associated with poor prognosis: higher risk of biochemical recurrence and clinically significant disease progression after radical prostatectomy. Conclusion: ERG-positive cancer was found in biopsy material from 47 % of patients and is characterized by enhanced proliferative activity, increased expression of AR, ERα, p53, TGFβ and EGFR, and decreased expression of BAX, ERβ, SRα and SRβ; it is associated with higher risk of unfavorable outcome.

L15 ANSWER 13 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052156602 EMBASE Full-text
DN 72194680
TI Targeting NANOG: Genes, proteins and response to viral RNAi in preclinical models.
AU Jessup, J. Milburn (correspondence); Mattoo, Abid R.; Korokhov, Nikolay
CS National Cancer Institute, Bethesda, MD, United States.
SO Cancer Research, (1 Aug 2015) Vol. 75, No. 15, Supp. SUPPL. 1. Abstract Number: 4216.
Meeting Info: 106th Annual Meeting of the American Association for Cancer Research, AACR 2015. Philadelphia, PA, United States. 18 Apr 2015-22 Apr 2015
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2015-4216
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 21 Mar 2016
Last Updated on Embase: 21 Mar 2016
AB Purpose: Since the NANOG family controls stemness and neoplastic progression in human colorectal carcinoma (CRC), our postulate is that targeting the dominant NANOG and NANOGP8 members with viral vector delivered shRNA will inhibit CRC progression in preclinical models and that replicating viral vectors are more active than non-replicating vectors. Methods: Cells were human CRC lines (Clone A, CX-1 and LS174T) and mouse fibroblasts (3T3). shRNA specific to NANOG (shNG-1), NANOGP8 (shNp8-1) or a control (shNEG) were created in lentivirus (LV) and chimeric adenovirus 5/3 (Ad5/3). CRC and 3T3 were cultured in monolayer with serum-containing medium or in suspension in ultra low attachment plates without serum. Nanostring 770 gene cancer panel was analyzed in 72 hr cultures with NMF clustering and GSEA analysis. Annexin V expression and caspase-3, 8 or 9 activation in suspension culture assessed Apoptosis. LV or Ad5/3 shRNAs were added to spheroids in 3-D suspension cultures to test therapy in vitro. Intratumoral injection of LV or Ad5/3 shRNA into 5-10 mm sub cutis nodules in groups of 5-10 NOD/SCID mice measured activity in vivo. Results: LV shNp8-1 in both Clone A and CX-1 caused significant inhibition of TGF-beta, EGFR, NRF2, E2F3 and the Cyclin D1 pathways by NMF and GSEA analysis in monolayer culture. LV shNp8-1 inhibited growth of LS174T, Clone A and CX-1 by 50% in 3 days in 3-D suspension cultures without further decrease. Apoptosis was due to Caspase 9 activation. In contrast, Ad5/3-shNp8-1 decreased spheroid growth by up to 94% at 9 -14 days while Ad5/3 decreases spheroid growth by 80%. Ad5/3-shNp8-1 but nit Ad5/3 was active in co-cultures with 3T3 to a 2:1 CRC:3T3 ratio. Transduction level was ~50% in LV treated cells but ~90% in Ad5/3 treated cells. Intratumoral injection of LVshNG-1 or LVshNp8-1, decreased tumor size by 50% compared to LVshNEG or untreated CX-1 tumors for 11 days after which tumor growth rebounded to match controls. Ad5/3-shNp8-1 injection into 5-9 mm nodules inhibited CX-1 and LS14T growth by ~50% until euthanized. Conclusions: Targeting NANOGP8 more than NANOG inhibits proliferation and activates apoptosis through multiple pathways. Nonreplicating LV delivered shRNA inhibited tumor growth in in vitro and in vivo preclinical models but replicating oncolytic Ad5/3 infects more cells and promotes shRNA efficacy. Replicating vectors targeting NANOG are important for further development.

L15 ANSWER 14 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051695487 EMBASE Full-text
DN 71723238
TI Insights into mechanisms of breast cancer metastasis.
AU Hynes, Nancy E. (correspondence)
CS Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland.
SO Cancer Research, (1 Oct 2014) Vol. 74, No. 19, Supp. SUPPL. 1. Abstract Number: SY20-02.
Meeting Info: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014. San Diego, CA, United States. 05 Apr 2014-09 Apr 2014
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2014-SY20-02
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 3 Feb 2015
Last Updated on Embase: 3 Feb 2015
AB Breast carcinoma is the most frequent cancer in women, affecting one million yearly. In the past decades there have been great improvements in surgery, screening and therapy. These have led to dramatic changes in the 5-year overall survival rates, which have gone from 40% in the 1950's up to 86% in the past decade (Maxmen 2012). However, many patients who present with early stage disease die from metastases, despite complete surgical removal of primary breast tumors. Indeed, if a tumor has spread to distant organs at the time of presentation, the 5-year overall survival is only 23% compared to 90% or higher for patients with localized tumors. Today, primary tumors are efficiently removed by surgical intervention, but there are essentially no successful therapeutic options for metastatic disease. Metastasis is a complex process whereby tumor cells detach from the primary site, acquire migratory properties, enter and survive in the circulation, and colonize and grow at distant sites (Gupta and Massague 2006). Metastatic relapse can occur years after surgery, suggesting that tumor cells have the ability to survive in a dormant state in metastatic niches (Karrison, Ferguson et al. 1999). Typical sites of relapse of breast cancer are the bone, lungs, liver and brain (Weigelt, Peterse et al. 2005; Nguyen, Bos et al. 2009). Thus, the most relevant clinical and experimental questions in the breast cancer field revolve around metastasis. Important research areas are: the identification of specific molecules and pathways contributing to metastatic spread, tumor cell survival and growth in distant sites, as well as uncovering metastatic therapies. My presentation will cover our recent work on: 1-targeting receptor tyrosine kinases (RTKs) in metastatic breast cancer models; 2-Memo, a novel enzyme that affects intracellular ROS production, and is essential for in vivo metastasis; 3- analyses aimed at uncovering molecular mechanisms involved in crosstalk between tumor cells and the bone marrow (BM) environment. 1-Targeting RTKs with antibodies or small molecular inhibitors is a clinically validated approach for cancer therapy. In breast cancer, the ErbB2/HER2 specific antibody trastuzumab is routinely given in combination with chemotherapy to ErbB2/HER2-positive breast cancer patients and has had a significant impact on patient mortality (Gianni, Dafni et al., 2011). Only a sub-set of patients, however, are eligible for this treatment, making it essential to uncover additional RTKs that could be useful in for therapy; the Ret kinase might be an interesting new target. Ret was discovered as an outlier kinase in breast cancer, with unexpectedly high expression levels detected in many breast tumors (Esseghir, Todd et al. 2007; Boulay, Breuleux et al. 2008; Kothari, Wei et al. 2013). Unlike thyroid or lung tumors that carry oncogenic Ret, as fusion proteins or with activating mutations, Ret appears to be wild type in breast cancer. We have shown that elevated Ret levels are found in different sub-types of human breast cancers and that high Ret correlates with decreased metastasis-free survival. Using a metastatic breast cancer model, we showed that in vivo blockade of Ret inhibits tumor outgrowth and metastatic potential (Gattelli, Nalvarte et al. 2013). Our results suggest that Ret has an important role in tumor growth and metastasis. Multiple RTKs are often active in cancer cells and combining RTK inhibitors has been shown to have strong anti-tumor activity

(e.g., Stommel, Kimmelman et al. 2007). Considering that breast tumors often co-express ErbB and FGFRs (Cancer Genome Atlas Network, 2012), we have tested the impact of blocking both in metastatic breast cancer models. We have recently shown that only when both RTKs are blocked do we observe: blockade of the ERK and PI3K pathways, prolonged tumor-stasis and a significant decrease in metastasis (Dey, Bianchi et al. 2010; Issa, Gill et al. 2013). 2-Our group originally identified Memo as being essential for breast cancer cell motility in response to several RTKs (Marone, Hess et al. 2004; Meira, Masson et al. 2009). The 2.1 A crystal structure of Memo revealed its structural homology with bacterial enzymes (Qiu, Lienhard et al. 2008); we have recently discovered that Memo is a metal-binding enzyme that requires Cu(II) for its oxidase-like activity. Memo knock-down (KD) in breast cancer models affects localized intracellular ROS production, cell migration and invasion, as well as in vivo spontaneous lung metastasis from xenografts. To investigate if Memo plays a role in human breast disease, immunohistochemistry (IHC) was carried out on breast cancer tissue microarrays (TMAs). Memo expression is low in non-neoplastic breast tissue and exhibits significantly higher expression in > 40% of tumors. Memo is diffusely localized to the cytoplasm and the nucleus and accumulates at the membrane upon growth factor stimulation (Schlatter, Meira et al. 2012). To examine if the sub-cellular localization of Memo correlates with clinical or histopathological parameters, we categorized the breast tumor samples according to expression and localization of Memo. We found that elevated Memo was prognostic of poor outcome; elevated levels of cytoplasmic Memo, but not nuclear Memo, significantly predicted early metastasis and death at 5 years in a multivariable Cox model. These data suggest that Memo has distinct roles in different cellular compartments and that its cytoplasmic function regulates pathways that promote tumor dissemination. 3- Bone marrow is particularly permissive for disseminated tumor cells since structural and environmental features needed to allow trafficking of hematopoietic stem cells and their progeny can also be employed by the tumor cells. The fenestration of bone sinusoidal capillaries facilitates the entrance of tumor cells. Moreover, bone stroma is a potent source of CXCL12 that attracts tumor cells expressing its receptor CXCR4, making BM a perfect soil for circulating tumor cells (Morrison and Spradling 2008). Metastatic tumors show different molecular features compared to primary tumors, which could reflect tumor-cell selection for particular conditions in the distant site and/or the influence of the surrounding stroma on a disseminated tumor cells (Kang, Siegel et al. 2003; Minn, Gupta et al. 2005). The BM niche is a complex, multicellular structure composed of osteoblasts, osteoclasts, stromal fibroblasts, endothelial cells, and mesenchymal progenitors, all of which contribute to general bone homeostasis (Mendez-Ferrer, Michurina et al. 2010; Ehninger and Trumpp 2011). Considering the strong interplay between these elements, it has been suggested that blocking the crosstalk between tumor and the bone environment would be a potential strategy to inhibit tumor expansion. To uncover molecular mechanisms involved in the crosstalk between tumor cells and the BM environment, we compared the transcriptome of different cell populations from the BM environment from tumor-bearing and tumor-free mice. For this, we used purified stromal cell subsets of: endothelial and osteoblastic cells, as well as mesenchymal and osteogenic progenitors. These analyses revealed that BM is strongly affected by breast cancer cell dissemination. Indeed, several components of key molecular pathways involved in tumor development, including TGFBR, PDGFRB, EGFR, HGFR, IGFR and JAK/Stat, are modulated in the BM of mice with tumor cells.

L15 ANSWER 15 OF 15 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 2004223470 EMBASE Full-text
DN 38657721 PMID: 15144206
TI A mammalian genetic system to screen for small molecules capable of disrupting protein-protein interactions.
AU Zhao, Hui-Fen; Kiyota, Taira; Chowdhury, Shafinaz; Purisima, Enrico; Banville, Denis; Konishi, Yasuo; Shen, Shi-Hsiang (correspondence)
CS Health Sector, Biotechnology Research Institute, National Research Council of Canada, 6100 Royalmount Avenue, Montreal, Que. H4P 2R2, Canada. shi.shen@nrc.ca
AU Shen, Shi-Hsiang (correspondence)
CS Department of Medicine, McGill University, Montreal, Que. H3G 1A4, Canada. shi.shen@nrc.ca

SO Analytical Chemistry, (15 May 2004) Vol. 76, No. 10, pp. 2922-2927.
    Refs: 18
    ISSN: 0003-2700 CODEN: ANCHAM
DOI 10.1021/ac035396m
PB American Chemical Society, 2540 Olentangy River Road, P.O. Box 3337,
    Columbus, OH 43210-3337, United States.
CY United States
DT Journal; Article
FS Intellectual Indexing
    022   Human Genetics
    037   Drug Literature Index
LA English
SL English
ED Entered Embase: 10 Jun 2004
    Last Updated on Embase: 10 Jun 2004
AB A mammalian two-hybrid system was developed for high-throughput screening
    of compounds that disrupt specific protein-protein interactions. The
    existing mammalian systems are unsatisfactory for drug screening due to
    non-regulated expression of interacting proteins. To construct a tightly
    regulated system, the tetracycline repressor was fused with the inhibitory
    KRAB domain as a suppressor. The binding of the suppressor to the tet
    operator entirely blocked expression of two interacting proteins. When
    both the inducer doxycycline and drugs were added to the culture, the
    reporter gene was either activated by interaction of the paired proteins
    with ineffective drugs or remained silent due to disruption of the protein
    interactions by the effective drugs. We demonstrate that interactions of
    the type I receptor for TGFβ with FKBP12 and the epidermal
    growth factor receptor (EGFR) with p85 are effectively disrupted by
    FK506 and EGFR kinase inhibitor AG 1478, respectively. The power of this
    system for drug screening was further demonstrated by rapid identification
    of inhibitors from a druglike library for the receptor kinases.

=> d his

    (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

    FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1   39 S E3
                E RAVI RAJANI/AU
L2   44 S E3-E4
L3   55 S L1-L2

    FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4   0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5   439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6   35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7   0 S L5 AND L6
L8   374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9   35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10   1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11   162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12   44 S L11 AND PY<=2010
L13   1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14   23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15   15 DUP REM L14 (8 DUPLICATES REMOVED)

=> s l15 and py<=2010

L16   4 L15 AND PY<=2010

=> d 1-4 bib ab

L16 ANSWER 1 OF 4   MEDLINE ® on STN
AN   2001689821   MEDLINE Full-text
DN   PubMed ID: 11737589
TI   Angiotensin II signaling and HB-EGF shedding via metalloproteinase in

glomerular mesangial cells.
AU Uchiyama-Tanaka Y
CS Department of Medicine II, Kansai Medical University, Osaka, Japan.
AU Matsubara H; Nozawa Y; Murasawa S; Mori Y; Kosaki A; Maruyama K; Masaki H; Shibasaki Y; Fujiyama S; Nose A; Iba O; Hasagawa T; Tateishi E; Higashiyama S; Iwasaka T
SO Kidney international, (2001 Dec) Vol. 60, No. 6, pp. 2153-63.
Journal code: 0323470. ISSN: 0085-2538. L-ISSN: 0085-2538.
DOI http://dx.doi.org/10.1046/j.1523-1755.2001.00067.x
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Print
EM 200201
ED Entered STN: 13 Dec 2001
Last Updated on STN: 30 Jan 2002
Entered Medline: 29 Jan 2002
OSC.G 20 There are 20 MEDLINE records that cite this record
AB BACKGROUND: Angiotensin II (Ang II) has been implicated in the development of glomerulosclerosis by stimulating fibronectin (FN) synthesis. The processing and release of heparin binding-endothelin growth factor (HB-EGF) are activated by protein kinase C (PKC) and Ca2+ signaling. We studied the roles of HB-EGF and endothelial growth factor (EGF) receptor (EGFR) in Ang II-induced FN expression using mesangial cells.

METHODS: Mesangial cells were prepared from mouse kidneys by the explant method and cells were used at passages 4 and 5.

RESULTS: Ang II stimulated FN mRNA levels dose-dependently with a maximal increase (3.4-fold) after 12 hours of incubation. This action was completely inhibited by PKC inhibitors and slightly blocked by Ca2+ chelating agents. FN mRNA accumulation by Ang II was abolished by tyrosine kinase inhibitors, a specific inhibitor for EGFR (AG1478) and extracellular signal-regulated kinase (ERK) inactivation. Addition of neutralizing anti-HB-EGF antibody, as well as pretreatment with heparin or the metalloproteinase inhibitor batimastat abolished induction of FN expression by Ang II. In mesangial cells stably transfected with a chimeric construct containing HB-EGF and alkaline phosphatase (ALP) genes, ALP activity in incubation medium was rapidly increased by Ang II (1.7-fold at 0.5 min) and reached a 4.1-fold increase at two minutes. Ang II phosphorylated EGFR (maximal at 2 min) and ERK (maximal at 8 min) in a PKC- and metalloproteinase-dependent manner. Ang II stimulated the expression and release of transforming growth factor-beta (TGF-beta) via EGFR-mediated signaling, and the released TGF-beta also contributed to Ang II-mediated FN expression via EGFR transactivation.

CONCLUSIONS: Ang II-mediated FN expression was regulated by autocrine effects of HB-EGF and TGF-beta, suggesting a novel paradigm for cross-talk between Ang II and growth factor receptor signaling pathways.

L16 ANSWER 2 OF 4 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2005:233362 BIOSIS Full-text
DN PREV200510021990
TI Bikunin down-regulates heterodimerization between CD44 and growth factor receptors and subsequently suppresses agonist-mediated signaling.
AU Wakahara, Kiyoshi; Kobayashi, Hiroshi [Reprint Author]; Yagyu, Tatsuo; Matsuzaki, Hidenori; Kondo, Toshiharu; Kurita, Noriyuki; Sekino, Hideo; Inagaki, Kiyokazu; Suzuki, Mika; Kanayama, Naohiro; Terao, Toshihiko
CS Hamamatsu Univ Sch Med, Dept Obstet and Gynecol, Handayama 1-20-1, Hamamatsu, Shizuoka 4313192, Japan
hirokoba@hama.med.ac.jp
SO Journal of Cellular Biochemistry, (APR 1 2005) Vol. 94, No. 5, pp. 995-1009.
CODEN: JCEBD5. ISSN: 0730-2312.
DOI 10.1002/jcb.20364
DT Article
LA English
ED Entered STN: 23 Jun 2005

Last Updated on STN: 11 Jun 2008

AB We provided evidence previously that bikunin, a Kunitz-type protease inhibitor, can disrupt dimerization of CD44 proteins, which may result in suppression of receptor-mediated MAP kinase signaling. However, to what extent dimerization may alter ligand-induced signaling has not been documented. Given the recent recognition that some growth factor receptors can form heterodimers with CD44, the present study was undertaken to determine whether the CD44 and growth factor receptors (e.g., EGFR, FGFR, HGFR, VEGFR, TGF-beta RI, or TGF-beta RII) can form heterodimers in cancer cells and, if so, to investigate the potential functional consequences of such heterodimerization. We also examined whether bikunin can abrogate these heterodimerizations and inhibit CD44/growth factor-dependent signaling. Here, we show direct evidence for heterodimerization of CD44-FGFR and CD44-TGF-beta RI in human chondrosarcoma HCS-2/8 cells, CD44-EGFR complex in human glioma U87MG cells, and CD44-TGF-beta RI heterodimer in human ovarian cancer HRA cells. Coupling of CD44 and growth factor receptor maybe selective, depending on a cell type. Bikunin does not alter the ligand binding, whereas functionally reduces heterodimerization between CD44 and growth factor receptors. The disruption of heterodimerization substantially reduces receptor-induced tyrosine phosphorylation and ERK1/2 activation. Taken together, our data suggest that bikunin-mediated suppression of heterodimerization between CD44 and growth factors may inhibit the agonist-promoted activation of the signaling pathway. (c) 2004 Wiley-Liss, Inc.

L16 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2020 ACS on STN

AN 2008:1102620 CAPLUS Full-text

DN 149:324137

TI Meroduplex gapped or nicked double-stranded RNAs specific for inhibiting transforming growth factor β receptor gene expression and their therapeutic use

IN Quay, Steven C.; McSwiggen, James; Vaish, Narendra K.; Ahmadian, Mohammad

PA MDRNA, Inc., USA

SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 80

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2008109546	A2	20080912	WO 2008-US55695	20080303
	WO 2008109546	A3	20081030		
	EP 2468864	A1	20120627	EP 2012-153919	20080228
	EP 2471920	A2	20120704	EP 2012-153915	20080303
	EP 2471920	A3	20121010		
	US 20100105134	A1	20100429	US 2009-552082	20090901
	US 20130011922	A1	20130110	US 2011-13327545	20111215
PRAI	US 2007-60934940	P	20070302		
	US 2007-60934930	P	20070316		
	US 2007-61016343	P	20071221		
	US 2007-60934931	P	20070420		
	US 2007-60934928	P	20070424		
	US 2007-60934934	P	20070424		
	US 2007-60934942	P	20070425		
	US 2007-60934943	P	20070425		
	US 2007-60932949	P	20070503		
	US 2007-61015611	P	20071220		
	EP 2008-731034	A3	20080228		
	WO 2008-US55353	A2	20080228		
	WO 2008-US55505	A2	20080229		
	WO 2008-US55511	A2	20080229		
	WO 2008-US55515	A2	20080229		
	WO 2008-US55516	A2	20080229		
	WO 2008-US55519	A2	20080229		
	WO 2008-US55524	A2	20080229		
	WO 2008-US55526	A2	20080229		
	WO 2008-US55527	A2	20080229		
	WO 2008-US55532	A2	20080229		
	WO 2008-US55533	A2	20080229		

WO 2008-US55542 A2 20080229
WO 2008-US55548 A2 20080229
WO 2008-US55550 A2 20080229
WO 2008-US55551 A2 20080229
WO 2008-US55554 A2 20080229
WO 2008-US55556 A2 20080229
WO 2008-US55560 A2 20080229
WO 2008-US55563 A2 20080229
EP 2008-731244 A3 20080303
WO 2008-US55597 A2 20080303
WO 2008-US55599 A2 20080303
WO 2008-US55601 A2 20080303
WO 2008-US55603 A2 20080303
WO 2008-US55604 A2 20080303
WO 2008-US55606 A2 20080303
WO 2008-US55608 A2 20080303
WO 2008-US55611 A2 20080303
WO 2008-US55612 A2 20080303
WO 2008-US55615 A2 20080303
WO 2008-US55618 A2 20080303
WO 2008-US55622 A2 20080303
WO 2008-US55625 A2 20080303
WO 2008-US55627 A2 20080303
WO 2008-US55631 A2 20080303
WO 2008-US55635 A2 20080303
WO 2008-US55644 A2 20080303
WO 2008-US55649 A2 20080303
WO 2008-US55651 A2 20080303
WO 2008-US55662 A2 20080303
WO 2008-US55676 A2 20080303
WO 2008-US55678 A2 20080303
WO 2008-US55693 A2 20080303
WO 2008-US55695 A2 20080303
WO 2008-US55697 A2 20080303
WO 2008-US55698 A2 20080303
WO 2008-US55701 A2 20080303
WO 2008-US55704 A2 20080303
WO 2008-US55708 A2 20080303
WO 2008-US55709 A2 20080303
WO 2008-US55711 A2 20080303
US 2009-552082 A1 20090901
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 149:324137
AB The present disclosure is based on the discovery that a nicked or gapped double-stranded RNA comprising at least three strands (termed meroduplex RNA or mdRNA) is a suitable substrate for Dicer or RISC and, therefore may be advantageously employed for gene silencing via, for example, the RNA interference pathway. An mdRNA comprises at least three strands that combine to form at least two non-overlapping double-stranded regions sepd. by a nick or gap wherein one strand is complementary to a mRNA. Partially duplexed dsRNA mols. (mdRNAs) are thus capable of initiating an RNA interference cascade that reduces expression of a target mRNA, such as a human transforming growth factor β receptor (TGFBR) mRNA. The introduction of substituted and modified nucleotides into mdRNA provides a powerful tool in overcoming potential limitations of in vivo stability and bioavailability inherent to nature RNA mols. The mean inhibitory concn. (IC50) of RISC and Dicer mdRNAs specific for influenza range from about 200 pM to about 15 nM; inclusion of a single locked nucleic acid reduced the IC50 of Dicer mdRNAs by up to 4-fold. In addn., the mdRNAs induce cytokines to a lesser extent than intact (i.e., not nicked) parent mols. Meroduplex RNAs are designed with the first strand complementary to a TGFBR mRNA, including TGFBR I, TGFBR II, and TGFBR III. Also provided are methods of decreasing expression of a TGFBR gene in a cell or in a subject to treat a TGFBR-related disease.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L16 ANSWER 4 OF 4 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 2004223470 EMBASE Full-text
DN 38657721 PMID: 15144206
TI A mammalian genetic system to screen for small molecules capable of

disrupting protein-protein interactions.
AU Zhao, Hui-Fen; Kiyota, Taira; Chowdhury, Shafinaz; Purisima, Enrico; Banville, Denis; Konishi, Yasuo; Shen, Shi-Hsiang (correspondence)
CS Health Sector, Biotechnology Research Institute, National Research Council of Canada, 6100 Royalmount Avenue, Montreal, Que. H4P 2R2, Canada. shi.shen@nrc.ca
AU Shen, Shi-Hsiang (correspondence)
CS Department of Medicine, McGill University, Montreal, Que. H3G 1A4, Canada. shi.shen@nrc.ca
SO Analytical Chemistry, (15 May 2004) Vol. 76, No. 10, pp. 2922-2927.
Refs: 18
ISSN: 0003-2700 CODEN: ANCHAM
DOI 10.1021/ac035396m
PB American Chemical Society, 2540 Olentangy River Road, P.O. Box 3337, Columbus, OH 43210-3337, United States.
CY United States
DT Journal; Article
FS Intellectual Indexing
022 Human Genetics
037 Drug Literature Index
LA English
SL English
ED Entered Embase: 10 Jun 2004
Last Updated on Embase: 10 Jun 2004
AB A mammalian two-hybrid system was developed for high-throughput screening of compounds that disrupt specific protein-protein interactions. The existing mammalian systems are unsatisfactory for drug screening due to non-regulated expression of interacting proteins. To construct a tightly regulated system, the tetracycline repressor was fused with the inhibitory KRAB domain as a suppressor. The binding of the suppressor to the tet operator entirely blocked expression of two interacting proteins. When both the inducer doxycycline and drugs were added to the culture, the reporter gene was either activated by interaction of the paired proteins with ineffective drugs or remained silent due to disruption of the protein interactions by the effective drugs. We demonstrate that interactions of the type I receptor for TGFβ with FKBP12 and the epidermal growth factor receptor (EGFR) with p85 are effectively disrupted by FK506 and EGFR kinase inhibitor AG 1478, respectively. The power of this system for drug screening was further demonstrated by rapid identification of inhibitors from a druglike library for the receptor kinases.

=> d his

(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5 439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6 35 S (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7 0 S L5 AND L6
L8 374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9 35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10 1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11 162 S L10 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12 44 S L11 AND PY<=2010
L13 1466 S L8 (5N) (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14 23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15 15 DUP REM L14 (8 DUPLICATES REMOVED)
L16 4 S L15 AND PY<=2010

=> s l8 (5n) (carcinoembryonic antigen or CEA or prostate-specific membrane antigen

```
 or PSMA or programmed death-ligand 1 or PD-L1)

L17        651 L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
               MEMBRANE ANTIGEN OR PSMA OR PROGRAMMED DEATH-LIGAND 1 OR PD-L1)

=> s l17 and (fusion or chimeric or heterodimer)

L18        133 L17 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> s l18 and py<=2010

L19          2 L18 AND PY<=2010

=> d 1-2 bib ab


L19  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2009:625581  CAPLUS Full-text
DN   151:377870
TI   Anaplastic lymphoma kinase (ALK)-induced malignancies: novel mechanisms of
     cell transformation and potential therapeutic approaches
AU   Wasik, Mariusz A.; Zhang, Qian; Marzec, Michal; Kasprzycka, Monika; Wang,
     Hong Yi; Liu, Xiaobin
CS   Department of Pathology and Laboratory Medicine, University of
     Pennsylvania, Philadelphia, PA, USA
SO   Seminars in Oncology (2009), 36(2, Suppl. 1), S27-S35
     CODEN: SOLGAV; ISSN: 0093-7754
DOI  10.1053/j.seminoncol.2009.02.007
PB   Elsevier Inc.
DT   Journal; General Review
LA   English
AB   A review.  Among the many oncogenic variants of the anaplastic lymphoma
     kinase (ALK), nucleophosmin 1 (NPM)/ALK fusion protein expressed in the
     subset of T-cell lymphoma (ALK+TCL) is currently the best characterized.
     NPM/ALK activates several signal transduction pathways, including
     PI3K/AKT, MEK/ERK, mTORC1, STAT3, and STAT5b.  In turn, the pathways
     modulate expression and function of many genes and proteins involved in
     the key cellular functions such as proliferation, growth, survival,
     metab., and angiogenesis.  Recent data indicate that NPM/ALK also promotes
     immune evasion of the ALK+TCL by inducing through STAT3 activation the
     expression of immunosuppressive cytokines interleukin-10 (IL-10) and
     transforming growth factor-beta (TGFβ) and cell surface protein
     CD274 (PD-L1, B7-H1).  In addn., NPM/ALK protects its own expression
     by mediating via STAT3 and at least one member of the DNA
     methyltransferase family DNMT1 epigenetic silencing of the SHP-1 and
     STAT5a genes.  In ALK+TCL cells, SHP-1 and STAT5a proteins act as potent
     tumor suppressors by promoting degrdn. of the NPM/ALK protein and
     inhibiting expression of the NPM/ALK gene, resp.  These findings provide
     further rationale to therapeutically target ALK and its effector proteins,
     foremost STAT3.  They also suggest that immunotherapeutic approaches to
     ALK+TCL and, possibly, other ALK-driven malignancies may require
     inhibition of ALK and STAT3 to achieve the optimal clin. efficacy.
OSC.G   8     THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
RE.CNT  78    THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT


L19  ANSWER 2 OF 2  EMBASE  COPYRIGHT (c) 2020 Elsevier B.V. All rights
     reserved on STN
AN   0050140648  EMBASE   Full-text
DN   70144356
TI   Adoptive transfer of PSMA-specific, TGF-β insensitive memory
     CD8+T cells: Suppression of human prostate cancer (CaP).
AU   Zhang, Qiang (correspondence); Helfand, Brian; Chen, Lin; Smith, Norm;
     Lee, Chung
CS   Chicago, IL, United States.
AU   Qin, Weijun
CS   Xian, China.
AU   Zhu, Julie
CS   Boston, MA, United States.
AU   Guo, Yinglu
CS   Beijing, China.
```

SO Journal of Urology, (April 2010) Vol. 183, No. 4, Supp. SUPPL. 1, pp. e265-e266. Abstract Number: 680.
Meeting Info: 2010 Annual Meeting of the American Urological Association, AUA. San Francisco, CA, United States. 29 May 2010-03 Jun 2010
ISSN: 0022-5347
DOI 10.1016/j.juro.2010.02.1079
PB Elsevier Inc..
PUI S 0022-5347(10)01335-2
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: Sep 2012
Last Updated on Embase: Sep 2012
AB INTRODUCTION AND OBJECTIVES: Tumor derived TGF-β is a potent immunosuppressant molecule which promotes CaP progression. Here we report a new immunotherapeutic approach using the adoptive transfer of PSMA-specific, TGF-β insensitive human memory CD8+ T cells to inhibit solid xenograft CaP. METHODS: Whole blood was collected from men with CaP prior to prostatectomy and CD45RAhighCD27-CD28-CCR7-memory CD8+ T cells were isolated using the EasySep CD8+ T cells enrichment kit, and then cultured in the presence of both fresh PSMA and irradiated autologous CD4+ T cells. We developed an anti-PSMA-vβ12-ζ-IRES-TβRIIDN chimeric T cell receptor construct (PZ-1-TβRIIDN) using an anti-PSMA IgTCR(ζ) gene (provided by Dr. Sadelain at Sloan-Kettering Cancer Center) and a dominant negative TGF-β type II receptor (TβRIIDN). Infection with a retroviral vector encoding this construct could induce memory T cells to be PSMA reactive and insensitive to TGF-β. Subcutaneous injection (5×105 cells) of either PC-3 CaP cells (PSMA negative; ATCC) or PSMA positive PC-3-PSMA cells (gift from Dr. Heston; Cleveland Clinic) into the right flank region of 15 immunodeficient RAG-1 mice was performed. Three weeks later, each set of animals was randomly assigned to one of three adoptive transfer groups: Group 1: memory CD8+ T cells infected with PZ-1-TβRIIDN; Group 2: memory CD8+ T cells infected with TβRIIDN only and Group 3: no treatment control. The animals were sacrificed after a total of 2 adoptive transfer treatments. The size and the weight of tumor and spleen were recorded. RESULTS: In Group 1 of PC-3-PSMA injected mice, the average tumor weight and volume of these mice was 2.62 g and 384.67 mm2, respectively. This was almost significantly less (~2-5 x) than that of animals in Group 2 (6.20g and 646.56 mm2) and Group 3 (11.66g and 752.24 mm2; P<0.05). Also, there was a significant difference between Groups 2 and 3. Interestingly, spleen weight of Group 1 (48.8mg) and Group 2 (64.5mg) increased compared to Group 3 (35.3 mg). Apoptosis in tumor cells was detected (TUNEL assay) only in animals of Group 1. There was no significant difference between the tumor size and weight in any of the three PC-3 injected groups. CONCLUSIONS: Tumor derived TGF-β decreases the function of host memory CD8+ T cells. Our approach combines TGF-β-insensitive with PSMA selectivity, which significantly enhance the specificity and tumor killing ability of multi-clonal CD8+ memory T cells. Therefore, this construct may offer a novel therapeutic intervention for both primary CaP treatment as well as for recurrence after prostatectomy.

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(FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
E BEDI ATUL/AU
L1 39 S E3
E RAVI RAJANI/AU
L2 44 S E3-E4
L3 55 S L1-L2

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4 0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)

```
L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010

=> s l18 and (linker or glycine linker)

L20           5 L18 AND (LINKER OR GLYCINE LINKER)

=> d 1-5


L20  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2020:1876680  CAPLUS Full-text
DN   173:674244
TI   preparation of sPD-1-Fc-sTGFβRII fusion protein for increasing
     cytotoxicity of immune cells and treating tumor
IN   Wu, Song; Zhu, Shimao; Wang, Fei; Sun, Haiyan; Lei, Qifang
PA   Shenzhen Following Precision Medical Research Institute, Peop. Rep. China
SO   Faming Zhuanli Shenqing, 20pp.
     CODEN: CNXXEV
DT   Patent
LA   Chinese
FAN.CNT 1
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ---------------------    --------
     CN 111690070         A    20200922    CN 2020-10403144         20200513
PRAI CN 2020-10403144          20200513


L20  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2020:1423434  CAPLUS Full-text
DN   173:293160
TI   Engineering bispecific antitumor antagonists targeting TGFβ1 and
     PD-1 or PD-L1 for treatment of cancer, infections and immune disorders
IN   Karow, Margaret; Sheng, Jackie; Zhang, Wei
PA   Gensun Biopharma, Inc., USA
SO   U.S. Pat. Appl. Publ., 284 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ---------------------    --------
     US 20200231665       A1   20200723    US 2019-16706187         20191206
PRAI US 2019-62869111     P    20190701
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT


L20  ANSWER 3 OF 5  CAPLUS  COPYRIGHT 2020 ACS on STN
AN   2018:1460154  CAPLUS Full-text
DN   169:281964
TI   TGFβ and/or ActRII antagonists for immunostimulation against immune
     exhaustion, for cancer immunotherapy and for potentiating vaccines
IN   Pearsall, Robert Scott; Kumar, Ravindra
PA   Acceleron Pharma Inc., USA
SO   PCT Int. Appl., 274pp.
     CODEN: PIXXD2
DT   Patent
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LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2018144542	A1	20180809	WO 2018-US16148	20180131
	CA 3051696	A1	20180809	CA 2018-3051696	20180131
	AU 2018214979	A1	20190815	AU 2018-214979	20180131
	KR 2019115037	A	20191010	KR 2019-7025689	20180131
	CN 110494155	A	20191122	CN 2018-80023489	20180131
	EP 3576773	A1	20191211	EP 2018-747362	20180131
	JP 2020505475	T	20200220	JP 2019-562229	20180131
	US 20200306340	A1	20201001	US 2019-16482869	20190801
PRAI	US 2017-62453413	P	20170201		
	WO 2018-US16148	W	20180131		

OS CASFORMULTNS 2018:1460154
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L20 ANSWER 4 OF 5 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052792557 EMBASE Full-text
DN 619156187
TI Preclinical evaluation and mechanistic characterization of M7824 (MSB0011359C), a novel bifunctional fusion protein targeting the PD-L1 and TGFβ pathways.
AU Lan, Yan (correspondence); Zhang, Dong; Xu, Chunxiao; Marelli, Bo; Qi, Jin; Qi, Huakui; Qin, Guozhong; Xu, Xiaomei; Wang, Hong; Sircar, Aroop; Brunkhorst, Beatrice; Austin, Eric; Radvanyi, Laszlo; Lo, Kin-Ming
CS EMD Serono Research and Development Institute, Inc., Billerica, MA, United States.
SO Cancer Research, (July 2017) Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 2615.
Meeting Info: American Association for Cancer Research Annual Meeting 2017. Washington, DC, United States. 01 Apr 2017-05 Apr 2017
ISSN: 1538-7445
DOI 10.1158/1538-7445.AM2017-2615
PB American Association for Cancer Research Inc..
CY Netherlands
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 14 Nov 2017
Last Updated on Embase: 14 Nov 2017
Indexing Added: 14 Nov 2017
First Entered Embase or Embase Alert: 14 Nov 2017

L20 ANSWER 5 OF 5 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0052750383 EMBASE Full-text
DN 618663162
TI Preclinical evaluation and mechanistic characterization of M7824 (MSB0011359C), a novel bifunctional fusion protein targeting the PD-L1 and TGFβ pathways.
AU Lan, Yan (correspondence); Zhang, Dong; Xu, Chunxiao; Marelli, Bo; Qi, Jin; Qi, Huakui; Qin, Guozhong; Xu, Xiaomei; Wang, Hong; Sircar, Aroop; Brunkhorst, Beatrice; Austin, Eric; Radvanyi, Laszlo; Lo, Kin-Ming
CS EMD Serono Research, Development Institute, Inc., Billerica, MA, United States.
SO Cancer Research, (July 2017) Vol. 77, No. 13, Supp. Supplement 1. Abstract Number: 2615.
Meeting Info: American Association for Cancer Research Annual Meeting 2017. Washington, DC, United States. 01 Apr 2017-05 Apr 2017
ISSN: 1538-7445
DOI 10.1158/1538-7445.AM2017-2615
PB American Association for Cancer Research Inc..
CY Netherlands
DT Journal; Conference; (Conference Abstract)
FS CONF

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FS   Intellectual Indexing
LA   English
SL   English
ED   Entered Embase: 13 Oct 2017
     Last Updated on Embase: 13 Oct 2017
     Indexing Added: 13 Oct 2017
     First Entered Embase or Embase Alert: 13 Oct 2017



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     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1           39 S E3
                E RAVI RAJANI/AU
L2           44 S E3-E4
L3           55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4            0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010
L20           5 S L18 AND (LINKER OR GLYCINE LINKER)

=> s l20 and py<=2010

L21           0 L20 AND PY<=2010

=> s l15 and l3

L22           0 L15 AND L3

=> s l12 and l3

L23           0 L12 AND L3

=> s l5 and l3

L24           0 L5 AND L3

=> d his


     (FILE 'HOME' ENTERED AT 15:50:49 ON 01 DEC 2020)

     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1           39 S E3
                E RAVI RAJANI/AU
L2           44 S E3-E4
L3           55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
L4            0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
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L5          439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6           35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7            0 S L5 AND L6
L8       374372 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L9        35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10        1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11         162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12          44 S L11 AND PY<=2010
L13        1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14          23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15          15 DUP REM L14 (8 DUPLICATES REMOVED)
L16           4 S L15 AND PY<=2010
L17         651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18         133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19           2 S L18 AND PY<=2010
L20           5 S L18 AND (LINKER OR GLYCINE LINKER)
L21           0 S L20 AND PY<=2010
L22           0 S L15 AND L3
L23           0 S L12 AND L3
L24           0 S L5 AND L3

=> s l3 and l8

L25          26 L3 AND L8

=> dup rem l25

PROCESSING COMPLETED FOR L25
L26           16 DUP REM L25 (10 DUPLICATES REMOVED)
                 ANSWERS '1-4' FROM FILE MEDLINE
                 ANSWERS '5-11' FROM FILE BIOSIS
                 ANSWERS '12-14' FROM FILE CAPLUS
                 ANSWERS '15-16' FROM FILE EMBASE

=> d 1-16 bib ab


L26  ANSWER 1 OF 16     MEDLINE ®  on STN           DUPLICATE 1
AN   2019540141     MEDLINE Full-text
DN   PubMed ID: 29467463
TI   Bifunctional immune checkpoint-targeted antibody-ligand traps that
     simultaneously disable TGFβ enhance the efficacy of cancer
     immunotherapy.
AU   Ravi Rajani; Pham Vui; Wysocki Piotr T; Sidransky David; Izumchenko
     Evgeny; Bedi Atul
CS   Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins
     University School of Medicine, Baltimore, MD, 21231, USA. abedil1@jhmi.edu
AU   Noonan Kimberly A; Borrello Ivan M
CS   Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School
     of Medicine, Baltimore, MD, 21231, USA.
AU   Bedi Rishi
CS   Department of Computer Science, Stanford University, Palo Alto, CA, 94305,
     USA.
AU   Zhavoronkov Alex; Ozerov Ivan V; Makarev Eugene; V Artemov Artem
CS   Insilico Medicine, Inc., Emerging Technology Centers, Johns Hopkins
     University at Eastern, B301, 1101 33rd Street, Baltimore, MD, 21218, USA.
AU   Mehra Ranee
CS   Department of Oncology, Johns Hopkins University School of Medicine,
     Baltimore, MD, 21231, USA.
AU   Nimmagadda Sridhar
AUID ORCID: https://orcid.org/0000-0002-6413-7191
CS   Department of Radiology and Radiological Science, Johns Hopkins Medical
     Institutions, Baltimore, MD, 21287, USA.
AU   Marchionni Luigi
CS   Center for Computational Genomics, Johns Hopkins University School of
     Medicine, Baltimore, MD, 21231, USA.
SO   Nature communications, (20180221) Vol. 9, No. 1, pp. 741.  Electronic
     Publication Date: 21 Feb 2018
     Journal code: 101528555. E-ISSN: 2041-1723. L-ISSN: 2041-1723.
     Report No.: PMC-PMC5821872.
DOI  http://dx.doi.org/10.1038/s41467-017-02696-6
CY   England: United Kingdom
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DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Electronic
EM 201803
ED Entered STN: 22 Feb 2018
Last Updated on STN: 23 Mar 2018
Indexing Added: 23 Mar 2018
Entered Medline: 22 Mar 2018
GO United States NCI NIH HHS
GN R01 CA184199
GO United States NIDCR NIH HHS
GN P50 DE019032
OSC.G 41 There are 41 MEDLINE records that cite this record
REM.CNT 68 There are 68 cited references available in MEDLINE for this document.
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd). a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L26 ANSWER 2 OF 16 MEDLINE ® on STN DUPLICATE 2
AN 2015468037 MEDLINE Full-text
DN PubMed ID: 25593015
TI A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma.
AU Gilbert Jill; Murphy Barbara
CS Vanderbilt University, Nashville, TN, United States. jill.gilbert@vanderbilt.edu; barbara.murphy@Vanderbilt.Edu
AU Schell Michael J; Zhao Xiuhua; Tanvetyanon Tawee; Leon Marino E
CS H. Lee Moffitt Cancer Center, Tampa, FL, United States. Michael.Schell@moffitt.org; Xiuhua.Zhao@moffitt.org; Tawee.Tanvetyanon@moffitt.org; Marino.Leon@Moffitt.org
AU Neil Hayes D
CS UNC Lineberger Cancer Center, Chapel Hill, NC, United States. hayes@med.unc.edu
AU Haigentz Missak Jr
CS Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, United States. mhaigent@montefiore.org
AU Saba Nabil
CS Emory Winship Cancer Institute, Atlanta, GA, United States. NFSABA@emory.edu
AU Nieva Jorge
CS University of Southern California, Los Angeles, CA, United States. Jorge.Nieva@med.usc.edu
AU Bishop Justin; Sidransky David; Ravi Rajani; Bedi Atul; Chung Christine H
CS Johns Hopkins Medical Institutions, Baltimore, MD, United States. jbishop@jhmi.edu; dsidrans@jhmi.edu; ravira@jhmi.edu; abedi1@jhmi.edu; cchung11@jhmi.edu
SO Oral oncology, (2015 Apr) Vol. 51, No. 4, pp. 376-82. Electronic Publication Date: 13 Jan 2015
Journal code: 9709118. E-ISSN: 1879-0593. L-ISSN: 1368-8375.

Report No.: PMC-PMC4459134; MID-NIHMS651330.
DOI http://dx.doi.org/10.1016/j.oraloncology.2014.12.011
CY England: United Kingdom
DT (CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201512
ED Entered STN: 17 Jan 2015
Last Updated on STN: 16 Dec 2015
Indexing Added: 16 Dec 2015
Entered Medline: 7 Dec 2015
GO United States NCI NIH HHS
GN HHSN261201100100C; R25 CA174664; P30 CA076292
GO United States NIDCR NIH HHS
GN P50 DE019032; P50DE019032
GO United States PHS HHS
GN N01 261201100100C
OSC.G 11 There are 11 MEDLINE records that cite this record
REM.CNT 24 There are 24 cited references available in MEDLINE for this document.
AB INTRODUCTION: A combination of cetuximab and sorafenib in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) were assessed for potential benefit.

MATERIAL AND METHODS: In a randomized phase II study, R/M HNSCC patients were treated with cetuximab 400mg/m(2) IV on day 1 followed by 250mg/m(2) IV weekly (Arm A), or cetuximab at the same dose/schedule plus sorafenib 400mg PO twice-a-day (Arm B). Each cycle was 21days. Tumor p16 and HPV status, and plasma immunomodulatory cytokine levels were assessed.

RESULTS: Of 55 patients enrolled (Arm A-27, Arm B-28), 52 patients received assigned treatments and 43 were evaluable for response. Overall response rate was 8% for both arms. Median overall survival (OS) and progression-free survival (PFS) were 9.0 and 3.0months in Arm A, and 5.7 and 3.2months in Arm B, respectively. Forty-four patients had tumors available for p16 staining (35-negative, 9-positive). Three of nine p16-positive tumors were also HPV positive. The p16-negative patients had significantly better PFS compared to the p16-positive patients (3.7 vs. 1.6months; p-value: 0.03), regardless of study arms. Twenty-four plasma samples were tested for 12 cytokine levels and patients with higher TGFβ1 levels had inferior PFS compared to lower levels (1.9 vs. 4.7months; adjusted p-value: 0.015), regardless of study arms.

CONCLUSIONS: A subset of R/M patients with p16-negative tumors or lower plasma TGFβ1 levels had longer PFS given the cetuximab-based therapy. However, both arms showed only modest response and sorafenib given with cetuximab did not demonstrate clinical benefit.
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L26 ANSWER 3 OF 16 MEDLINE ® on STN DUPLICATE 3
AN 2014730904 MEDLINE Full-text
DN PubMed ID: 24830724
TI The TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors.
AU Izumchenko Evgeny; Chang Xiaofei; Michailidi Christina; Kagohara Luciane; Ravi Rajani; Brait Mariana; Hoque Mohammad O; Ling Shizhang; Bedi Atul; Sidransky David
CS Authors' Affiliations: Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, and. dsidrans@jhmi.edu
AU Paz Keren
CS Champions Oncology, Inc., Baltimore, Maryland.
SO Cancer research, (2014 Jul 15) Vol. 74, No. 14, pp. 3995-4005. Electronic Publication Date: 15 May 2014
Journal code: 2984705R. E-ISSN: 1538-7445. L-ISSN: 0008-5472.
Report No.: PMC-PMC4122100; MID-NIHMS597285.

DOI http://dx.doi.org/10.1158/0008-5472.CAN-14-0110
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201409
ED Entered STN: 17 May 2014
Last Updated on STN: 27 Sep 2014
Indexing Added: 27 Sep 2014
Entered Medline: 26 Sep 2014
GO United States NCI NIH HHS
GN P50 CA058184; U01CA084986; U01 CA084986
GO United States NIDCR NIH HHS
GN R37DE012588; P50 DE019032; R37 DE012588
OSC.G 46 There are 46 MEDLINE records that cite this record
REM.CNT 42 There are 42 cited references available in MEDLINE for this document.
AB Although specific mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) identify tumors that are responsive to EGFR tyrosine kinase inhibitors (TKI), these genetic alterations are present in only a minority of patients. Patients with tumors expressing wild-type EGFR lack reliable predictive markers of their clinical response to EGFR TKIs. Although epithelial-mesenchymal transition (EMT) has been inversely correlated with the response of cancers to EGFR-targeted therapy, the precise molecular mechanisms underlying this association have not been defined and no specific EMT-associated biomarker of clinical benefit has been identified. Here, we show that during transforming growth factor β (TGFβ)-mediated EMT, inhibition of the microRNAs 200 (miR200) family results in upregulated expression of the mitogen-inducible gene 6 (MIG6), a negative regulator of EGFR. The MIG6-mediated reduction of EGFR occurs concomitantly with a TGFβ-induced EMT-associated kinase switch of tumor cells to an AKT-activated EGFR-independent state. In a panel of 25 cancer cell lines of different tissue origins, we find that the ratio of the expression levels of MIG6 and miR200c is highly correlated with EMT and resistance to erlotinib. Analyses of primary tumor xenografts of patient-derived lung and pancreatic cancers carrying wild-type EGFR showed that the tumor MIG6(mRNA)/miR200 ratio was inversely correlated with response to erlotinib in vivo. Our data demonstrate that the TGFβ-miR200-MIG6 network orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors, and identify a low ratio of MIG6 to miR200 as a promising predictive biomarker of the response of tumors to EGFR TKIs.
©2014 American Association for Cancer Research.

L26 ANSWER 4 OF 16 MEDLINE ® on STN DUPLICATE 4
AN 2012918323 MEDLINE Full-text
DN PubMed ID: 22927667
TI Inhibition of TGF-β enhances the in vivo antitumor efficacy of EGF receptor-targeted therapy.
AU Bedi Atul
CS Head and Neck Cancer Research Division, Department of Otolaryngology-Head and Neck Surgery, 1550 Orleans Street, Johns Hopkins University School of Medicine, Cancer Research Building II, Baltimore, MD 21231, USA.
AU Chang Xiaofei; Noonan Kimberly; Pham Vui; Bedi Rishi; Fertig Elana J; Considine Michael; Califano Joseph A; Borrello Ivan; Chung Christine H; Sidransky David; Ravi Rajani
SO Molecular cancer therapeutics, (2012 Nov) Vol. 11, No. 11, pp. 2429-39.
Electronic Publication Date: 27 Aug 2012
Journal code: 101132535. E-ISSN: 1538-8514. L-ISSN: 1535-7163.
Report No.: PMC-PMC3640459; MID-NIHMS438147.
DOI http://dx.doi.org/10.1158/1535-7163.MCT-12-0101-T
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201304
ED Entered STN: 29 Aug 2012

Last Updated on STN: 24 Apr 2013
Entered Medline: 23 Apr 2013
GO United States NCI NIH HHS
GN K25CA141053; P30 CA006973; K25 CA141053; 5P50CA096784-05; P50 CA096784; R01 CA123277; R01CA123277; R01 CA184199
GO United States NIDCR NIH HHS
GN R01 DE017982; P50 DE019032
OSC.G 24 There are 24 MEDLINE records that cite this record
REM.CNT 46 There are 46 cited references available in MEDLINE for this document.
AB EGF receptor (EGFR)-targeted monoclonal antibodies (mAb), such as cetuximab, execute their antitumor effect in vivo via blockade of receptor-ligand interactions and engagement of Fcγ receptors on immune effector cells that trigger antibody-dependent cell-mediated cytotoxicity (ADCC). We show that tumors counteract the in vivo antitumor activity of anti-EGFR mAbs by increasing tumor cell-autonomous expression of TGF-β. We show that TGF-β suppresses the expression of key molecular effectors of immune cell-mediated cytotoxicity, including Apo2L/TRAIL, CD95L/FasL, granzyme B, and IFN-γ. In addition to exerting an extrinsic inhibition of the cytotoxic function of immune effectors, TGF-β-mediated activation of AKT provides an intrinsic EGFR-independent survival signal that protects tumor cells from immune cell-mediated apoptosis. Treatment of mice-bearing xenografts of human head and neck squamous cell carcinoma with cetuximab resulted in emergence of resistant tumor cells that expressed relatively higher levels of TGF-β compared with untreated tumor-bearing mice. Although treatment with cetuximab alone forced the natural selection of TGF-β-overexpressing tumor cells in nonregressing tumors, combinatorial treatment with cetuximab and a TGF-β-blocking antibody prevented the emergence of such resistant tumor cells and induced complete tumor regression. Therefore, elevated levels of TGF-β in the tumor microenvironment enable tumor cells to evade ADCC and resist the antitumor activity of cetuximab in vivo. Our results show that TGF-β is a key molecular determinant of the de novo and acquired resistance of cancers to EGFR-targeted mAbs, and provide a rationale for combinatorial targeting of TGF-β to improve anti-EGFR-specific antibody therapy of EGFR-expressing cancers.
©2012 AACR.

L26 ANSWER 5 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2019:842991 BIOSIS Full-text
DN PREV201900942198
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 10442860 20191015
SO Official Gazette of the United States Patent and Trademark Office Patents, (OCT 15 2019)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 6 Nov 2019
Last Updated on STN: 6 Nov 2019
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 6 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2018:318724 BIOSIS Full-text
DN PREV201800318724
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGF beta enhance the efficacy of cancer immunotherapy.
AU Ravi, Rajani; Noonan, Kimberly A.; Vui Pham; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; Artemov, Artem V.; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul [Reprint Author]
CS Johns Hopkins Univ, Sch Med, Dept Otolaryngol Head and Neck Canc Res, Baltimore, MD 21231 USA
abedi1@jhmi.edu
SO Nature Communications, (FEB 21 2018) Vol. 9, pp. Article No.: 741. http://www.nature.com/ncomms/index.html.
ISSN: 2041-1723.
DOI 10.1038/s41467-017-02696-6
DT Article
LA English
ED Entered STN: 28 Mar 2018
Last Updated on STN: 28 Mar 2018
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-beta (TGF beta), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and T(H)1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGF beta receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGF beta in the target cell microenvironment (alpha-CTLA4-TGF beta RIIecd and alpha-PDL1-TGF beta RIIecd). alpha-CTLA4-TGF beta RIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, alpha-PDL1-TGF beta RIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGF beta-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L26 ANSWER 7 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2018:123836 BIOSIS Full-text
DN PREV201800123836
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09850306 20171226
SO Official Gazette of the United States Patent and Trademark Office Patents, (DEC 26 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 17 Jan 2018
Last Updated on STN: 17 Jan 2018
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional

in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2016:751124 BIOSIS Full-text
DN PREV201600751124
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09441044 20160913
SO Official Gazette of the United States Patent and Trademark Office Patents, (SEP 13 2016)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 5 Oct 2016
Last Updated on STN: 5 Oct 2016
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By conteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L26 ANSWER 9 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2015:392017 BIOSIS Full-text
DN PREV201500392017
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 08993524 20150331
SO Official Gazette of the United States Patent and Trademark Office Patents, (MAR 31 2015)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 13 May 2015
Last Updated on STN: 13 May 2015
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immune suppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant

or disseminated cancer cells.

L26 ANSWER 10 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2014:713314 BIOSIS Full-text
DN PREV201400713314
TI The TGF beta-miR200-Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors (vol 74, pg 3995, 2014).
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hogue, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
SO Cancer Research, (SEP 1 2014) Vol. 74, No. 17, pp. 4950.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/0008-5472.CAN-14-2153
DT Article
Errata
LA English
ED Entered STN: 15 Oct 2014
Last Updated on STN: 15 Oct 2014

L26 ANSWER 11 OF 16 BIOSIS COPYRIGHT (c) 2020 Clarivate Analytics on STN
AN 2015:430029 BIOSIS Full-text
DN PREV201500430029
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. [Reprint Author]; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins Univ, Baltimore, MD USA
SO Cancer Research, (OCT 1 2014) Vol. 74, No. 19, Suppl. S, pp. 4382.
Meeting Info.: 105th Annual Meeting of the American-Association-for-Cancer-Research (AACR). San Diego, CA, USA. April 05 -09, 2014. Amer Assoc Canc Res.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/1538-7445.AM2014-4382
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 27 May 2015
Last Updated on STN: 27 May 2015

L26 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2018:1128946 CAPLUS Full-text
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy
AU Ravi, Rajani; Noonan, Kimberly A.; Pham, Vui; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; V. Artemov, Artem; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul
CS Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SO Nature Communications (2018), 9(1), 1-14
CODEN: NCAOBW; ISSN: 2041-1723
DOI 10.1038/s41467-017-02696-6
PB Nature Research
DT Journal; (online computer file)
LA English
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8+ and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd).

a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). The study demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2014:1471342 CAPLUS Full-text
DN 161:625200
TI The TGFβ-miR200-MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors [Erratum to document cited in CA161:458236]
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hoque, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
CS Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SO Cancer Research (2014), 74(17), 4950
CODEN: CNREA8; ISSN: 0008-5472
DOI 10.1158/0008-5472.CAN-14-2153
PB American Association for Cancer Research
DT Journal
LA English
AB On page 3995, the authors list was published with typog. errors; the correct authors list is given.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2020 ACS on STN
AN 2011:1138357 CAPLUS Full-text
DN 155:404869
TI Fusion proteins of targeting antibody and immunomodulatory moiety for targeted antitumor therapy
IN Bedi, Atul ; Ravi, Rajani
PA The Johns Hopkins University, USA
SO PCT Int. Appl., 154pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011109789	A2	20110909	WO 2011-US27317	20110304
WO 2011109789	A3	20120405		
CA 2791383	A1	20110909	CA 2011-2791383	20110304
CA 3083324	A1	20110909	CA 2011-3083324	20110304
IL 221607	A	20121031	IL 2011-221607	20110304
EP 2542590	A2	20130109	EP 2011-751481	20110304
EP 2542590	B1	20170503		
EP 2542590	B2	20200401		
JP 2013521311	T	20130610	JP 2012-556279	20110304
JP 6066732	B2	20170125		
ES 2638521	T3	20171023	ES 2011-751481	20110304
EP 3260470	A1	20171227	EP 2017-168491	20110304
IL 266971	A	20190731	IL 2011-266971	20110304
IN 2012CN08417	A	20140214	IN 2012-CN8417	20121001
US 20130039911	A1	20130214	US 2012-13582717	20121017
US 8993524	B2	20150331		
US 20150183881	A1	20150702	US 2015-14645282	20150311
US 9441044	B2	20160913		
JP 2017043600	A	20170302	JP 2016-145162	20160725
JP 6378262	B2	20180822		

	US 20160340430	A1	20161124	US 2016-15231309	20160808
	US 9850306	B2	20171226		
	US 20170158770	A1	20170608	US 2016-15362632	20161128
	US 10442860	B2	20191015		
	JP 2018172439	A	20181108	JP 2018-140050	20180726
	IN 201948021756	A	20191018	IN 2019-48021756	20190531
	US 20200115455	A1	20200416	US 2019-16601347	20191014
PRAI	US 2010-61311255	P	20100305		
	US 2011-61435671	P	20110124		
	CA 2011-2791383	A3	20110304		
	EP 2011-751481	A3	20110304		
	IL 2011-221607	A3	20110304		
	JP 2012-556279	A3	20110304		
	WO 2011-US27317	W	20110304		
	IN 2012-CN8417	A3	20121001		
	US 2012-13582717	A1	20121017		
	US 2015-14645282	A1	20150311		
	JP 2016-145162	A3	20160725		
	US 2016-15231309	A3	20160808		
	US 2016-15362632	A1	20161128		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2011:1138357

AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF -.beta .)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compns. and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

OSC.G 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)

L26 ANSWER 15 OF 16 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN

AN 20170658529 EMBASE Full-text

DN 618271173 PMID: 28522603

TI SMAD4 loss is associated with cetuximab resistance and induction of MAPK/JNK activation in head and neck cancer cells.

AU Ozawa, Hiroyuki; Ranaweera, Ruchira S.; Fertig, Elana J.; Howard, Jason D.; Markovic, Ana; Perez, Jimena; Wang, Hao; Kang, Hyunseok; Chung, Christine H. (correspondence)

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AU Izumchenko, Evgeny; Bedi, Atul; Ravi, Rajani; Sidransky, David

CS Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, School of Medicine, Baltimore, MD, United States.

AU Makarev, Eugene; Zhavoronkov, Alex

CS Insilico Medicine, Inc., ETC, Johns Hopkins University, Baltimore, MD, United States.

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AU Le, Quynh-Thu; Kong, Christina S.

CS Department of Pathology, Stanford University, School of Medicine, Stanford, CA, United States.

AU Jordan, Richard C.

CS Department of Orofacial Sciences and Pathology, University of California, San Francisco, San Francisco, CA, United States.

AU Quon, Harry

CS Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, MD, United States.

AU Chung, Christine H. (correspondence)

CS Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, H.

Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL, 33612, United States. Christine.Chung@Moffitt.Org
SO Clinical Cancer Research, (1 Sep 2017) Vol. 23, No. 17, pp. 5162-5175.
Refs: 65
ISSN: 1078-0432; E-ISSN: 1557-3265 CODEN: CCREF4
DOI 10.1158/1078-0432.CCR-16-1686
PB American Association for Cancer Research Inc..
CY United States
DT Journal; Article
FS Intellectual Indexing
016 Cancer
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered Embase: 26 Sep 2017
Last Updated on Embase: 5 Jul 2018
Indexing Added: 26 Sep 2017
First Entered Embase or Embase Alert: 26 Sep 2017
AB Purpose: We previously demonstrated an association between decreased SMAD4 expression and cetuximab resistance in head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to further elucidate the clinical relevance of SMAD4 loss in HNSCC. Experimental Design: SMAD4 expression was assessed by IHC in 130 newly diagnosed and 43 patients with recurrent HNSCC. Correlative statistical analysis with clinicopathologic data was also performed. OncoFinder, a bioinformatics tool, was used to analyze molecular signaling in TCGA tumors with low or high SMAD4 mRNA levels. The role of SMAD4 was investigated by shRNA knockdown and gene reconstitution of HPV-negative HNSCC cell lines in vitro and in vivo. Results: Our analysis revealed that SMAD4 loss was associated with an aggressive, HPV-negative, cetuximab-resistant phenotype. We found a signature of prosurvival and antiapoptotic pathways that were commonly dysregulated in SMAD4-low cases derived from TCGA-HNSCC dataset and an independent oral cavity squamous cell carcinoma (OSCC) cohort obtained from GEO. We show that SMAD4 depletion in an HNSCC cell line induces cetuximab resistance and results in worse survival in an orthotopic mouse model in vivo. We implicate JNK and MAPK activation as mediators of cetuximab resistance and provide the foundation for the concomitant EGFR and JNK/MAPK inhibition as a potential strategy for overcoming cetuximab resistance in HNSCCs with SMAD4 loss. Conclusions: Our study demonstrates that loss of SMAD4 expression is a signature characterizing the cetuximab-resistant phenotype and suggests that SMAD4 expression may be a determinant of sensitivity/resistance to EGFR/MAPK or EGFR/JNK inhibition in HPV-negative HNSCC tumors.

L26 ANSWER 16 OF 16 EMBASE COPYRIGHT (c) 2020 Elsevier B.V. All rights reserved on STN
AN 0051693676 EMBASE Full-text
DN 71721427
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. (correspondence); Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins University, Baltimore, MD, United States.
SO Cancer Research, (1 Oct 2014) Vol. 74, No. 19, Supp. SUPPL. 1. Abstract Number: 4382.
Meeting Info: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014. San Diego, CA, United States. 05 Apr 2014-09 Apr 2014
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2014-4382
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 3 Feb 2015
Last Updated on Embase: 3 Feb 2015
AB While sensitizing mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) render tumors more sensitive to EGFR

tyrosine kinase inhibitors (TKIs), these genetic alterations are present in only a minority of patients who respond to treatment and are rare in tumors other than NSCLCs. Thus, clinical benefit of TKIs in a subset of patients with wild-type EGFR may be underestimated due to the lack of appropriate predictive markers to stratify them from larger number of patients who do not response. It has long been observed that the response of anti-EGFR agents is associated with epithelial and mesenchymal transition (EMT) in multiple types of tumors without known EGFR mutations. However, little is known about the molecular mechanisms underlying this association, and no EMT-associated biomarkers of clinical utility have been successfully developed. Here we show that during the TGFβ-induced EMT, upregulation of mitogen-inducible gene 6 (Mig6), a negative regulator of EGFR, by microRNAs 200 (miR200) family is leading to reduced EGFR dependence, initiation of kinase switch in mesenchymal cells and subsequent insensitivity of these cells to EGFR inhibition. Moreover, we found that the ratio between mRNA levels of Mig6 and miR200c highly correlated with erlotinib sensitivity and EMT status in panel of 25 cancer cell lines of different tissue origins. Furthermore, analysis of directly xenografted human lung and pancreatic tumors (tumorgrafts) bearing wtEGFR demonstrated a higher response to EGFR inhibitor erlotinib for models with low Mig6 (mRNA)/miR200 ratio. Collectively, our data demonstrates that during the EMT-associated evolution of resistance to EGFR inhibitors, Mig6 expression is highly correlated with EMT status and identifies the ratio of Mig6 mRNA to miR200 as a novel, reliable and cost-effective predictor of biologic and clinical response to TKIs.

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     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
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                E RAVI RAJANI/AU
L2            44 S E3-E4
L3            55 S L1-L2

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L4             0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5           439 S (POLYPEPTIDE AND BINDS AND TUMOR CELL)
L6            35 S (TARGETING MOIETY FUSED OR  IMMUNOMODULATORY MOIETY)
L7             0 S L5 AND L6
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L9         35612 S L8 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L10         1487 S L9 AND (FUSION OR CHIMERIC OR HETERODIMER)
L11          162 S L10 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L12           44 S L11 AND PY<=2010
L13         1466 S L8 (5N)  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L14           23 S L13 AND (FUSION OR CHIMERIC OR HETERODIMER)
L15           15 DUP REM L14 (8 DUPLICATES REMOVED)
L16            4 S L15 AND PY<=2010
L17          651 S L8 (5N) (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFI
L18          133 S L17 AND (FUSION OR CHIMERIC OR HETERODIMER)
L19            2 S L18 AND PY<=2010
L20            5 S L18 AND (LINKER OR GLYCINE LINKER)
L21            0 S L20 AND PY<=2010
L22            0 S L15 AND L3
L23            0 S L12 AND L3
L24            0 S L5 AND L3
L25           26 S L3 AND L8
L26           16 DUP REM L25 (10 DUPLICATES REMOVED)

=> s l16 AND (LINKER OR GLYCINE LINKER)

L27            0 L16 AND (LINKER OR GLYCINE LINKER)

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     FILE 'HCAPLUS' ENTERED AT 15:51:08 ON 01 DEC 2020
                E BEDI ATUL/AU
L1            39 S E3
                E RAVI RAJANI/AU
L2            44 S E3-E4
L3            55 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:52:04 ON 01 DEC 2020
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=>  file hcaplus

COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
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FULL ESTIMATED COST                                 0.21             0.21

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FILE COVERS 1907 - 13 Sep 2021 VOL 176 ISS 1
FILE LAST UPDATED: 12 Sep 2021 (20210912/ED)

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substance identification.

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E3           40 --> BEDI ATUL/AU
E4            2     BEDI B/AU
E5            1     BEDI B R/AU
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=> e  ravi rajani/au

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E2            1     RAVI RAJAMANICKAM/AU
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=> s l1-l2

L3           73 (L1 OR L2)

=> file .medline

COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
                                                   ENTRY          SESSION
FULL ESTIMATED COST                               16.22            16.43

FILE 'MEDLINE' ENTERED AT 07:49:37 ON 13 SEP 2021

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=> s (targeting moiety fused with immunomodulatory moiety)

L4            0 (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
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=> s (targeting moiety fused and immunomodulatory moiety)

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=> s l8 and (fusion or chimeric or heterodimer)

L9        1650 L8 AND (FUSION OR CHIMERIC OR HETERODIMER)

=> s l9 and  (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediat
or or HVEM)

L10        187 L9 AND (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES VIRU
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=> s l9 and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen
or PSMA or programmed death-ligand 1 or PD-L1)

L11        312 L9 AND (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
               MEMBRANE ANTIGEN OR PSMA OR PROGRAMMED DEATH-LIGAND 1 OR PD-L1)

=> d ab


L11  ANSWER 1 OF 312     MEDLINE ®  on STN
AB   Background:  For patients with recurrent glioblastoma (rGBM), there are
     few options following treatment failure with radiotherapy plus
     temozolomide.  Bintrafusp alfa is a first-in-class bifunctional fusion
     protein composed of the extracellular domain of the TGF-βRII
     receptor (a TGF-β "trap") fused to a human IgG1 antibody blocking
     PD-L1.

     Methods:  In this phase I, open-label expansion cohort (NCT02517398),
     patients with rGBM that progressed after radiotherapy plus temozolomide
     received bintrafusp alfa 1200 mg Q2W until disease progression,
     unacceptable toxicity, or trial withdrawal.  Response was assessed per
     RANO criteria.  The primary endpoint was disease control rate (DCR);
     secondary endpoints included safety.

     Results:  As of August 24, 2018, 35 patients received bintrafusp alfa for
     a median of 1.8 (range, 0.5-20.7) months.  Eight patients (22.9%)
     experienced disease control as assessed by an independent review
     committee: 2 had a partial response, 4 had stable disease, and 2 had
     non-complete response/non-progressive disease.  Median progression-free
     survival (PFS) was 1.4 (95% confidence interval [CI], 1.2-1.6) months; 6-
     and 12-month PFS rates were 15.1% and 11.3%, respectively.  Median overall
     survival (OS) was 5.3 (95% CI, 2.6-9.4) months; 6- and 12-month OS rates
     were 44.5% and 30.8%, respectively.  The DCR (95% CI) was 66.7%
     (22.3-95.7%) for patients with IDH-mutant GBM (n = 6) and 13.8%
     (3.9-31.7%) for patients with IDH-wild-type GBM (n = 29).  Disease control
     was seen regardless of PD-L1 expression.  Twenty-five patients (71.4%)
     experienced treatment-related adverse events (grade ≥3; 17.1% [n =
     6]).

     Conclusions:  The percentage of patients achieving disease control and the
     manageable safety profile may warrant further investigation of bintrafusp
     alfa in GBM.
     © The Author(s) 2021. Published by Oxford University Press, the
     Society for Neuro-Oncology and the European Association of Neuro-Oncology.
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=> d his


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                E  RAVI RAJANI/AU
L2            50 S E1-E4
L3            73 S L1-L2

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L5             0 S (TARGETING MOIETY FUSED AND IMMUNOMODULATORY MOIETY)
L6            38 S  (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
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L8         37645 S L7 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L9          1650 S L8 AND (FUSION OR CHIMERIC OR HETERODIMER)
L10          187 S L9 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L11          312 S L9 AND (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC

=> s l11 and py<=2010

L12          24 L11 AND PY<=2010

=> dup rem l12

PROCESSING COMPLETED FOR L12
L13           22 DUP REM L12 (2 DUPLICATES REMOVED)
                 ANSWERS '1-21' FROM FILE CAPLUS
                 ANSWER '22' FROM FILE EMBASE

=> d 1-22 bib ab


L13  ANSWER 1 OF 22  CAPLUS  COPYRIGHT 2021 ACS on STN DUPLICATE 1
AN   2005:248644  CAPLUS Full-text
DN   142:274057
TI   Sequences of human schizophrenia related genes and use for diagnosis,
     prognosis and therapy
IN   Liew, Choong-chin
PA   Chondrogene Limited, Can.
SO   U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 51
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
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     CA 2702148           A1   20000713    CA 2000-2702148          20000105
     CA 2702148           C    20140304

     CA 2833366           A1   20000713    CA 2000-2833266          20000105

     US 20040014059       A1   20040122    US 2002-268730           20021009
     US 7598031           B2   20091006

     US 20070031841       A1   20070208    US 2003-601518           20030620

     US 20060134635       A1   20060622    US 2004-802875           20040312

     US 20050191637       A1   20050901    US 2004-803737           20040318
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CA 2702148	C	Dead	20201107
CA 2832266	A1	Dead	20201107
US 20040014059	A1	Dead	20201107
US 7598031	B2	Dead	20201107
US 20070031841	A1	Dead	20201121

US 20060134635 A1 Dead 20201121
US 20050191637 A1 Dead 20201106
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US 20120165212 A1 Dead 20201121
US 20130190197 A1 Dead 20201107
US 8669058 B2 Dead 20201107

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention is directed to detection and measurement of gene transcripts and their equiv. nucleic acid products in blood. Specifically provided is anal. performed on a drop of blood for detecting, diagnosing and monitoring diseases using gene-specific and/or tissue-specific primers. The present invention also describes methods by which delineation of the sequence and/or quantitation of the expression levels of disease-specific genes allows for an immediate and accurate diagnostic/prognostic test for disease or to assess the effect of a particular treatment regimen. [This abstr. record is one of 3 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.]

L13 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2016:1876135 CAPLUS Full-text
DN 166:338726
TI Methods and compositions related to th-1 dendritic cells
IN Decker, William K.; Shpall, Elizabeth J.; Komanduri, Krishna V.; Xing, Dongxia
PA The Board of Regents, The University of Texas System, USA
SO U.S., No pp. given
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 8728806	B2	20140520	US 2011-13132517	20110829
US 20110306948	A1	20111215		
WO 2010065876	A2	20100610	WO 2009-US66807	20091204
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US 20140286975	A1	20140925	US 2014-14248908	20140409
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US 20160263206	A1	20160915	US 2016-15133204	20160419
US 9993537	B2	20180612		

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PRAI US 2008-61120437     P    20081206
     WO 2009-US66807      W    20091204
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     WO 2010065876        A3   Dead            20201202
     US 20140286975       A1   Alive           20201121
     US 9333248           B2   Alive           20201120
     US 20160263206       A1   Alive           20201120
     US 9993537           B2   Alive           20201121
     US 20190262442       A1   Alive           20201120
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB   Certain embodiments of the invention are directed to methods for inducing
     an immunol. response to a tumor in a patient using mature dendritic cells
     transfected with a nucleic acid compn. encoding one or more tumor antigens
     and loaded with a corresponding tumor antigen compn.
OSC.G   2     THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)


L13  ANSWER 3 OF 22  CAPLUS  COPYRIGHT 2021 ACS on STN
AN   2016:2121702  CAPLUS Full-text
DN   167:477322
TI   Aptamer-targeted costimulatory ligand aptamer
IN   Gilboa, Eli; Pastor, Fernando
PA   University of Miami, USA
SO   U.S. Pat. Appl. Publ., No pp. given
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
     ---------------     ----  --------    ----------------------   --------
     US 20130209514       A1   20130815    US 2012-13376873         20120628

     WO 2010144295        A1   20101216    WO 2010-US37164          20100603
PRAI US 2009-61185251     P    20090609
     WO 2010-US37164      W    20100603
PSPI
     PATENT NO.          KIND  STATUS          STATUS DATE
     ---------------     ----  -------------   -----------
     US 20130209514       A1   Dead            20201120
     WO 2010144295        A1   Dead            20201202
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS   CASFORMULTNS 2016:2121702
AB   Compns. for inducing or enhancing immunogenicity of a tumor comprise bi-
     and multi-specific aptamers binding to a tumor cell and an immune cell.
     These compns. have broad applicability in the treatment of many diseases,
     including cancer.


L13  ANSWER 4 OF 22  CAPLUS  COPYRIGHT 2021 ACS on STN
AN   2016:1977575  CAPLUS Full-text
DN   167:78908
TI   Vaccine immunotherapy
IN   Hadden, John W.; Signorelli, Kathy; Egan, James; Naylor, Paul
PA   IRX Therapeutics, Inc., USA
SO   U.S. Pat. Appl. Publ., No pp. given
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
PI
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
```

US 20120064035	A1	20120315	US 2011-13320584	20111115
US 9539320	B2	20170110		
CA 3017298	A1	20101118	CA 2010-3017298	20100517
WO 2010132867	A1	20101118	WO 2010-US35060	20100517
US 20130243723	A1	20130919	US 2013-13771622	20130220
US 9566331	B2	20170214		
AU 2013203561	A1	20130502	AU 2013-203561	20130410
AU 2013203561	B2	20151126		
JP 2015155432	A	20150827	JP 2015-79745	20150409
PRAI US 2009-61178741	P	20090515		
WO 2010-US35060	W	20100517		
AU 2010-248761	A3	20100517		
CA 2010-2799081	A3	20100517		
JP 2012-511064	A3	20100517		
US 2011-13320584	A3	20111115		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
US 20120064035	A1	Alive	20201121
US 9539320	B2	Alive	20201120
CA 3017298	A1	Alive	20201120
WO 2010132867	A1	Dead	20201202
US 20130243723	A1	Alive	20201121
US 9566331	B2	Alive	20201121
AU 2013203561	A1	Alive	20201121
AU 2013203561	B2	Alive	20201121
JP 2015155432	A	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A compn. for treating cancer, including synergistic amts. of a primary cell-derived biol. having the cytokines IL-1, IL-2, IL-6, IL-8, TNF-α, and IFN-γ, and a cancer vaccine having at least one antigen. A compn. comprising synergistic amts. of the primary cell-derived biol. in combination with at least one adjuvant. A method of treating cancer by administering the compn. A method of reversing immune suppression and gaining immunity to cancer. A method of producing an immune response to an exogenous antigen. A method of enhancing an immune response in a patient by administering the primary cell-derived biol. in combination with at least one adjuvant, and enhancing the immune response of the patient by a synergistic interaction of the primary cell-derived biol. and the adjuvant. A method of increasing function of an immune system.

OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN

AN 2011:51492 CAPLUS Full-text

DN 154:152967

TI Method for generating aptamers with improved off-rates for histology reagents

IN Zichi, Dominic; Wilcox, Sheri K.; Bock, Chris; Schneider, Daniel J.; Eaton, Bruce; Gold, Larry; Jarvis, Thale C.; Carter, Jeffrey D.

PA SomaLogic, Inc., USA

SO PCT Int. Appl., 134 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 11

PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2011006075	A1	20110113	WO 2010-US41540	20100709
US 20100055695	A1	20100304	US 2009-499967	20090709
US 7964356	B2	20110621		
CA 2765857	A1	20110113	CA 2010-2765857	20100709
CA 2765857	C	20180306		
AU 2010271271	A1	20120119	AU 2010-271271	20100709
AU 2010271271	B2	20150129		
EP 2451981	A1	20120516	EP 2010-797920	20100709

	EP 2451981	B1	20161019		
	JP 2012532612	T	20121220	JP 2012-519765	20100709
	JP 5926178	B2	20160525		
	ES 2610633	T3	20170428	ES 2010-797920	20100709
	US 20120115752	A1	20120510	US 2012-13382493	20120105
	US 8975026	B2	20150310		
	US 20120264117	A1	20121018	US 2012-13525271	20120615
	US 8703416	B2	20140422		
	HK 1169682	A1	20170901	HK 2012-110456	20121019
	AU 2013203360	A1	20130502	AU 2013-203360	20130410
	AU 2013203360	B2	20151210		
	AU 2013203374	A1	20130502	AU 2013-203374	20130410
	AU 2013203374	B2	20150409		
	AU 2013203386	A1	20130502	AU 2013-203386	20130410
	AU 2013203386	B2	20151008		
	AU 2013203588	A1	20130502	AU 2013-203588	20130411
	AU 2013203588	B2	20151029		
	AU 2013248169	A1	20140130	AU 2013-248169	20131129
	AU 2013248169	B2	20151210		
	US 20150148237	A1	20150528	US 2015-14606134	20150127
	US 9382533	B2	20160705		
	AU 2015249081	A1	20151112	AU 2015-249081	20151028
	AU 2015249081	B2	20170302		
	AU 2015249082	A1	20151112	AU 2015-249082	20151028
	AU 2015249082	B2	20170302		
	AU 2015255156	A1	20151126	AU 2015-255156	20151109
	AU 2015255156	B2	20170119		
	AU 2015261546	A1	20151210	AU 2015-261546	20151124
	AU 2015261546	B2	20170928		
	AU 2017202051	A1	20170420	AU 2017-202051	20170328
	AU 2017202051	B2	20190131		
	AU 2017202493	A1	20170504	AU 2017-202493	20170418
	AU 2017202493	B2	20190228		
	AU 2019201066	A1	20190307	AU 2019-201066	20190215
	AU 2019201066	B2	20200924		

PRAI	US 2009-499967	A	20090709
	AU 2007-205974	A3	20070116
	US 2007-623535	A2	20070116
	US 2007-623580	A2	20070116
	US 2007-60950281	P	20070717
	US 2007-60950283	P	20070717
	US 2007-60950293	P	20070717
	US 2008-61031420	P	20080226
	US 2008-61051594	P	20080508
	AU 2008-275915	A3	20080717
	AU 2008-275917	A3	20080717
	US 2008-175434	A2	20080717
	US 2008-175446	A2	20080717
	AU 2010-271271	A3	20100709
	WO 2010-US41540	W	20100709
	US 2010-958620	A2	20101202
	US 2011-61498224	P	20110617
	US 2012-13382493	A2	20120105
	AU 2013-203360	A3	20130410
	AU 2013-203386	A3	20130410
	AU 2013-203588	A3	20130411
	AU 2015-249081	A3	20151028
	AU 2015-261546	A3	20151124
	AU 2017-202051	A3	20170328

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2011006075	A1	Dead	20201201
US 20100055695	A1	Alive	20201121
US 7964356	B2	Alive	20201121
CA 2765857	A1	Alive	20201120
CA 2765857	C	Alive	20201120
AU 2010271271	A1	Alive	20201120
AU 2010271271	B2	Alive	20201121
EP 2451981	A1	Indeterminate	20201107
EP 2451981	B1	Indeterminate	20201106
JP 5926178	B2	Alive	20201121

ES 2610633	T3	Alive	20201121
US 20120115752	A1	Alive	20201121
US 8975026	B2	Alive	20201121
US 20120264117	A1	Alive	20201121
US 8703416	B2	Alive	20201120
AU 2013203360	A1	Alive	20201121
AU 2013203360	B2	Alive	20201121
AU 2013203374	A1	Alive	20201121
AU 2013203374	B2	Alive	20201121
AU 2013203386	A1	Alive	20201121
AU 2013203386	B2	Alive	20201120
AU 2013203588	A1	Alive	20201121
AU 2013203588	B2	Alive	20201121
AU 2013248169	A1	Alive	20201121
AU 2013248169	B2	Alive	20201121
US 20150148237	A1	Alive	20201120
US 9382533	B2	Alive	20201121
AU 2015249081	A1	Alive	20201120
AU 2015249081	B2	Alive	20201121
AU 2015249082	A1	Alive	20201120
AU 2015249082	B2	Alive	20201120
AU 2015255156	A1	Alive	20201121
AU 2015255156	B2	Alive	20201121
AU 2015261546	A1	Alive	20201120
AU 2015261546	B2	Alive	20201120
AU 2017202051	A1	Alive	20201121
AU 2017202051	B2	Alive	20201121
AU 2017202493	A1	Alive	20201121
AU 2017202493	B2	Alive	20201121
AU 2019201066	A1	Alive	20201120
AU 2019201066	B2	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present disclosure describes the identification and use of aptamers and photoaptamers having slower dissocn. rate consts. than those obtained using previously described methods. Specifically, the present disclosure describes methods for the identification and use of aptamers to one or more targets within a histol. or cytol. sample, which have slow rates of dissocn. The aptamers may be used to assess localization, relative d., and presence or absence of one or more targets in cytol. and histol. samples. Targets may be selected that are specific and diagnostic of a given disease state for which the sample was collected. The aptamers may also be used to introduce target specific signal moieties. In addn. to target identification, the aptamers may be used to amplify signal generation through a variety of methods. High affinity 5-(N-benzylcarboxyamide)-dUTP-contg. aptamers to Her2 were generated. Aptamer 2616-24 had an equil. binding const. of 1.5 × 10-8 M. The aptamer was synthesized with 5' addn. of a biotin Cy3 label and used to stain HER2 protein in frozen breast carcinoma tissue sections. In the presence of 1 mM dextran sulfate, the HER2 aptamer bound to cell membranes in the expected morphol. pattern in frozen breast tumors that had been classified by immunohistochem. (IHC) as having 3+ HER2 expression, but it did not bind to breast tumors classified by IHC as 0/neg., or non-breast neg. control tissues.

OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2016:1994714 CAPLUS Full-text
DN 167:149933
TI Composition comprising a complexed (m)rna and a naked mrna for providing or enhancing an immunostimulatory response in a mammal and uses thereof
IN Fotin-Mleczek, Mariola; Voss, Soehnke
PA CureVac GmbH, Germany
SO U.S. Pat. Appl. Publ., No pp. given
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

	US 20110250225	A1	20111013	US 2010-994407	20101123
	US 9572874	B2	20170221		
	WO 2010037408	A1	20100408	WO 2008-EP8304	20080930
	WO 2010037539	A1	20100408	WO 2009-EP7032	20090930
	US 20170202957	A1	20170720	US 2017-15408339	20170117
	US 20210046179	A1	20210218	US 2020-16907130	20200619
PRAI	WO 2008-EP8304	A	20080930		
	WO 2009-EP7032	W	20090930		
	US 2010-994407	A1	20101123		
	US 2017-15408339	A1	20170117		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
US 20110250225	A1	Alive	20201121
US 9572874	B2	Alive	20201120
WO 2010037408	A1	Dead	20201202
WO 2010037539	A1	Dead	20201202
US 20170202957	A1	Dead	20210401
US 20210046179	A1	Alive	20210225

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The present invention relates to an immunostimulatory compn. comprising a) an adjuvant component, comprising or consisting of at least one (m)RNA, complexed with a cationic or polycationic compd., and b) at least one free mRNA, encoding at least one therapeutically active protein, antigen, allergen and/or antibody, wherein the immunostimulatory compn. is capable to elicit or enhance an innate and optionally an adaptive immune response in a mammal. The inventive immunostimulatory compn. may be a pharmaceutical compn. or a vaccine. The invention furthermore relates to a method of prepn. of the inventive immunostimulatory compn. The invention also relates to the use of the inventive immunostimulatory compn. or its components (for the prepn. of a pharmaceutical compn. or a vaccine) for the treatment of various diseases. Finally, the invention relates to kits contg. the inventive immunostimulatory compn., its components and/or the pharmaceutical compn. or vaccine.

OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L13 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN

AN 2010:1570638 CAPLUS Full-text

DN 154:55967

TI Bispecific aptamers target tumor antigens and co-stimulatory molecules and their use in cancer vaccines

IN Gilboa, Eli; Pastor, Fernando

PA University of Miami, USA

SO PCT Int. Appl., 80pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2010144295	A1	20101216	WO 2010-US37164	20100603
	US 20130209514	A1	20130815	US 2012-13376873	20120628
PRAI	US 2009-61185251	P	20090609		
	WO 2010-US37164	W	20100603		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2010144295	A1	Dead	20201202
US 20130209514	A1	Dead	20201120

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Methods of inducing the presentation of tumor antigens and co-stimulatory mols. to immune cells using aptamers binding the antigen and the costimulatory mol. are described. Presentation of the antigen in a preferred stoichiometry with a costimulatory mol. improves the immune response to the tumor. Use of an aptamer binding prostate-specific membrane antigen and two mols. of 4-1BB receptors is demonstrated.

The aptamer was as effective as anti-4-1BB antibody in costimulating CD8-pos. T cells presented with prostate-specific membrane antigen.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2010:1433100 CAPLUS Full-text
DN 153:616648
TI Cancer vaccine immunotherapy
IN Hadden, John W.; Signorelli, Kathy; Egan, James; Naylor, Paul
PA IRX Therapeutics, Inc., USA
SO PCT Int. Appl., 158pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2010132867	A1	20101118	WO 2010-US35060	20100517
	CA 2799081	A1	20101118	CA 2010-2799081	20100517
	CA 2799081	C	20181030		
	CA 3017298	A1	20101118	CA 2010-3017298	20100517
	AU 2010248761	A1	20120112	AU 2010-248761	20100517
	AU 2010248761	B2	20160211		
	EP 2429585	A1	20120321	EP 2010-775661	20100517
	EP 2429585	B1	20180418		
	JP 2012526853	T	20121101	JP 2012-511064	20100517
	JP 5797190	B2	20151021		
	ES 2679043	T3	20180821	ES 2010-775661	20100517
	MX 2011012147	A	20120619	MX 2011-12147	20111111
	US 20120064035	A1	20120315	US 2011-13320584	20111115
	US 9539320	B2	20170110		
	IN 2011MN02702	A	20120504	IN 2011-MN2702	20111214
	HK 1168541	A1	20190628	HK 2012-109265	20120920
	US 20130243723	A1	20130919	US 2013-13771622	20130220
	US 9566331	B2	20170214		
	AU 2013203561	A1	20130502	AU 2013-203561	20130410
	AU 2013203561	B2	20151126		
	JP 2015155432	A	20150827	JP 2015-79745	20150409
PRAI	US 2009-61178741	P	20090515		
	AU 2010-248761	A3	20100517		
	CA 2010-2799081	A3	20100517		
	JP 2012-511064	A3	20100517		
	WO 2010-US35060	W	20100517		
	US 2011-13320584	A3	20111115		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2010132867	A1	Dead	20201202
CA 2799081	A1	Alive	20201121
CA 2799081	C	Alive	20201121
CA 3017298	A1	Alive	20201120
AU 2010248761	A1	Alive	20201121
AU 2010248761	B2	Alive	20201120
EP 2429585	A1	Indeterminate	20201107
EP 2429585	B1	Indeterminate	20201106
JP 5797190	B2	Alive	20201121
ES 2679043	T3	Alive	20201121
MX 2011012147	A	Dead	20201121
US 20120064035	A1	Alive	20201121
US 9539320	B2	Alive	20201120
US 20130243723	A1	Alive	20201121
US 9566331	B2	Alive	20201121
AU 2013203561	A1	Alive	20201121
AU 2013203561	B2	Alive	20201121
JP 2015155432	A	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS CASFORMULTNS 2010:1433100
AB A compn. for treating cancer, including synergistic amts. of a primary cell-derived biol. having the cytokines IL-1, IL-2, IL-6, IL-8, TNF-α, and IFN-γ, and a cancer vaccine having at least one antigen. A compn. comprising synergistic amts. of the primary cell-derived biol. in combination with at least one adjuvant. A method of treating cancer by administering the compn. A method of reversing immune suppression and gaining immunity to cancer. A method of producing an immune response to an exogenous antigen. A method of enhancing an immune response in a patient by administering the primary cell-derived biol. in combination with at least one adjuvant, and enhancing the immune response of the patient by a synergistic interaction of the primary cell-derived biol. and the adjuvant. A method of increasing function of an immune system.
OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2010:717746 CAPLUS Full-text
DN 153:60379
TI Methods and compositions related to Th1 cell polarization by dendritic cells
IN Decker, William K.; Shpall, Elizabeth J.; Kamanduri, Krishna V.; Xing, Dongxia
PA University of Texas System, USA
SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2010065876	A2	20100610	WO 2009-US66807	20091204
	WO 2010065876	A3	20101125		
	US 8728806	B2	20140520	US 2011-13132517	20110829
	US 20110306948	A1	20111215		
	US 20140286975	A1	20140925	US 2014-14248908	20140409
	US 9333248	B2	20160510		
	US 20160263206	A1	20160915	US 2016-15133204	20160419
	US 9993537	B2	20180612		
	US 20190262442	A1	20190829	US 2019-16241358	20190107
PRAI	US 2008-61120437	P	20081206		
	WO 2009-US66807	W	20091204		
	US 2011-13132517	A1	20110829		
	US 2014-14248908	A1	20140409		
	US 2016-15133204	A1	20160419		
	US 2018-15974122	B3	20180508		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2010065876	A2	Dead	20201201
	WO 2010065876	A3	Dead	20201202
	US 8728806	B2	Alive	20201121
	US 20110306948	A1	Alive	20201121
	US 20140286975	A1	Alive	20201121
	US 9333248	B2	Alive	20201120
	US 20160263206	A1	Alive	20201120
	US 9993537	B2	Alive	20201121
	US 20190262442	A1	Alive	20201120

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS CASFORMULTNS 2010:717746
AB The authors disclose methods for inducing an immunol. response to a tumor in a patient using mature dendritic cells transfected with a nucleic acid encoding one or more tumor antigens in conjunction with loading with a corresponding tumor antigen compn.
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L13 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2010:439558 CAPLUS Full-text
DN 152:475584
TI Complexed (m)RNA and a naked mRNA for providing or enhancing an immunostimulatory response in a mammal
IN Fotin-Mleczek, Mariola; Voss, Soehnke
PA CureVac GmbH, Germany
SO PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010037539	A1	20100408	WO 2009-EP7032	20090930
WO 2010037408	A1	20100408	WO 2008-EP8304	20080930
AU 2009300113	A1	20100408	AU 2009-300113	20090930
AU 2009300113	B2	20130418		
CA 2730261	A1	20100408	CA 2009-2730261	20090930
CA 2730261	C	20161129		
KR 2011023889	A	20110308	KR 2011-7001541	20090930
KR 1343043	B1	20131220		
EP 2331129	A1	20110615	EP 2009-736823	20090930
EP 2331129	B1	20140618		
CN 102123733	A	20110713	CN 2009-80131936	20090930
CN 102123733	B	20160113		
JP 2012502074	T	20120126	JP 2011-526423	20090930
JP 5859853	B2	20160216		
ES 2502915	T3	20141006	ES 2009-736823	20090930
RU 2545756	C2	20150410	RU 2011-116931	20090930
BR 2009015844	A2	20151103	BR 2009-15844	20090930
BR 2009015844	B1	20210713		
US 20110250225	A1	20111013	US 2010-994407	20101123
US 9572874	B2	20170221		
MX 2010013071	A	20101220	MX 2010-13071	20101129
IN 2010DN08454	A	20120302	IN 2010-DN8454	20101129
IN 291696	B	20180119		
US 20170202957	A1	20170720	US 2017-15408339	20170117
US 20210046179	A1	20210218	US 2020-16907130	20200619

PRAI WO 2008-EP8304 A 20080930
WO 2009-EP7032 W 20090930
US 2010-994407 A1 20101123
US 2017-15408339 A1 20170117

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2010037539	A1	Dead	20201202
WO 2010037408	A1	Dead	20201202
AU 2009300113	A1	Alive	20201121
AU 2009300113	B2	Alive	20201121
CA 2730261	A1	Alive	20201121
CA 2730261	C	Alive	20201120
KR 2011023889	A	Alive	20201121
KR 1343043	B1	Alive	20201121
EP 2331129	A1	Indeterminate	20201106
EP 2331129	B1	Indeterminate	20201106
CN 102123733	A	Alive	20201120
CN 102123733	B	Alive	20201121
JP 5859853	B2	Alive	20201121
ES 2502915	T3	Alive	20201121
RU 2545756	C2	Alive	20201120
BR 2009015844	A2	Alive	20201202
BR 2009015844	B1	Alive	20210902
US 20110250225	A1	Alive	20201121
US 9572874	B2	Alive	20201120

MX 2010013071 A Alive 20201121
US 20170202957 A1 Dead 20210401
US 20210046179 A1 Alive 20210225
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS CASFORMULTNS 2010:439558
AB The authors disclose immunostimulatory compns. comprising (a) an adjuvant component of at least one (m)RNA complexed with a cationic or polycationic compd. and (b) at least one free mRNA encoding at least one therapeutically active protein, antigen, allergen and/or antibody. The immunostimulatory compns. are capable of eliciting or enhancing an innate and optionally an adaptive immune response in a mammal. In one example, a partial protamine complex of mRNA encoding ovalbumin as a model tumor antigen is shown to elicit an enhanced antitumor response compared to fully complexed mRNA or free mRNA alone.
OSC.G 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2010:436046 CAPLUS Full-text
DN 152:462950
TI Composition comprising a complexed (m)RNA and a naked mRNA for providing or enhancing an immunostimulatory response in a mammal and uses thereof
IN Fotin-Mleczek, Mariola; Voss, Soehnke
PA CureVac GmbH, Germany
SO PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2010037408	A1	20100408	WO 2008-EP8304	20080930
AU 2009300113	A1	20100408	AU 2009-300113	20090930
AU 2009300113	B2	20130418		
CA 2730261	A1	20100408	CA 2009-2730261	20090930
CA 2730261	C	20161129		
WO 2010037539	A1	20100408	WO 2009-EP7032	20090930
KR 2011023889	A	20110308	KR 2011-7001541	20090930
KR 1343043	B1	20131220		
EP 2331129	A1	20110615	EP 2009-736823	20090930
EP 2331129	B1	20140618		
CN 102123733	A	20110713	CN 2009-80131936	20090930
CN 102123733	B	20160113		
JP 2012502074	T	20120126	JP 2011-526423	20090930
JP 5859853	B2	20160216		
EP 2762165	A2	20140806	EP 2013-5251	20090930
EP 2762165	A3	20141029		
EP 2762165	B1	20170809		
PT 2331129	E	20140826	PT 2009-736823	20090930
ES 2502915	T3	20141006	ES 2009-736823	20090930
RU 2545756	C2	20150410	RU 2011-116931	20090930
BR 2009015844	A2	20151103	BR 2009-15844	20090930
BR 2009015844	B1	20210713		
US 20110250225	A1	20111013	US 2010-994407	20101123
US 9572874	B2	20170221		
MX 2010013071	A	20101220	MX 2010-13071	20101129
IN 2010DN08454	A	20120302	IN 2010-DN8454	20101129
IN 291696	B	20180119		
JP 2014196306	A	20141016	JP 2014-96387	20140507
JP 5931120	B2	20160608		
US 20170202957	A1	20170720	US 2017-15408339	20170117
US 20210046179	A1	20210218	US 2020-16907130	20200619
PRAI WO 2008-EP8304	A	20080930		
EP 2009-736823	A3	20090930		

JP 2011-526423 A3 20090930
WO 2009-EP7032 W 20090930
US 2010-994407 A1 20101123
US 2017-15408339 A1 20170117

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2010037408	A1	Dead	20201202
AU 2009300113	A1	Alive	20201121
AU 2009300113	B2	Alive	20201121
CA 2730261	A1	Alive	20201121
CA 2730261	C	Alive	20201120
WO 2010037539	A1	Dead	20201202
KR 2011023889	A	Alive	20201121
KR 1343043	B1	Alive	20201121
EP 2331129	A1	Indeterminate	20201106
EP 2331129	B1	Indeterminate	20201106
CN 102123733	A	Alive	20201120
CN 102123733	B	Alive	20201121
JP 5859853	B2	Alive	20201121
EP 2762165	A2	Indeterminate	20201107
EP 2762165	A3	Indeterminate	20201107
EP 2762165	B1	Indeterminate	20201106
PT 2331129	E	Alive	20201120
ES 2502915	T3	Alive	20201121
RU 2545756	C2	Alive	20201120
BR 2009015844	A2	Alive	20201202
BR 2009015844	B1	Alive	20210902
US 20110250225	A1	Alive	20201121
US 9572874	B2	Alive	20201120
MX 2010013071	A	Alive	20201121
JP 2014196306	A	Alive	20201121
JP 5931120	B2	Alive	20201121
US 20170202957	A1	Dead	20210401
US 20210046179	A1	Alive	20210225

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2010:436046

AB The present invention relates to an immunostimulatory compn. comprising (i) an adjuvant component, comprising or consisting of at least one (m)RNA, complexed with a cationic or polycationic compd., and (ii) at least one free mRNA, encoding at least one therapeutically active protein, antigen, allergen and/or antibody, wherein the immunostimulatory compn. is capable to elicit or enhance an innate and optionally an adaptive immune response in a mammal. The inventive immunostimulatory compn. may be a pharmaceutical compn. or a vaccine. The invention furthermore relates to a method of prepn. of the inventive immunostimulatory compn. The invention also relates to the use of the inventive immunostimulatory compn. or its components (for the prepn. of a pharmaceutical compn. or a vaccine) for the treatment of various diseases. Finally, the invention relates to kits contg. the inventive immunostimulatory compn., its components and/or the pharmaceutical compn. or vaccine. Thus, the mRNA was complexed with protamine by addn. of protamine to the mRNA in the ratios of 1:1 to 1:4. After incubation for 10 min, the free RNA was added to obtain a compn. suitable for vaccine.

OSC.G 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN

AN 2010:410483 CAPLUS Full-text

DN 152:427645

TI Dual-specific ligand comprising two single variable domains for synergistic therapy of disease such as tumor and rheumatoid arthritis

IN Grant, Steven; Basran, Amrik; Ignatovich, Olga; De Wildt, Rudolph Maria T.; Jones, Philip; Brewis, Neil; Woolven, Ben; De Angelis, Elena; Holt, Lucy J.; Winter, Greg; Tomlinson, Ian; Moulder, Kevin

PA SmithKline Beecham Corporation, USA

SO U.S. Pat. Appl. Publ., 341 pp., Cont.-in-part of U.S. Ser. 141,661.
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 37
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	US 20100081792	A1	20100401	US 2007-981821	20071031
	WO 2003002609	A2	20030109	WO 2002-GB3014	20020628
	WO 2003002609	A3	20030821		
	WO 2004003019	A2	20040108	WO 2003-GB2804	20030630
	WO 2004003019	A3	20040910		
	US 20040219643	A1	20041104	US 2003-744774	20031223
	WO 2004058821	A2	20040715	WO 2003-GB5646	20031224
	WO 2004058821	A3	20040819		
	US 20050271663	A1	20051208	US 2004-925366	20040824
	MY 142617	A	20101215	MY 2004-5336	20041223
	US 20060106203	A1	20060518	US 2004-23959	20041228
	US 20060073141	A1	20060406	US 2005-98758	20050404
	US 20060257406	A1	20061116	US 2005-141661	20050531
	WO 2009058383	A2	20090507	WO 2008-US12404	20081031
	WO 2009058383	A3	20091230		
	JP 2009082141	A	20090423	JP 2008-311997	20081208
	AU 2013273775	A1	20140116	AU 2013-273775	20131220
PRAI	GB 2001-15841	A	20010628		
	WO 2002-GB3014	A2	20020628		
	GB 2002-30202	A	20021227		
	WO 2003-GB2804	A2	20030630		
	US 2003-60509613	P	20031008		
	GB 2003-22770	A	20031128		
	US 2003-744774	A2	20031223		
	WO 2003-GB5646	A1	20031224		
	US 2004-925366	B2	20040824		
	US 2004-23959	A2	20041228		
	US 2005-98758	A2	20050404		
	US 2005-141661	A2	20050531		
	JP 2003-508989	A3	20020628		
	GB 2003-27706	A	20031128		
	US 2004-60535076	P	20040108		
	WO 2004-GB2829	A2	20040630		
	US 2007-981821	A	20071031		
	AU 2008-212682	A3	20080208		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	US 20100081792	A1	Dead	20201121
	WO 2003002609	A2	Dead	20201202
	WO 2003002609	A3	Dead	20201202
	WO 2004003019	A2	Dead	20201202
	WO 2004003019	A3	Dead	20201202
	US 20040219643	A1	Dead	20201121
	WO 2004058821	A2	Dead	20201202
	WO 2004058821	A3	Dead	20201202
	US 20050271663	A1	Dead	20201121
	MY 142617	A	Alive	20201209
	US 20060106203	A1	Dead	20201121
	US 20060073141	A1	Dead	20201120
	US 20060257406	A1	Dead	20201120
	WO 2009058383	A2	Dead	20201202
	WO 2009058383	A3	Dead	20201202
	JP 2009082141	A	Alive	20201121
	AU 2013273775	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention provides a dual-specific ligand, antibody or scFv comprising a first and second single variable domain, each having binding specificity for a antigenic target. The invention also provides for a single variable domain monomer ligand that specifically binds to an antigenic target.
OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L13 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2009:857946 CAPLUS Full-text
DN 151:167076
TI Construction of N-linked glycosylation sites in therapeutic proteins and their glycoconjugation using oligosaccharyltransferases
IN Defrees, Shawn
PA Neose Technologies, Inc., USA
SO PCT Int. Appl., 238pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009089396	A2	20090716	WO 2009-US30503	20090108
WO 2009089396	A3	20091015		
CA 2711503	A1	20090716	CA 2009-2711503	20090108
EP 2242505	A2	20101027	EP 2009-700164	20090108
JP 2011512121	T	20110421	JP 2010-542355	20090108
JP 5647899	B2	20150107		
CN 102037004	A	20110427	CN 2009-80106134	20090108
IN 2010CN04502	A	20101022	IN 2010-CN4502	20100716
US 20100286067	A1	20101111	US 2010-811963	20100720
PRAI US 2008-61019805	P	20080108		
WO 2009-US30503	W	20090108		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2009089396	A2	Dead	20201202
WO 2009089396	A3	Dead	20201201
CA 2711503	A1	Dead	20201121
EP 2242505	A2	Dead	20201203
JP 5647899	B2	Dead	20201121
CN 102037004	A	Dead	20201121
US 20100286067	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OS MARPAT 151:167076
AB The invention relates to a method of prepg. glycosylated polypeptides using short enzyme-recognized N-linked glycosylation sequences. The current invention provides therapeutic polypeptides and polypeptide conjugates that include an exogenous N-linked glycosylation sequence. The N-linked glycosylation sequence is preferably a substrate for an oligosaccharyltransferase (e.g., bacterial PgIB), which can catalyze the transfer of a glycosyl moiety from a lipid-bound glycosyl donor mol. (e.g., a lipid-pyrophosphate-linked glycosyl moiety) to an asparagine (N) residue of the glycosylation sequence. In one example, the asparagine residue is part of an exogenous N-linked glycosylation sequence of the invention. The invention further provides methods of making the polypeptide conjugates that include contacting a polypeptide having an N-linked glycosylation sequence of the invention and a lipid-pyrophosphate-linked glycosyl moiety (or phospholipid-linked glycosyl moiety) in the presence of an oligosaccharyltransferase under conditions sufficient for the enzyme to transfer the glycosyl moiety to an asparagine residue of the N-linked glycosylation sequence. Exemplary glycosyl moieties that can be conjugated to the glycosylation sequence include GlcNAc, GlcNH, bacillosamine, 6-hydroybacillosamine, GalNAc, GaINH, GlcNAc-GlcNAc, GlcNAc-GlcNH, GlcNAc-Gal, GlcNAc-GlcNAc-Gal-Sia, GlcNAc-Gal-Sia, GlcNAc-GlcNAc-Man, and GlcNAc-GlcNAc-Man(Man)2. The transferred glycosyl moiety is optionally modified with a modifying group,

such as a polymer (e.g., PEG). In one example, the modified glycosyl moiety is a GlcNAc or a sialic acid moiety. Exemplary human BMP-7 variant polypeptides contg. exogenous N-linked glycosylation sites are listed.
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)

L13 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2008:1477039 CAPLUS Full-text
DN 150:48001
TI Methods for selecting protease-resistant peptide ligands for a target protein for therapeutic use
IN Jespers, Laurent; Pupecka, Malgorzata; Tomlinson, Ian; Enever, Carolyn
PA Domantis Limited, UK
SO PCT Int. Appl., 245 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 37
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008149143	A2	20081211	WO 2008-GB50399	20080603
WO 2008149143	A3	20090402		
AU 2008259590	A1	20081211	AU 2008-259590	20080603
CA 2688433	A1	20081211	CA 2008-2688433	20080603
KR 2010018040	A	20100216	KR 2010-7000188	20080603
EP 2162465	A2	20100317	EP 2008-750794	20080603
JP 2010528645	T	20100826	JP 2010-510882	20080603
CN 101848935	A	20100929	CN 2008-80102138	20080603
SG 182170	A1	20120730	SG 2012-4143	20080603
BR 2008013898	A2	20190924	BR 2008-13898	20080603
AR 66847	A1	20090916	AR 2008-102362	20080604
AR 66848	A1	20090916	AR 2008-102363	20080604
AR 66849	A1	20090916	AR 2008-102364	20080604
AR 66850	A1	20090916	AR 2008-102365	20080604
SG 182141	A1	20120730	SG 2012-3954	20080604
SG 182151	A1	20120730	SG 2012-4027	20080604
EP 2746290	A2	20140625	EP 2013-184209	20080604
EP 2746290	A3	20140910		
EP 2746290	B1	20190814		
EP 2746291	A2	20140625	EP 2013-184211	20080604
EP 2746291	A3	20140903		
EP 2746291	B1	20190814		
CN 104311663	A	20150128	CN 2014-10440384	20080604
CN 104311663	B	20181102		
PT 2162467	E	20151029	PT 2008-750800	20080604
US 20090148437	A1	20090611	US 2008-323632	20081126
AU 2008334605	A1	20090618	AU 2008-334605	20081211
AU 2008334605	B2	20130718		
CA 2707986	A1	20090618	CA 2008-2707986	20081211
WO 2009074634	A2	20090618	WO 2008-EP67295	20081211
WO 2009074634	A3	20100923		
EP 2220115	A2	20100825	EP 2008-860530	20081211
KR 2010098697	A	20100908	KR 2010-7015536	20081211
JP 2011506396	T	20110303	JP 2010-537443	20081211

	CN 102131827	A	20110720	CN 2008-80127160	20081211
	SG 185286	A1	20121129	SG 2012-7487	20081211
	BR 2008019932	A2	20190730	BR 2008-19932	20081211
	ZA 2009008339	A	20110223	ZA 2009-8339	20091125
	IN 3009KN04135	A	20100319	IN 3009-KN4135	20091130
	ZA 2009008454	A	20110223	ZA 2009-8454	20091130
	ZA 2009008470	A	20110223	ZA 2009-8470	20091130
	MX 2009013137	A	20100430	MX 2009-13137	20091202
	CO 6251320	A2	20110221	CO 2009-142777	20091214
	CO 6251321	A2	20110221	CO 2009-142781	20091214
	CO 6251322	A2	20110221	CO 2009-142782	20091214
	CR 11195	A	20100524	CR 2010-11195	20100106
	CR 11193	A	20100628	CR 2010-11193	20100106
	CR 11194	A	20100628	CR 2010-11194	20100106
	US 20100254972	A1	20101007	US 2010-663491	20100608
	ZA 2010004093	A	20111130	ZA 2010-4093	20100608
	US 20100260853	A1	20101014	US 2010-747203	20100610
	MX 2010006533	A	20100702	MX 2010-6533	20100611
	US 20120134982	A1	20120531	US 2011-13299030	20111117
	US 20140141093	A1	20140522	US 2013-13763768	20130211
	US 9562090	B2	20170207		
	AU 2013273775	A1	20140116	AU 2013-273775	20131220
	US 20170174775	A1	20170622	US 2016-15386141	20161221
	US 10072089	B2	20180911		
	US 20190040148	A1	20190207	US 2018-16047197	20180727
PRAI	US 2007-60933632	P	20070606		
	GB 2007-24331	A	20071213		
	AU 2008-212682	A3	20080208		
	BD 2008-127	A	20080522		
	BD 2008-128	A	20080522		
	BD 2008-129	A	20080522		
	BD 2008-130	A	20080522		
	WO 2008-GB50399	W	20080603		
	WO 2008-GB50400	A2	20080603		
	WO 2008-GB50403	A2	20080603		
	WO 2008-GB50404	A2	20080603		
	CN 2008-80102207	A3	20080604		
	EP 2008-750800	A3	20080604		
	WO 2008-GB50405	PD	20080604		
	WO 2008-GB50406	A2	20080604		
	WO 2008-GB50407	A2	20080604		
	US 2008-323632	B1	20081126		
	WO 2008-EP67295	W	20081211		
	US 2010-663502	A1	20100608		
	US 2013-13763768	A3	20130211		
	US 2016-15386141	A1	20161221		

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PATENT NO.	KIND	STATUS	STATUS DATE
WO 2008149143	A2	Dead	20201202
WO 2008149143	A3	Dead	20201202
AU 2008259590	A1	Dead	20201121
CA 2688433	A1	Dead	20201121
KR 2010018040	A	Dead	20201120
EP 2162465	A2	Dead	20201201
CN 101848935	A	Dead	20201121
SG 182170	A1	Alive	20201121
BR 2008013898	A2	Dead	20201121
AR 66847	A1	Alive	20201121
AR 66848	A1	Dead	20201121
AR 66849	A1	Dead	20201121
AR 66850	A1	Dead	20201120
SG 182141	A1	Alive	20201121
SG 182151	A1	Alive	20201121

EP 2746290	A2	Indeterminate	20201106
EP 2746290	A3	Indeterminate	20201107
EP 2746290	B1	Indeterminate	20201106
EP 2746291	A2	Indeterminate	20201106
EP 2746291	A3	Indeterminate	20201107
EP 2746291	B1	Indeterminate	20201106
CN 104311663	A	Alive	20201120
CN 104311663	B	Alive	20201120
PT 2162467	E	Alive	20201121
US 20090148437	A1	Dead	20201121
AU 2008334605	A1	Dead	20201121
AU 2008334605	B2	Dead	20201121
CA 2707986	A1	Dead	20201120
WO 2009074634	A2	Dead	20201202
WO 2009074634	A3	Dead	20201202
EP 2220115	A2	Dead	20201202
KR 2010098697	A	Dead	20201120
CN 102131827	A	Dead	20201120
SG 185286	A1	Alive	20201121
BR 2008019932	A2	Dead	20201120
MX 2009013137	A	Dead	20201120
CO 6251320	A2	Alive	20201121
CO 6251321	A2	Dead	20201121
CO 6251322	A2	Dead	20201121
CR 11195	A	Alive	20201121
CR 11193	A	Alive	20201121
CR 11194	A	Dead	20201121
US 20100254972	A1	Dead	20201121
US 20100260853	A1	Dead	20201121
US 20120134982	A1	Dead	20201121
US 20140141093	A1	Alive	20201121
US 9562090	B2	Alive	20201120
AU 2013273775	A1	Dead	20201121
US 20170174775	A1	Alive	20201121
US 10072089	B2	Alive	20201120
US 20190040148	A1	Alive	20201121

AB Methods of selecting peptide ligands for a target protein that are resistant to proteinases found in a target tissue are described. This may include proteinases of the respiratory and digestive tracts of human. A library of peptides is incubated with a proteinase of interested and the enzyme is allowed to catalyze hydrolysis of the peptides. The library is then screened for peptides that retain binding activity for the target protein. The process may take place in soln., or in a peptide array. These peptides may be used as therapeutic ligands for a target protein, and because of their resistance to proteolysis, they may be active for longer, and at lower dosages. The development of proteinase-resistant peptide ligands for type 1 tumor necrosis factor receptors from domain antibodies is demonstrated. Random and site-directed mutagenesis were used to develop variants of the sequence that were selected first for optimal binding, then for trypsin resistance. The peptides could be effectively nebulized under physiol. conditions. The use of fusion proteins of these peptides with Fc fragments of Igs to increase serum half-lives is demonstrated.

OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

L13 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2008:607789 CAPLUS Full-text
DN 148:555109
TI Microorganisms as carriers of nucleotide sequences coding for antigens and protein toxins for use in disease treatment
IN Gentschev, Ivaylo; Fensterle, Joachim; Rapp, Ulf R.; Goebel, Werner
PA Aeterna Zentaris G.m.b.H., Germany
SO PCT Int. Appl., 114pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

	WO 2008058944	A1	20080522	WO 2007-EP62237	20071113
	EP 1921149	A1	20080514	EP 2006-123974	20061113
	AU 2007321266	A1	20080522	AU 2007-321266	20071113
	AU 2007321266	B2	20121115		
	CA 2669219	A1	20080522	CA 2007-2669219	20071113
	EP 2092067	A1	20090826	EP 2007-822513	20071113
	EP 2092067	B1	20100602		
	KR 2009092803	A	20090901	KR 2009-7012089	20071113
	KR 1505413	B1	20150325		
	CN 101595219	A	20091202	CN 2007-80044576	20071113
	CN 101595219	B	20160127		
	JP 2010508861	T	20100325	JP 2009-536716	20071113
	JP 5479102	B2	20140423		
	AT 469971	T	20100615	AT 2007-822513	20071113
	NZ 576947	A	20111222	NZ 2007-576947	20071113
	RU 2447145	C2	20120410	RU 2009-122560	20071113
	IL 198736	A	20120830	IL 2007-198736	20071113
	BR 2007019003	A2	20131217	BR 2007-19003	20071113
	IN 2009KN01749	A	20090612	IN 2009-KN1749	20090511
	MX 2009005038	A	20090525	MX 2009-5038	20090512
	NO 2009002278	A	20090813	NO 2009-2278	20090612
	HK 1138314	A1	20161007	HK 2010-100634	20100121
PRAI	EP 2006-123974	A	20061113		
	US 2006-60865484	P	20061113		
	US 2007-60939140	P	20070521		
	WO 2007-EP62237	W	20071113		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2008058944	A1	Dead	20201201
EP 1921149	A1	Dead	20201201
AU 2007321266	A1	Alive	20201121
AU 2007321266	B2	Alive	20201121
CA 2669219	A1	Dead	20201120
EP 2092067	A1	Indeterminate	20201106
EP 2092067	B1	Indeterminate	20201107
KR 2009092803	A	Alive	20201121
KR 1505413	B1	Alive	20201120
CN 101595219	A	Alive	20201121
CN 101595219	B	Alive	20201121
JP 5479102	B2	Dead	20201120
AT 469971	T	Alive	20201121
NZ 576947	A	Alive	20201121
RU 2447145	C2	Alive	20201121
BR 2007019003	A2	Dead	20201121
MX 2009005038	A	Alive	20201121
HK 1138314	A1	Alive	20201121

AB The invention relates to a microorganism as a carrier of nucleotide sequences coding for antigens and protein toxins comprising the following 4 components.: (I) at least one nucleotide sequence coding for at least one complete or partial antigen of at least one wild-type or mutated protein. First (1), there is at least one nucleotide sequence coding for at least one complete or partial antigen of at least one wild-type or mutated protein. Second (2), there is at least one nucleotide sequence coding for at least one protein toxin and/or at least one protein toxin subunit. Third (3) is (a) at least one nucleotide sequence coding for at least one secretion/transport system which enables the expression of the expression products of component (1) and component (2) on the outer surface of the microorganism and/or enables the secretion of the expression products of component (1) and component (2), and/or (b) optionally, at least one nucleotide sequence coding for at least one

protein for lysing the microorganism in the cytosol of mammalian cells and for intracellularly releasing plasmids or expression vectors, which are contained in the lysed microorganism. Fourth (4) is at least one nucleotide sequence for at least one activation sequence for the expression of one or more of components (1) to (3), wherein said activation sequence can be activated in the microorganism and/or is tissue cell-specific, tumor cell-specific, macrophage-specific, dendrite-specific, lymphocyte-specific, function-specific. or non-cell-specific". Also disclosed are a process of manufg. thereof, corresponding plasmids or expression vectors and uses of the microorganism as a medicament. Also disclosed are a process of manufg. thereof, corresponding plasmids or expression vectors and uses of the microorganism as a medicament. Thus, for example, immune response and protection against tumor cell challenge is demonstrated in mice immunized with Salmonella strains secreting fusion proteins of tumor antigens (human prostate-specific antigen or human B-Raf protein), cholera toxin subunit B, and Escherichia coli hemolysin A.

OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2007:1064219 CAPLUS Full-text
DN 147:383999
TI Detection of gene expression by specific cell types in mixed samples or tissues such as mouse thymus cortex or medullary stromal cells using DGEM (differential gene expression mapping)
IN Petrie, Howard T.
PA USA
SO PCT Int. Appl., 257pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2007106507	A2	20070920	WO 2007-US6363	20070314
	WO 2007106507	A3	20090205		
PRAI	US 2006-60782124	P	20060314		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2007106507	A2	Dead	20201203
WO 2007106507	A3	Dead	20201201

AB Differential gene expression mapping (DGEM) utilizes (1) laser capture microdissection or other methods of microdissection of the tissue regions of interest; (2) microarray screening of RNA isolated from the microdissected regions and anal. of purified individual cellular components from the tissue; and (3) computational profiling or subtraction to identify gene expression by specific cell types in situ. The method was applied to stromal cells from whole cortical and medullary regions of C57BL6 mouse thymus. As a result, DGEM, a reverse identification approach, solves previously insurmountable problems, as the lymphoid progenitors can be readily isolated, allowing fluctuations in receptor expression on lymphoid cells to be used to predict stratified stromal signals. An algorithmic approach can be used for calcg. the expression profile of a tissue/sample of interest that consists of at least two types of cells. Specifically, the approach electronically subtracts the expression profile of one component of a sample from the expression profile of the total sample, thus revealing the profiles of the other component. To confirm the robustness of the DGEM procedure, the gene expression profiles from each sample of whole medulla, whole cortex, cortical thymocytes and medullary thymocytes was sorted based only on the expression data.

L13 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2005:283610 CAPLUS Full-text
DN 142:353382

TI Gene expression profiles for diagnosing breast cancer and identification of gene targets for therapy
IN Nakamura, Yusuke; Katagiri, Toyomasa; Nakatsuru, Shuichi
PA Oncotherapy Science, Inc., Japan; The University of Tokyo
SO PCT Int. Appl., 143 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005028676	A2	20050331	WO 2004-JP14438	20040924
WO 2005028676	A3	20050915		
EP 1668156	A2	20060614	EP 2004-773526	20040924
EP 1668156	B1	20110504		
CN 1890381	A	20070103	CN 2004-80034701	20040924
CN 1890381	B	20110622		
JP 2007506426	T	20070322	JP 2006-527773	20040924
JP 4620670	B2	20110126		
AT 508202	T	20110515	AT 2004-773526	20040924
ES 2365732	T3	20111010	ES 2004-773526	20040924
US 20070269432	A1	20071122	US 2007-573297	20070409
US 7531300	B2	20090512		
JP 2008092949	A	20080424	JP 2007-237927	20070913
US 20090286856	A1	20091119	US 2009-416900	20090401
US 8044193	B2	20111025		
US 20120010090	A1	20120112	US 2011-13238273	20110921

PRAI US 2003-60505571 P 20030924
JP 2006-527773 A3 20040924
WO 2004-JP14438 W 20040924
US 2007-573297 A3 20070409
US 2009-416900 A3 20090401

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2005028676	A2	Dead	20201202
WO 2005028676	A3	Dead	20201202
EP 1668156	A2	Indeterminate	20201106
EP 1668156	B1	Indeterminate	20201107
CN 1890381	A	Dead	20201120
CN 1890381	B	Dead	20201121
JP 4620670	B2	Dead	20201121
AT 508202	T	Dead	20201121
ES 2365732	T3	Alive	20201121
US 20070269432	A1	Transitional	20210624
US 7531300	B2	Transitional	20210624
JP 2008092949	A	Alive	20201121
US 20090286856	A1	Dead	20201121
US 8044193	B2	Dead	20201121
US 20120010090	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Methods for detecting and diagnosing breast cancer (BRC) are provided. Gene expression profiles of cancer cells from 81 BRCs, including 12 DCISs (ductal carcinoma in situ) and 69 IDCs (invasive ductal carcinoma), were analyzed using a cDNA microarray representing 23,040 genes coupled with laser microdissection. By comparing expression patterns between cancer cells from patients diagnosed with BRC and normal ductal epithelial cells purely selected with laser microdissection, 102 genes were identified as commonly up-regulated in BRC cells and among them 100 genes were selected as BRC-assocd. genes of the present invention. Similarly, 288 genes were also identified as being commonly down-regulated in BRC cells. The diagnostic method involves detg. the expression level of a BRC-assocd. gene that discriminates among BRC cells, between DCIS and IDC cells. The present invention further provides means for predicting and preventing

breast cancer metastasis using BRC-assocd. genes having unique altered expression patterns in breast cancer cells with lymph-node metastasis. Finally, the present invention provides methods of screening for therapeutic agents useful in the treatment of breast cancer, methods of treating breast cancer, and method for vaccinating a subject against breast cancer.

OSC.G 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (25 CITINGS)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2004:1020014 CAPLUS Full-text
DN 142:5477
TI Recombinant virus expressing an intact anti-tumor antibody containing human immunoglobulin constant regions and the therapeutic use thereof
IN Qian, Qijun; Yang, Qin
PA Sino-Gene Biotechnology Ltd., Peop. Rep. China
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA Chinese
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2004101777	A1	20041125	WO 2004-CN430	20040429
	CN 1542132	A	20041103	CN 2003-116733	20030430
	CN 1777672	A	20060524	CN 2004-80010578	20040429
	CN 100549164	C	20091014		
	US 20080241103	A1	20081002	US 2006-554902	20061108
	US 9029133	B2	20150512		
PRAI	CN 2003-116733	A	20030430		
	WO 2004-CN430	W	20040429		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2004101777	A1	Dead	20201201
CN 1542132	A	Dead	20201120
CN 1777672	A	Alive	20201121
CN 100549164	C	Alive	20201120
US 20080241103	A1	Alive	20201121
US 9029133	B2	Alive	20201121

AB The present invention provides a recombinant virus comprising a chimeric gene which encodes an intact anti-tumor antibody contg. human Ig const. regions and the therapeutic use thereof. By inserting into the genome of a recombinant virus a nucleotides acid sequence which simultaneously comprises. The cDNA sequences of both light chain and heavy chain gene of an intact anti-tumor antibody with human Ig const. regions are inserted into the genome of a recombinant virus, and the intact anti-tumor antibody can be expressed in tumor cells with high efficiency, thereby inhibit the growth and metastasis of tumors. In particular embodiments, the cDNA expressing human anti-EGFR antibody, or humanized antibody specific to human Her2, and chimeric human-mouse anti-CD20 antibody are prepd. and inserted into a replication deficient adenovirus. The anti-tumor activity of chimeric human-mouse anti-CD20 antibody is tested in breast cancer cell line BT-474 and a nude mouse implemented with breast cancer cell line SK-OV-3.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2004:449883 CAPLUS Full-text
DN 140:402911
TI Binary prediction tree modeling with many predictors and its uses in clinical and genomic applications
IN Nevins, Joseph R.; West, Mike; Huang, Andrew T.

PA Duke University, USA
SO PCT Int. Appl., 886 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2004038376	A2	20040506	WO 2003-XA33946	20031024
	WO 2004038376	A3	20040826		
	WO 2004038376	A2	20040506	WO 2003-US33946	20031024
	WO 2004038376	A3	20040826		
PRAI	US 2002-60420729	P	20021024		
	US 2002-60421062	P	20021025		
	US 2002-60421102	P	20021025		
	US 2002-60424715	P	20021108		
	US 2002-60424718	P	20021108		
	US 2002-60424701	P	20021108		
	US 2002-60425256	P	20021112		
	US 2003-60448462	P	20030221		
	US 2003-60448461	P	20030221		
	US 2003-60457877	P	20030327		
	US 2003-60458373	P	20030331		
	WO 2003-US33946		20031024		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2004038376	A2	Dead	20201201
WO 2004038376	A3	Dead	20201202
WO 2004038376	A2	Dead	20201201
WO 2004038376	A3	Dead	20201202

AB The statistical anal. described and claimed is a predictive statistical tree model that overcomes several problems obsd. in prior statistical models and regression analyses, while ensuring greater accuracy and predictive capabilities. Although the claimed use of the predictive statistical tree model described herein is directed to the prediction of a disease in individuals, the claimed model can be used for a variety of applications including the prediction of disease states, susceptibility of disease states or any other biol. state of interest, as well as other applicable non-biol. states of interest. This model first screens genes to reduce noise, applies kmeans correlation-based clustering targeting a large no. of clusters, and then uses singular value decompns. (SVD) to ext. the single dominant factor (principal component) from each cluster. This generates a statistically significant no. of cluster-derived singular factors, that are referred to as metagenes, that characterize multiple patterns of expression of the genes across samples. The strategy aims to ext. multiple such patterns while reducing dimension and smoothing out gene-specific noise through the aggregation within clusters. Formal predictive anal. then uses these metagenes in a Bayesian classification tree anal. This generates multiple recursive partitions of the sample into subgroups (the 'leaves' of the classification tree), and assocs. Bayesian predictive probabilities of outcomes with each subgroup. Overall predictions for an individual sample are then generated by averaging predictions, with appropriate wts., across many such tree models. The model includes the use of iterative out-of-sample, cross-validation predictions leaving each sample out of the data set one at a time, refitting the model from the remaining samples and using it to predict the hold-out case. This rigorously tests the predictive value of a model and mirrors the real-world prognostic context where prediction of new cases as they arise is the major goal. [This abstr. record is one of 3 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L13 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2004:287758 CAPLUS Full-text
DN 140:302345
TI Genes showing altered patterns of expression in the central nervous system in multiple sclerosis and their diagnostic and therapeutic use

IN Dangond, Fernando; Hwang, Daehee; Gullans, Steven R.
PA Brigham and Women's Hospital, Inc., USA
SO PCT Int. Appl., 139 pp.
    CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004028339	A2	20040408	WO 2003-US29451	20030925
WO 2004028339	A3	20040805		
AU 2003275029	A1	20040419	AU 2003-275029	20030925
US 20040156826	A1	20040812	US 2003-670766	20030925
PRAI US 2002-60414219	P	20020927		
WO 2003-US29451	W	20030925		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2004028339	A2	Dead	20201203
WO 2004028339	A3	Dead	20201202
AU 2003275029	A1	Dead	20201120
US 20040156826	A1	Dead	20201120

AB The present invention identifies a no. of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addn., these genes identify therapeutic targets, the modification of which may prevent MS development or progression.
OSC.G 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
           ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2001:828415 CAPLUS Full-text
DN 137:89412
TI Detection of variations in the DNA methylation profile of genes in the determining the risk of disease
IN Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PA Epigenomics A.-G., Germany
SO PCT Int. Appl., 636 pp.
    CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 69
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077373	A2	20011018	WO 2001-XA1486	20010406
DE 10019058	A1	20011220	DE 2000-10019058	20000406
WO 2001077373	A3	20011018	WO 2001-DE1486	20010406
AU 2001077487	A	20011023	AU 2001-77487	20010406
EP 1360319	A2	20031112	EP 2001-955278	20010406
EP 2014776	A2	20090114	EP 2008-12765	20010406
EP 2014776	A3	20090401		
AT 339520	T	20061015	AT 2002-90203	20020605
ES 2272636	T3	20070501	ES 2002-90203	20020605
US 20040067491	A1	20040408	US 2003-240454	20030311
AU 2003204553	A1	20040108	AU 2003-204553	20030605

	AU 2003204553	B2	20071129		
	JP 2004008217	A	20040115	JP 2003-160375	20030605
	US 20040023279	A1	20040205	US 2003-455212	20030605
	US 8577615	B2	20131105		
	AU 2006203475	A1	20060831	AU 2006-203475	20060811
	AU 2006213968	A1	20061019	AU 2006-213968	20060915
	AU 2006225250	A1	20061026	AU 2006-225250	20061005
PRAI	DE 2000-10019058	A	20000406		
	WO 2001-DE1486		20010406		
	DE 2000-10019173	A	20000407		
	DE 2000-10032529	A	20000630		
	DE 2000-10043826	A	20000901		
	AU 2001-275663	A	20010406		
	AU 2001-276331	A3	20010406		
	AU 2001-75663	A	20010406		
	EP 2001-969303	A3	20010406		
	WO 2001-EP4016	W	20010406		
	EP 2002-90203	A	20020605		
	AU 2006-230475	A	20060811		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2001077373	A2	Dead	20201202
DE 10019058	A1	Dead	20201106
WO 2001077373	A2	Dead	20201202
AU 2001077487	A	Dead	20201121
EP 1360319	A2	Dead	20201202
EP 2014776	A2	Dead	20201203
EP 2014776	A3	Dead	20201203
AT 339520	T	Dead	20201121
ES 2272636	T3	Alive	20201121
US 20040067491	A1	Dead	20201120
AU 2003204553	A1	Dead	20201120
AU 2003204553	B2	Dead	20201121
JP 2004008217	A	Alive	20201120
US 20040023279	A1	Dead	20201120
US 8577615	B2	Dead	20201121
AU 2006203475	A1	Dead	20201120
AU 2006213968	A1	Dead	20201121
AU 2006225250	A1	Dead	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for detg. the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for detg. the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or assocd. syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. [This abstr. record is one of 3 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.]

L13 ANSWER 22 OF 22 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN

AN 0050140648 EMBASE Full-text

DN 70144356
TI Adoptive transfer of PSMA-specific, TGF-β insensitive memory CD8+T cells: Suppression of human prostate cancer (CaP).
AU Zhang, Qiang (correspondence); Helfand, Brian; Chen, Lin; Smith, Norm; Lee, Chung
CS Chicago, IL, United States.
AU Qin, Weijun
CS Xian, China.
AU Zhu, Julie
CS Boston, MA, United States.
AU Guo, Yinglu
CS Beijing, China.
SO Journal of Urology, (April 2010) Vol. 183, No. 4, Supp. SUPPL. 1, pp. e265-e266. Abstract Number: 680.
Meeting Info: 2010 Annual Meeting of the American Urological Association, AUA. San Francisco, CA, United States. 29 May 2010-03 Jun 2010
ISSN: 0022-5347
DOI 10.1016/j.juro.2010.02.1079
PB Elsevier Inc..
PUI S 0022-5347(10)01335-2
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: Sep 2012
Last Updated on Embase: Sep 2012
AB INTRODUCTION AND OBJECTIVES: Tumor derived TGF-β is a potent immunosuppressant molecule which promotes CaP progression. Here we report a new immunotherapeutic approach using the adoptive transfer of PSMA-specific, TGF-β insensitive human memory CD8+ T cells to inhibit solid xenograft CaP. METHODS: Whole blood was collected from men with CaP prior to prostatectomy and CD45RAhighCD27-CD28-CCR7-memory CD8+ T cells were isolated using the EasySep CD8+ T cells enrichment kit, and then cultured in the presence of both fresh PSMA and irradiated autologous CD4+ T cells. We developed an anti-PSMA-vβ12-ζ-IRES-TβRIIDN chimeric T cell receptor construct (PZ-1-TβRIIDN) using an anti-PSMA IgTCR(ζ) gene (provided by Dr. Sadelain at Sloan-Kettering Cancer Center) and a dominant negative TGF-β type II receptor (TβRIIDN). Infection with a retroviral vector encoding this construct could induce memory T cells to be PSMA reactive and insensitive to TGF-β. Subcutaneous injection (5×105 cells) of either PC-3 CaP cells (PSMA negative; ATCC) or PSMA positive PC-3-PSMA cells (gift from Dr. Heston; Cleveland Clinic) into the right flank region of 15 immunodeficient RAG-1 mice was performed. Three weeks later, each set of animals was randomly assigned to one of three adoptive transfer groups: Group 1: memory CD8+ T cells infected with PZ-1-TβRIIDN; Group 2: memory CD8+ T cells infected with TβRIIDN only and Group 3: no treatment control. The animals were sacrificed after a total of 2 adoptive transfer treatments. The size and the weight of tumor and spleen were recorded. RESULTS: In Group 1 of PC-3-PSMA injected mice, the average tumor weight and volume of these mice was 2.62 g and 384.67 mm2, respectively. This was almost significantly less (~2-5 x) than that of animals in Group 2 (6.20g and 646.56 mm2) and Group 3 (11.66g and 752.24 mm2; P<0.05). Also, there was a significant difference between Groups 2 and 3. Interestingly, spleen weight of Group 1 (48.8mg) and Group 2 (64.5mg) increased compared to Group 3 (35.3 mg). Apoptosis in tumor cells was detected (TUNEL assay) only in animals of Group 1. There was no significant difference between the tumor size and weight in any of the three PC-3 injected groups. CONCLUSIONS: Tumor derived TGF-β decreases the function of host memory CD8+ T cells. Our approach combines TGF-β-insensitive with PSMA selectivity, which significantly enhance the specificity and tumor killing ability of multi-clonal CD8+ memory T cells. Therefore, this construct may offer a novel therapeutic intervention for both primary CaP treatment as well as for recurrence after prostatectomy.

=> d his

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     (FILE 'HOME' ENTERED AT 07:47:50 ON 13 SEP 2021)

     FILE 'HCAPLUS' ENTERED AT 07:48:36 ON 13 SEP 2021
                E BEDI ATUL/AU
L1           51 S E3-E6
                E  RAVI RAJANI/AU
L2           50 S E1-E4
L3           73 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 07:49:37 ON 13 SEP 2021
L4            0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5            0 S (TARGETING MOIETY FUSED AND IMMUNOMODULATORY MOIETY)
L6           38 S  (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7       396043 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L8        37645 S L7 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L9         1650 S L8 AND (FUSION OR CHIMERIC OR HETERODIMER)
L10         187 S L9 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L11         312 S L9 AND (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
L12          24 S L11 AND PY<=2010
L13          22 DUP REM L12 (2 DUPLICATES REMOVED)

=> s l13 and l3

L14           0 L13 AND L3

=> s l7 and l3

L15          27 L7 AND L3

=> dup rem l15

PROCESSING COMPLETED FOR L15
L16          17 DUP REM L15 (10 DUPLICATES REMOVED)
                ANSWERS '1-4' FROM FILE MEDLINE
                ANSWERS '5-11' FROM FILE BIOSIS
                ANSWERS '12-15' FROM FILE CAPLUS
                ANSWERS '16-17' FROM FILE EMBASE

=> d 1-17 bib ab


L16  ANSWER 1 OF 17     MEDLINE ®  on STN           DUPLICATE 1
AN   2019540141     MEDLINE Full-text
DN   PubMed ID: 29467463
TI   Bifunctional immune checkpoint-targeted antibody-ligand traps that
     simultaneously disable TGFβ enhance the efficacy of cancer
     immunotherapy.
AU   Ravi Rajani; Pham Vui; Wysocki Piotr T; Sidransky David; Izumchenko
     Evgeny; Bedi Atul
CS   Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins
     University School of Medicine, Baltimore, MD, 21231, USA. abedi1@jhmi.edu
AU   Noonan Kimberly A; Borrello Ivan M
CS   Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School
     of Medicine, Baltimore, MD, 21231, USA.
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CS   Department of Computer Science, Stanford University, Palo Alto, CA, 94305,
     USA.
AU   Zhavoronkov Alex; Ozerov Ivan V; Makarev Eugene; V Artemov Artem
CS   Insilico Medicine, Inc., Emerging Technology Centers, Johns Hopkins
     University at Eastern, B301, 1101 33rd Street, Baltimore, MD, 21218, USA.
AU   Mehra Ranee
CS   Department of Oncology, Johns Hopkins University School of Medicine,
     Baltimore, MD, 21231, USA.
AU   Nimmagadda Sridhar
AUID ORCID: https://orcid.org/0000-0002-6413-7191
CS   Department of Radiology and Radiological Science, Johns Hopkins Medical
     Institutions, Baltimore, MD, 21287, USA.
AU   Marchionni Luigi
CS   Center for Computational Genomics, Johns Hopkins University School of
     Medicine, Baltimore, MD, 21231, USA.
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SO Nature communications, (20180221) Vol. 9, No. 1, pp. 741. Electronic Publication Date: 21 Feb 2018
Journal code: 101528555. E-ISSN: 2041-1723. L-ISSN: 2041-1723.
Report No.: PMC-PMC5821872.
DOI http://dx.doi.org/10.1038/s41467-017-02696-6
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS MEDLINE; Priority Journals
FS Electronic
EM 201803
ED Entered STN: 22 Feb 2018
Last Updated on STN: 23 Mar 2018
Indexing Added: 23 Mar 2018
Entered Medline: 22 Mar 2018
GO United States NCI NIH HHS
GN R01 CA184199
GO United States NIDCR NIH HHS
GN P50 DE019032
OSC.G 69 There are 69 MEDLINE records that cite this record
REM.CNT 68 There are 68 cited references available in MEDLINE for this document.
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd). a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L16 ANSWER 2 OF 17 MEDLINE ® on STN DUPLICATE 2
AN 2015468037 MEDLINE Full-text
DN PubMed ID: 25593015
TI A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma.
AU Gilbert Jill; Murphy Barbara
CS Vanderbilt University, Nashville, TN, United States. jill.gilbert@vanderbilt.edu; barbara.murphy@Vanderbilt.Edu
AU Schell Michael J; Zhao Xiuhua; Tanvetyanon Tawee; Leon Marino E
CS H. Lee Moffitt Cancer Center, Tampa, FL, United States. Michael.Schell@moffitt.org; Xiuhua.Zhao@moffitt.org; Tawee.Tanvetyanon@moffitt.org; Marino.Leon@Moffitt.org
AU Neil Hayes D
CS UNC Lineberger Cancer Center, Chapel Hill, NC, United States. hayes@med.unc.edu
AU Haigentz Missak Jr
CS Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, United States. mhaigent@montefiore.org
AU Saba Nabil
CS Emory Winship Cancer Institute, Atlanta, GA, United States. NFSABA@emory.edu
AU Nieva Jorge
CS University of Southern California, Los Angeles, CA, United States. Jorge.Nieva@med.usc.edu
AU Bishop Justin; Sidransky David; Ravi Rajani; Bedi Atul; Chung Christine H

CS Johns Hopkins Medical Institutions, Baltimore, MD, United States. jbishop@jhmi.edu; dsidrans@jhmi.edu; ravira@jhmi.edu; abedi1@jhmi.edu; cchung11@jhmi.edu
SO Oral oncology, (2015 Apr) Vol. 51, No. 4, pp. 376-82. Electronic Publication Date: 13 Jan 2015
Journal code: 9709118. E-ISSN: 1879-0593. L-ISSN: 1368-8375.
Report No.: PMC-PMC4459134; MID-NIHMS651330.
DOI http://dx.doi.org/10.1016/j.oraloncology.2014.12.011
CY England: United Kingdom
DT (CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201512
ED Entered STN: 17 Jan 2015
Last Updated on STN: 16 Dec 2015
Indexing Added: 16 Dec 2015
Entered Medline: 7 Dec 2015
GO United States NCI NIH HHS
GN HHSN261201100100C; R25 CA174664; P30 CA076292
GO United States NIDCR NIH HHS
GN P50 DE019032; P50DE019032
GO United States PHS HHS
GN N01 261201100100C
OSC.G 14 There are 14 MEDLINE records that cite this record
REM.CNT 24 There are 24 cited references available in MEDLINE for this document.
AB INTRODUCTION: A combination of cetuximab and sorafenib in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) were assessed for potential benefit.

MATERIAL AND METHODS: In a randomized phase II study, R/M HNSCC patients were treated with cetuximab 400mg/m(2) IV on day 1 followed by 250mg/m(2) IV weekly (Arm A), or cetuximab at the same dose/schedule plus sorafenib 400mg PO twice-a-day (Arm B). Each cycle was 21days. Tumor p16 and HPV status, and plasma immunomodulatory cytokine levels were assessed.

RESULTS: Of 55 patients enrolled (Arm A-27, Arm B-28), 52 patients received assigned treatments and 43 were evaluable for response. Overall response rate was 8% for both arms. Median overall survival (OS) and progression-free survival (PFS) were 9.0 and 3.0months in Arm A, and 5.7 and 3.2months in Arm B, respectively. Forty-four patients had tumors available for p16 staining (35-negative, 9-positive). Three of nine p16-positive tumors were also HPV positive. The p16-negative patients had significantly better PFS compared to the p16-positive patients (3.7 vs. 1.6months; p-value: 0.03), regardless of study arms. Twenty-four plasma samples were tested for 12 cytokine levels and patients with higher TGFβ1 levels had inferior PFS compared to lower levels (1.9 vs. 4.7months; adjusted p-value: 0.015), regardless of study arms.

CONCLUSIONS: A subset of R/M patients with p16-negative tumors or lower plasma TGFβ1 levels had longer PFS given the cetuximab-based therapy. However, both arms showed only modest response and sorafenib given with cetuximab did not demonstrate clinical benefit.
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L16 ANSWER 3 OF 17 MEDLINE ® on STN DUPLICATE 3
AN 2014730904 MEDLINE Full-text
DN PubMed ID: 24830724
TI The TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors.
AU Izumchenko Evgeny; Chang Xiaofei; Michailidi Christina; Kagohara Luciane; Ravi Rajani; Brait Mariana; Hoque Mohammad O; Ling Shizhang; Bedi Atul; Sidransky David
CS Authors' Affiliations: Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, and. dsidrans@jhmi.edu

AU Paz Keren
CS Champions Oncology, Inc., Baltimore, Maryland.
SO Cancer research, (2014 Jul 15) Vol. 74, No. 14, pp. 3995-4005. Electronic Publication Date: 15 May 2014
Journal code: 2984705R. E-ISSN: 1538-7445. L-ISSN: 0008-5472.
Report No.: PMC-PMC4122100; MID-NIHMS597285.
DOI http://dx.doi.org/10.1158/0008-5472.CAN-14-0110
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201409
ED Entered STN: 17 May 2014
Last Updated on STN: 27 Sep 2014
Indexing Added: 27 Sep 2014
Entered Medline: 26 Sep 2014
GO United States NCI NIH HHS
GN P50 CA058184; U01CA084986; U01 CA084986
GO United States NIDCR NIH HHS
GN R37DE012588; P50 DE019032; R37 DE012588
OSC.G 55 There are 55 MEDLINE records that cite this record
REM.CNT 42 There are 42 cited references available in MEDLINE for this document.
AB Although specific mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) identify tumors that are responsive to EGFR tyrosine kinase inhibitors (TKI), these genetic alterations are present in only a minority of patients. Patients with tumors expressing wild-type EGFR lack reliable predictive markers of their clinical response to EGFR TKIs. Although epithelial-mesenchymal transition (EMT) has been inversely correlated with the response of cancers to EGFR-targeted therapy, the precise molecular mechanisms underlying this association have not been defined and no specific EMT-associated biomarker of clinical benefit has been identified. Here, we show that during transforming growth factor β (TGFβ)-mediated EMT, inhibition of the microRNAs 200 (miR200) family results in upregulated expression of the mitogen-inducible gene 6 (MIG6), a negative regulator of EGFR. The MIG6-mediated reduction of EGFR occurs concomitantly with a TGFβ-induced EMT-associated kinase switch of tumor cells to an AKT-activated EGFR-independent state. In a panel of 25 cancer cell lines of different tissue origins, we find that the ratio of the expression levels of MIG6 and miR200c is highly correlated with EMT and resistance to erlotinib. Analyses of primary tumor xenografts of patient-derived lung and pancreatic cancers carrying wild-type EGFR showed that the tumor MIG6(mRNA)/miR200 ratio was inversely correlated with response to erlotinib in vivo. Our data demonstrate that the TGFβ-miR200-MIG6 network orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors, and identify a low ratio of MIG6 to miR200 as a promising predictive biomarker of the response of tumors to EGFR TKIs.
©2014 American Association for Cancer Research.

L16 ANSWER 4 OF 17 MEDLINE ® on STN DUPLICATE 4
AN 2012918323 MEDLINE Full-text
DN PubMed ID: 22927667
TI Inhibition of TGF-β enhances the in vivo antitumor efficacy of EGF receptor-targeted therapy.
AU Bedi Atul
CS Head and Neck Cancer Research Division, Department of Otolaryngology-Head and Neck Surgery, 1550 Orleans Street, Johns Hopkins University School of Medicine, Cancer Research Building II, Baltimore, MD 21231, USA.
AU Chang Xiaofei; Noonan Kimberly; Pham Vui; Bedi Rishi; Fertig Elana J; Considine Michael; Califano Joseph A; Borrello Ivan; Chung Christine H; Sidransky David; Ravi Rajani
SO Molecular cancer therapeutics, (2012 Nov) Vol. 11, No. 11, pp. 2429-39. Electronic Publication Date: 27 Aug 2012
Journal code: 101132535. E-ISSN: 1538-8514. L-ISSN: 1535-7163.
Report No.: PMC-PMC3640459; MID-NIHMS438147.
DOI http://dx.doi.org/10.1158/1535-7163.MCT-12-0101-T
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 201304
ED Entered STN: 29 Aug 2012
Last Updated on STN: 24 Apr 2013
Entered Medline: 23 Apr 2013
GO United States NCI NIH HHS
GN K25CA141053; P30 CA006973; K25 CA141053; 5P50CA096784-05; P50 CA096784; R01 CA123277; R01CA123277; R01 CA184199
GO United States NIDCR NIH HHS
GN R01 DE017982; P50 DE019032
OSC.G 30 There are 30 MEDLINE records that cite this record
REM.CNT 46 There are 46 cited references available in MEDLINE for this document.
AB EGF receptor (EGFR)-targeted monoclonal antibodies (mAb), such as cetuximab, execute their antitumor effect in vivo via blockade of receptor-ligand interactions and engagement of Fcγ receptors on immune effector cells that trigger antibody-dependent cell-mediated cytotoxicity (ADCC). We show that tumors counteract the in vivo antitumor activity of anti-EGFR mAbs by increasing tumor cell-autonomous expression of TGF-β. We show that TGF-β suppresses the expression of key molecular effectors of immune cell-mediated cytotoxicity, including Apo2L/TRAIL, CD95L/FasL, granzyme B, and IFN-γ. In addition to exerting an extrinsic inhibition of the cytotoxic function of immune effectors, TGF-β-mediated activation of AKT provides an intrinsic EGFR-independent survival signal that protects tumor cells from immune cell-mediated apoptosis. Treatment of mice-bearing xenografts of human head and neck squamous cell carcinoma with cetuximab resulted in emergence of resistant tumor cells that expressed relatively higher levels of TGF-β compared with untreated tumor-bearing mice. Although treatment with cetuximab alone forced the natural selection of TGF-β-overexpressing tumor cells in nonregressing tumors, combinatorial treatment with cetuximab and a TGF-β-blocking antibody prevented the emergence of such resistant tumor cells and induced complete tumor regression. Therefore, elevated levels of TGF-β in the tumor microenvironment enable tumor cells to evade ADCC and resist the antitumor activity of cetuximab in vivo. Our results show that TGF-β is a key molecular determinant of the de novo and acquired resistance of cancers to EGFR-targeted mAbs, and provide a rationale for combinatorial targeting of TGF-β to improve anti-EGFR-specific antibody therapy of EGFR-expressing cancers.
©2012 AACR.

L16 ANSWER 5 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2019:842991 BIOSIS Full-text
DN PREV201900942198
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 10442860 20191015
SO Official Gazette of the United States Patent and Trademark Office Patents, (OCT 15 2019)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 6 Nov 2019
Last Updated on STN: 6 Nov 2019
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention

provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L16 ANSWER 6 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2018:318724 BIOSIS Full-text
DN PREV201800318724
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGF beta enhance the efficacy of cancer immunotherapy.
AU Ravi, Rajani; Noonan, Kimberly A.; Vui Pham; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; Artemov, Artem V.; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul [Reprint Author]
CS Johns Hopkins Univ, Sch Med, Dept Otolaryngol Head and Neck Canc Res, Baltimore, MD 21231 USA
abedi1@jhmi.edu
SO Nature Communications, (FEB 21 2018) Vol. 9, pp. Article No.: 741. http://www.nature.com/ncomms/index.html.
ISSN: 2041-1723.
DOI 10.1038/s41467-017-02696-6
DT Article
LA English
ED Entered STN: 28 Mar 2018
Last Updated on STN: 28 Mar 2018
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-beta (TGF beta), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8(+) and T(H)1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGF beta receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGF beta in the target cell microenvironment (alpha-CTLA4-TGF beta RIIecd and alpha-PDL1-TGF beta RIIecd). alpha-CTLA4-TGF beta RIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, alpha-PDL1-TGF beta RIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). Our data demonstrate that Y-traps counteract TGF beta-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.

L16 ANSWER 7 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2018:123836 BIOSIS Full-text
DN PREV201800123836
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09850306 20171226
SO Official Gazette of the United States Patent and Trademark Office Patents, (DEC 26 2017)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 17 Jan 2018
Last Updated on STN: 17 Jan 2018
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and

such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L16 ANSWER 8 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2016:751124 BIOSIS Full-text
DN PREV201600751124
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 09441044 20160913
SO Official Gazette of the United States Patent and Trademark Office Patents, (SEP 13 2016)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 5 Oct 2016
Last Updated on STN: 5 Oct 2016
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By conteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L16 ANSWER 9 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2015:392017 BIOSIS Full-text
DN PREV201500392017
TI Compositions and methods for targeted immunomodulatory antibodies and fusion proteins.
AU Bedi, Atul [Inventor]; Anonymous; Ravi, Rajani [Inventor]
CS Lutherville Timonium, MD USA
ASSIGNEE: The Johns Hopkins University
PI US 08993524 20150331
SO Official Gazette of the United States Patent and Trademark Office Patents, (MAR 31 2015)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 13 May 2015
Last Updated on STN: 13 May 2015
AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immune suppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF-beta) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By

counteracting tumor-induced immune tolerance, the present invention provides effective compositions and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

L16 ANSWER 10 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2014:713314 BIOSIS Full-text
DN PREV201400713314
TI The TGF beta-miR200-Mig6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors (vol 74, pg 3995, 2014).
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hogue, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
SO Cancer Research, (SEP 1 2014) Vol. 74, No. 17, pp. 4950.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/0008-5472.CAN-14-2153
DT Article
Errata
LA English
ED Entered STN: 15 Oct 2014
Last Updated on STN: 15 Oct 2014

L16 ANSWER 11 OF 17 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
AN 2015:430029 BIOSIS Full-text
DN PREV201500430029
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. [Reprint Author]; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins Univ, Baltimore, MD USA
SO Cancer Research, (OCT 1 2014) Vol. 74, No. 19, Suppl. S, pp. 4382.
Meeting Info.: 105th Annual Meeting of the American-Association-for-Cancer-Research (AACR). San Diego, CA, USA. April 05 -09, 2014. Amer Assoc Canc Res.
CODEN: CNREA8. ISSN: 0008-5472. E-ISSN: 1538-7445.
DOI 10.1158/1538-7445.AM2014-4382
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 27 May 2015
Last Updated on STN: 27 May 2015

L16 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2021:108362 CAPLUS Full-text
DN 174:345147
TI Engineering antibody fusion proteins with ligand traps for cancer immunotherapy
IN Bedi, Atul; Bedi, Rishi
PA The Johns Hopkins University, USA; Y-Trap, Inc.
SO PCT Int. Appl., 387pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2021007428	A2	20210114	WO 2020-US41403	20200709
	WO 2021007428	A3	20210311		
	US 20210107969	A1	20210415	US 2020-16925068	20200709
PRAI	US 2019-62872194	P	20190709		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE

WO 2021007428 A2 Alive 20210128
WO 2021007428 A3 Alive 20210318
US 20210107969 A1 Alive 20210422
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention relates generally to the field of multifunctional fusion proteins to counteract immune dysfunction in the tumor microenvironment and more specifically to compns. and methods employing such fusion proteins (either alone or in combination regimens) for treatment of cancer.

L16 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2018:1128946 CAPLUS Full-text
DN 175:79670
TI Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFβ enhance the efficacy of cancer immunotherapy
AU Ravi, Rajani; Noonan, Kimberly A.; Pham, Vui; Bedi, Rishi; Zhavoronkov, Alex; Ozerov, Ivan V.; Makarev, Eugene; V. Artemov, Artem; Wysocki, Piotr T.; Mehra, Ranee; Nimmagadda, Sridhar; Marchionni, Luigi; Sidransky, David; Borrello, Ivan M.; Izumchenko, Evgeny; Bedi, Atul
CS Department of Otolaryngology-Head and Neck Cancer Research, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SO Nature Communications (2018), 9(1), 1-14
CODEN: NCAOBW; ISSN: 2041-1723
DOI 10.1038/s41467-017-02696-6
PB Nature Research
DT Journal; (online computer file)
LA English
AB A majority of cancers fail to respond to immunotherapy with antibodies targeting immune checkpoints, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1)/PD-1 ligand (PD-L1). Cancers frequently express transforming growth factor-β (TGFβ), which drives immune dysfunction in the tumor microenvironment by inducing regulatory T cells (Tregs) and inhibiting CD8+ and TH1 cells. To address this therapeutic challenge, we invent bifunctional antibody-ligand traps (Y-traps) comprising an antibody targeting CTLA-4 or PD-L1 fused to a TGFβ receptor II ectodomain sequence that simultaneously disables autocrine/paracrine TGFβ in the target cell microenvironment (a-CTLA4-TGFβRIIecd and a-PDL1-TGFβRIIecd). a-CTLA4-TGFβRIIecd is more effective in reducing tumor-infiltrating Tregs and inhibiting tumor progression compared with CTLA-4 antibody (Ipilimumab). Likewise, a-PDL1-TGFβRIIecd exhibits superior antitumor efficacy compared with PD-L1 antibodies (Atezolizumab or Avelumab). The study demonstrate that Y-traps counteract TGFβ-mediated differentiation of Tregs and immune tolerance, thereby providing a potentially more effective immunotherapeutic strategy against cancers that are resistant to current immune checkpoint inhibitors.
OSC.G 30 THERE ARE 30 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2014:1471342 CAPLUS Full-text
DN 161:625200
TI The TGFβ-miR200-MIG6 Pathway Orchestrates the EMT-Associated Kinase Switch That Induces Resistance to EGFR Inhibitors [Erratum to document cited in CA161:458236]
AU Izumchenko, Evgeny; Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Paz, Keren; Brait, Mariana; Hoque, Mohammad O.; Ling, Shizhang; Bedi, Atul; Sidransky, David
CS Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
SO Cancer Research (2014), 74(17), 4950
CODEN: CNREA8; ISSN: 0008-5472
DOI 10.1158/0008-5472.CAN-14-2153
PB American Association for Cancer Research
DT Journal
LA English
AB On page 3995, the authors list was published with typog. errors; the

correct authors list is given.
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2021 ACS on STN
AN 2011:1138357 CAPLUS Full-text
DN 155:404869
TI Fusion proteins of targeting antibody and immunomodulatory moiety for targeted antitumor therapy
IN Bedi, Atul ; Ravi, Rajani
PA The Johns Hopkins University, USA
SO PCT Int. Appl., 154pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2011109789	A2	20110909	WO 2011-US27317	20110304
	WO 2011109789	A3	20120405		
	CA 2791383	A1	20110909	CA 2011-2791383	20110304
	CA 3083324	A1	20110909	CA 2011-3083324	20110304
	IL 221607	A	20121031	IL 2011-221607	20110304
	EP 2542590	A2	20130109	EP 2011-751481	20110304
	EP 2542590	B1	20170503		
	EP 2542590	B2	20200401		
	JP 2013521311	T	20130610	JP 2012-556279	20110304
	JP 6066732	B2	20170125		
	ES 2638521	T3	20171023	ES 2011-751481	20110304
	EP 3260470	A1	20171227	EP 2017-168491	20110304
	IL 266971	A	20190731	IL 2011-266971	20110304
	EP 3798237	A1	20210331	EP 2020-205164	20110304
	IN 2012CN08417	A	20140214	IN 2012-CN8417	20121001
	US 20130039911	A1	20130214	US 2012-13582717	20121017
	US 8993524	B2	20150331		
	US 20150183881	A1	20150702	US 2015-14645282	20150311
	US 9441044	B2	20160913		
	JP 2017043600	A	20170302	JP 2016-145162	20160725
	JP 6378262	B2	20180822		
	US 20160340430	A1	20161124	US 2016-15231309	20160808
	US 9850306	B2	20171226		
	US 20170158770	A1	20170608	US 2016-15362632	20161128
	US 10442860	B2	20191015		
	JP 2018172439	A	20181108	JP 2018-140050	20180726
	IN 201948021756	A	20191018	IN 2019-48021756	20190531
	US 20200115455	A1	20200416	US 2019-16601347	20191014
PRAI	US 2010-61311255	P	20100305		
	US 2011-61435671	P	20110124		
	CA 2011-2791383	A3	20110304		
	EP 2011-751481	A3	20110304		
	EP 2017-168491	A3	20110304		
	IL 2011-221607	A3	20110304		
	JP 2012-556279	A3	20110304		
	WO 2011-US27317	W	20110304		
	IN 2012-CN8417	A3	20121001		
	US 2012-13582717	A1	20121017		
	US 2015-14645282	A1	20150311		
	JP 2016-145162	A3	20160725		
	US 2016-15231309	A3	20160808		
	US 2016-15362632	A1	20161128		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2011109789	A2	Dead	20201201
	WO 2011109789	A3	Dead	20201202
	CA 2791383	A1	Alive	20201121
	CA 3083324	A1	Alive	20201120
	IL 221607	A	Alive	20201120
	EP 2542590	A2	Indeterminate	20201107
	EP 2542590	B1	Indeterminate	20201106

EP 2542590	B2	Indeterminate	20201106
JP 6066732	B2	Alive	20201120
ES 2638521	T3	Alive	20201121
EP 3260470	A1	Transitional	20210408
EP 3798237	A1	Alive	20210401
US 20130039911	A1	Alive	20201121
US 8993524	B2	Alive	20201121
US 20150183881	A1	Alive	20201120
US 9441044	B2	Alive	20201121
JP 2017043600	A	Alive	20201121
JP 6378262	B2	Alive	20201120
US 20160340430	A1	Alive	20201120
US 9850306	B2	Alive	20201120
US 20170158770	A1	Alive	20201121
US 10442860	B2	Alive	20201120
JP 2018172439	A	Alive	20201121
US 20200115455	A1	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASFORMULTNS 2011:1138357

AB The present invention is based on the seminal discovery that targeted immunomodulatory antibodies and fusion proteins can counter act or reverse immune tolerance of cancer cells. Cancer cells are able to escape elimination by chemotherapeutic agents or tumor-targeted antibodies via specific immunosuppressive mechanisms in the tumor microenvironment and such ability of cancer cells is recognized as immune tolerance. Such immunosuppressive mechanisms include immunosuppressive cytokines (for example, Transforming growth factor beta (TGF -.beta .)) and regulatory T cells and/or immunosuppressive myeloid dendritic cells (DCs). By counteracting tumor-induced immune tolerance, the present invention provides effective compns. and methods for cancer treatment, optional in combination with another existing cancer treatment. The present invention provides strategies to counteract tumor-induced immune tolerance and enhance the antitumor efficacy of chemotherapy by activating and leveraging T cell-mediated adaptive antitumor immunity against resistant or disseminated cancer cells.

OSC.G 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (22 CITINGS)

L16 ANSWER 16 OF 17 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN

AN 20170658529 EMBASE Full-text

DN 618271173 PMID: 28522603

TI SMAD4 loss is associated with cetuximab resistance and induction of MAPK/JNK activation in head and neck cancer cells.

AU Ozawa, Hiroyuki; Ranaweera, Ruchira S.; Fertig, Elana J.; Howard, Jason D.; Markovic, Ana; Perez, Jimena; Wang, Hao; Kang, Hyunseok; Chung, Christine H. (correspondence)

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AU Quon, Harry

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AU Chung, Christine H. (correspondence)

CS Department of Head and Neck-Endocrine Oncology, Moffitt Cancer Center, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL, 33612, United States. Christine.Chung@Moffitt.Org

SO Clinical Cancer Research, (1 Sep 2017) Vol. 23, No. 17, pp. 5162-5175.

Refs: 65
ISSN: 1078-0432; E-ISSN: 1557-3265 CODEN: CCREF4
DOI 10.1158/1078-0432.CCR-16-1686
PB American Association for Cancer Research Inc..
CY United States
DT Journal; Article
FS Intellectual Indexing
016 Cancer
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered Embase: 26 Sep 2017
Last Updated on Embase: 5 Jul 2018
Indexing Added: 26 Sep 2017
First Entered Embase or Embase Alert: 26 Sep 2017
AB Purpose: We previously demonstrated an association between decreased SMAD4 expression and cetuximab resistance in head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to further elucidate the clinical relevance of SMAD4 loss in HNSCC. Experimental Design: SMAD4 expression was assessed by IHC in 130 newly diagnosed and 43 patients with recurrent HNSCC. Correlative statistical analysis with clinicopathologic data was also performed. OncoFinder, a bioinformatics tool, was used to analyze molecular signaling in TCGA tumors with low or high SMAD4 mRNA levels. The role of SMAD4 was investigated by shRNA knockdown and gene reconstitution of HPV-negative HNSCC cell lines in vitro and in vivo. Results: Our analysis revealed that SMAD4 loss was associated with an aggressive, HPV-negative, cetuximab-resistant phenotype. We found a signature of prosurvival and antiapoptotic pathways that were commonly dysregulated in SMAD4-low cases derived from TCGA-HNSCC dataset and an independent oral cavity squamous cell carcinoma (OSCC) cohort obtained from GEO. We show that SMAD4 depletion in an HNSCC cell line induces cetuximab resistance and results in worse survival in an orthotopic mouse model in vivo. We implicate JNK and MAPK activation as mediators of cetuximab resistance and provide the foundation for the concomitant EGFR and JNK/MAPK inhibition as a potential strategy for overcoming cetuximab resistance in HNSCCs with SMAD4 loss. Conclusions: Our study demonstrates that loss of SMAD4 expression is a signature characterizing the cetuximab-resistant phenotype and suggests that SMAD4 expression may be a determinant of sensitivity/resistance to EGFR/MAPK or EGFR/JNK inhibition in HPV-negative HNSCC tumors.

L16 ANSWER 17 OF 17 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
AN 0051693676 EMBASE Full-text
DN 71721427
TI Relative expression of miR200 microRNAs and ERBB family negative regulator Mig6 in estimation of EMT status and erlotinib sensitivity.
AU Izumchenko, Eugene G. (correspondence); Chang, Xiaofei; Michailidi, Christina; Kagohara, Luciane; Ravi, Rajani; Brait, Mariana; Bedi, Atul; Sidransky, David
CS Johns Hopkins University, Baltimore, MD, United States.
SO Cancer Research, (1 Oct 2014) Vol. 74, No. 19, Supp. SUPPL. 1. Abstract Number: 4382.
Meeting Info: 105th Annual Meeting of the American Association for Cancer Research, AACR 2014. San Diego, CA, United States. 05 Apr 2014-09 Apr 2014
ISSN: 0008-5472
DOI 10.1158/1538-7445.AM2014-4382
PB American Association for Cancer Research Inc..
DT Journal; Conference; (Conference Abstract)
FS CONF
FS Intellectual Indexing
LA English
SL English
ED Entered Embase: 3 Feb 2015
Last Updated on Embase: 3 Feb 2015
AB While sensitizing mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) render tumors more sensitive to EGFR tyrosine kinase inhibitors (TKIs), these genetic alterations are present in only a minority of patients who respond to treatment and are rare in tumors other than NSCLCs. Thus, clinical benefit of TKIs in a subset of

patients with wild-type EGFR may be underestimated due to the lack of appropriate predictive markers to stratify them from larger number of patients who do not response. It has long been observed that the response of anti-EGFR agents is associated with epithelial and mesenchymal transition (EMT) in multiple types of tumors without known EGFR mutations. However, little is known about the molecular mechanisms underlying this association, and no EMT-associated biomarkers of clinical utility have been successfully developed. Here we show that during the TGFβ-induced EMT, upregulation of mitogen-inducible gene 6 (Mig6), a negative regulator of EGFR, by microRNAs 200 (miR200) family is leading to reduced EGFR dependence, initiation of kinase switch in mesenchymal cells and subsequent insensitivity of these cells to EGFR inhibition. Moreover, we found that the ratio between mRNA levels of Mig6 and miR200c highly correlated with erlotinib sensitivity and EMT status in panel of 25 cancer cell lines of different tissue origins. Furthermore, analysis of directly xenografted human lung and pancreatic tumors (tumorgrafts) bearing wtEGFR demonstrated a higher response to EGFR inhibitor erlotinib for models with low Mig6 (mRNA)/miR200 ratio. Collectively, our data demonstrates that during the EMT-associated evolution of resistance to EGFR inhibitors, Mig6 expression is highly correlated with EMT status and identifies the ratio of Mig6 mRNA to miR200 as a novel, reliable and cost-effective predictor of biologic and clinical response to TKIs.

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=> d his

     (FILE 'HOME' ENTERED AT 07:47:50 ON 13 SEP 2021)

     FILE 'HCAPLUS' ENTERED AT 07:48:36 ON 13 SEP 2021
                 E BEDI ATUL/AU
L1             51 S E3-E6
                 E  RAVI RAJANI/AU
L2             50 S E1-E4
L3             73 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 07:49:37 ON 13 SEP 2021
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
L5              0 S (TARGETING MOIETY FUSED AND IMMUNOMODULATORY MOIETY)
L6             38 S  (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7         396043 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L8          37645 S L7 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L9           1650 S L8 AND (FUSION OR CHIMERIC OR HETERODIMER)
L10           187 S L9 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L11           312 S L9 AND (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
L12            24 S L11 AND PY<=2010
L13            22 DUP REM L12 (2 DUPLICATES REMOVED)
L14             0 S L13 AND L3
L15            27 S L7 AND L3
L16            17 DUP REM L15 (10 DUPLICATES REMOVED)

=> s l16 and py<=2010

L17             0 L16 AND PY<=2010

=> d his

     (FILE 'HOME' ENTERED AT 07:47:50 ON 13 SEP 2021)

     FILE 'HCAPLUS' ENTERED AT 07:48:36 ON 13 SEP 2021
                 E BEDI ATUL/AU
L1             51 S E3-E6
                 E  RAVI RAJANI/AU
L2             50 S E1-E4
L3             73 S L1-L2

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 07:49:37 ON 13 SEP 2021
L4              0 S (TARGETING MOIETY FUSED WITH IMMUNOMODULATORY MOIETY)
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L5            0 S (TARGETING MOIETY FUSED AND IMMUNOMODULATORY MOIETY)
L6           38 S  (TARGETING MOIETY FUSED OR IMMUNOMODULATORY MOIETY)
L7       396043 S (TRANSFORMING GROWTH FACTOR-BETA RECEPTOR TYPE OR TGF-B OR TG
L8        37645 S L7 AND (TGFBRII OR TYPE 2 OR TYPE II OR EXTRACELLULAR DOMAIN
L9         1650 S L8 AND (FUSION OR CHIMERIC OR HETERODIMER)
L10         187 S L9 AND  (EPIDERMAL GROWTH FACTOR RECEPTOR OR EGFR OR HERPES
L11         312 S L9 AND (CARCINOEMBRYONIC ANTIGEN OR CEA OR PROSTATE-SPECIFIC
L12          24 S L11 AND PY<=2010
L13          22 DUP REM L12 (2 DUPLICATES REMOVED)
L14           0 S L13 AND L3
L15          27 S L7 AND L3
L16          17 DUP REM L15 (10 DUPLICATES REMOVED)
L17           0 S L16 AND PY<=2010

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WEST Search History for Application 16601347

Creation Date: 2021091307:47

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
10442860.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
9850306.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	5	ADJ	YES		12-01-2020
16601347	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	1	ADJ	YES		12-01-2020
9441011.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
9441044.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
8993524.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(8993524.pn.) and (TGF)		2	ADJ	YES		12-01-2020

	PGPB, USPT, EPAB, JPAB, DWPI, FPRS					
7795389.pn.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(7795389.pn.) and TGF-beta	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	2	ADJ	YES		12-01-2020
(bedi atul or ravi rajani).in.	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	45	ADJ	YES		12-01-2020
(targeting moiety fused with immunomodulatory moiety)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety)) and (polypeptide and binds and tumor cell)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell)) and ((targeting moiety fused with immunomodulatory moiety))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety)) and	PGPB, USPT, EPAB, JPAB,	28	ADJ	YES		12-01-2020

(Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)	DWPI, FPRS					
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)) and (TGFbRII or type 2 or type II or extracellular domain)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain)) and (linker or glycine linker)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-(10442860.pn.))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	24	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and (Transforming growth factor-beta receptor type	PGPB, USPT, EPAB, JPAB, DWPI,	10	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 485 of 498
Bicara v. JHU - PGR2026-00025

or TGF-b or TGF-beta or TGFbR) and (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-L1)) and ((bedi atul or ravi rajani).in.)	FPRS					
(Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	66911	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)) with (TGFbRII or type 2 or type II or extracellular domain)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	3014	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain)) and (linker or glycine linker)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	1384	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	586	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker)) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-(10442860.pn.))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	388	ADJ	YES		12-01-2020
((Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR) with (TGFbRII or type 2 or type II or extracellular domain) and (linker or glycine linker) and (carcinoembryonic antigen or CEA or	PGPB, USPT, EPAB, JPAB, DWPI,	1	ADJ	YES		12-01-2020

Bicara Ex. 1006, Page 486 of 498
Bicara v. JHU - PGR2026-00025

prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD-L1)) and (10442860.pn.)	FPRS					
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety)) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/00 | C07K16/32 | C07K7/08 | C07K19/00 | C07K1/00 | C07K14/475 | C07K14/715 | C07K16/18 | C07K16/22 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/16 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 | A61B18/18 | C12P21/08).IPCR.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	29	ADJ	YES		12-01-2020
((targeting moiety fused with immunomodulatory moiety) and (polypeptide and binds and tumor cell) and (targeting moiety fused with immunomodulatory moiety) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/00 | C07K16/32 | C07K7/08 | C07K19/00 | C07K1/00 | C07K14/475 | C07K14/715 | C07K16/18 | C07K16/22 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/16 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 | A61B18/18 | C12P21/08).IPCR.)) and ((bedi atul or ravi rajani).in.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	10	ADJ	YES		12-01-2020
(bedi atul or ravi rajani).in.	PGPB, USPT, EPAB,	55	ADJ	YES		09-13-2021

Bicara Ex. 1006, Page 487 of 498
Bicara v. JHU - PGR2026-00025

	JPAB, DWPI, FPRS					
(targeting moiety fused with immunomodulatory moiety)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	33	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety)) and (polypeptide or antibody or antigen)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	33	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (polypeptide or antibody or antigen)) and (tumor cell)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	32	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (polypeptide or antibody or antigen)) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	32	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (polypeptide or antibody or antigen) and (Transforming growth factor-beta receptor type or TGF-b or TGF-beta or TGFbR)) and ((bedi atul or ravi rajani).in.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	10	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety)) and (TGFbRII or type 2 or type II or extracellular domain)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	27	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety)) and (fusion or chimeric or heterodimer)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	33	ADJ	YES		09-13-2021

((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer)) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	33	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and (carcinoembryonic antigen or CEA or prostate-specific membrane antigen or PSMA or programmed death-ligand 1 or PD- ((bedi atul or ravi rajani).in.))	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	26	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and ((bedi atul or ravi rajani).in.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	10	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and (linker or glycine linker)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	32	ADJ	YES		09-13-2021
((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM)) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/32 | C07K7/08 | C07K16/00 | C07K19/00 | C07K1/00 | C07K16/18 | C07K16/22 | C07K14/475 | C07K14/715 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K38/16 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 |	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	33	ADJ	YES		09-13-2021

A61B18/18 | A61N5/10 | C12P21/08 | A01K67/027).IPCR.)						
((targeting moiety fused with immunomodulatory moiety) and (fusion or chimeric or heterodimer) and (Epidermal Growth Factor Receptor or EGFR or Herpes virus entry mediator or HVEM) and ((C07K16/28 | C07K14/71 | C07K14/705 | C07K14/495 | C07K16/30 | C07K14/00 | C07K14/65 | C07K16/32 | C07K7/08 | C07K16/00 | C07K19/00 | C07K1/00 | C07K16/18 | C07K16/22 | C07K14/475 | C07K14/715 | C07K16/24 | A61K39/395 | A61K45/06 | A61K39/00 | A61K38/17 | A61K38/10 | A61K38/00 | A61K48/00 | A61K31/704 | A61K39/385 | A61K47/48 | A61K47/68 | A61K38/16 | A61K35/12 | A61K35/13 | A61K35/15 | A61K35/17 | A61K38/18 | A61K45/00 | C12N15/62 | C12N5/00 | C12N5/078 | C12N5/09 | C12N5/0784 | G01N33/68 | A61P35/00 | A61P29/00 | A61P37/00 | A61P37/02 | A61P37/04 | A61P37/06 | A61P43/00 | A61B18/02 | A61B18/04 | A61B18/18 | A61N5/10 | C12P21/08 | A01K67/027).IPCR.)) and ((bedi atul or ravi rajani).in.)	PGPB, USPT, EPAB, JPAB, DWPI, FPRS	10	ADJ	YES		09-13-2021

Bicara Ex. 1006, Page 490 of 498
Bicara v. JHU - PGR2026-00025

PATENT
Attorney Docket No.: JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	F.M. Hamud
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL SHEET

Sir:

Transmitted herewith for the above-identified application, please find:

1. Response to Notice of Allowance mailed November 2, 2021 (1 page); and
2. Form PTOL-85B Issue Fee Transmittal (1 page).

The fees for this filing total $600.00, which consist of $600.00 for the Issue Fee pursuant to 37 CFR § 1.18(a). The Commissioner is hereby authorized to charge this fee and any other fees associated with the filing submitted herewith or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

Date: February 1, 2022

/Pamela E. Hwang/
Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
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USPTO Customer No. 100899
DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

297254809.2
331323-001301

PATENT
Attorney Docket No.: JHU3260-8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1647
Application No.:	16/601,347	Examiner:	F.M. Hamud
Filed:	October 14, 2019	Conf. No.:	9807
Title:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS		

Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF ALLOWANCE

Sir:

In response to the Notice of Allowance mailed November 2, 2021, attached is the completed Issue Fee Transmittal Form PTOL-85B.

The Commissioner is hereby authorized to charge $600.00 to Deposit Account No. 07-1896 consisting of $600.00 for the required Issue Fees. The Commissioner is also authorized to charge any other fees associated with the filing submitted herewith or credit any overpayment to the aforementioned Deposit Account.

Respectfully submitted,

Date: February 1, 2022

/Pamela E. Hwang/
Pamela E. Hwang, J.D., Ph.D.
Registration No. 54,984
Telephone: (858) 677-1473
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DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133

297254991.2
331323-001301

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

100899 7590 11/02/2021
The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Aldon Griffis	(Typed or printed name)
/Aldon Griffis/	(Signature)
February 1, 2022	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	10/14/2019	Atul Bedi	JHU3260-8	9807

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	02/02/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
HAMUD, FOZIA M	1647	530-387100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 DLA Piper LLP (US)
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: The Johns Hopkins University

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Baltimore, Maryland

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies .....

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 07-1896

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☒ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Pamela E. Hwang/ Date February 1, 2022

Typed or printed name Pamela E. Hwang, J.D., Ph.D. Registration No. 54,984

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	16601347
Filing Date:	14-Oct-2019
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Filer:	Aldon Griffis
Attorney Docket Number:	JHU3260-8

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	600	600

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**600**

Electronic Acknowledgement Receipt

EFS ID:	44892583
Application Number:	16601347
International Application Number:	
Confirmation Number:	9807
Title of Invention:	COMPOSITIONS AND METHODS FOR TARGETED IMMUNOMODULATORY ANTIBODIES AND FUSION PROTEINS
First Named Inventor/Applicant Name:	Atul Bedi
Customer Number:	100899
Filer:	Aldon Griffis
Filer Authorized By:	
Attorney Docket Number:	JHU3260-8
Receipt Date:	01-FEB-2022
Filing Date:	14-OCT-2019
Time Stamp:	16:58:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$600
RAM confirmation Number	E202221G58343761
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		C11123-P11123-37_20220201_OTH_DLAP_IssueFeeEFS.pdf	328591 a7a7637f48d86e6d3f5b43ad25f0273f6e6efb70	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Issue Fee Payment (PTO-85B)	3	3

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	37915 a0b9726ad544b3d15e5390a1dca1277033cd5d5f	no	2

Warnings:

Information:

Total Files Size (in bytes):	366506

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/601,347	03/15/2022	11274156	JHU3260-8	9807

100899 7590 02/23/2022

The John Hopkins University
c/o DLA Piper LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Atul Bedi, Timonium, MD;
Rajani Ravi, Ruxton, MD;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

The Johns Hopkins University, Baltimore, MD;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.