の機能的な抗体をほとんど産生できない抗体重鎖欠損ホモ接合体を得ることができる（期待される確率は1/4である、膜型μ鎖欠損マウスにおける結果：Kitamuraら，Nature，350，423-，1991参照）。清浄な環境で飼育したホモ接合体雌雄個体の交配により得られる胚をキメラマウス作成の際の宿主として利用できる。この場合キメラマウスにおいて機能的なB細胞はほとんど注入したES細胞に由来する。RAG-2欠損マウス（Shinkaiら，Cell，68，855-，1992）等、機能的なB細胞を自ら作ることができない他のマウス系統もこの目的に同様に利用できる。このシステムにおいて（実施例62、63、64）で得られる内在性抗体重鎖及び軽鎖欠損かつヒト14番＋2番あるいは14番＋22番あるいは14番＋2番＋22番染色体（断片）を保持するマウスES細胞株を使用し（実施例10）等に示した方法でキメラマウスを作成する。得られるキメラマウスではES細胞由来のB細胞において機能的なヒト抗体重鎖（14番染色体上）、軽鎖κ（2番染色体上）、軽鎖λ（22番染色体上）遺伝子より主にヒト重鎖及びヒト軽鎖からなる抗体を生産する。

（実施例68）ヒト14番染色体（断片）導入ES細胞由来キメラマウス子孫におけるヒト染色体の保持

（実施例9）と同様な方法及び、（実施例9）のマウスES細胞をTT2F（39、XO、実施例39）に置き換えた方法を利用して得られるヒト14番染色体（断片）を保持するキメラマウスと野生型ICRマウス（アルビノ、日本クレア社）を混合して交配する。誕生する野生色の子マウスの尻尾より調製したゲノムDNAについてヒト14番染色体断片の保持をPCR法により検討する（実施例9、42、43参照）。ヒト14番染色体（断片）を保持するマウスES細胞株は（実施例42）及び（実施例43）で示した通りにキメラマウス中で機能的な卵子あるいは精子に分化し、それ由来の子孫にヒト14番染色体（断片）が伝達可能である。すなわちヒト抗体重鎖遺伝子を含む14番染色体（断片）を保持する継代可能なマウス系統を確立することができる。本実施例及び以下の実施例69～74において、ヒト14番染色体（断片）はヒト抗体重鎖遺伝子、ヒト2番染色体（断片）はヒト抗体κ鎖遺伝子を、ヒト22番染色体（断片）はヒト抗体λ鎖遺伝子を、それぞれ含むものを指す。

（実施例69）ヒト22番染色体（断片）導入ES細胞由来キメラマウス子孫におけるヒト染色体の保持



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（実施例30）と同様な方法及び、（実施例30）のマウスES細胞をTT2F（39、XO）に置き換えた方法を利用して得られるヒト22番染色体（断片）を保持するキメラマウスとICRマウスを混合して交配する。誕生する野生色の子マウスの尻尾より調製したゲノムDNAについてヒト22番染色体断片の保持をPCR法により検討する（実施例30、42、43参照）。ヒト22番染色体あるいはその部分断片を保持するマウスES細胞株は（実施例42）及び（実施例43）で示した通りにキメラマウス中で機能的な卵子あるいは精子に分化し、それ由来の子孫にヒト22番染色体（断片）が伝達可能である。すなわちヒト抗体軽鎖λ遺伝子を含む22番染色体（断片）を保持する継代可能なマウス系統を確立することができる。

（実施例70）ヒト2番染色体断片及び14番染色体（断片）を同時に保持するマウス個体の交配による作成

（実施例42）あるいは（実施例43）で得られたヒト2番染色体断片を保持するマウス系統と（実施例68）で得られるヒト14番染色体（断片）を保持するマウス系統を交配することにより生まれる子マウスの尻尾より調製したゲノムDNAをPCR法等（実施例9、42、43）により解析して、ヒト2番染色体部分断片及びヒト14番染色体（断片）を同時に保持する個体を得る。

（実施例71）ヒト22番染色体（断片）及び14番染色体（断片）を同時に保持するマウス個体の交配による作成

（実施例69）で得られるヒト22番染色体（断片）を保持するマウス系統と（実施例68）で得られるヒト14番染色体（断片）を保持するマウス系統を交配することにより生まれる子マウスの尻尾より調製したゲノムDNAをPCR法等（実施例30、42、43）により解析して、ヒト22番染色体（断片）及びヒト14番染色体（断片）を同時に保持する個体を得る。

（実施例72）ヒト2番染色体断片、14番染色体（断片）及び22番染色体（断片）を同時に保持するマウス個体の交配による作成

（実施例71）で得られるヒト22番染色体（断片）及びヒト14番染色体（断片）を保持するマウス系統を（実施例42、43）で得られたヒト2番染色体断片を保持するマウス系統と交配することにより生まれる子マウスの尻尾より調製したゲノムDNAをPCR法等（実施例9、30、42、43）により解析して、ヒト22番染色体（



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断片）及びヒト14番染色体（断片）及びヒト2番染色体部分断片の3種のヒト染色体を同時に保持する個体を得る。あるいは（実施例70）で得られるヒト2番染色体（断片）及びヒト14番染色体（断片）を保持するマウス系統と（実施例69）で得られるヒト22番染色体断片を保持するマウス系統と交配することによっても同様に3種のヒト染色体を同時に保持するマウス個体を得る。

（実施例73）完全なヒト抗体を主として産生するマウス系統の交配による作成

ヒト2番＋14番（実施例70）、14番＋22番（実施例71）、2番＋14番＋22番（実施例72）染色体を保持するマウス系統を内在性抗体重鎖（実施例67; Kitamuraら, Nature, 350, 423-, 1991)、軽鎖κ（Zouら, EMBO J., 12, 811-, 1993; Chen ら, EMBO J., 12, 821-, 1993)遺伝子を欠損しているマウス系統と交配を繰り返し、ヒト2番＋14番、14番＋22番、または2番＋14番＋22番染色体を保持するマウスをPCR解析等（実施例9、30、42、43）により選抜し、主に完全なヒトを産生するマウス系統を確立する（Greenら, Nature Genetics, 7, 13-, 1994, Lonbergら, Nature, 368, 856-, 1994）。

（実施例74）交配により得られるヒト抗体遺伝子を含むヒト染色体を保持するマウス系統からのヒト抗体産生ハイブリドーマ取得

（実施例25）と同様に（実施例42、43、68、69、70、71、72、73）で得られるヒト抗体遺伝子を含むヒト染色体を保持するマウス個体に目的とする抗原で免疫し、脾臓を取り出し、ミエローマ細胞と細胞融合し、ハイブリドーマを作成する。1～3週間培養し培養上清をELISA法で解析する。ELISA法は（実施例14、15、21、22、25、33、34、37、38）に示した方法で行ない、ヒト抗体陽性及びヒト抗体陽性かつ免疫した抗原特異的クローンを得る。

（実施例75）マウス抗体重鎖両側アレル破壊TT2F細胞株由来キメラマウスの血清中のマウスIgMの検出および定量

（実施例51）で取得されたマウス抗体重鎖両側アレル破壊TT2F細胞株(#131-3)より（実施例40）に示した方法で誕生した子マウスのうちキメラ率がそれぞれ0%、50% 、99% の3個体について血清中のマウスIgMの検出および定量を行った。生後約2週齢のキメラマウスより採血し血清中のマウスIgM濃度を（実施例14）のELISA 法を用いて定量した。PBSで希釈した抗マウスIgM抗体(Kirkegaard & Pe



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rry Laboratories Inc., 01-18-03)を固定し、次いで5%FBSを添加したPBSで希釈した血清試料を加えた。ペルオキシダーゼ標識抗マウスIgM抗体(Kirkegaard & Perry Laboratories Inc., 074-1803)を加え、TMBZを基質とし、450 nmの吸光度を測定した。精製されたマウスIgM(ファーミンジェン、03081D) を標準とし段階的にFBS添加のPBSで希釈した。結果を第20表に示す。マウス抗体重鎖の両側アレルが破壊されたTT2F細胞由来のキメラマウスのうち、キメラ率が99% のものはマウスIgM濃度が低く、ES細胞のマウス重鎖遺伝子がほとんど機能しないことが確認された。

第20表. キメラマウス中のマウスIgM濃度 (ELISA)

| キメラ率% | IgM (mg/l) |
|---|---|
| 0 | 12 |
| 50 | 11 |
| 99 | 1.5 |

産業上の利用可能性

本発明により、単一または複数の外来染色体またはその断片を保持し、該染色体またはその断片上の遺伝子を発現するキメラ非ヒト動物が提供された。本発明のキメラ非ヒト動物を利用して、生物学的に活性な物質を製造することができる。

本発明により、単一または複数の外来染色体またはその断片を保持し、該染色体またはその断片上の遺伝子を発現する分化多能性を持つ細胞が提供された。該細胞を利用して、骨髄移植等による遺伝病治療を行うことができる。



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# 配 列 表

配列番号：1

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGGAAGGTGG ATAACGCCCT　20

配列番号：2

配列の長さ：２２

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TCATTCTCCT CCAACATTAG CA　22

配列番号：3

配列の長さ：２１

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGTAGGGGAC CTGGAGCCTT G　21

配列番号：4



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配列の長さ：２１

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TTGACAACTC ACCTGGACTA G 21

配列番号：５

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CTCTCCTGCA GGGCCAGTCA 20

配列番号：６

配列の長さ：２２

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGCTGATGGT GAGAGTGAAC TC 22

配列番号：７

配列の長さ：２０

配列の型：核酸



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鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

AGTCAGGGCA TTAGCAGTGC 20

配列番号：8

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GCTGCTGATG GTGAGAGTGA 20

配列番号：9

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGGTGGCTGA AAGCTAAGAA 20

配列番号：１０

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状



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配列の種類：他の核酸　合成DNA

配列

CCAGAAGAAT GGTGTCATTA 20

配列番号：１１

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TCCAGGTTCT GCAGAGCAAG 20

配列番号：１２

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGTAGTTGGA GGCCATGTCC 20

配列番号：１３

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列



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CCCCACCCAT GATCCAGTAC 20

配列番号：１４
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GCCCTCAGAA GACGAAGCAG 20

配列番号：１５
配列の長さ：２２
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GAGAGTTGCA GAAGGGGTGA CT 22

配列番号：１６
配列の長さ：２２
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GGAGACCACC AAACCCTCCA AA 22



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配列番号：１７

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GGCTATGGGG ACCTGGGCTG 20

配列番号：１８

配列の長さ：２２

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CAGAGACACA GGCACGTAGA AG 22

配列番号：１９

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TTAAGGGTCA CCCAGAGACT 20

配列番号：２０

配列の長さ：２０



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配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGTAGTTGGA GGCCATGTCC 20

配列番号：２１

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CAAAAAGTCC AACCCTATCA 20

配列番号：２２

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GCCCTCAGAA GACGAAGCAG 20

配列番号：２３

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖



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トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
TCGTTCCTGT CGAGGATGAA 20

配列番号：２４
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
TCACTCCGAA GCTGCCTTTC 20

配列番号：２５
配列の長さ：２１
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
ATGTACAGGA TGCAACTCCT G 21

配列番号：２６
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA



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配列

TCATCTGTAA ATCCAGCAGT 20

配列番号：２７

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GATCCCATCG CAGCTACCGC 20

配列番号：２８

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TTCGCCGAGT AGTCGCACGG 20

配列番号：２９

配列の長さ：２２

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GATGAACTAG TCCAGGTGAG TT 22



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配列番号：３０
配列の長さ：２２
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
CCTTTTGGCT TCTACTCCTT CA 22

配列番号：３１
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
ATAGAGGGTA CCCACTCTGG 20

配列番号：３２
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
AACCAGGTAG GTTGATATGG 20

配列番号：３３



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配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

AAGTTCCTGT GATGTCAAGC 20

配列番号：３４

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TCATGAGCAG ATTAAACCCG 20

配列番号：３５

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGTGAAGGAG GACCAGGTGT 20

配列番号：３６

配列の長さ：２０

配列の型：核酸



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鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGTAGGGGTT GACAGTGACA 20

配列番号：３７

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CTGAGAGATG CCTCTGGTGC 20

配列番号：３８

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GGCGGTTAGT GGGGTCTTCA 20

配列番号：３９

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状



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配列の種類：他の核酸　合成DNA

配列

GGTGTCGTGG AACTCAGGCG 20

配列番号：４０

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CTGGTGCAGG ACGGTGAGGA 20

配列番号：４１

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

GCATCCTGAC CGTGTCCGAA 20

配列番号：４２

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列



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GGGTCAGTAG CAGGTGCCAG 20

配列番号：４３
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
AGTGAGATAA GCAGTGGATG 20

配列番号：４４
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GTTGTGCTAC TCCCATCACT 20

配列番号：４５
配列の長さ：２１
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
TTGTATTTCC AGGAGAAAGT G 21



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配列番号：４６
配列の長さ：２０
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GGAGACGAGG GGGAAAAGGG 20

配列番号：４７
配列の長さ：２７
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
ATGGACTGGA CCTGGAGGRT CYTCTKC 27

配列番号：４８
配列の長さ：２７
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
ATGGAGYTTG GGCTGASCTG GSTTTYT 27

配列番号：４９
配列の長さ：２７



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配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

ATGRAMMWAC TKTGKWBCWY SCTYCTG 27

配列番号：５０

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CAGAGGCAGT TCCAGATTTC 20

配列番号：５１

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGGGATAGAA GTTATTCAGC 20

配列番号：５２

配列の長さ：２０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状



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配列の種類：他の核酸　合成DNA

配列

ATGGACATGR RRDYCCHVGY KCASCTT 27

配列番号：５３

配列の長さ：２８

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CCAAGCTTCA GGAGAAAGTG ATGGAGTC

配列番号：５４

配列の長さ：２８

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CCAAGCTTAG GCAGCCAACG GCCACGCT

配列番号：５５

配列の長さ：２８

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列



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CCAAGCTTCA GAGGCAGTTC CAGATTTC

配列番号：５６
配列の長さ：２８
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GGGAATTCGG GTAGAAGTCA CTGATCAG

配列番号：５７
配列の長さ：２８
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GGGAATTCGG GTAGAAGTCA CTTATGAG

配列番号：５８
配列の長さ：２８
配列の型：核酸
鎖の数：一本鎖
トポロジー：直鎖状
配列の種類：他の核酸　合成DNA
配列
GGGAATTCGG GTAGAAGTCA CTTACGAG



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配列番号：５９

配列の長さ：６０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

ACCTTCATCG TCCTCTTCCT CCTGAGCCTC TTCTACAGCA CCACCGTCAC CCTGTTCAAG

配列番号：６０

配列の長さ：６０

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

TGATGCTGCA CCAACTGTAT CCATCTTCCC ACCATCCAGT GAGCAGTTAA CATCTGGAGG

配列番号：６１

配列の長さ：２２

配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CTGGGGTGAG CCGGATGTTT TG

配列番号：６２

配列の長さ：２２



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配列の型：核酸

鎖の数：一本鎖

トポロジー：直鎖状

配列の種類：他の核酸　合成DNA

配列

CCAACCCAGC TCAGCCCAGT TC



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# 請 求 の 範 囲

1．単一または複数の外来染色体あるいはその断片を含むミクロセルを作製し、該ミクロセルとの融合により、分化多能性を保持する細胞へ前記単一または複数の外来染色体あるいはその断片を移入させることを特徴とする、キメラ非ヒト動物の作製法。

2. 単一または複数の外来染色体あるいはその断片を含むミクロセルを作製し、該ミクロセルとの融合により、分化多能性を保持する細胞へ前記単一または複数の外来染色体あるいはその断片を移入させることを特徴とする、単一または複数の外来染色体あるいはその断片を含む分化多能性を保持する細胞の作製方法。

3. 単一または複数の外来染色体あるいはその断片が１Ｍｂ（百万塩基対）以上の大きさを有するものである請求の範囲第１項または第２項記載の方法。

4. 外来染色体あるいはその断片が抗体をコードする領域を含むものである請求の範囲第１項または第２項記載の方法。

5. 単一または複数の外来染色体あるいはその断片を含むミクロセルが、単一または複数の外来染色体あるいはその断片を含む細胞とミクロセル形成能の高い細胞とを融合させて作製されたハイブリッド細胞から誘導されたものである請求の範囲第１項または第２項記載の方法。

6. 単一または複数の外来染色体あるいはその断片を含むミクロセルが、前記ハイブリッド細胞から誘導されたミクロセルをさらにミクロセル形成能の高い細胞と融合させて作製された細胞から誘導されたものである請求の範囲第５項記載の方法。

7. 単一または複数の外来染色体あるいはその断片を含む細胞がヒト正常２倍体細胞である請求の範囲第５項記載の方法。

8. ミクロセル形成能の高い細胞がマウスＡ９細胞である請求の範囲第５項～第７項のいずれか一項に記載の方法。

9. 分化多能性を保持する細胞がＥＳ細胞である請求の範囲第１項または第２項記載の方法。

10. 外来染色体あるいはその断片が目的の遺伝子を含むものであり、分化多能性を保持する細胞がその外来染色体あるいはその断片上の該目的の遺伝子と同じあ



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るいは相同の遺伝子が破壊されているものである請求の範囲第1項または第2項記載の方法。

11. その外来染色体あるいはその断片上の前記の目的の遺伝子と同じあるいは相同の遺伝子が破壊されている分化多能性を保持する細胞に、該目的の遺伝子と同じあるいは相同の遺伝子を含む外来染色体あるいはその断片を移入した後、該細胞と前記目的の遺伝子と同じあるいは相同の遺伝子が欠損している系統の非ヒト動物の胚とのキメラを作製する請求の範囲第1項記載の方法。

12. 前記目的の遺伝子と同じあるいは相同の遺伝子が欠損している系統の非ヒト動物が標的遺伝子相同組み換え法により作製されたものである請求の範囲第11項記載の方法。

13. キメラ非ヒト動物が、単一または複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現し、該外来染色体あるいはその断片を子孫に伝達可能なものである請求の範囲第1項記載の方法。

14. キメラ非ヒト動物が哺乳動物である請求の範囲第1項記載の方法。

15. 哺乳動物がマウスである請求の範囲第14項記載の方法。

16. 請求の範囲第2項に記載の方法により作製することができ、単一または複数の外来染色体あるいはその断片を含む分化多能性を保持する細胞。

17. キメラ非ヒト動物を作製するための請求の範囲第16項記載の分化多能性を保持する細胞の使用。

18. 請求の範囲第1項および第3項～第15項のいずれか一項に記載の方法により作製することができ、単一または複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現するキメラ非ヒト動物、または、前記の単一もしくは複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現するその子孫。

19. 請求の範囲第18項記載のキメラ非ヒト動物またはその子孫の交配により得られる単一または複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現する非ヒト動物、または、単一もしくは複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現するその子孫。



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20. 請求の範囲第18項記載のキメラ非ヒト動物もしくはその子孫または請求の範囲第19項記載の非ヒト動物もしくはその子孫に由来する組織。

21. 請求の範囲第18項記載のキメラ非ヒト動物もしくはその子孫または請求の範囲第19項記載の非ヒト動物もしくはその子孫に由来する細胞。

22. Ｂ細胞である請求の範囲第21項記載の細胞。

23. 請求の範囲第21項記載の細胞とミエローマ細胞との融合により作製されたハイブリドーマ。

24. 単一または複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現する請求の範囲第18項記載のキメラ非ヒト動物もしくはその子孫または請求の範囲第19項記載の非ヒト動物もしくはその子孫を、該遺伝子と同じあるいは相同の遺伝子が欠損している系統の非ヒト動物と交配させることにより作製された非ヒト動物、または、前記の単一もしくは複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現するその子孫。

25. 請求の範囲第18項記載のキメラ非ヒト動物もしくはその子孫または請求の範囲第19項記載の非ヒト動物もしくはその子孫の個体、組織または細胞において、単一または複数の外来染色体あるいはその断片上の遺伝子を発現させ、その産物としての生物学的に活性な物質を回収することを特徴とする、生物学的に活性な物質の製造法。

26. キメラ非ヒト動物の細胞がＢ細胞である請求の範囲第25項記載の方法。

27. Ｂ細胞がミエローマ細胞と融合して、不死化されている請求項26記載の方法。

28. 生物学的に活性な物質が抗体である請求の範囲第25項～第27項のいずれか一項に記載の方法。

29. 抗体が哺乳動物の抗体である請求の範囲第28項記載の方法。

30. 哺乳動物の抗体がヒト抗体である請求の範囲第29項記載の方法。

31. 単一または複数の外来染色体あるいはその断片を保持し、該外来染色体あるいはその断片上の遺伝子を発現する請求の範囲第18項記載のキメラ非ヒト動物もしくはその子孫または請求の範囲第19項記載の非ヒト動物もしくはその子孫を、該遺伝子と同じあるいは相同の遺伝子が欠損している系統の非ヒト動物と交配さ



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せ、誕生した子動物の個体、組織または細胞において、前記の単一または複数の外来染色体あるいはその断片上の遺伝子を発現させ、その産物としての生物学的に活性な物質を回収することを特徴とする、生物学的に活性な物質の製造法。



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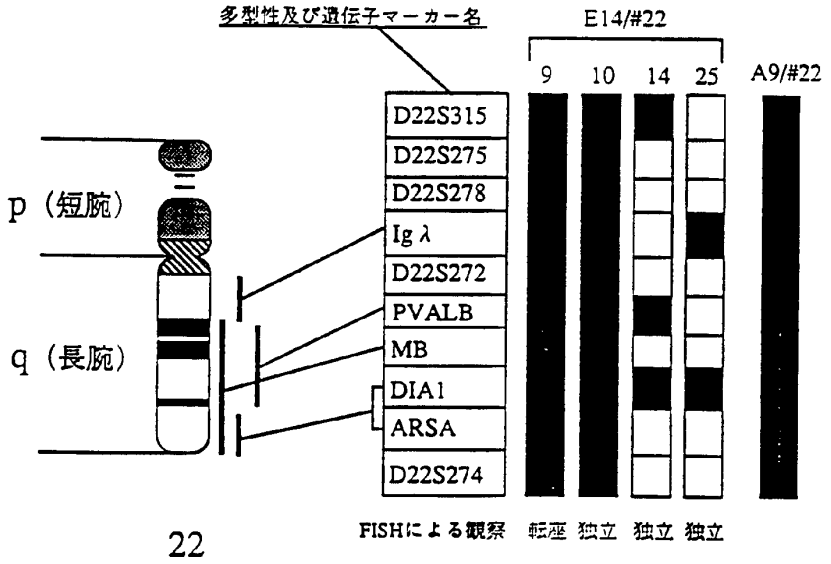
| | | ミクロセル融合株 | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | B-5 | B-24 | C8他 | D-1 | D-2 | D-8 | D-14 | E-21 | I-23 | L-34 | M-16 | N2他 | T-9 | W-23 | Y-68 | Z-15 |
| 多型性および遺伝子マーカー | S207 | × | × | × | × | × | ● | ● | ● | ● | × | × | × | × | × | × | ● |
| | S177 | × | × | × | × | × | ● | ● | ● | ● | ● | × | × | ● | × | × | ● |
| | Vk1-2 | ● | ● | ● | × | × | ● | ● | ● | ● | ● | × | ● | × | ● | × | ● |
| | Vk3-2 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| | Ck | ● | ● | ● | × | × | ● | ● | ● | ● | ● | × | ● | × | ● | × | ● |
| | S156 | × | × | × | × | × | ● | ● | ● | ● | ● | × | × | × | × | × | ● |
| | S159 | × | × | × | × | × | ● | ● | ● | ● | ● | × | × | × | × | × | ● |
| | 染色体 | 独立 | 独立 | 転座 | | 独立 | 独立 | 独立 | 独立 | 独立 | | | 転座 | | 独立 | | 独立 |

第１図　ヒト2番染色体（断片）を保持するA9細胞のPCR解析





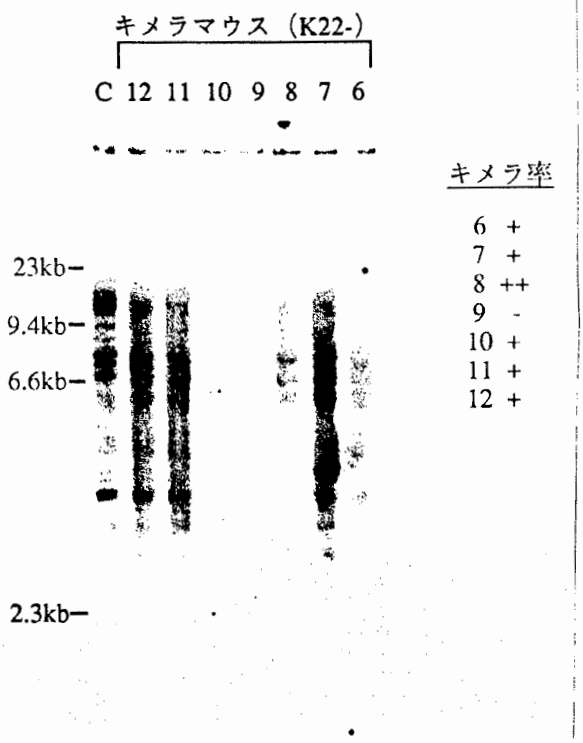
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第 2 図 E14耐性株におけるヒト22番染色体（断片）の保持（PCR解析）



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第 3 図

22番染色体導入ES細胞由来キメラマウスにおけるヒトL1配列の保持
（サザン解析）



差 替 え 用 紙 (規則26)

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DIA1：ヒト-チトクローム b5 レダクターゼ

B：脳
L：肝臓
SM：骨格筋
H：心臓
Sp：ひ臓
Th：胸腺
Ov：卵巣
K：腎臓
nc：陰性コントロール
pc：陽性コントロール

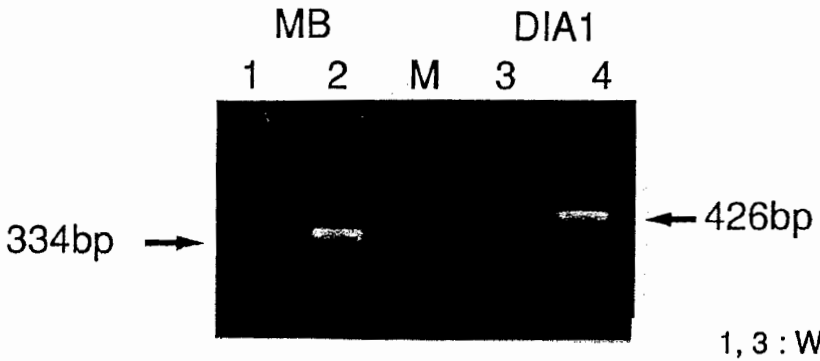
第 4 図 ヒト22番染色体導入キメラマウス臓器におけるヒト染色体の保持（PCR解析）







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1, 3 : WT（野性型マウス）

2, 4 : K22-7

MB：ヒト-ミオグロビン

DIA1 ：ヒト-チトクローム b5 レダクターゼ

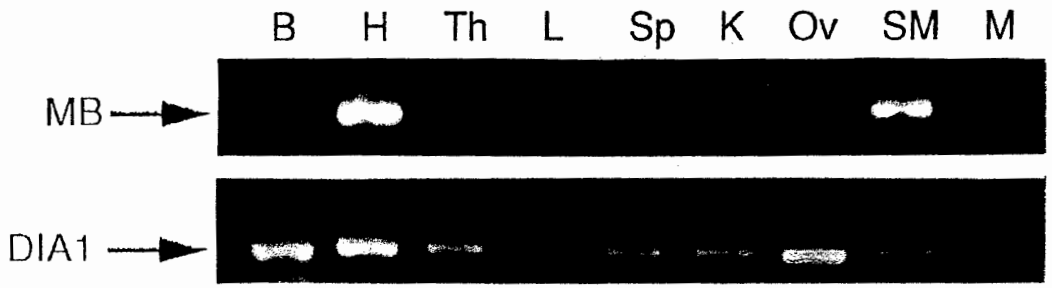
第 5 図 22番染色体導入キメラマウスにおけるヒト遺伝子発現







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B：脳
H：心臓
Th：胸腺
L：肝臓
Sp：ひ臓
K：腎臓
Ov：卵巣
SM：骨格筋
M：分子量マーカー

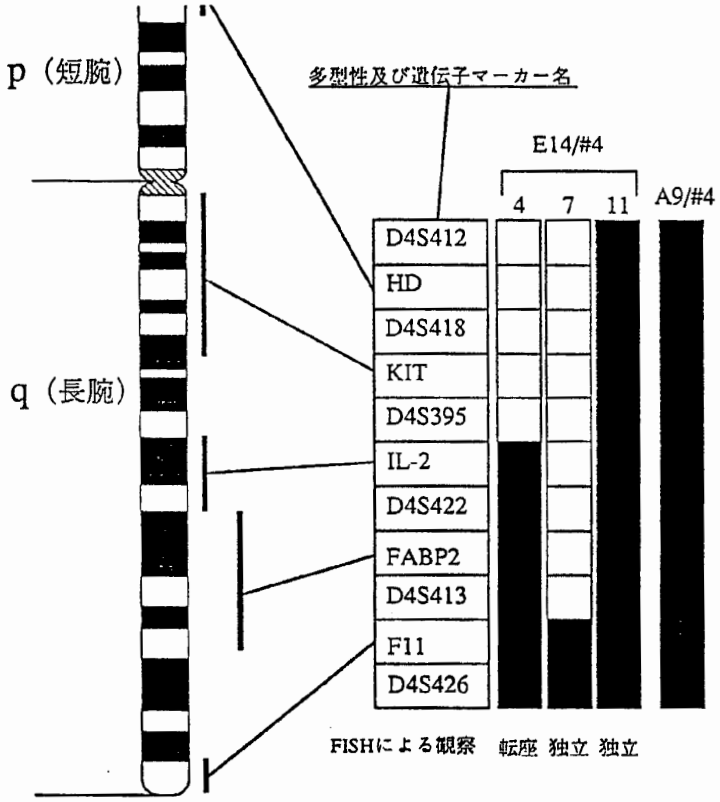
MB：ヒト-ミオグロビン

DIA1：ヒト-チトクローム b5 レダクターゼ

第 6 図 22番染色体導入キメラマウス臓器におけるヒト遺伝子発現



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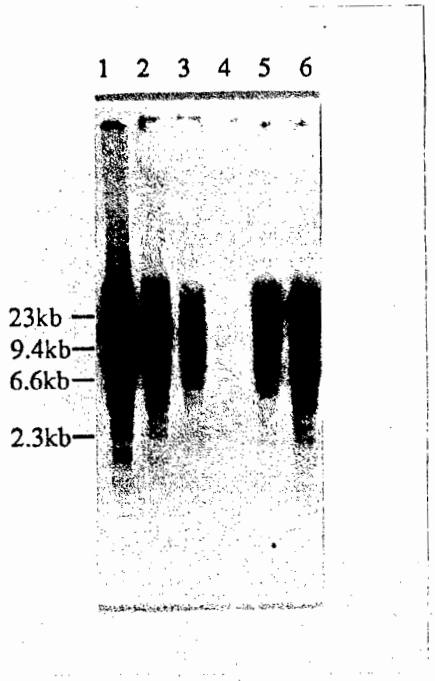



4

第 7 図 E14耐性株におけるヒト4番染色体（断片）の保持（PCR解析）



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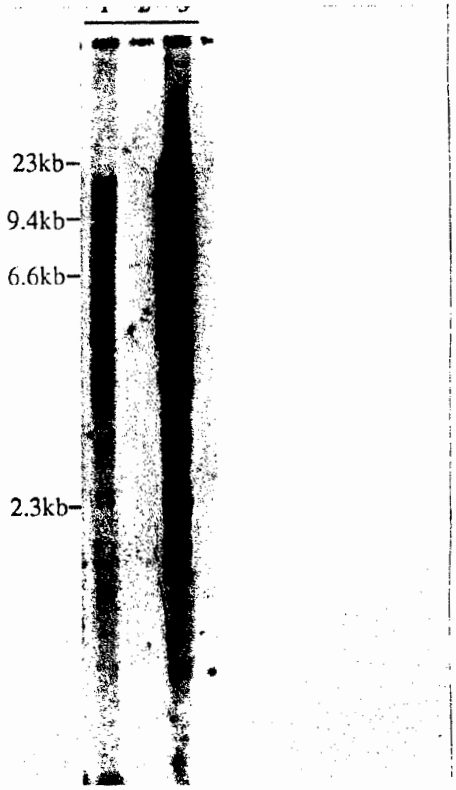

第 8 図

ヒト4番染色体導入E14細胞株におけるヒトL1配列の検出（サザン解析）



差替え用紙（規則26）

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Dana-Farber v. BMS, IPR2023-00501
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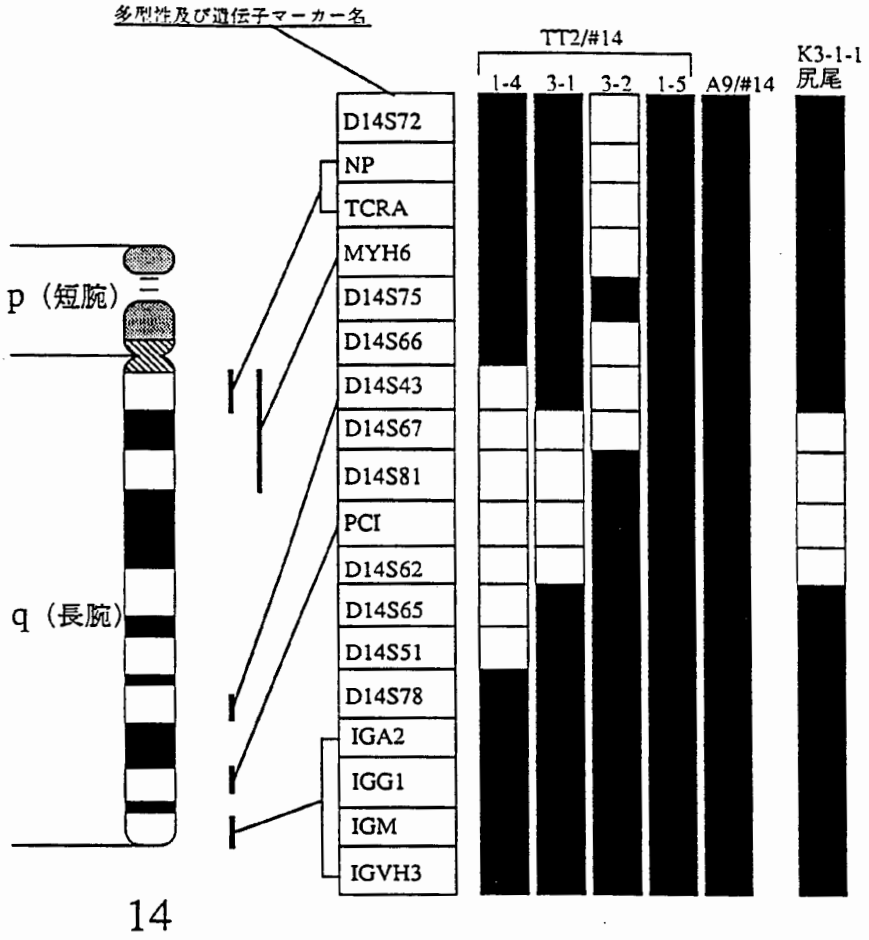

第 9 図

4番染色体導入ES細胞由来キメラマウスにおけるヒトL1配列の保持
(サザン解析)





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第１０図 TT2耐性株におけるヒト14番染色体（断片）の保持（PCR解析）



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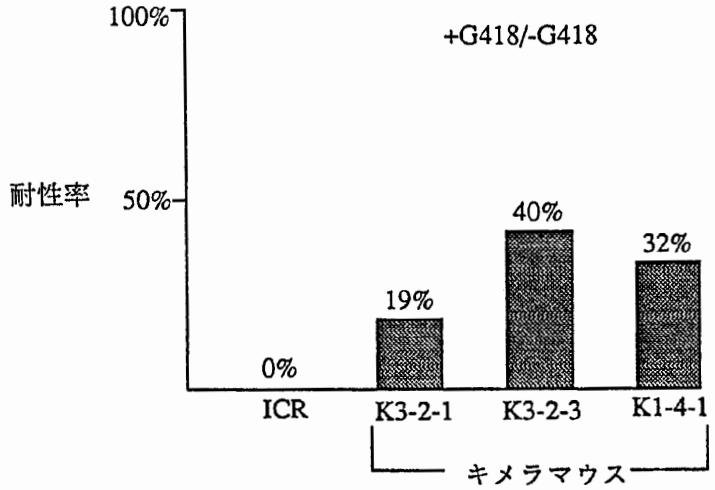
B：脳
K：腎臓
Sp：ひ臓
H：心臓
L：肝臓
Th：胸腺
pc：陽性コントロール
nc：陰性コントロール
M：分子量マーカー

IgM：ヒト-免疫グロブリンμ鎖

第１１図ヒト14番染色体導入キメラマウス臓器におけるヒト染色体の保持（PCR解析）



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Dana-Farber v. BMS, IPR2023-00501
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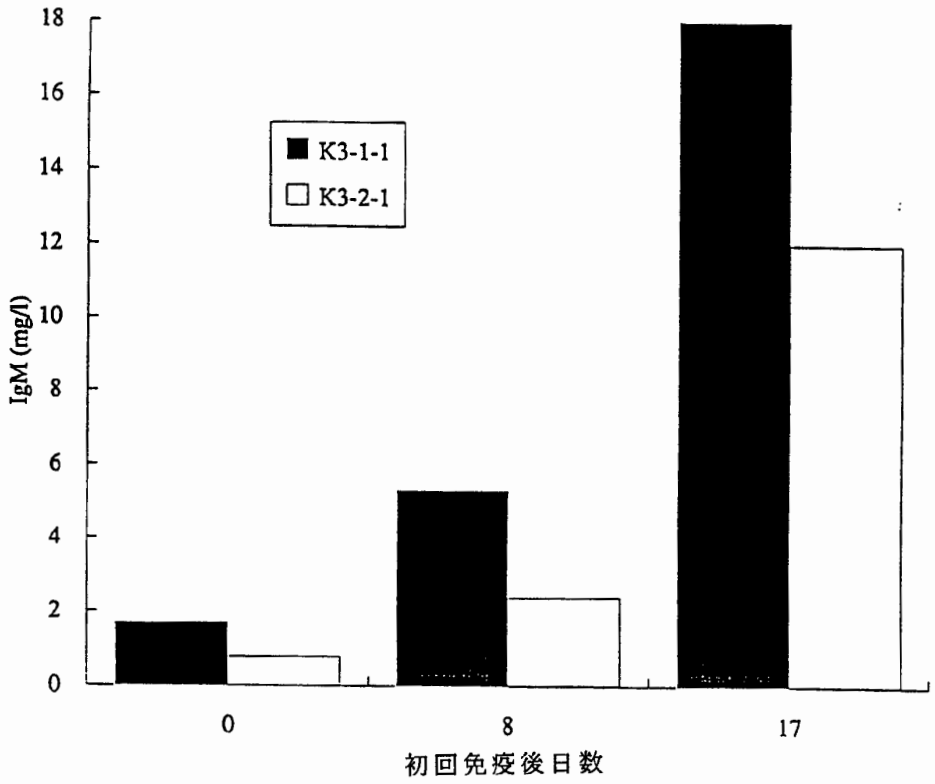



第１２図 尻尾由来繊維芽細胞G418耐性テスト



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Dana-Farber v. BMS, IPR2023-00501
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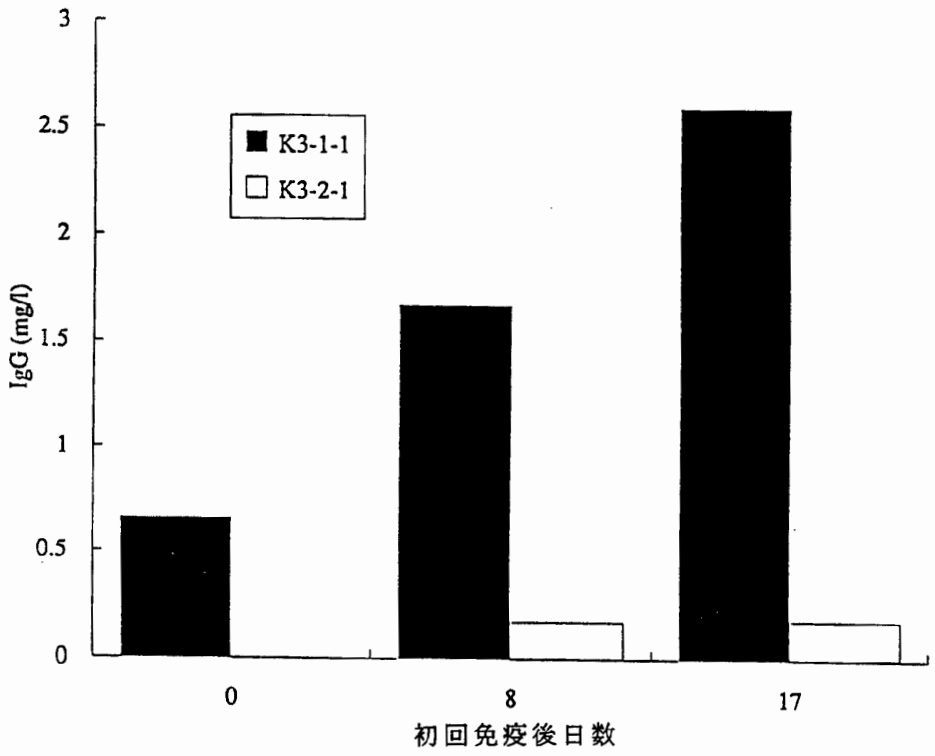
第１３図 ヒト血清アルブミン免疫キメラマウス血清中のヒト抗体IgM濃度（ELISA）






Dana-Farber EX1017
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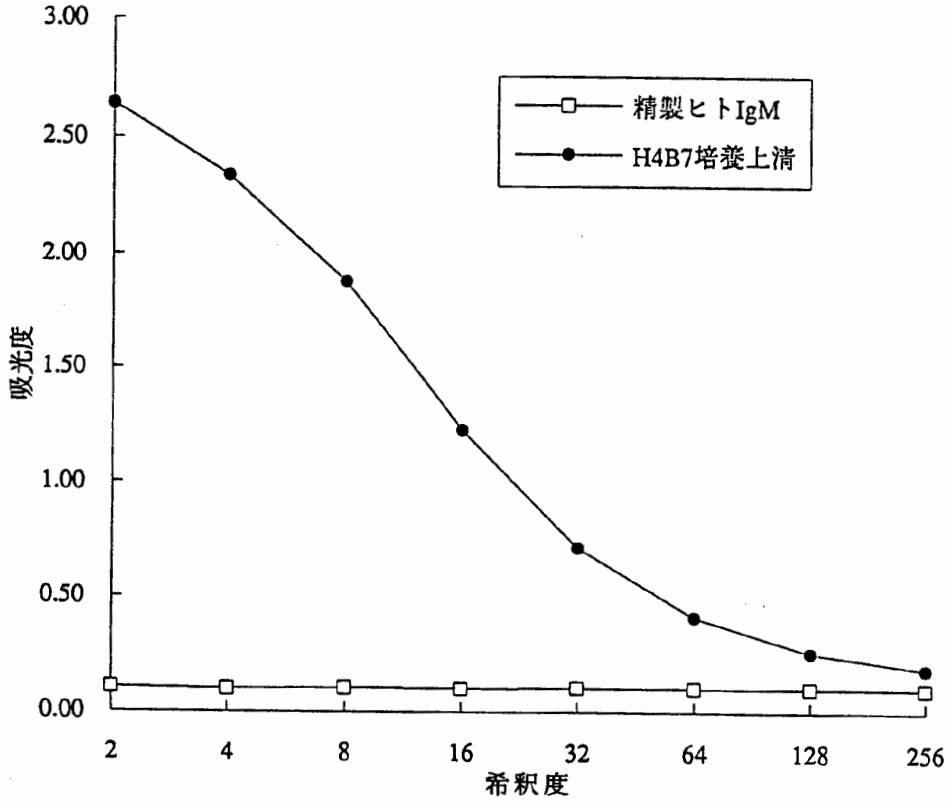
第１４図ヒト血清アルブミン免疫キメラマウス血清中のヒト抗体IgG濃度（ELISA）





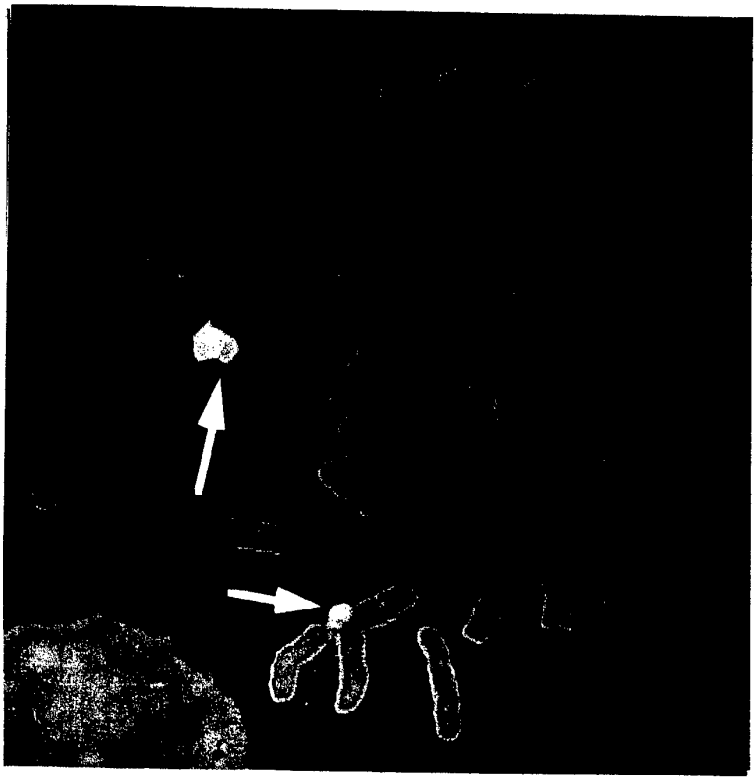

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Dana-Farber v. BMS, IPR2023-00501
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第１５図 抗HSAーヒトIgM産生ハイブリドーマH4B7株の解析






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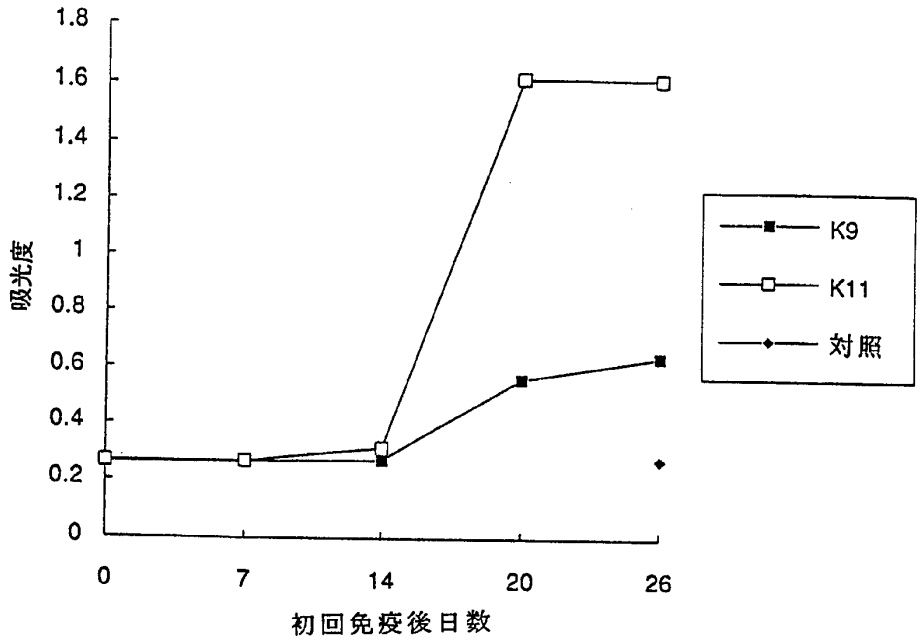
第16図



差替え用紙(規則26)

Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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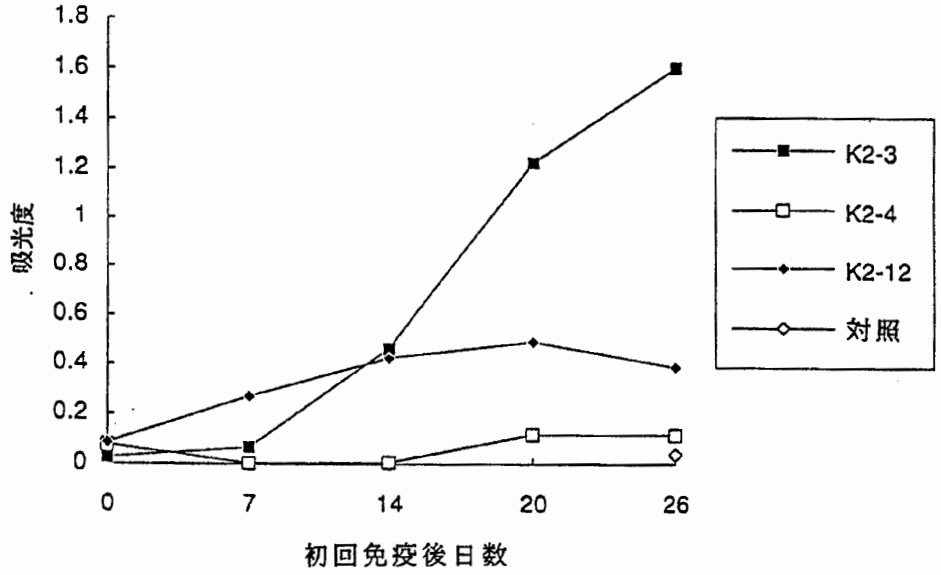
第１７図 HSA免疫キメラマウス血清中の抗HSAヒトIgG抗体価の増加






Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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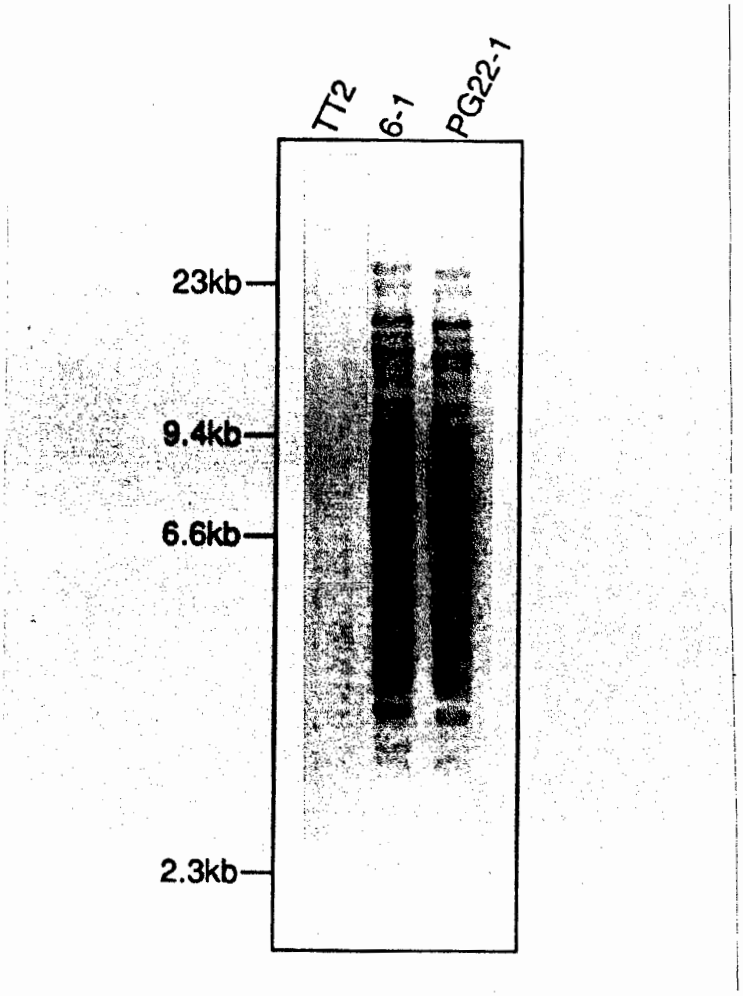
第１８図 HSA免疫キメラマウス血清中の抗HSAヒトIgκ抗体価の増加






Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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# 第１９図

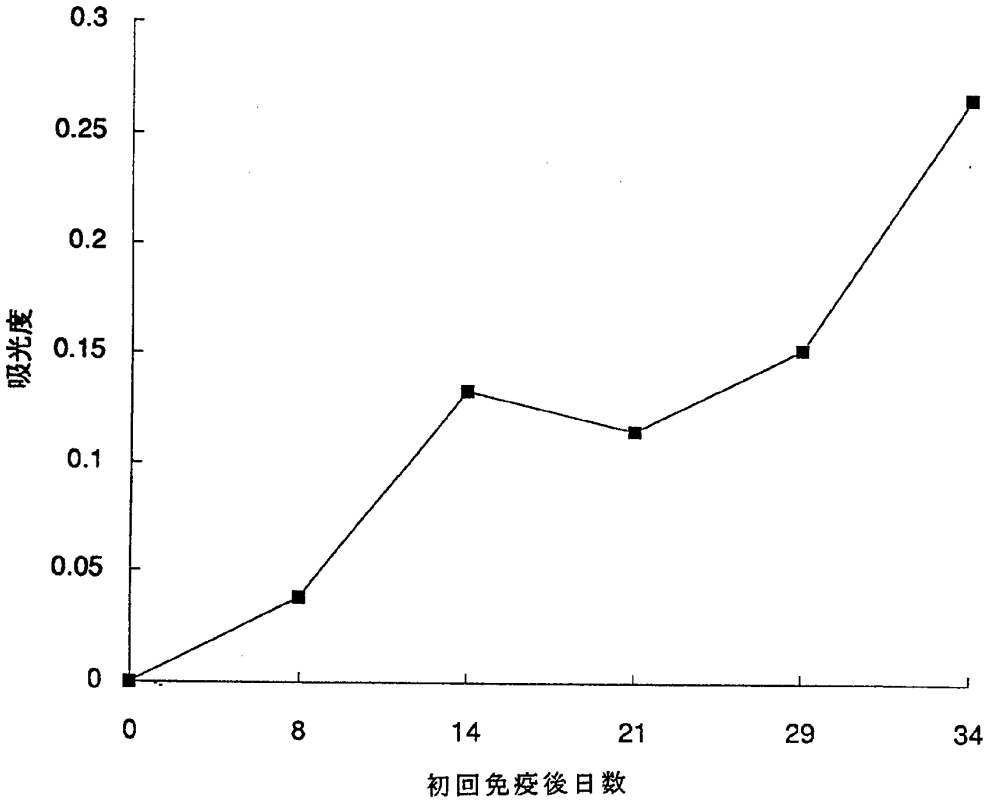





差替え用紙（規則26）

Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1437 of 2058

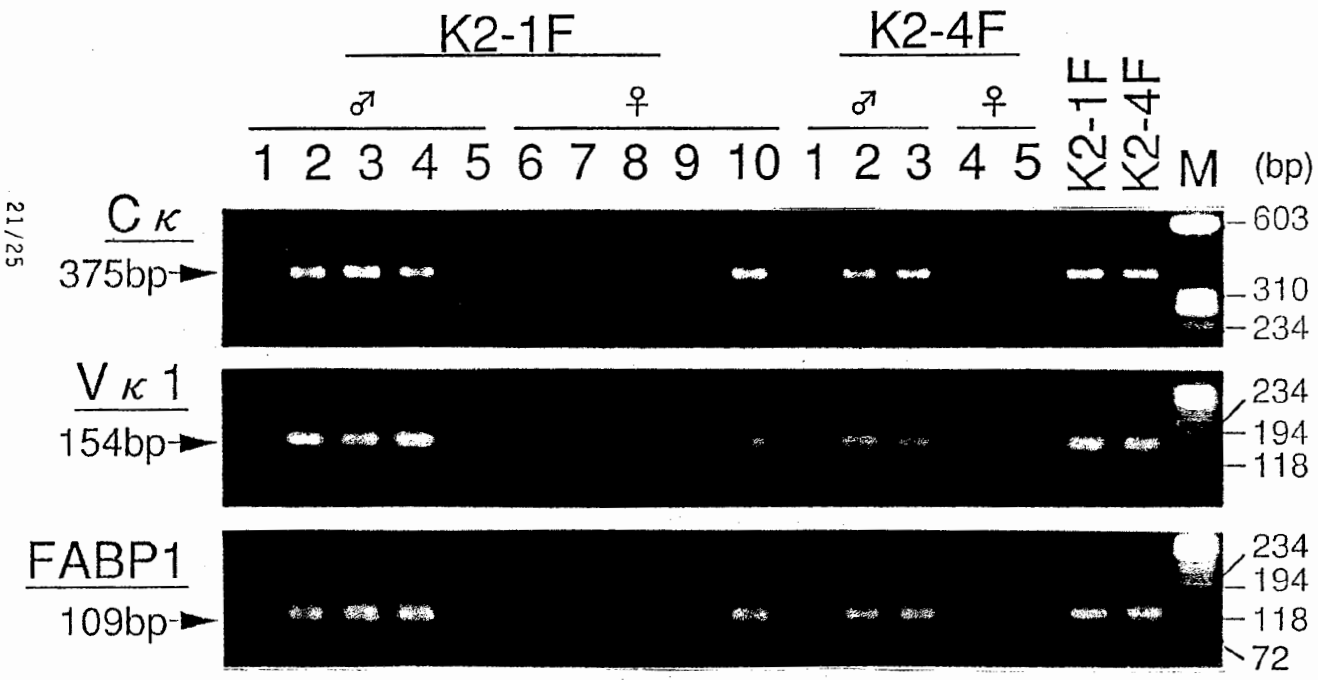
第２０図 HSA免疫キメラマウス血清中の抗HSAヒトIgλ抗体価

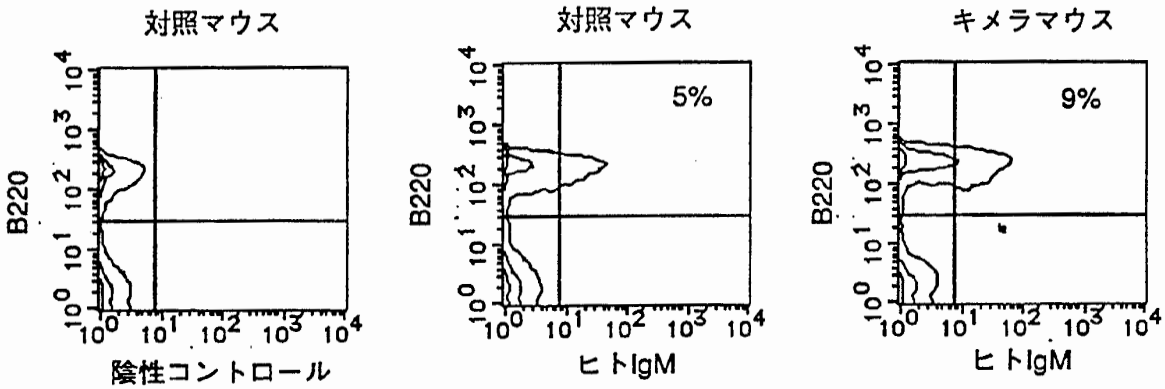





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# 第２１図


K2-1F
K2-4F
♂
♀
♂
♀
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 K2-1F K2-4F M (bp)
Cκ
375bp
603
310
234
Vκ1
154bp
234
194
118
FABP1
109bp
234
194
118
72



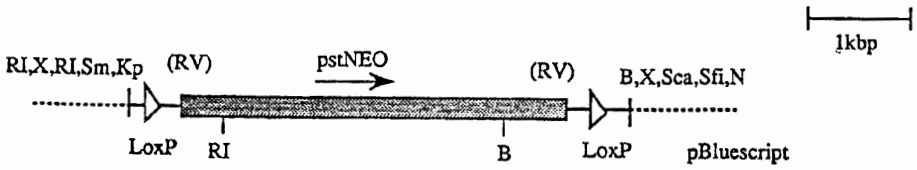

第２２図 ヒト染色体導入キメラマウスひ臓細胞の解析



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Dana-Farber v. BMS, IPR2023-00501
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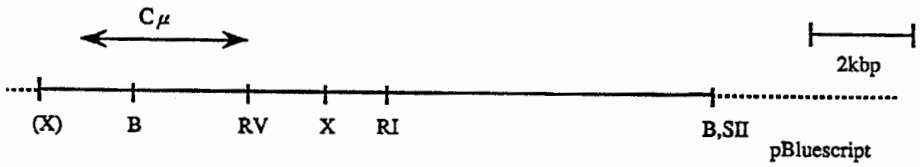
# 第２３図

LoxP-pstNEOプラスミドＤＮＡ



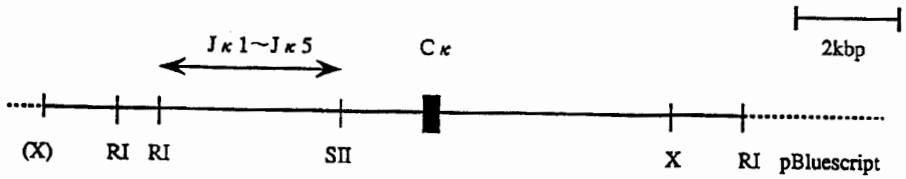

# 第２４図

マウス抗体重鎖Cμゲノム DNA




# 第２５図

マウス抗体軽鎖κゲノム DNA

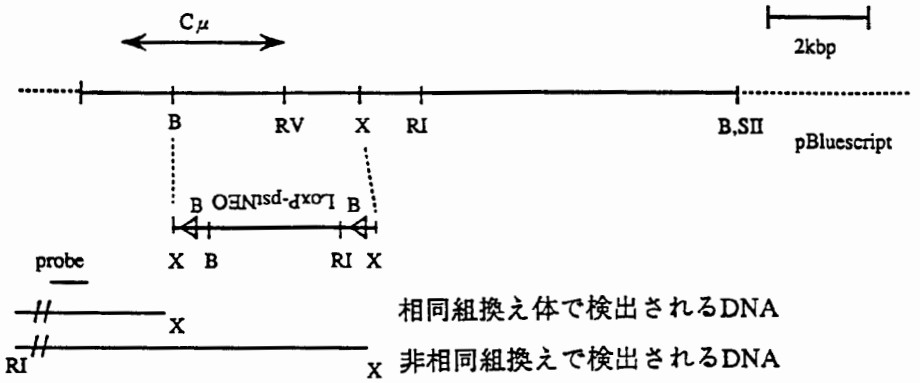





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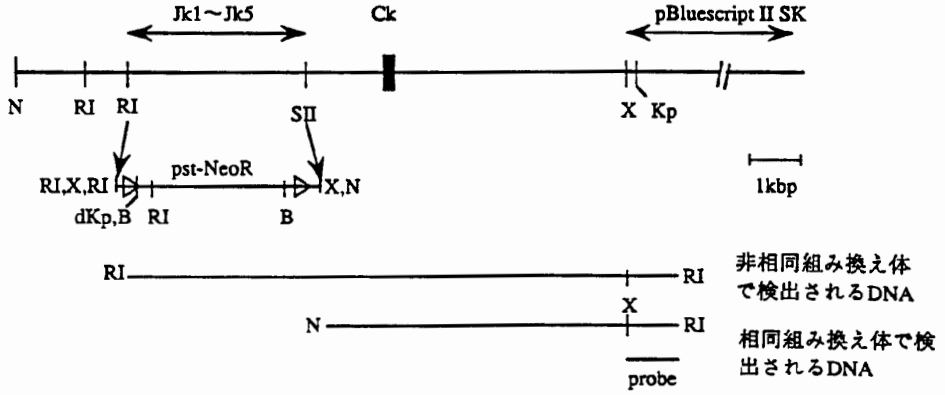
# 第２６図

マウス抗体重鎖Cμターゲッティングベクターと
形質転換体TT2細胞ゲノムDNAのサザンブロットに使用するプローブと相同
組換え体で検出されるべきDNA断片




# 第２７図

マウス抗体軽鎖κターゲッティングベクターと形質転換体TT2(TT2F)
細胞ゲノムDNAのサザンブロットに使用するプローブと相同組み換え体で検出
されるべきDNA断片



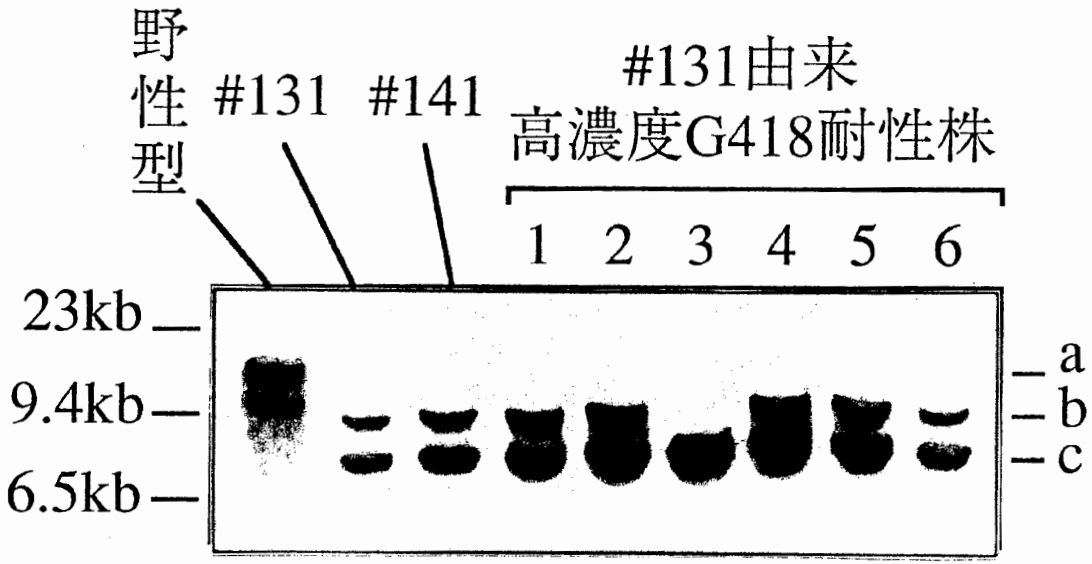

制限酵素：
Kp: KpnI, B: BamHI, RI: EcoRI, RV: EcoRV, N: NotI, SII: SacII, Sca: ScaI, Sfi: SfiI, Sm: SmaI
X: XhoI, (X)：ラムダベクター由来のXhoI切断部位
点線部分：pBluescript SKII(+) プラスミドDNA

◁▷ ：LoxP配列



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第２８図








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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/02427

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl$^6$ A01K67/027, C12N5/16, C12P21/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl$^6$ A01K67/027, C12N5/16, C12P21/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | Ted K. Choi et al., Nature Genetics Vol. 4, p. 117-123 (1993) | 1 - 31 |
| Y | I. Jean McGowan-Jordan et al., Cancer Res. Vol. 54, p. 2568-2572 (1994) | 1 - 31 |
| Y | P.J. Saxon et al., EMBO J. Vol. 5, No. 13, p. 3461-3466 (1986) | 1 - 31 |
| Y | M. Koi et al., Jpn. J. Cancer Res. Vol. 80, p. 413-418 (1989) | 1 - 31 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| November 22, 1996 (22. 11. 96) | December 3, 1996 (03. 12. 96) |
| Name and mailing address of the ISA/ Japanese Patent Office<br>Facsimile No. | Authorized officer<br>Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号　PCT／JP96／02427

A.　発明の属する分野の分類（国際特許分類（IPC））

Int. Cl.[6]　A01K　67／027,　C12N　5／16,　C12P　21／08

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl.[6]　A01K　67／027,　C12N　5／16,　C12P　21／08

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

BIOSIS

C.　関連すると認められる文献

| 引用文献のカテゴリー＊ | 引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示 | 関連する請求の範囲の番号 |
|---|---|---|
| Y | Ted K. Choi et al, Nature Genetics vol. 4, p. 117-123 (1993) | 1－31 |
| Y | I. Jean McGowan-Jordan et al, Cancer Res. vol. 54, p. 2568-2572 (1994) | 1－31 |
| Y | P. J. Saxon et al, EMBO J. vol. 5 no. 13, p. 3461-3466 (1986) | 1－31 |
| Y | M. Koi et al, Jpn. J. Cancer Res. vol. 80 p. 413-418 (1989) | 1－31 |

☐ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

| 国際調査を完了した日 | 国際調査報告の発送日 |
|---|---|
| 22. 11. 96 | 03.12.96 |

| 国際調査機関の名称及びあて先 | 特許庁審査官（権限のある職員） | 2B | 9123 |
|---|---|---|---|
| 日本国特許庁（ISA／JP）<br>郵便番号100<br>東京都千代田区霞が関三丁目4番3号 | 長井　啓子　印 | | |
| | 電話番号　03－3581－1101　内線　3236 | | |

様式PCT／ISA／210（第2ページ）（1992年7月）

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 5217282 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Perry Moy |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 24-APR-2009 |
| **Filing Date:** | |
| **Time Stamp:** | 16:47:39 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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 | Information Disclosure Statement (IDS) Filed (SB/08) | 0773750499IDS.PDF | 104907<br>56c98a6731080b20bda11327406e561b1c68e577 | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| This is not an USPTO supplied IDS fillable form | | | | | |
|---|---|---|---|---|---|
| 2 | Foreign Reference | JP7291996.pdf | 890375<br>f92c58048413d966e14ab409fe13422989ff6d85 | no | 11 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | NPL Documents | Wongetal2007.pdf | 502194<br>edd55bdb54b3519ca334d6b9b17341637ec6c9fb | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | WO1997007671A.pdf | 5896765<br>9d8afeee76c5816ee0867ad9e76ab6e7bd025938 | no | 144 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 7394241 | |

**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 APPLICATION FEE DETERMINATION RECORD
Effective December 8, 2004

Application or Docket Number: 11/913217

### CLAIMS AS FILED - PART I

| | (Column 1) | (Column 2) | SMALL ENTITY RATE | SMALL ENTITY FEE | OR | LARGE ENTITY RATE | LARGE ENTITY FEE |
|---|---|---|---|---|---|---|---|
| U.S. NATIONAL STAGE FEES | | | | | | | |
| BASIC FEE | | | BASIC FEE | | OR | BASIC FEE | 310 |
| EXAMINATION FEE | | | EXAM. FEE | | | EXAM. FEE | 210 |
| SEARCH FEE | | | SEARCH FEE | | | SEARCH FEE | 410 |
| FEE FOR EXTRA SPEC. PGS. | minus 100 = | / 50 = | X $ 125 = | | | X $ 250 = | 500 |
| TOTAL CHARGEABLE CLAIMS | 30 minus 20 = | 10 | X $ 25 = | | OR | X $ 50 = | 550 |
| INDEPENDENT CLAIMS | 7 minus 3 = | 4 | X $ 100 = | | OR | X $ 200 = | 800 |
| MULTIPLE DEPENDENT CLAIM PRESENT | | ☐ | + $ 180 = | | OR | + $ 360 = | |
| * If the difference in column 1 is less than zero, enter "0" in column 2 | | | TOTAL | | OR | TOTAL | 2850 |

### CLAIMS 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 | * | Minus | ** | = | X $ 25 = | | OR | X $ 50 = | |
| | Independent | * | Minus | *** | = | X $ 100 = | | OR | X $ 200 = | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | | ☐ | + $ 180 = | | OR | + $ 360 = | |
| | | | | | | TOTAL ADDIT. FEE | | OR | TOTAL ADDIT. 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 | * | Minus | ** | = | X $ 25 = | | OR | X $ 50 = | |
| | Independent | * | Minus | *** | = | X $ 100 = | | OR | X $ 200 = | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM | | | | ☐ | + $ 180 = | | OR | + $ 360 = | |
| | | | | | | TOTAL ADDIT. FEE | | OR | TOTAL ADDIT. 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 number found in the appropriate box in column 1.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1448 of 2058

# U.S NATIONAL STAGE WORKSHEET (DO/EO)

U.S. APPL. NO. 11/913217 INTERNATIONAL APPL. IP06/309606

APPLICATION FILED BY: 20 MOS., ____ OR 30 MOS., X SCREENED BY

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- X International application
- X Article 19 amendments
- X Priority Document(s) No. 3
- ___ Request Form PCT/RO/101
- ___ PCT/IB/302
- ___ PCT/IB/304
- ___ PCT/IB/306
- ___ PCT/IB/308
- ___ PCT/IB/331
- ___ OTHER PCT/IB/_____
- ___ PCT/IPEA/409 also 416
- ___ 409 annexes to IPER
- X PCT/ISA/210 (Search report)
- ___ Search report References
- ___ Other Papers filed

*WIPO PUBLICATION*
PUBLICATION NO. WO 06/121168
PUBLICATION DATE 16-NOV-06
PUBLICATION LANG., ENGLISH
*NOT PUBLISHED*
_____U.S. only _____Requested

RECEIVED FROM THE APPLICANT: (other than checked above)

- X National application basic fee paid
- ___ Express Processing Requested
- ___ Translation of the International Application
- X Used the IB copy of the IA
- X Description
- X Claims
- X Drawings 58
- ___ Foreign Language in drawing
- ___ Article 19 Amendments
- ___ Amendment used in application
- ___ Article 34 Amendment
- ___ Amendment used in application
- ___ DNA
- ___ 1194 transaction done
- X Preliminary Amendment(s) filed 10-31-07
- X second submission 3-3-08
- X Information Disclosure Statement 10-7-08
- X second submission 4-24-09
- X Assignment
- ____Forward to Assignment Branch
- ____Substitute Specification_____
- ___ Small Entity Statement _____
- type _____
- X Oath/Declaration (date submitted 24 SEP 09)
- ___ Not executed
- X Executed
- ___ Power of Attorney
- ___ Change of Address

Data Sheet

35 USC Receipt of Request (PTO – 1399 Transmittal Letter) 21 OCT 2009
Date Acceptable oath/declaration received 1-29-09
102(e) Date 1-29-09
Date complete 35 USC 371 requirements met 1-29-09

**DATE NOTICE COMPLETED**

DO/EO 903 Notice of Acceptance
DO/EO 905 Notice of Missing Requirements
DO/EO 917 Notice of A defective oath or declaration
DO/EO 916 Notice of defective response
DO/EO 913 Notice of defective translation
DO/EO 909 Notifilcation of Abandonment

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | 1656 | 2980 | 077375.0499 | 31 | 7 |

**CONFIRMATION NO. 1207**

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

**FILING RECEIPT**

*OC000000036016738*

Date Mailed: 05/21/2009

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

**Applicant(s)**

Alan J. Korman, Piedmont, CA;
Mohan Srinivasan, San Jose, CA;
Changyu Wang, Fremont, CA;
Mark J. Selby, San Francisco, CA;
Bing Chen, Alameda, CA;
Josephine M. Cardarelli, San Carlos, CA;

**Assignment For Published Patent Application**

MEDAREX, INC, Princeton, NJ

**Power of Attorney:** The patent practitioners associated with Customer Number 63367

**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/JP2006/309606 05/02/2006
which claims benefit of 60/679,466 05/09/2005
and claims benefit of 60/738,434 11/21/2005
and claims benefit of 60/748,919 12/08/2005

**Foreign Applications**

**If Required, Foreign Filing License Granted:** 05/15/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/913,217**

**Projected Publication Date:** 08/27/2009

**Non-Publication Request:** No

**Early Publication Request:** No



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1450 of 2058

**Title**

Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics

**Preliminary Class**

435

## 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 (1-866-999-4158).

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## Title 37, Code of Federal Regulations, 5.11 & 5.15

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| U.S. APPLICATION NUMBER NO. | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
|---|---|---|
| 11/913,217 | Alan J. Korman | 077375.0499 |

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| INTERNATIONAL APPLICATION NO. | |
|---|---|
| PCT/JP2006/309606 | |
| I.A. FILING DATE | PRIORITY DATE |
| 05/02/2006 | 05/09/2005 |

**CONFIRMATION NO. 1207**
**371 ACCEPTANCE LETTER**

*OC0000000036016739*

Date Mailed: 05/21/2009

## NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

| | |
|---|---|
| 01/29/2009 | 01/29/2009 |
| DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS | DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS |

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 10/31/2007
- Copy of the International Search Report filed on 10/31/2007
- Preliminary Amendments filed on 03/03/2008
- Information Disclosure Statements filed on 10/07/2008
- Biochemical Sequence Diskette filed on 03/03/2008
- Oath or Declaration filed on 01/29/2009
- Biochemical Sequence Listing filed on 03/03/2008
- U.S. Basic National Fees filed on 10/31/2007
- Priority Documents filed on 10/31/2007
- Specification filed on 10/31/2007
- Claims filed on 10/31/2007
- Abstracts filed on 10/31/2007
- Drawings filed on 10/31/2007
- Paper nucleotide sequence listings filed on 10/31/2007



FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

VONDA M WALLACE

Telephone: (703) 756-1425



FORM PCT/DO/EO/903 (371 Acceptance Notice)

Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1454 of 2058

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman, *et al.* | Customer No. | : 63367 |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| Filed | : 10/31/2007 | Group Art Unit | : 1632 |
| Examiner | : TBD | | |
| For | : Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics | | |

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT**

**FILED VIA EFS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicants bring to the attention of the Examiner the documents listed on the attached Form PTO 1449 and respectfully request that the listed documents be considered by the Examiner and made of record in the above-captioned application.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed document is material or constitutes "prior art." If the Examiner applies the documents as prior art against any claim in the application and applicants determine that the cited documents do not constitute "prior art" under United States law, applicants reserve the right to present to the Office the relevant facts and law regarding the appropriate status of the documents.



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Dana-Farber v. BMS, IPR2023-00501
Page 1455 of 2058

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the documents be applied against the claims of the present application.

Applicants believe no fee is due in connection with this submission. If any additional fee is due, or if any overpayment has been made, the Commissioner is authorized to charge any such fee or credit any overpayment, to our Deposit Account No. 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

July 8, 2009
Date

Lisa D. Tyner
Patent Office Reg. No. 51,619

30 Rockefeller Plaza
45th Floor
New York, NY 10012-4498
Attorney for Applicant(s)
212-408-2500



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1456 of 2058

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, *et al.* |
| | Art Unit | 1632 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

## U.S. PATENT DOCUMENTS

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 1. | US 5,897,862 | 04/27/1999 | HARDY *et al.* |
| | 2. | US 6,803,192 | 10/12/2004 | CHEN |
| | 3. | US 6,936,704 | 08/30/2005 | FREEMAN *et al.* |
| | 4. | US 7,029,674 | 04/18/2006 | CARRENO *et al.* |
| | 5. | US 7,041,474 | 05/09/2006 | KINGSBURY |
| | 6. | US 7,122,372 | 10/17/2006 | HARDY *et al.* |
| | 7. | US 7,329,639 | 02/12/2008 | HARDY *et al.* |
| | 8. | US 7,332,582 | 02/19/2008 | HARDY *et al.* |
| | 9. | US 7,488,802 | 02/10/2009 | COLLINS *et al.* |

## FOREIGN PATENT DOCUMENTS

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 10. | WO 03/033644 | 04/24/2003 | CURE TECH LTD *et al.* |
| | 11. | WO 2006/021955 | 03/02/2006 | MOR RESEARCH APPLICATIONS LTD *et al.* |
| | 12. | EP 0742795 | 09/23/1998 | MOR RESEARCH APPLICATIONS LTD |
| | 13. | EP 1537878 | 06/08/2005 | ONO PHARMACEUTICAL CO., LTD *et al.* |

| Exam Initial | No. | **OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, Etc.)** |
|---|---|---|
| | | |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:659012.1

* Examiner: Initial citation 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.

| Substitute for form 1449/PTO<br><br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br><br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, *et al.* |
| | Art Unit | 1632 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

| | | |
|---|---|---|
| | 14 | BERGER *et al.*, "Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies," *Clin Cancer Res.* (2008); 14(10):3044-51. |
| | 15 | BLANK *et al.*, "PD-L1/B7H-1 Inhibits the Effector Phase of Tumor Rejection by T Cell Receptor (TCR) Transgenic $CD8^+$ T Cells"; *Cancer Research*; (2004); 64:1140-1145. |
| | 16 | COX *et al.*, "A directory of human germ-line $V_\kappa$ segments reveals a strong bias in their usage"; *Eur. J. Immunol.*; (1994); 24:827-836. |
| | 17 | KOGA *et al.*, "Blockade of the Interaction Between PD-1 and PD-L1 Accelerates Graft Arterial Disease in Cardiac Allografts"; *Arterioscler. Thromb. Vasc. Biol.*; (2004); 24(11):2057-2062. |
| | 18 | TOMLINSON *et al.*, "The Repertoire of Human Germline $V_H$ Sequences Reveals about Fifty Groups of $V_H$ Segments with Different Hypervariable Loops"; *J. Mol. Biol.*; (1992); 227:776-798. |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:659012.1

* Examiner: Initial citation 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number
WO 03/033644 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number: PCT/IL02/00831

(22) International Filing Date: 15 October 2002 (15.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
145926 15 October 2001 (15.10.2001) IL

(71) Applicants *(for all designated States except US)*: **CURE TECH LTD.** [IL/IL]; Hayarkon Street 42, 81227 Yavne (IL). **MOR-RESEARCH APPLICATIONS LTD.** [IL/IL]; Hasivim Street 23, P.O. Box 7590, Kiryat Matalon, 49170 Petach Tikva (IL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HARDY, Britta** [IL/IL]; Eliahu Hakim Street 6, 69120 Tel Aviv (IL). **RAITER, Annat** [IL/IL]; Imbar Street 21/21, 44451 Kfar Saba (IL). **KLAPPER, Leah** [IL/IL]; Ben-Zion Street 10, 53230 Givataim 53230 (IL).

(74) Agent: **WEBB, Cynthia**; Webb & Associates, P.O. Box 2189, 76121 Rehovot (IL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 03/033644 A2

(54) Title: PEPTIDE USEFUL IN IMMUNOMODULATION

(57) Abstract: The present invention provides peptides and polynucleotides, and their use for immunomodulation, immunotherapy and vaccine particularly for anti-cancer therapy, and for diagnosis purposes. The immunomodulatory effect includes induction of proliferation and activation of peripheral blood lymphocytes and induction of an anti-tumor effect upon administration of peptides of the invention to subjects suffering from cancer.

# PEPTIDES USEFUL IN IMMUNOMODULATION

## FIELD OF THE INVENTION

The present invention relates to the field of immunotherapeutic vaccines and particularly the identification and use of peptides recognized by the immunomodulatory monoclonal antibodies designated BAT, to polynucleotides encoding these peptides, to pharmaceutical compositions comprising the peptides or the polynucleotides and to use thereof in immunomodulation, especially in anti-cancer therapy, and for diagnostic purposes.

## BACKGROUND OF THE INVENTION

Cancer in its different forms is a major cause of death in humans. The most widely used therapeutic treatments of cancer are local therapy, such as surgery and radiation, or chemotherapy. The rapid increase of knowledge in recent years about the molecular and cellular bases of immune regulation, particularly at the level of T-cell responses, provides a new arsenal of immunotherapeutic approaches including the development of tumor vaccines. Tumor vaccine is administered for therapeutic or preventive purposes. This can include administration of immuno-potentiating agents as well as biological response modifiers such as interferons and interleukins, in order to stimulate the immune system.

Vaccination with an antigen molecule, such as a peptide or a protein, generally leads to an antibody response or CD4+ helper T cell response (Raychaudhuri et al., 1993 Immunol Today 14:344). This immune response is initiated by the binding of the antigen to selected major histocompatibility complex (MHC) molecules of either Class I or Class II. The latter molecules are expressed primarily on cells involved in initiating and sustaining immune responses such as T lymphocytes, B lymphocytes and macrophages. Class II molecules are recognized by CD4+ helper T cell and induce their proliferation and the amplification of the immune response to the epitope that is displayed. Class I MHC molecules are found on most nucleated cells and are recognized by cytotoxic T lymphocytes (CTLs) which destroy the antigen bearing cells. The CTL response is a major component of the immune system, active in immune surveillance and destruction of infected or malignant cells and invading organisms expressing foreign antigens on their surface. The ligand of the antigen-





Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1460 of 2058

specific T lymphocyte receptor is a complex made up of a peptide fragment of a foreign antigen 8 to 10 amino acids in length, presented in the groove of MHC class I molecules. Unlike B cells, T cells do not recognize intact native antigen molecules. In general, cytotoxic T cell activation requires that the antigen be processed endogenously and cleaved into specific peptide fragments which are presented on the surface of antigen processing cells in association with class I MHC molecules.

Accordingly, a successful vaccine for cancer immunotherapy requires the identification of a target antigen and the production of a cytotoxic T cell response. Moreover, identification of cell surface antigens expressed exclusively or preferentially on certain tumors allows the formation of selective treatment strategies.

Numerous disclosures exist concerning immunomodulatory peptides. WO 94/20127 discloses means and methods for selecting immunogenic peptides capable of specifically binding HLA-A2.1 allele and inducing T-cell activation. WO 95/19783 relates to peptides based on an epitope derived from the product of the tumor associated gene MAGE-3. WO 97/11715 discloses a peptide which mimics MUCI or other cancer peptides. WO 00/06723 discloses tumor specific antigen peptides and use thereof as anti-tumor vaccines. US 6,406,700 discloses methods for isolating immunogenic complexes by using a cDNA library from cancer cell RNA.

International patent applications WO 95/20605 and WO 00/58363 which are incorporated herein by reference, describe a novel monoclonal antibody designated BAT-1, also designated herein BAT, which induces lymphocyte proliferation and cytolytic activity against tumor target cells. A single intravenous administration of BAT into mice bearing various tumors resulted in striking anti-tumor effects manifested by regression of tumors and prolongation of survival. BAT also induced regression of human tumor xenografts transplanted into SCID mice that were engrafted with human peripheral blood lymphocytes. The anti-tumor activity of BAT is mediated by its immune stimulatory properties as was evident from adoptive transfer experiments in which splenocytes from BAT treated mice injected to mice bearing tumors induced regression of tumors. The membrane determinant recognized by BAT has not yet been identified or characterized.

Several alternative methods of identifying the peptide epitopes bound by monoclonal antibodies are recognized in the art. These methods include the use of phage display libraries such as disclosed in US Patents Nos.: 5,223,409; 5,403,484; 5,571,698; 5,837,500 and continuations thereto. Phage display involves a selection



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technique enabling identification and isolation of a protein against a chosen target. The selection procedure is based on DNA molecules, each encoding a protein and a structural signal calling for the display of the protein on the outer surface of a bacteriophage. The protein is expressed and the potential binding domain is displayed on the outer surface of the phage. The cells or viruses bearing the binding domains which recognize the target molecule are isolated, by a repetitive selection process called biopanning, and amplified. The successful binding domains are then characterized.

Epitope libraries can also be screened for epitope sequences which mimic the epitope, i.e., sequences which do not identify a continuous linear native sequence that necessarily occurs within a natural protein sequence. These mimicking peptides are called mimotopes. In most cases mimotopes are short peptides which can be readily synthesized in large amounts. Mimotopes of various binding sites have been found. For example, US 5,877,155 provides an isolated peptide that functionally mimics a binding site for a monoclonal antibody, the monoclonal antibody recognizing an epitope within the human platelet glycoprotein Ib/IX complex.

There is an unmet medical need for peptides capable of eliciting or stimulating an anti-tumor immune response in vivo.

## SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide peptides that are useful as immunomodulatory agents, for example, in stimulating immune responses and in tumor growth inhibition.

It is another object of some aspects of the present invention to provide peptides that are useful in treatment of cancer and in treatment of autoimmune diseases.

It is a further object of some aspects of the present invention to provide peptides that are recognized by BAT monoclonal antibody.

It is yet a further object of some aspects of the invention to provide a diagnostic agent and method for diagnosing cancer in a subject.

It is yet a further object of some aspects of the invention to provide peptides that comprise epitopes or mimotopes recognized by the immunomodulatory antibody designated BAT-1.



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It is a further object of some aspects of the present invention to provide an antibody recognizing at least one epitope encompassed within any of the peptides of the invention.

The term 'epitope' referred to herein, relates to that part of an antigenic molecule that is recognized and bound by a T-cell receptor or by a B-cell receptor (i.e. a determinant on a large molecule against which an antibody can be produced and to which it will bind). The term as used herein is intended to include antigenic determinants of naturally occurring molecules or synthetic molecules that can mimic naturally occurring antigenic determinants. Molecules which mimic the naturally occurring antigenic determinants may also be referred to as 'mimotopes', and these terms may be used interchangeably in reference to epitopes which are not formed by a contiguous segment of the primary sequence of an antigen.

The peptides of the invention are recognized by the BAT-1 monoclonal antibody, also denoted herein as BAT, which is disclosed in WO 95/20605 and WO 00/58363. The peptides of the invention are further recognized by genetically modified antibodies which retain the biological activity of BAT, including chimeras or CDR-grafted antibodies. A chimeric human-mouse BAT antibody, containing mouse variable regions joined to human constant regions, is disclosed in WO 00/58363.

It has previously been shown that BAT monoclonal antibody is beneficial in treating a variety of tumors including but not limited to: melanoma, lung carcinoma, prostate cancer, breast cancer, lymphomas and leukemias, colon carcinoma, and fibrosarcomas. The peptides and polynucleotides of the present invention are useful to elicit an immune response that will obviate the necessity to treat an individual with the antibodies themselves. Thus, the peptides and polynucleotides may be used to elicit antibodies that share the attributes of the previously known BAT antibody.

In addition, the peptides of the invention are immunomodulatory. The peptides of the invention may serve as immunostimulatory agents to elicit anti-tumor activity or may serve as agents for immunotherapy or as immune-stimulators against infections, including in immunization procedures. Conversely, they can serve to inhibit undesirable immune responses such as immune responses that are involved in inflammatory conditions, including but not limited to autoimmune diseases. As immunomodulators, these peptides can induce shifts in the immune system from undesirable responses to beneficial responses. Thus, for example the peptides of the



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invention could be used to induce shifts from T helper 1 (TH1) to T helper 2 (TH2) responses that have been postulated to be of therapeutic value for suppressing or preventing autoimmune diseases or disorders.

There is thus provided, according to one embodiment of the invention, a peptide comprising at least one epitope recognized by a BAT monoclonal antibody, selected from:

(SEQ ID NO 1) Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 2) Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln-amide
(SEQ ID NO 3) Pro Arg Arg Phe Lys Pro Arg Lys Ile Asn/Asp Leu Gln
(SEQ ID NO 4) Pro Arg Arg Ile Lys Pro Arg Lys Ile Asn/Asp Phe Gln
(SEQ ID NO 5) Pro Arg Arg Ile Lys Pro Arg Lys Ile Asn/Asp Leu Gln
(SEQ ID NO 6) Pro Arg Arg Ile Lys Ala Arg Lys Ile Met Leu Gln
(SEQ ID NO 7) Pro Arg Lys Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 8) - - Arg Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 9) Pro Arg Arg Ile Lys Pro Arg Lys Ile Met - -
(SEQ ID NO 10) acetyl-Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 11) Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro Arg Ile
(SEQ ID NO 12) Gln Arg Ile Leu Gln Gln Ile Asn Leu Ala Arg Ile
(SEQ ID NO 13) Gln Arg Ile Leu Gln Glu Ile Asn Leu Pro Arg Ile
(SEQ ID NO 14) Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro Lys Ile
(SEQ ID NO 15) - - Ile Leu Gln Gln Ile Asn Leu Pro Arg Ile
(SEQ ID NO 16) Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro - -
(SEQ ID NO 17) Asn Arg Ile Arg Thr Asn Thr Lys Leu Met Asn Ser

According to certain currently preferred embodiments, the present invention provides a peptide comprising at least one epitope recognized by a BAT monoclonal antibody selected from SEQ ID NOs 1, 6, 8, 9, 10, 14 and 16.

According to another particular embodiment, the present invention provides a peptide comprising at least one epitope recognized by a BAT monoclonal antibody, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to yet another particular embodiment, the present invention provides a combination of any one of the peptides comprising at least one epitope recognized by a BAT monoclonal antibody, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one



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of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to certain currently preferred embodiments, the present invention provides a peptide comprising at least one epitope recognized by a BAT monoclonal antibody, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

According to yet another currently preferred embodiments, the present invention provides a combination of any one of the peptides comprising at least one epitope recognized by a BAT monoclonal antibody, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

According to yet another particular embodiment, the peptide of the present invention is capable of inhibiting binding of BAT monoclonal antibody to lymphoma cells, for example, to Daudi or Jurkat cells.

Furthermore, in another embodiment, the present invention provides a peptide useful for inhibiting tumor growth, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to yet another particular embodiment, the present invention provides a combination of any one of the peptides useful for inhibiting tumor growth, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

In certain currently preferred embodiments, the present invention provides a peptide useful for inhibiting tumor growth, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

According to another certain currently preferred embodiments, the present invention provides a combination of any one of the peptides useful for inhibiting



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tumor growth, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

In another embodiment, the present invention provides a peptide capable of inducing an immune response against tumor cells, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to yet another particular embodiment, the present invention provides a combination of any one of the peptides capable of inducing an immune response against tumor cells, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

In certain currently preferred embodiments, the present invention provides a peptide capable of inducing an immune response against tumor cells, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

According to currently preferred embodiments, the present invention provides a combination of any one of the peptides capable of inducing an immune response against tumor cells, selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16, wherein the biological activity of said peptides or fragments is retained.

Further provided according to another embodiment of the invention, is a polynucleotide encoding at least one peptide recognized by BAT monoclonal antibodies. The nucleic acid sequences include both the DNA sequence that is transcribed into RNA and the RNA sequence that is translated into a peptide.

According to certain embodiments of the present invention, the polynucleotide comprises a sequence selected from the group consisting of:

(SEQ ID NO 18) CCTCGACGAATAAAGCCCAGGAAGATCATGCTGCAA

(SEQ ID NO 26) CAGAGGATACTGCAGCAAATTAATCTTCCCAGGATC



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(SEQ ID NO 32) AACCGAATCAGGACAAATACTAAGCTCATGAACAGC

According to other embodiments, the polynucleotides of the invention are inferred from the amino acid sequence of the peptides of the invention. As is known in the art several alternative polynucleotides are possible due to redundant codons, while retaining the biological activity of the translated peptides.

Thus, according to further embodiments, the polynucleotide of the invention comprise a sequences selected from:

(SEQ ID NO 19) CCTCGACGATTYAAGCCCAGGAAGATCRAYCTGCAA

(SEQ ID NO 20) CCTCGACGAATAAAGCCCAGGAAGATCRAYTTYCAA

(SEQ ID NO 21) CCTCGACGAATAAAGCCCAGGAAGATCRAYCTGCAA

(SEQ ID NO 22) CCTCGACGAATAAAGGCXAGGAAGATCATGCTGCAA

(SEQ ID NO 23) CCTCGAAAYATAAAGCCCAGGAAGATCATGCTGCAA

(SEQ ID NO 24) CGAATAAAGCCCAGGAAGATCATGCTGCAA

(SEQ ID NO 25) CCTCGACGAATAAAGCCCAGGAAGATCATG

(SEQ ID NO 27) CAGAGGATACTGCAGCAAATTAATCTTGCXAGGATC

(SEQ ID NO 28) CAGAGGATACTGCAGGARATTAATCTTCCCAGGATC

(SEQ ID NO 29) CAGAGGATACTGCAGCAAATTAATCTTCCCAAYATC

(SEQ ID NO 30) ATACTGCAGCAAATTAATCTTCCCAGGATC

(SEQ ID NO 31) CAGAGGATACTGCAGCAAATTAATCTTCCC

wherein Y=T or C; R=A or G; X= T or C or A or G)

The nomenclature used to describe peptide and polynucleotide compounds of the invention follows the conventional practice wherein the amino group (N-terminus) and the 5' are presented to the left and the carboxyl group (C-terminus) and 3' to the right.

It is to be understood explicitly that the scope of the present invention encompasses homologs, analogs, variants, derivatives and salts, including shorter and longer peptides and polynucleotides, as well as peptide and polynucleotide analogs with one or more amino acid or nucleic acid substitution, as well as amino acid or nucleic acid derivatives, non-natural amino or nucleic acids and synthetic amino or nucleic acids as are known in the art, with the stipulation that these modifications must preserve the biological activity of the original molecule. Specifically any active fragments of the active peptides as well as extensions, conjugates and mixtures are disclosed according to the principles of the present invention.



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Also provided, according to another embodiment of the invention, is a construct comprising a polynucleotide encoding for at least one peptide recognized by a BAT monoclonal antibody.

Furthermore, in another embodiment, the present invention provides a vector, for example, a plasmid or a virus, comprising a polynucleotide encoding at least one peptide recognized by a BAT monoclonal antibody.

Further provided, according to other embodiment of the invention, is a host cell comprising a polynucleotide encoding at least one peptide recognized by the BAT monoclonal antibody.

In one embodiment the host cell is capable of expressing at least one epitope recognized by BAT monoclonal antibody.

In yet another embodiment, the present invention provides a method and a composition for treating cancer in a subject in need thereof, comprising the step of administering to a patient a therapeutically effective amount of a pharmaceutical composition of the present invention.

In one embodiment the pharmaceutical composition comprises a pharmaceutical carrier and an active ingredient, which is a peptide according to embodiments of the invention.

In another embodiment the pharmaceutical composition comprises a pharmaceutical carrier and an active ingredient, which is a polynucleotide encoding at least one peptide recognized by a BAT monoclonal antibody.

In one embodiment the polynucleotide comprises a sequence selected from SEQ ID NOs 18 through 31.

In currently preferred embodiments the polynucleotide comprises a sequence selected from SEQ ID NOs 18, 22, 24, 25, 29, 31.

Also provided according to an embodiment of the invention is an immunomodulatory vaccine comprising a pharmaceutically acceptable adjuvant, selected from the group of an aluminum salt and an oil emulsion, and at least one peptide recognized by a BAT monoclonal antibody.

In one embodiment, the peptide comprises a sequence selected from SEQ ID NOs 1 to 17.

The term "vaccine" or "vaccination" referred to herein relates to a modality or process that induces modulation of the immune system, for example, but not limited



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to, a composition or process that induce the activation of T- lymphocytes or that induces the production of antibodies.

According to another embodiment of the invention there is provided a diagnostic agent for detecting the presence of tumor cells comprising a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to yet another particular embodiment, the present invention provides a diagnostic agent for detecting the presence of tumor cells comprising a combination of any one of the peptides, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

In certain currently preferred embodiments, the peptide comprises the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, and 16.

Furthermore, in another embodiment the present invention provides a method for diagnosing cancer comprising the steps of: contacting a sample from a subject with a peptide recognized by a BAT monoclonal antibody; determining the extent of binding of said peptide to the sample; and comparing the extent of binding of said peptide to the sample with a known control (such as a predetermined calibration scale) thereby obtaining information regarding the occurrence of cancer in the sample.

Furthermore, in another embodiment the present invention provides a method for diagnosing an inflammatory disorder or autoimmune disease comprising the steps of: obtaining a sample of immune cells from an individual; exposing said immune cells to at least one peptide recognized by a BAT monoclonal antibody; and monitoring the response of said immune cells compared to the response of said immune cells not exposed to the peptide.

According to another embodiment, the present invention provides an antibody recognizing at least one epitope selected from: a peptide, a fragment of a peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

According to currently preferred embodiments, the present invention provides an antibody a combination of any one of the peptides comprising at least one epitope recognized by a BAT monoclonal antibody, selected from: a peptide, a fragment of a



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peptide, a homolog, a variant, a derivative or a salt of a peptide having the sequence of any one of SEQ ID NOs 1 through 17, wherein the biological activity of said peptides or fragments is retained.

Other objects, features and advantages of the present invention will become apparent from the following detailed description and appended claims.

## BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** shows the inhibition of BAT monoclonal antibody binding to immobilized phage bearing the insert of SEQ ID NO 1 (Peptide A) by the free peptide.

**Figure 2** shows the results of a flow cytometry experiment in which Peptide A inhibition of BAT mAb binding to B-lymphoblastoid cells was determined.

**Figure 3** is a graph showing growth inhibition of melanoma s.c. tumord, by immunization with the synthetic Peptide A.

**Figure 4** is a graph showing binding of sera from Peptide A immunized mice to Peptide A coated plates.

**Figure 5** shows the binding of BAT monoclonal antibody to selected peptides, from the phage-library, in the second experiment.

**Figure 6** presents growth inhibition of lung tumosr by Peptide A and its analogues.

**Figure 7** presents growth inhibition of lung tumors by Peptide B and its analogues.

**Figures 8A, 8B and 8C** exhibit cytolytic activity in splenocytes of mice immunized with Peptides A and B.

**Figures 9A-9D** show inhibition of BAT monoclonal antibody binding to Daudi cells by anti-Peptides A and B antibodies.

**Figure 10** presents induction of human lymphocyte proliferation by anti-Peptides A and B antibodies.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns peptides, polynucleotides and pharmaceutical and vaccine compositions including same which are useful in modulation of immune responses, in inhibition of tumor growth, both primary tumor and metastases, in treatment of cancer and of inflammatory disorders including autoimmune diseases by way of prevention and cure. Specifically, the present invention provides vaccines which include peptides recognized by the immune modulator BAT monoclonal



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antibody which is disclosed in the above-mentioned International Patent Applications WO 95/20605 and WO 00/58363.

a. Preferred modes for carrying out the invention

According to a first aspect of the present invention there are provided peptides recognized by BAT monoclonal antibody. Several methods for identifying peptides that are capable of binding to the BAT antibody are known in the art. For example, raising peptides against the BAT antibody whereas the peptides may be selected from peptide libraries, such as, bacteriophage library, chemical library, hybridoma cell library; cells preferably B lymphocytes and T cell and more preferably Daudi cells and Jurkat cells; chemical syntheses that might produce a set or a subset of molecules having high affinity for the sequence of BAT monoclonal antibody; designing molecules intended to have a high affinity for BAT sequences using computer-assisted or other theoretical approaches; using in-vitro evolution of nucleic acids capable of binding to the sequence of BAT.

According to preferred embodiments of the present invention a phage epitope library is employed in order to identify peptides that bind BAT monoclonal antibody and to prepare an immunotherapy modality. Most preferably, a 12-mer-phage peptide library constructed using phage M13 is used to identify peptides as the putative antibody binding epitope and consequently to identify the polynucleotide sequence encoding the peptides.

Although the peptide will preferably be substantially free of other naturally occurring host cell proteins or protein fragments, in some embodiments the peptides can be synthetically conjugated to native fragments or particles.

According to a certain preferred embodiments, the 12-mer peptides of the present invention are:

SEQ ID NO 1, also termed hereinafter Peptide A:

Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln

SEQ ID NO 11, also termed hereinafter Peptide B:

Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro Arg Ile

SEQ ID NO 17, also termed hereinafter Peptide C:

Asn Arg Ile Arg Thr Asn Thr Lys Leu Met Asn Ser



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According to the principles of the present invention the scope of the invention further includes any variants, derivative or salts of the above peptides.

The term "variant" as used herein refers to a peptide sequence that possesses at least one modified structural property compared to the original peptide while substantially retaining the biological activity of the resulting peptide as compared with the original peptide or the BAT monoclonal antibody. For example, one or more of the amino acid residues of the original peptides are replaced by different amino acid residues, or are deleted, or one or more amino acid residues are added to the original peptides, a peptide bond is modified, cyclization is introduced to the structure of the original peptide, a backbone is modified. A variant may have altered binding to BAT monoclonal antibody than the original peptide. A variant may have at least 70% identity with the original peptide, preferably 80% or 90% identity. A variant may also be referred to as 'analog' or 'homolog', and these terms may be used interchangeably.

In one embodiment, the present invention comprises a salt of peptide of the invention. The term "salt" includes acid addition salts which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. The term also includes base addition salts which are formed from inorganic bases such as, for example, sodium, potassium, ammonium, and calcium, and from organic bases such as isopropylamine, trimethylamine, histidine, and the like.

In another embodiment the present invention comprises a derivative of a peptide of the invention. The term "derivative" of a peptide as used herein refers to a peptide that contains additional chemical moieties not normally a part of the peptide. Such modifications may be introduced into the molecule by reacting targeted amino acid residues of the peptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues. Examples of chemical derivatives, by way of illustration and not by way of limitation, include a peptide in which the C-terminus or the N-terminus of the peptides of the present invention, or both, are substituted with a carboxylic acid protecting group or an amine protecting group, respectively. Suitable protecting groups are described in Green and Wuts, "Protecting Groups in organic Synthesis", John Wiley and Sons, Chapters 5 and 7, 1991. Examples of N-terminal protecting groups include acyl groups (-CO-$R_1$) and alkoxy carbonyl or aryloxy carbonyl groups (-CO-O-$R_1$), wherein $R_1$ is an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or a substituted aromatic



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group. Examples of acyl groups include acetyl, (ethyl)-CO-, n-propyl-CO-, iso-propyl-CO-, n-butyl-CO-, sec-butyl-CO-, t-butyl-CO- and phenyl-CO-. Examples of alkoxy carbonyl and aryloxy carbonyl groups include $CH_3$ -O-CO-, (ethyl)-O-CO-, n-propyl-O-CO-, iso-propyl-O-CO-, n-butyl-O-CO-, sec-butyl-O-CO-, t-butyl-O-CO-, phenyl-O-CO-. The carboxyl group at the C-terminus can be protected, for example, as an amide (i.e., the hydroxyl group at the C-terminus is replaced with $-NH_2$, $-NHR_2$ and $-NR_2$ $R_3$) or ester (i.e. the hydroxyl group at the C-terminus is replace with $-OR_2$). $R_2$ and $R_3$ are independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or a substituted aryl group.

A variant, derivative or salt of a peptide of the invention may be advantageous, as compared to the original peptide, if they possess at least one of the following properties: improved solubility, prolonged duration of action, superior biological activity, increased stability to degradation by enzymes and therefore increased in vivo half lives, eliminated or attenuated undesirable side effects and the like.

The term "biological activity" as used herein, includes at least one of the following activities: induction of anti-tumor effect, modification of immune response, stimulation of immune response against tumor cells, inhibition of the binding of BAT monoclonal antibody to lymphoma cells – particularly Daudi or Jurkat cells, detection of cancer, detection of an inflammatory disorder or autoimmune disease or, prevention of tumor development.

The term "anti-tumor effect" as used herein, refers to a biological effect which can be manifested by a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in the number of metastases, an increase in life expectancy, or amelioration of various physiological symptoms associated with the cancerous condition. An "anti-tumor effect" can also be manifested by the ability of the peptides, polynucleotides, and antibodies of the invention in prevention of the occurrence of tumor in the first place.

The peptide or variant may be generated through recombinant DNA technologies, well known to those skilled in the art, following cloning into an expression vector, transfection into host cells and the protein harvesting according to methods known in the art. In a preferred embodiment the peptides and variants are prepared by known peptide synthesis techniques.



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Currently preferred embodiments of the invention are variants obtained by conservative modifications introduced to SEQ ID NO 1 (Peptide A). Currently most preferred embodiments include the following variants:

(SEQ ID NO 2) Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln-amide
(SEQ ID NO 3) Pro Arg Arg Phe Lys Pro Arg Lys Ile Asn/Asp Leu Gln
(SEQ ID NO 4) Pro Arg Arg Ile Lys Pro Arg Lys Ile Asn/Asp Phe Gln
(SEQ ID NO 5) Pro Arg Arg Ile Lys Pro Arg Lys Ile Asn/Asp Leu Gln
(SEQ ID NO 6) Pro Arg Arg Ile Lys Ala Arg Lys Ile Met Leu Gln
(SEQ ID NO 7) Pro Arg Lys Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 8) - - Arg Ile Lys Pro Arg Lys Ile Met Leu Gln
(SEQ ID NO 9) Pro Arg Arg Ile Lys Pro Arg Lys Ile Met - -
(SEQ ID NO 10) acetyl-Pro Arg Arg Ile Lys Pro Arg Lys Ile Met Leu Gln

Additional currently preferred embodiments of the invention are variants obtained by conservative modifications introduced to SEQ ID NO 11 (Peptide B). Currently most preferred embodiments include the following variants:

(SEQ ID NO 12) Gln Arg Ile Leu Gln Gln Ile Asn Leu Ala Arg Ile
(SEQ ID NO 13) Gln Arg Ile Leu Gln Glu Ile Asn Leu Pro Arg Ile
(SEQ ID NO 14) Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro Lys Ile
(SEQ ID NO 15) - - Ile Leu Gln Gln Ile Asn Leu Pro Arg Ile
(SEQ ID NO 16) Gln Arg Ile Leu Gln Gln Ile Asn Leu Pro - -

The biological activity of the variants is monitored and compared with that of the selected peptides and of the BAT monoclonal antibody as exemplified hereinbelow.

Without wishing to be bound by any theory, it is possible that the peptides of the invention elicit an immune response similar to that obtained by the BAT monoclonal antibody.

Thus, preferred methods for monitoring the biological activity of the peptides and the variants include: competitive inhibition with BAT monoclonal antibody to determinants recognized by BAT, e.g. Daudi cells and Jurkat cells; competitive inhibition to determinants recognized by BAT, e.g. Daudi cells and Jurkat cells, between sera of immunized subjects and BAT monoclonal antibody; immunizing with the peptides tumor-bearing animals and monitoring tumor growth; immunizing with the peptides naive animals and monitoring tumor development upon induction of cancer; monitoring immune response upon immunization, preferably monitoring the



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cytolytic activity of NK and CTL cells upon immunization with the peptides; monitoring lymphocyte proliferation upon immunization with anti-peptides antibodies.

According to a second aspect of the present invention there is provided a construct comprising a polynucleotide encoding for the peptides recognized by the BAT monoclonal antibody.

In several preferred embodiments the polynucleotides of the invention are isolated from the phage clones expressing peptides recognized by BAT monoclonal antibody, and are selected from: SEQ ID NO 18, encoding the peptide of SEQ ID NOS 1 (Peptide A), 2 and 10; SEQ ID NO 26 encoding the peptide of SEQ ID NO 11 (Peptide B); SEQ ID NO 32 encoding the peptide of SEQ ID NO 17 (Peptide C);

According to other general embodiments, the polynucleotides of the invention are derived from the amino acid sequence of the peptides of the invention, including variations due to redundant codons providing that the biological activity of the translated peptide is retained.

Thus, according to further embodiments the polynucleotide of the invention are selected from the group of sequences consisting of:

SEQ ID NO 19 encoding the peptide of SEQ ID NO 3;
SEQ ID NO 20 encoding the peptide of SEQ ID NO 4;
SEQ ID NO 21 encoding the peptide of SEQ ID NO 5;
SEQ ID NO 22 encoding the peptide of SEQ ID NO 6;
SEQ ID NO 23 encoding the peptide of SEQ ID NO 7;
SEQ ID NO 24 encoding the peptide of SEQ ID NO 8;
SEQ ID NO 25 encoding the peptide of SEQ ID NO 9;
SEQ ID NO 26 encoding the peptide of SEQ ID NO 10;
SEQ ID NO 27 encoding the peptide of SEQ ID NO 12;
SEQ ID NO 28 encoding the peptide of SEQ ID NO 13;
SEQ ID NO 29 encoding the peptide of SEQ ID NO 14;
SEQ ID NO 30 encoding the peptide of SEQ ID NO 15;
SEQ ID NO 31 encoding the peptide of SEQ ID NO 16;

The constructs comprising the polynucleotides encoding the peptides of the invention may further include promoters, enhancers and other regulatory sequences necessary for expression, transcription and translation, as are well known in the art. The constructs can be further provided with appropriate linkers and can be ligated into



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expression vectors available in the art. The vectors can be used to transform suitable hosts to produce the desired peptides. Vectors may include restriction enzyme sites for the insertion of additional genes and for selection markers, as well as elements necessary for propagation and maintenance of vectors within cells.

Cells presenting peptides recognized by the monoclonal antibody BAT are also included in the present invention, for instance, antigen presenting cells including dendritic cells or macrophages which are also known as useful immunogens.

An antibody recognizing an epitope within any one of SEQ ID NOs 1 through 17 is further provided in the present invention.

The term "antibody" is used herein in the broadest sense and covers monoclonal antibodies (including full length monoclonal antibodies) and antibody fragments so long as they exhibit the desired biological activity. "Antibody fragments" comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Methods for the production of antibodies are well known in the arts, including eliciting antibodies from the sera of subjects immunized with the target determinant of said antibodies, as well as recombinant techniques.

b. Pharmacology

The present invention further relates to a pharmaceutical composition which includes at least one epitope recognized by the BAT monoclonal antibody as the pharmaceutically active ingredient. The pharmaceutically active ingredient is selected from the group containing: a peptide comprising at least one epitope, a polynucleotide encoding at least one epitope, a polynucleotide encoding at least one of said peptide, a construct comprising at least one of said polynucleotide, a vector comprising at least one of said construct.

The peptide of the present invention, or a pharmacologically acceptable salt thereof may be mixed with an excipient, carrier, diluent, and optionally, a preservative or the like, pharmacologically acceptable vehicles as known in the art. Examples of excipients include, glucose, mannitol, inositol, sucrose, lactose, fructose, starch, cornstarch, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, polyvinylpyrrolidone and the like. Optionally, a thickener may be



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added, such as a natural gum, a cellulose derivative, an acrylic or vinyl polymer, or the like. The pharmaceutical composition including the peptide may further comprise a biodegradable polymer selected from poly-1,4-butylene succinate, poly-2,3-butylene succinate, poly-1,4-butylene fumarate and poly-2,3-butylene succinate, incorporating the peptide of the invention as the pamoate, tannate, stearate or palmitate thereof. Such compositions are known in the art as described, for example, in U.S. Patent 5,439,688.

The pharmaceutically active ingredient of the composition may be conjugated to a matrix or to a proteinaceous carrier, for example tetanus or diphtheria toxoids or oxidized KLH, in order to stimulate T cell help, or to other immuno-potentiating agents as well as biological response modifiers such as interferons, interleukins etc., in order to stimulate the immune system. The compositions for administration to humans may further comprise adjuvants that are suitable for human use, such as alum, which is approved for human use, or submicron emulsions that are intended for human use as disclosed for example in WO 95/11700. Appropriate ranges of ingredients for preparing compositions with or without additional diluents, carriers or adjuvants are known in the art.

The preparation of pharmaceutical compositions comprising peptides is well known in the art, as disclosed for example in U.S. Patents 5,736,519, 5,733,877, 5,418,219, 5,354,900, 5,298,246, 5,164,372, 4,900,549 and 4,457,917. Means for processing the pharmaceutical compositions of the present invention include, without limitations, conventional mixing, dissolving, granulating, grinding, pulverizing, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

According to yet another aspect of the present invention a peptide vaccine is provided. The two major types of peptide vaccine are: peptides mixed with adjuvant substances and peptides which are introduced together with an antigen presenting cell (APC; Mayordomo et al., Nature Med. 1:1297, 1995). The most common cells used for the latter type of vaccine bone marrow and peripheral blood derived dendritic cells, as this cells express costimulatory molecules that help activation of CTL. WO 00/06723 discloses a cellular vaccine composition which includes an antigen presenting cell presenting tumor associated antigen peptides. Presenting the peptide can be effected by loading the APC with a polynucleotide (e.g., DNA, RNA) encoding the peptide or loading the APC with the peptide itself.



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In accordance with the first type of peptide vaccine, adjuvant substances that stimulate immunogenicity are mixed with the peptide in order to improve the immune response to the peptide. Immunological adjuvants have generally been divided into two basic types: aluminum salts and oil emulsions. Aluminum phosphate and hydroxide (alum) adjuvants induce elevated levels of antibody against antigens in alum-based vaccines above those obtained with the corresponding aqueous vaccine. Numerous alum-based vaccines, including methods of preparation thereof, were developed as, for example, disclosed in US Patents 5,747,653, 6,013,264, 6,306,404 and 6,372,223. However, aluminum compounds have not always enhanced the immunogenicity of vaccines.

The main components of the oil-based adjuvants are: oil, emulsifier and immunostimulant. The earliest types of emulsified oil-based adjuvants are Incomplete Freund's Adjuvant (IFA), consisting of an approximately 50:50 water-in-oil emulsion, and complete Freund's adjuvant (CFA), a similar preparation with inclusion of killed mycobacteria. The powerful antibody-stimulating effect of CFA has not been surpassed by any other adjuvant. However, because of severe toxic reactions CFA can be used only for experimental purposes and not in human or veterinary vaccines. The use of IFA in humans has been limited to those clinical situations in which aqueous vaccines are relatively impotent and aluminum compounds have not provided enough adjuvant activity. Example of improved emulsions as vaccine adjuvants, by enhancing the immunogenicity of the antigen, include submicron emulsions as disclosed in US Patent 5,961,970 and solid fat nanoemulsions as disclosed in 5,716,637 for example.

Preferred means for administering peptides are through intravenous, intramuscular or subcutaneous administration. Oral administration is expected to be less effective, because a peptide may be digested before being taken up. Decomposition in the digestive tract may be lessened by use of certain compositions, for instance, by confining the peptide of the invention in microcapsules such as liposomes. The pharmaceutical composition of the invention may also be administered to other mucous membranes. The pharmaceutical composition is then provided in the form of a suppository, nasal spray or sublingual tablet.

The uptake of a peptide of the invention may be facilitated by a number of methods. For instance, a non-toxic derivative of the cholera toxin B subunit, or of the structurally related subunit B of the heal-labile enterotoxin of enterotoxic *Eschericia coli* may be added to the composition, as disclosed in U.S. Patent 5,554,378.



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The peptides according to an embodiment of the invention may be also administered via liposomes, slow releasing particles and the like, as known in the art, so as to increase the immunogenicity of the peptides.

A composition according to an embodiment of the invention can be directly administered to an individual for immunizing the individual. Alternatively, in accordance with an embodiment of the invention, the peptides may be used to generate new antibodies with the attribute and activities of known BAT monoclonal antibodies. Ex-vivo activation of T-cells by these peptides may also elicit the desired activity of immunostimulation. Thus, the composition can be used for inducing antibodies in an ex-vivo system and the induced antibodies can then be administered to an individual for treating an autoimmune disease, an infection or cancer. The composition can also be used in an ex-vivo system to stimulate T-cells to be administered in a process of adoptive immunotherapy, as described in the art.

The present invention also includes the use of the peptide or polynucleotide as a diagnostic agent for diagnosing cancer in an individual. According to an embodiment of the invention a sample from a individual, such as a blood sample or a sample from a patient's GI tract fluids, or cerebrospinal fluid or any other relevant sample can be contacted, in vivo or in vitro, with a peptide or polynucleotide according to the invention and the extent of binding of the peptide or polynucleotide to the sample can be determined, such as by ELISA, so as to provide information regarding the occurrence of BAT in the sample. For example antibodies to the peptides of the invention may be used to diagnose cancer or to monitor its progression if present in a body fluid especially serum or plasma. Conversely, in the patient's lymph nodes especially in draining lymph nodes in proximity to a suspected tumor, it may be possible to screen the T cells using the peptides of the invention.

The present invention provides methods for the treatment of autoimmune diseases, cancer and for anti-cancer vaccination. Pharmaceutical compositions suitable for use in context of the present invention include compositions wherein the active ingredients are contained in an amount effective to achieve the intended purpose. All formulations for administration should be in dosages suitable for the chosen route of administration. More specifically, a "therapeutically effective" dose means an amount of a compound effective to prevent, alleviate or ameliorate symptoms of a disease of the subject being treated. Determination of a therapeutically



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effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

Toxicity and therapeutic efficacy of the compositions described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the $IC_{50}$ (the concentration which provides 50% inhibition) and the maximal tolerated dose for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. Depending on the severity and responsiveness of the condition to be treated, dosing can also be a single administration of a slow release composition, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved. The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, and all other relevant factors.

The present invention will be further described and exemplified by the following non-limitative examples.

## EXAMPLES

### Example 1. Preparation of BAT monoclonal antibody

BAT was generated, purified and characterized as previously disclosed in WO 95/20605, WO 00/58363 and subsequent publications. In brief, BALB-C mice were immunized with membranes of Daudi cells. Spleen cells were fused with myeloma NSO cells. Clones producing BAT were selected by the ability of supernatants to bind Daudi cells and to induce proliferation of peripheral blood mononuclear cells. Hybridoma cells were grown in RPMI 1640 supplemented with 10% fetal calf serum (for Experiment 1 in Example 2) or with PFHM serum free protein media (GIBCO; for Experiment 2 in Example 2), sodium pyruvate, glutamine, and antibiotics and incubated at 37°C in a humidified atmosphere containing 5% $CO_2$. BAT was purified on a protein G Sepharose column according to manufacturer's instructions (Pharmacia Corp.



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NJ, USA). Biotinylation, was performed as follows: 100 μg of the immunoglobulin fraction of BAT monoclonal antibody in 1ml of 0.1 M NaHCO3, pH 8.6, was incubated for 2 hours at room temperature with 5 μg of biotin amidocoproate N–hydroxysuccinimide ester (SIGMA, Israel) from a stock solution of 1mg/ml in dimethylformamide and dialyzed at 4°C against phosphate buffered saline pH 7.4.

**Example 2. Isolation of peptides by phage-display analysis**

**Experiment 1**

Materials and Methods

a. Isolation of epitope-presenting phage from a phage epitope library

The phage display peptide library was based on a combinatorial library of random 12-mer peptides fused to a minor coat protein (pIII) of M13 phage. A library sample containing $4x10^{10}$ infectious phage particles was subjected to 6 rounds of panning and amplification. For each selection cycle 100μg of biotinylated BAT monoclonal antibody was used. The phage was pre-incubated with the biotinylated antibody at room temperature for 1 hour. The reaction mixtures were then layered in 1 ml of TBS 0.5% Tween on streptavidin coated and blocked 60-mm polystyrene Petri dishes for 30 minutes at room temperature. Unbound phages were removed by 10 times washings in TBS 0.5% Tween. The remaining phages were eluted with 1ml 0.2M Glycine –HCl (pH 2.2), 1mg/ml BSA. The eluate was neutralized and used to infect E. coli stain ER2537. After each round of panning phage was titer on LB/IPTG/Xgal plates. The unamplified last round was titered and plaques were used for sequencing.

b. Phage-ELISA

Wells of microtiter plates were coated with 100 μl of a 1:1000 dilution (0.1M NaHCO3, pH 8.6) of rabbit anti-phage M13 serum by incubation overnight at 4°C. Coated plates were washed 3 times with PBS 0.05% Tween 20 and 100μl of enriched phage clones, containing $10^9$ phage particles, were then added to the wells and incubated for 1 hour at 37°C. Wells were blocked with 1% BSA



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in PBS for 1 hour at room temperature, washed and incubated with the antibody overnight at 4°C. For inhibition experiments, peptides were pre-incubated with the antibody for 30 minutes, before their addition to phage coated wells. After washing, bound antibody was detected by incubation with anti-mouse IgG Peroxidase conjugated (Fab specific) for 45 minutes. After washing with o-phenylene diamine (OPD), substrate was added and the color developed was determined by an ELISA reader at 450nm.

c. FACS analysis of peptide-inhibition experiments

BAT mAb biotinylated (20μg/ml) was incubated with different concentrations of the peptide selected from the phage display analysis (0.01-40μg/ml) overnight at 4°C. Daudi cells ($0.5x10^6$) were incubated with the antibody or either with the combination of antibody and peptide for 2 hours on ice. After washing streptavidin FITC was added for 30 minutes. Cells were analyzed by a FACScan (Becton Dickinson & Co., NJ, USA).

d. In vivo effect of the peptide selected from the phage display analysis

C57BL mice were injected with 20μg of peptide in CFA (complete Freund's adjuvant) into the footpad. Control mice were injected with CFA alone. After seven days a boost was given with 20μg of the peptide in PBS. B16 melanoma cells ($0.5x10^6$ cells/mouse) were inoculated, subcutaneous (s.c.), on day 1 or on day 8 after peptide injection and volume of tumor was measured every two days. Blood was taken from mice on day 14, 21 and 28 after peptide injection for testing specific anti-peptide antibody in sera using ELISA method.

Results

a. Isolation of Peptide A (SEQ ID NO 1)

Increased enrichment in the number of plaque forming units (pfu) of phages which were positive for binding to BAT mAb was observed after each panning. Following the $4^{th}$ panning pfu was $2x10^4$ and after the $6^{th}$ panning a number of $1.5x10^5$ pfu was observed. The number of phages used in each panning was $1x10^9$. After the sixth panning, 100% of the phages were positive



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for binding to BAT mAb. DNA from 40 positive clones was sequenced. The 40 phage clones exhibited the amino acid sequence:

(Peptide A, SEQ ID NO 1) PRRIKPRKIMLQ

and the nucleic acid sequence:

(SEQ ID NO 18) CCTCGACGAATAAAGCCCAGGAAGATCATGCTGCAA.

Binding of the phage was highly specific. Moreover, binding to control antibodies including nonrelated antibody like IgG-3 mAb was not observed.

b. Inhibition of BAT binding to the selected phages by the synthetic peptide

To ensure that the interaction between the selected phages and BAT mAb is caused by the insert sequences, peptides encompassing this region were synthesized (i.e. Peptide A) and their ability to compete with BAT mAb binding to the phage was assessed. Immobilized phage on microtiter ELISA plates coated with rabbit anti-phage M13 serum was incubated with 6μg/ml of the antibody. BAT mAb was pre-incubated with increasing amount of synthetic Peptide A. Peptide A inhibited the binding of the antibody in a dose dependent manner with an inhibition concentration ($IC_{50}$) value of $6.6x10^{-7}$ M (Fig. 1).

c. FACS analysis of peptide inhibition experiments

BAT mAb were shown to bind a membrane determinant on Daudi cells. Accordingly, the ability of the synthetic Peptide A to inhibit this binding was assessed. Biotinylated BAT (20μg/ml) was pre-incubated with increased amounts of Peptide A. The mixture was added to Daudi cells and antibody bound was stained with strept-avidin FITC. Peptide A (1 to 40μg/ml) inhibited the binding of BAT mAb to Daudi cells in a dose dependent manner (Fig. 2).

d. In vivo anti-tumor effect of the selected peptides.

C57BL mice (n=4), inoculated s.c. with B16 melanoma cells, were immunized with 20μg of the peptides. Control animals were injected only with CFA. The average melanoma tumor volume was found to decrease in mice immunized with the peptides (Fig. 3).

Blood samples were withdrawn from control and immunized mice on day 21 and 28 after immunization. Sera from 4 control mice and 4 immunized mice were incubated on microtiter ELISA plates with immobilized peptide. ELISA results



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indicated that higher concentrations of anti-Peptide A antibodies were observed in the sera of the immunized mice as compared with the sera of control mice (Fig. 4). These results explain the tumor growth inhibition in the treated mice (see Fig. 3).

**Experiment 2**

Materials and Methods

a. Isolation of epitope-presenting phage from a phage epitope library

The phage display peptide library is based on a combinatorial library of random peptide 12-mer fused to a minor coat protein (pIII) of M13 phage. A library sample containing $2x10^{10}$ infectious phage particles was subjected to 3 rounds of panning. For biopanning selection cycles, 20μg of biotinylated BAT monoclonal antibody was used. The phage was pre-incubated with the biotinylated antibody at room temperature for 1 hour. The reaction mixture was then layered in 1 ml of TBS 0.5% Tween on strept-avidin coated and blocked 60-mm polystyrene Petri dishes for 30 minutes at room temperature. Unbound phages were removed by 10 times washings in TBS 0.5%tween. The remaining phages were eluted with 1ml 0.2M Glycine-HCl (pH 2.2), 1mg/ml BSA. The eluate was neutralized and used to infect E.coli strain ER2537. After each round of panning phage was titer on LB/IPTG/Xgal plates. After the second cycle of biopanning, the number of phages was amplified. The an-amplified last round was tittered and plaques were used for DNA sequencing.

b. Phage-ELISA

Wells of microtiter plates were coated with 100 μl of a 1:1000 dilution (0.1M NaHCO3, pH 8.6) of rabbit anti-phage M13 serum by incubation overnight at 4°C. Coated plates were washed 3 times with PBS 0.05% Tween. Then, 100μl of enriched phage clones, containing $10^9$ phage particles, were then added to the wells and incubated for 1 hour at 37°C. After incubation, wells were blocked with 1% BSA in PBS for 1 hour at room temperature, washed and incubated with the antibody overnight at 4°C. After washing bound antibody was detected with IgG Peroxidase conjugated (Fab specific) for 45 minutes. After washing OPD subtract was added and the color developed was determined by an ELISA reader at 450nm.



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Results

a. Isolation of Peptide B (SEQ ID NO 11) and Peptide C (SEQ ID NO 17)

In view of the anti-tumor effect of BAT mAb, it was aimed to select a peptide that binds specifically the antibody from a 12-mer random phage epitope library. After each panning enrichment in the number of plaque forming units (pfu) was observed. Resulting from 1st panning a number of $5.6x10^6$ pfu was obtained, from the 2nd one, $2x10^2$ pfu, after amplification the number of pfu was $2x10^8$ and after the last round of biopanning $1x10^3$ pfu were counted (Table 1).

**Table 1: Screening for BAT binding peptide.**

| | Panning 1 | Panning 2 | Panning 3 |
|---|---|---|---|
| **Number of phages** | $2x10^{10}$ | $5.6x10^6$ | $2x10^8$ |
| **PFU obtained** | $5.6x10^6$ | $2x10^2$ | $2x10^3$ (sequenced 52) |
| **Percent (%)** | 0.028 | 0.004 | 0.0005 |

DNA from 42 positive clones was sequenced. The DNA from 31 of the phage clones exhibited the sequence:

CAGAGGATACTGCAGCAAATTAATCTTCCCAGGATC (SEQ ID NO 28) encoding for a peptide of SEQ ID NO 11, also termed Peptide B.

The DNA from 3 of the phage clones exhibited the sequence:

AACCGAATCAGGACAAATACTAAGCTCATGAACAGC (SEQ ID NO 34) encoding for a peptide of SEQ ID NO 17, also termed Peptide C.

The rest of the 8 positive clones exhibited different sequences.

b. Phage ELISA on anti-M13 plates.

To ensure that the interaction between the selected phages and BAT mAb is caused by the insert sequences, ELISA on anti M13 binding plates was performed. The ability of the positive phage to bind BAT mAb (5µg/ml) was assessed. $1x10^9$ phages from positive pfu were incubated on anti-M13 plates and binding to BAT mAb was assessed. ELISA detected only phages with peptide B in the insert (Fig. 5, phages N51 and N52). Phages with other sequences did not bind to BAT monoclonal antibody (Fig. 5, phages N40, N6, N7, and N37).



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**Example 3. In vivo effect of peptides**

Materials and Methods:

Peptides: Peptide A and Peptide B and variants, are shown in Table 2 (SEQ ID NO 1-17). Peptide were produced by amino-acid synthesis as known in the art.

Mice: C57BL female mice, 6-8 weeks old.

Tumors: B16 syngeneic melanoma cells were inoculated in order to induce the formation of lung metastases. Cells were inoculated i.v. on day 1 following the first peptide injection. Metastases were detected in the lung by their dark coloration, resulting from melanin production in the cells. Tumor growth was monitored by lung weight compared to control mice.

Vaccine composition and dose: A vaccine immunization composed: 10μg of a peptide and 100 μl of complete Freund's adjuvant (CFA) or PBS.

Vaccination Protocol: C57BL mice were injected with the above dose of peptide vaccine in CFA into the footpads, followed by two boosts of the above dose in PBS on the $7^{th}$ and $14^{th}$ day following the first immunization. Control mice were injected with vehicle alone. BAT (10μg) monoclonal antibody was injected on day 10 post tumor- inoculation as a positive control. Lung weight was measured on day 24 post tumor inoculation.

Results:

Peptide A (SEQ ID NO 1) and several of the variants based on the sequence of Peptide A (SEQ ID NOS 6 and 8-10; Fig. 6) and on the sequence of Peptide B (SEQ ID NOS 14 and 16; Fig. 7) exhibited anti tumor activity similar to that of BAT monoclonal antibody. The anti-tumor activity as a measure of lung weight was approximately twice higher as compared with control (non-treated tumors). Other peptides were found less effective than BAT monoclonal antibody.



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**TABLE 2. Peptide analogs**

| Peptide SEQ ID NO | Peptide sequence | DNA SEQ ID NO |
|---|---|---|
| 1 (Peptide A) | PRRIKPRKIMLQ | 18 |
| 2 | PRRIKPRKIMLQ-amide | 18 |
| 3 | PRRFKPRKIBLQ | 19 |
| 4 | PRRIKPRKIBFQ | 20 |
| 5 | PRRIKPRKIBLQ | 21 |
| 6 | PRRIKARKIMLQ | 22 |
| 7 | PRKIKPRKIMLQ | 23 |
| 8 | --RIKPRKIMLQ | 24 |
| 9 | PRRIKPRKIM-- | 25 |
| 10 | acetyl-PRRIKPRKIMLQ | 18 |
| 11 (Peptide B) | QRILQQINLPRI | 26 |
| 12 | QRILQQINLARI | 27 |
| 13 | QRILQEINLPRI | 28 |
| 14 | QRILQQINLPKI | 29 |
| 15 | --ILQQINLPRI | 30 |
| 16 | QRILQQINLP-- | 31 |
| 17 (Peptide C) | NRIRTNTKLMNS | 32 |

**Example 4. NK and CTL cytolytic activity in peptide-immunized mice**

Material and Methods

Cytotoxicity was examined by measuring the release of radiolabeled chromium from target cells. Cells (2-4x$10^6$ YAC, B16 or 3LL) were labeled with 200 μCi [$^{51}$Cr]-chromate, in serum free media for 1 h at 37°C. Following three washes, cells were resuspended in complete medium and plated at $10^4$ cells/well. Mouse splenocytes were removed on the indicated days (YAC- day 7, B16 and 3LL- day 21) following peptide immunization. Vaccination regimen was identical to that used in tumor-inhibition experiments (see Example 3). Splenocytes were mixed with target cells at the indicated ratios and incubated for 12 h at 37°C. Supernatants were monitored for radioactivity. Cytotoxicity was determined as follows,

$$\% \text{ Lysis} = 100x(Re-Rs)/Rmax-Rs).$$

where Re is the measured release, Rs is the spontaneous release in the presence of medium alone and Rmax stands for the maximal release obtained by incubating target



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cells with Triton x100. $^{51}Cr$ release was determined at effector-to-target cell ratios of 1:5, 1:25 and 1:50.

Results

Tumor inhibition by peptide vaccines may depend on both humoral and cellular effects elicited by the immunization. To examine whether peptides A and B induce cellular toxicity, mice immunized with the peptides were studied for their ability to mount tumor-cell lysis in vitro. Following an immunization regimen that elicits an anti-tumor response, splenocyte cytotoxicity against a variety of tumor cells was observed (Fig. 8). Interestingly, this activity was induced against both NK sensitive cells (YAC; FIG. 8A) as well as NK insensitive cells (B16 and 3LL; FIG. 8B and FIG. 8C, respectively), suggesting involvement of both populations in the response. Characteristically, NK-dependent lysis could be observed as early as 7 days following immunization, in accordance with early stimulation of NK cells. NK-independent lysis of B16 and 3LL cells followed a classical time-response of maximal efficacy around day 21.

The above effects could be induced to a similar extent by both peptides A and B, reaching an impressive activity of up to %80 lysis. Peptide N, a non-relevant control peptide could not elicit a similar response, in accordance with its inability to inhibit tumor growth.

**Example 5. Anti-Peptide A and B antibodies compete with BAT monoclonal antibody binding to Daudi cells**

Materials and Methods:

a. Antibody purification:

To examine the ability of BAT-selected peptide-vaccines to elicit BAT-like antibodies, serum from peptide-immunized mice was collected and purified on protein-G sepharose beads according to manufacturer's instructions (Pharmacia Corp. NJ, USA).

b. Inhibition of BAT binding:

Daudi cells ($0.5x10^6$) were pre-incubated with anti-peptide purified serum, 5, 10 and 20 μg/ml of each purified antibody, for 2 hours on ice. Biotinylated BAT monoclonal antibody (40 μg/ml) was added and cells were incubated for an additional 2 h period at 4°C. Following extensive washing streptavidin FITC was added for 30



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minutes. Cells were analyzed by FACScan (Becton Dickinson & Co., NJ, USA). Binding of anti-peptide antibodies alone (20μg/ml) was determined in a similar manner, however, the detection was performed by incubation with a secondary antibody against mouse IgG conjugated to FITC. In a control sample, cells were exposed only to the secondary antibody.

Results

It is plausible that peptides mimicking the antigenic site of BAT monoclonal antibody can elicit production of antibodies in the serum with similar binding characteristics to those of the original BAT. To examine this possibility, antibodies purified from the serum of peptide-immunized mice were studied for their ability to inhibit the binding of BAT to its antigen (FIG. 9). The binding of anti-A and anti-B antibodies to Daudi cells was verified (FIG. 9B) with respect to control (FIG. 9A), suggesting recognition of BAT antigen.

Determination of BAT binding in the presence of anti-A (FIG. 9C) and anti-B (FIG. 9D) antibodies revealed a common epitope. Both peptides induced mouse antibodies capable of significantly inhibiting BAT binding to its target cells, as demonstrated by the decrease in fluorescent labeling by BAT. This observation is explained by the fact that in the presence of the purified anti-peptide antibodies, BAT antibody could occupy less antigenic determinants on the surface of antigen expressing cells.

**Example 6. Anti-Peptide A and B antibodies induce human lymphocyte proliferation**

Materials and Methods:

a. Human-PBL (peripheral blood lymphocytes) preparation

Human normal donor blood was diluted 1:1 in PBS. Histopaque (1077-1 SIGMA) was added (1:2 v/v) and the solution was centrifuged for 30 min, 1600 rpm at 4°C. The lymphocyte inter-phase ring was collected, cells washed and incubated in complete media for one hour at 37°C to remove adherent cells. PBL were collected from supernatant.

b. Thymidine incorporation



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PBL were dispensed at a concentration of $2x10^6$ cells/ml (200µl) in 96-well flat-bottom plates in complete medium. BAT or anti-peptide antibodies (1µg/ml) were added for 5 days followed by incubation in the presence of $^3$[H]Thymidine (1µCi/well) for 16 h at 37°C. Cells were harvested and radioactivity determined using a liquid B-scintillation counter.

Results

Human PBL incubated in the presence of antibodies purified from peptide-immunized mice, demonstrated an increased proliferation, similar to that induced by BAT (Fig 10). These antibodies were effective at a similar concentration and time interval as those of BAT antibody, suggesting a resemblance in efficacy and may be in mechanism. The results suggest that lymphocyte stimulation is correlated with the ability of the vaccine of the invention to elicit an anti-tumor effect. The results further indicate that the antigenic epitope recognized by BAT is involved in lymphocyte activation.

The ability of the peptide-induced antibodies to stimulate lymphocyte proliferation is, most probably, the mechanism underlying their ability to trigger anti-tumor cytotoxicity (as shown in Example 4). In the setting of disease, anti-cancer lymphocytes that are present but beneath a threshold require an efficient immune-response such as the stimulation that is represented by the peptide of the invention in the present example.

**Example 7. Peptide vaccination in cancer patients**

Vaccination of human subjects with peptides recognized by BAT monoclonal antibody is tested in several studies. The target population for these studies is, in the first case, cancer patients. In these patients, the vaccine is expected to elicit an anti-tumor immune response, allowing to alleviate, reduce, cure or at least partially arrest the disease.

Phase I - Safety study: Double-blind, rising dose, Placebo - controlled.

Phase II - Safety & Efficacy study: Double-blind, rising dose, Placebo-controlled.

Patients who sign informed consent and fulfill inclusion criteria are randomized in a 1:1 ratio to receive the peptide vaccine or placebo (vehicle or adjuvant only). Peptide vaccine and placebo are diluted in sterile saline to generate the administered



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dosage form. The medication is administered by a suitable route of administration, for example, a fast drip intravenous infusion or peristaltic pump or subcutaneously.

The primary efficacy endpoints of the trial are: the reduction in tumor size, NK and CTL activation, proliferation of lymphocytes and humoral and cellular immune responses to tumor antigens, evaluation of peptide concentration in the blood (pharmacokinetics).

Treatment of cancer patients may exclusively include the peptide vaccine or may include another vaccine comprising a BAT monoclonal antibody. In the latter type of treatment the two vaccines may be administered separately at similar time points or at different time points of the treatment.

Safety is assessed by comparing the rate of adverse events, classified according to body system, severity and relation to treatment, between the two groups.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention. Thus the expressions "means to..." and "means for...", or any method step language, as may be found in the specification above and/or in the claims below, followed by a functional statement, are intended to define and cover whatever structural, physical, chemical or electrical element or structure, or whatever method step, which may now or in the future exist which carries out the recited function, whether or not precisely equivalent to the embodiment or embodiments disclosed in the specification above, i.e., other means or steps for carrying out the same functions can be used; and it is intended that such expressions be given their broadest interpretation.



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**CLAIMS**

1. A peptide comprising at least one epitope recognized by a BAT monoclonal antibody, selected from:
   (a) a peptide having the sequence of any one of SEQ ID NOs 1 through 17; or
   (b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or
   (c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or
   (d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof;
   (e) a combination of peptides according to (a), (b), (c) or (d).
2. The peptide according to claim 1, wherein the peptide is selected from:
   (a) a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16; or
   (b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or
   (c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or
   (d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof; or
   (e) a combination of peptides according to (a), (b), (c) or (d) which retains the biological activity thereof.
3. A peptide capable of inhibiting binding of BAT monoclonal antibody to lymphoma cells.
4. The peptide according to claim 3, wherein the lymphoma cells are Daudi or Jurkat cells.
5. The peptide according to claim 3, selected from:
   (a) a peptide having the sequence of any one of SEQ ID NOs 1 through 17; or
   (b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or



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(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or

(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof; or

(e) a combination of peptides according to (a), (b), (c) or (d) which retains the biological activity thereof.

6. The peptide according to claim 3, selected from:

(a) a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16; or

(b) a peptide having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or

(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or

(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof; or

(e) a combination of peptides according to (a), (b), (c) or (d).

7. A peptide useful for inhibiting tumor growth selected from:

(a) a peptide having the sequence of any one of SEQ ID NOs 1 through 17; or

(b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or

(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or

(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof;

(e) a combination of peptides according to (a), (b), (c) or (d).

8. The peptide according to claim 7, wherein the peptide is selected from:

(a) a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16; or

(b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or

(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or



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(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof; or

(e) a combination of peptides according to (a), (b), (c) or (d).

9. A peptide capable of inducing an immune response against tumor cells, selected from:

(a) a peptide having the sequence of any one of SEQ ID NOs 1 through 17; or

(b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or

(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or

(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof;

(e) a combination of peptides according to (a), (b), (c) or (d).

10. The peptide according to claim 9, wherein the peptide is selected from:

(a) a peptide having the sequence of any one of SEQ ID NOs 1, 6, 8, 9, 10, 14, 16; or

(b) a homolog having at least 70% identity with a peptide of (a) and retains the biological activity thereof; or

(c) a fragment of a peptide of (a) or (b) having the biological activity thereof; or

(d) a variant, derivative or salt of a peptide of (a), (b) or (c) which retains the biological activity thereof; or

(e) a combination of peptides according to (a), (b), (c) or (d).

11. A polynucleotide encoding at least one peptide recognized by a BAT monoclonal antibody.

12. The polynucleotide according to claim 11, having a sequence selected from SEQ ID NOs 18 through 32.

13. The polynucleotide according to claim 11, having a sequence selected from SEQ ID NOs 18, 22, 24, 25, 29, 31.

14. A construct comprising a polynucleotide encoding for at least one peptide recognized by a BAT monoclonal antibody.

15. The construct according to claim 14, wherein the polynucleotide comprises a sequence selected from SEQ ID NOs 18 through 32.



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16. The construct according to claim 14, wherein the polynucleotide comprises a sequence selected from SEQ ID NOs 18, 22, 24, 25, 29, 31.
17. A vector comprising a polynucleotide encoding at least one peptide recognized by a BAT monoclonal antibody.
18. The vector according to claim 17, wherein the polynucleotide comprises a sequence selected from SEQ ID NOs 18 through 32.
19. The vector according to claim 17, wherein the polynucleotide comprises a sequence selected from SEQ ID NOs 18, 22, 24, 25, 29, 31.
20. The vector according to claim 17, wherein the vector is a plasmid or a virus.
21. A host cell comprising a vector comprising a polynucleotide encoding at least one peptide recognized by a BAT monoclonal antibody.
22. The host cell according to claim 21, comprising a polynucleotide having a sequence selected from SEQ ID NOs 18 through 32.
23. The host cell according to claim 21, comprising a polynucleotide having a sequence selected from SEQ ID NOs 18, 22, 24, 25, 29, 31.
24. The host cell according to any one of claims 21 to 23, capable of expressing at least one epitope recognized by BAT monoclonal antibody.
25. A pharmaceutical composition comprising as an active ingredient at least one peptide according to any one of claims 1 through 10 and a pharmaceutically acceptable carrier.
26. A pharmaceutical composition comprising as an active ingredient a polynucleotide according to any one of claims 11 through 13 and a pharmaceutically acceptable carrier.
27. A method for treating cancer in a subject in need thereof comprising the step of administering a therapeutically effective amount of a composition according to any one of claims 25 to 26.
28. An immunomodulatory vaccine comprising at least one peptide recognized by a BAT monoclonal antibody and a pharmaceutically acceptable adjuvant.
29. The vaccine according to claim 28, wherein the peptide comprises a sequence according to claims 1 through 10.
30. The vaccine according to claim 28, wherein the adjuvant is selected from the group of an aluminum salt and an oil in water emulsion.
31. A diagnostic agent for detecting cancer comprising a peptide recognized by a BAT monoclonal antibody, according to claims 1 through 10.



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32. An antibody recognizing at least one peptide according to any one of claims 1 through 10.

33. The antibody according to claims 32, selected from the group of: intact antibody, an antibody fragment selected from: Fv, F(ab'), $F(ab')_2$ or a single chain antibody.

34. The antibody according to claims 33 to 35, selected from the group of: monoclonal antibody, polyclonal antibody, recombinant antibody, synthetic antibody fragment.



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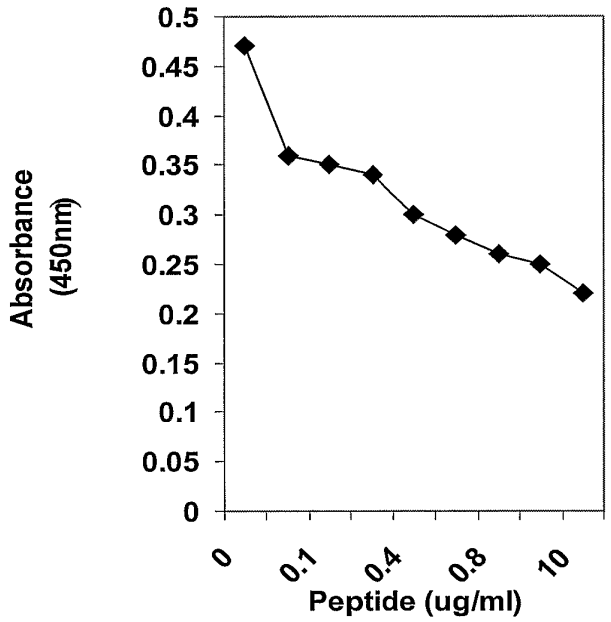

Absorbance (450nm)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.1
0.4
0.8
10
Peptide (ug/ml)

FIG. 1

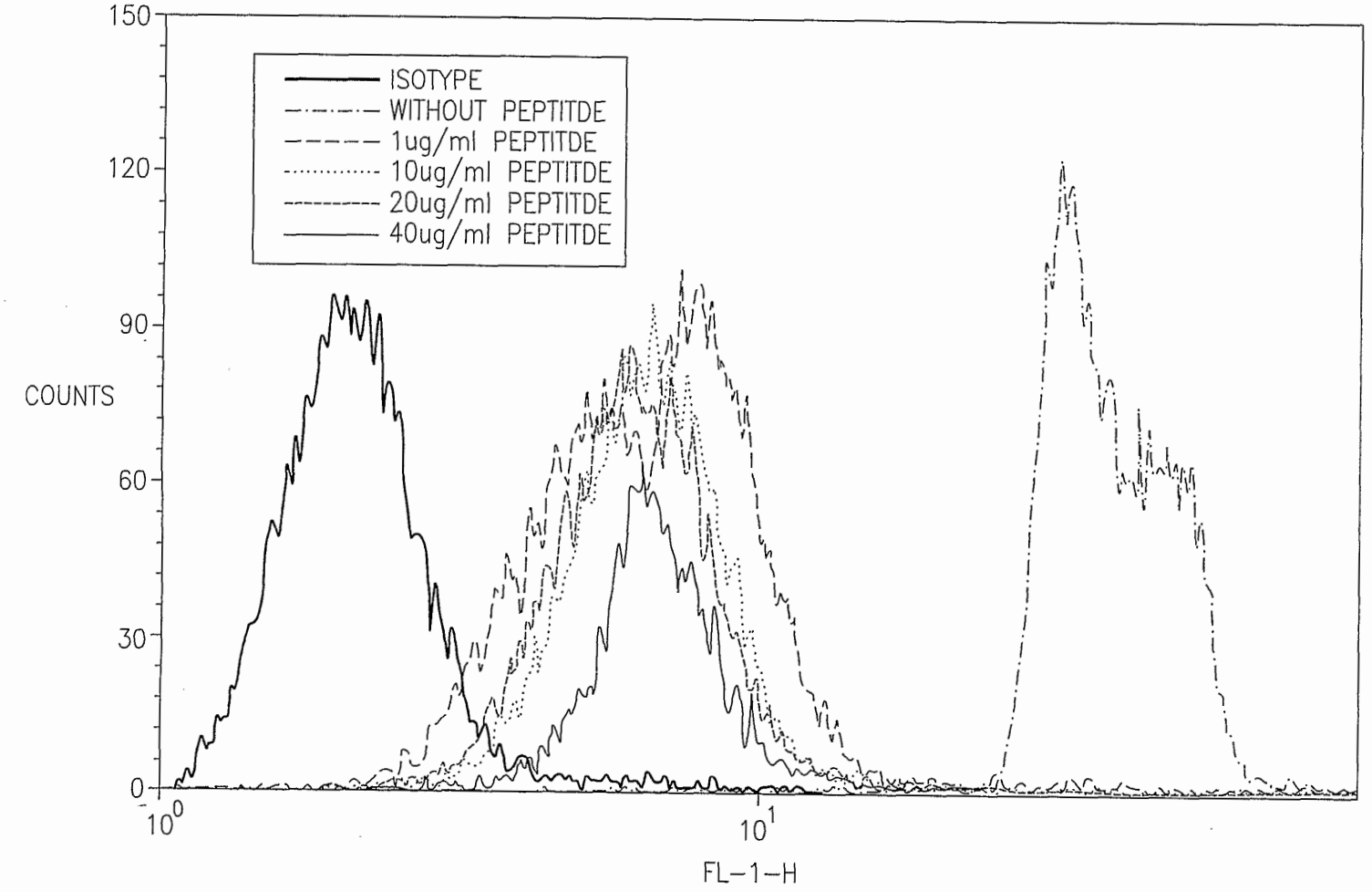



FIG. 2

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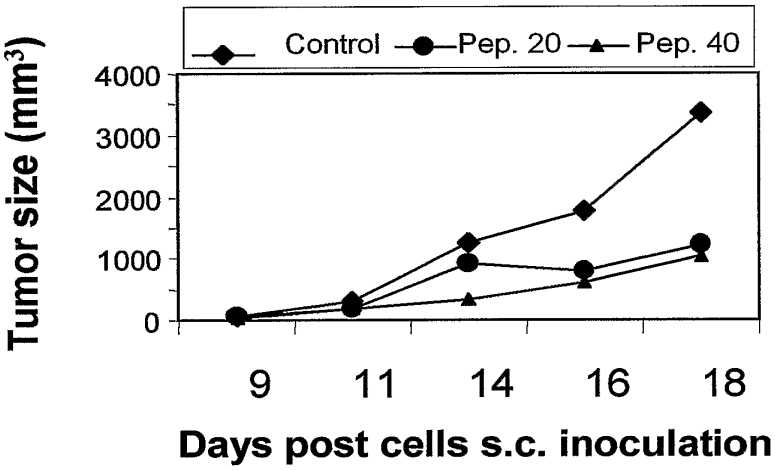

Control
Pep. 20
Pep. 40
Tumor size (mm3)
4000
3000
2000
1000
0
9
11
14
16
18
Days post cells s.c. inoculation

FIG. 3

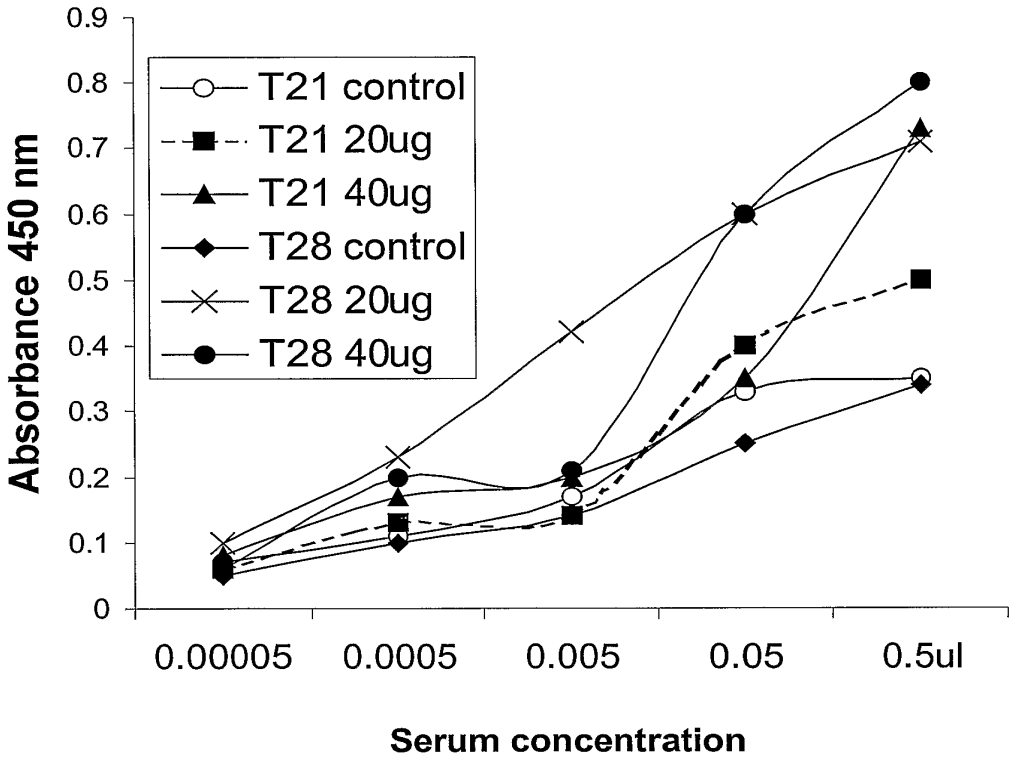

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Absorbance 450 nm
T21 control
T21 20ug
T21 40ug
T28 control
T28 20ug
T28 40ug
0.00005
0.0005
0.005
0.05
0.5ul
Serum concentration

FIG. 4

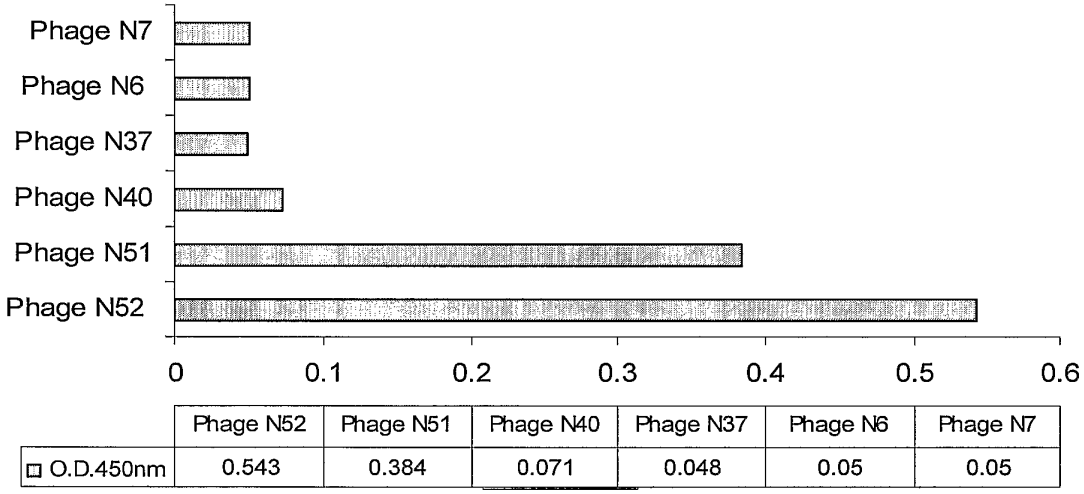

Phage N7
Phage N6
Phage N37
Phage N40
Phage N51
Phage N52
0
0.1
0.2
0.3
0.4
0.5
0.6
Phage N52 Phage N51 Phage N40 Phage N37 Phage N6 Phage N7
O.D.450nm 0.543 0.384 0.071 0.048 0.05 0.05

FIG. 5

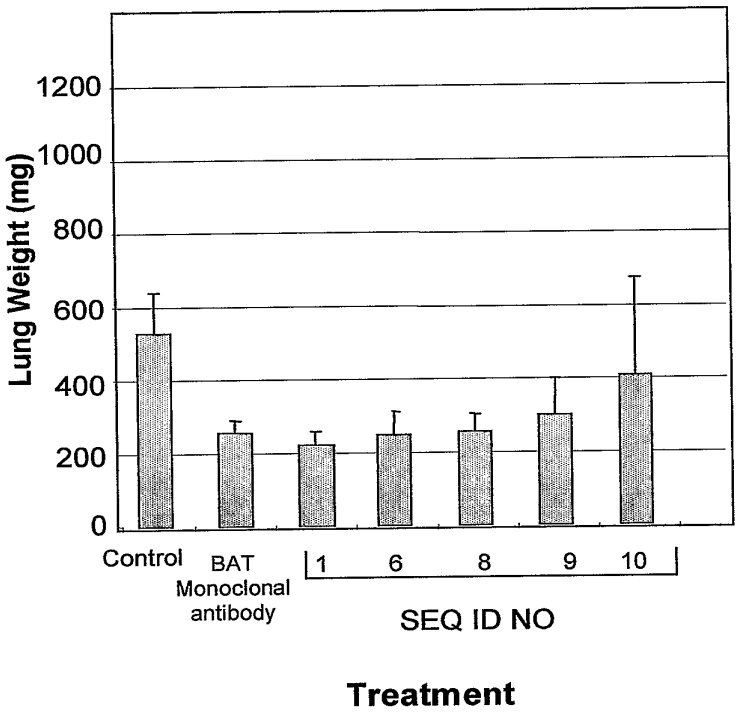

Lung Weight (mg)
1200
1000
800
600
400
200
0
Control
BAT Monoclonal antibody
1
6
8
9
10
SEQ ID NO
Treatment

FIG. 6

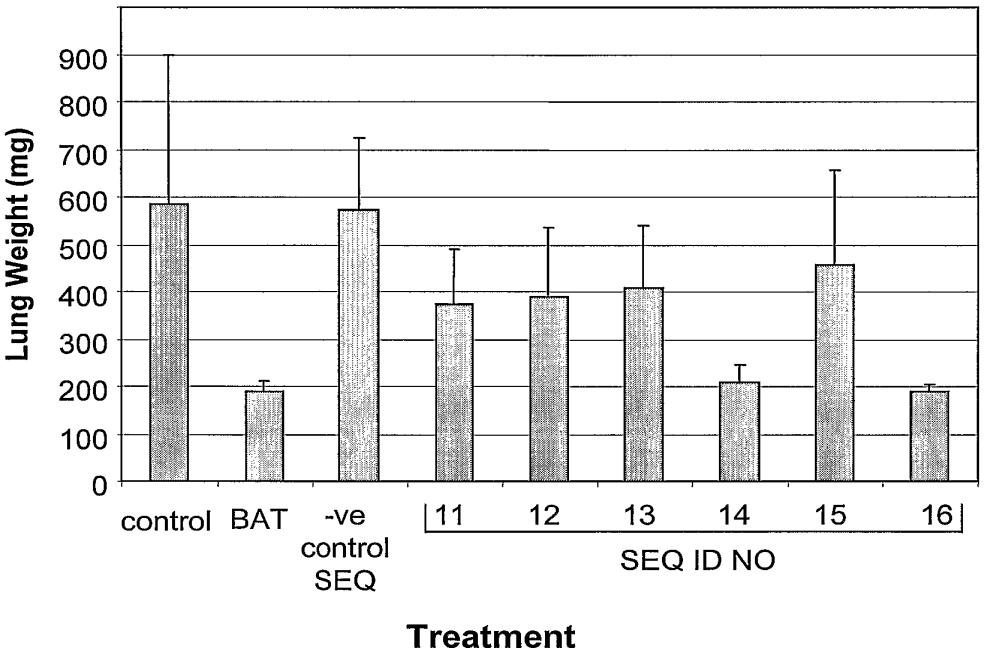

900
800
700
600
500
400
300
200
100
0
Lung Weight (mg)
control
BAT
-ve control SEQ
11
12
13
14
15
16
SEQ ID NO
Treatment

FIG. 7

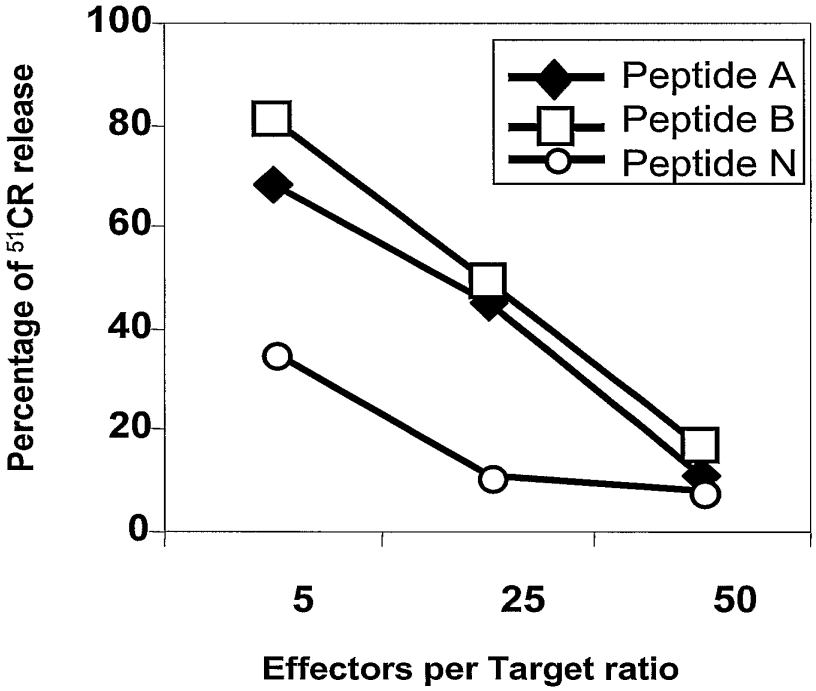

100
80
60
40
20
0
Percentage of 51CR release
Peptide A
Peptide B
Peptide N
5
25
50
Effectors per Target ratio

FIG. 8A

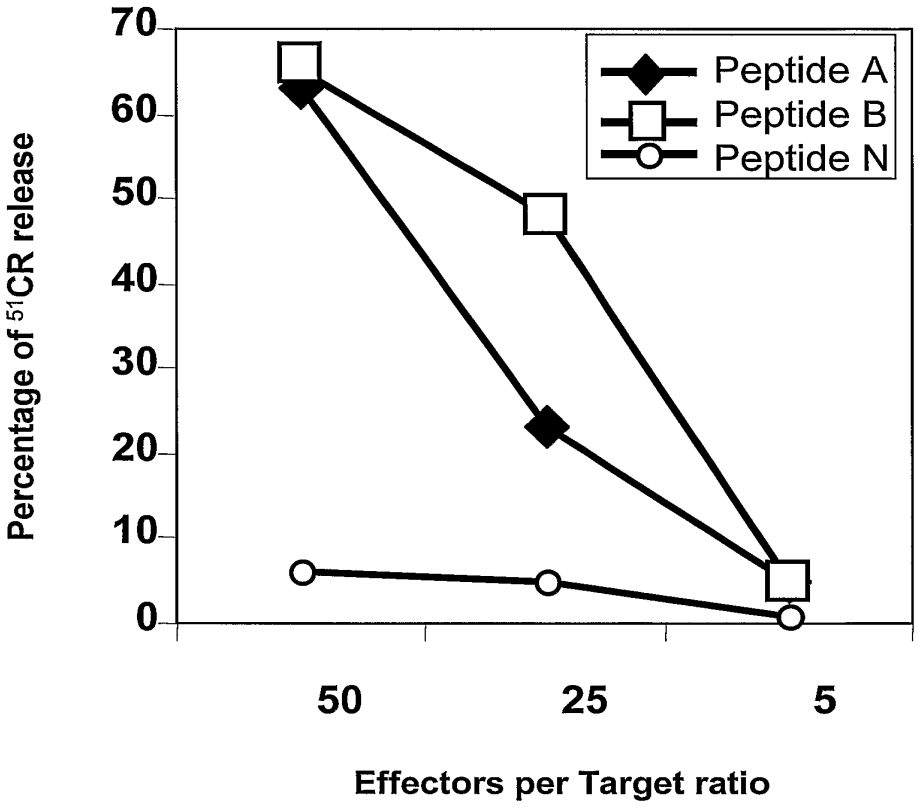

70
60
50
40
30
20
10
0
Percentage of 51CR release
Peptide A
Peptide B
Peptide N
50
25
5
Effectors per Target ratio

FIG. 8B

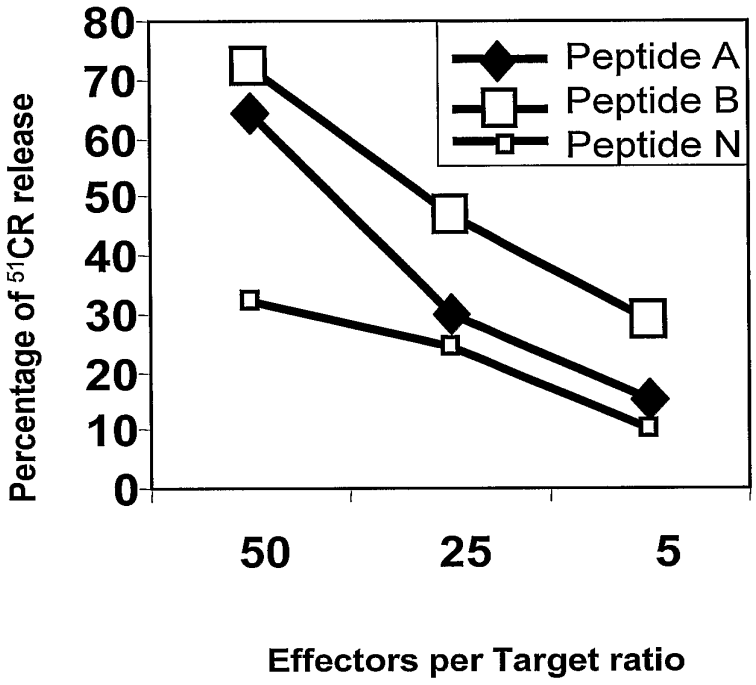

80
70
60
50
40
30
20
10
0
Percentage of 51CR release
Peptide A
Peptide B
Peptide N
50
25
5
Effectors per Target ratio

FIG. 8C

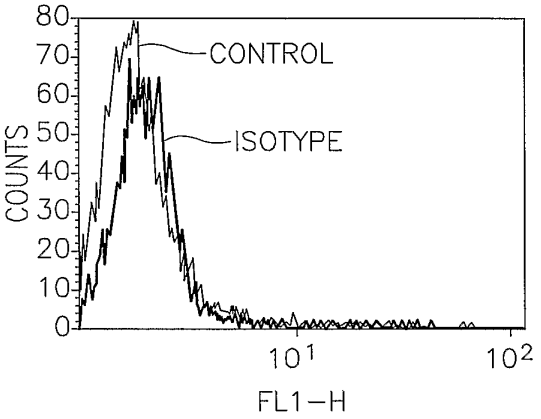



FIG.9A

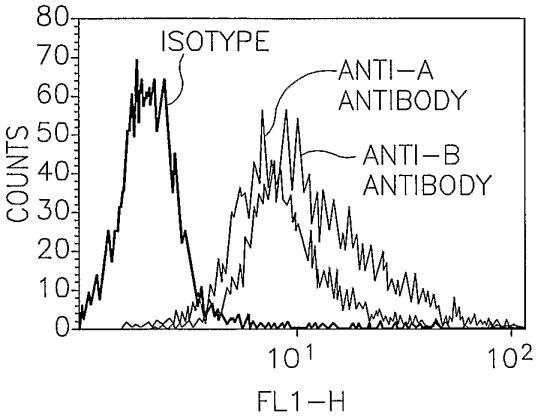



FIG.9B

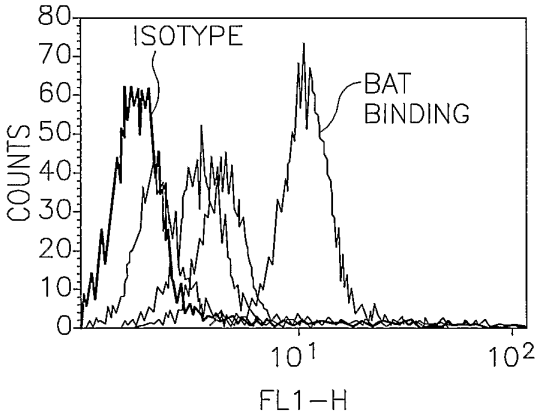



FIG.9C

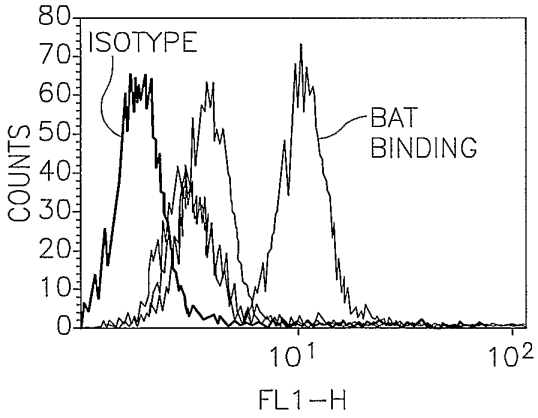



FIG.9D



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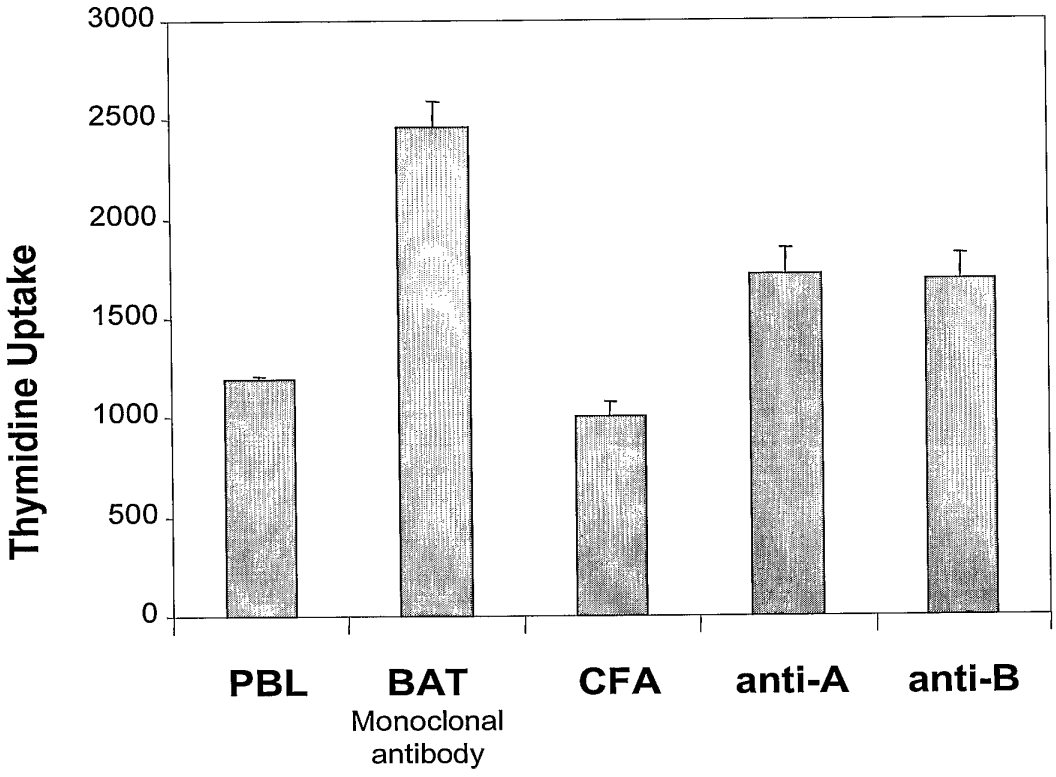

3000
2500
2000
1500
1000
500
0
Thymidine Uptake
PBL
BAT
CFA
anti-A
anti-B
Monoclonal antibody

FIG. 10

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**Published:**
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(54) Title: PEPTIDE USEFUL IN IMMUNOMODULATION

(57) Abstract: The present invention provides peptides and polynucleotides, and their use for immunomodulation, immunotherapy and vaccine particularly for anti-cancer therapy, and for diagnosis purposes. The immunomodulatory effect includes induction of proliferation and activation of peripheral blood lymphocytes and induction of an anti-tumor effect upon administration of peptides of the invention to subjects suffering from cancer.

WO 2003/033644 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL02/00831

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC(7) : A61K 38/00; C07K 2/00, 4/00, 5/00, 7/00, 14/00, 16/00, 17/00
US CL : 530/300, 350
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/300, 350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GenCore amino acid databases, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | GenCore amino acid database, Accession number A72330, 11 June 1999, one sheet. | 1-34 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 February 2004 (16.02.2004) | 17 JUN 2004 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Authorized officer<br>Alana M. Harris, Ph.D.<br>Telephone No. (703) 308-0196 |

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(54) Title: USE OF BAT MONOCLONAL ANTIBODY FOR IMMUNOTHERAPY

(57) Abstract: The present invention relates to immunotherapy and more specifically concerns the use of immunostimulatory BAT monoclonal antibodies for treatment of a variety of immunodeficiency related diseases and disorders and malfunction or incompetence of the immune system.

# USE OF BAT MONOCLONAL ANTIBODY FOR IMMUNOTHERAPY

## FIELD OF THE INVENTION

The present invention relates to immunotherapy and more specifically concerns the use of immunostimulatory BAT monoclonal antibodies for treatment of a variety of immuno-deficiency related diseases and disorders and malfunction or incompetence of the immune system.

## BACKGROUND OF THE INVENTION

Cancer immunotherapeutics are aimed by and large at modulating the response of the immune system to induce or enhance killing of tumor cells. This approach utilizes using various immunomodulators including monoclonal antibodies that selectively bind to a specific determinant on T cells thereby either initiating an activation pathway or inducing an inhibitory effect (Kohler, G. and Milstein, C., 1995, Nature 256:495).

The main tumor-cell-killing effector cells are cytotoxic T lymphocytes, though accumulating evidence suggests that T-helper cells are also essential for priming the immune system against tumors (Pardoll, D. M. and Topalian, S. L., 1998, Cur. Opinions Immunol. 10:588). T-helper cells activate nonspecific immune effector mechanisms in the course of tumor destruction by secreting appropriate cytokines such as interferon-gamma among others (Sadanaga, N. et al., 1999, J. Immunother., 22:315).

BAT is a monoclonal antibody that was generated against a membrane preparation of a Burkitt lymphoma cell line (Daudi) and exhibits anti-tumor and immunostimulatory effects towards various types of tumors (Hardy et al., 2001, Int. J. Oncol. 19:897). BAT monoclonal antibody was initially disclosed in US Patent No. 5,897,862 to Hardy et al., an inventor of the present invention, which is incorporated in its entirety by reference, as is fully set forth herein.

The polynucleotide and amino-acid sequences of murine BAT are disclosed in WO 00/58363, to Hardy et al., and US Patent Publication No. 20030026800, both publications incorporated herein by reference.

A humanized monoclonal BAT antibody is disclosed in WO 03/099196 to Hardy et al., which is incorporated in its entirety herein by reference. The humanized monoclonal BAT antibody appears to induce a greater anti-tumor effect than those induced by the parent murine BAT antibody.

Among other model systems tested, the BAT anti-tumor activity was studied in SCID (severe combined immunodeficiency disease) mice, beige mice that are deficient in NK cells and nude mice that are deficient in T cells. (Hardy, B., 1997, Proc. Natl. Acad. Sci. USA 94:5756). All mice were injected i.v. with murine B16 melanoma that subsequently develops tumors in the lungs. BAT exerted an anti-tumor effect only in SCID mice that were engrafted with either murine or human lymphocytes. In the athymic nude mice and the beige mice BAT exerted an anti-tumor activity, though this activity was less effective as compared to the anti-tumor activity of BAT in the wild-type mice.

The immunomodulatory effect of BAT was studied also *in vitro*. Murine BAT activates $CD4^+$ T cells and induces the secretion of IFN-$\gamma$ from these cells (Hardy et al., 2000, Int. Immunol. 12:1623 and Quaglino E. et al., 2005, Vaccine 9:23(25):3280-7, respectively). In addition, Hardy et al. showed that BAT triggers the proliferation of T cells and increases their cytolytic activity (Hardy, B. et al., 1997, Hum. Antibodies, 8:95).

Nowhere in the background art is the use of BAT monoclonal antibody for immunotherapy or immunostimulation of immunodeficient patients, including AIDS or SCID patients, taught or suggested. There is an unmet need for compositions and methods for the treatment of immunodeficiency disorders, depletion of lymphocytes, reduction in lymphocyte number and malfunction of lymphocytes.

## SUMMARY OF THE INVENTION

In accordance with some aspects of the present invention, the BAT monoclonal antibody is disclosed as a therapeutic agent for the treatment of immunodeficiency disorders, including, but not limited to, severe combined immunodeficiency disease, acquired immunodeficiency syndrome, and any disorder that involves depletion, attenuation and/or malfunctioning of lymphocytes, specifically T cells, NK cells, NK-T cells, B cells, monocytes, macrophages or any combination thereof. The present



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invention further discloses use of BAT monoclonal antibody for the treatment of immunodeficiency, immune malfunction or immune incompetence, collectively referred to hereinafter as immunodeficiency disorders, established after chemotherapy or irradiation. According to certain embodiments, BAT monoclonal antibody is used in conjunction with autologous, allogeneic or syngeneic stem cell transplantation derived from the bone marrow, umbilical cord blood or peripheral blood and donor leukocyte infusion. In particular, the BAT monoclonal antibody, including any variation comprising at least the antigen binding portion thereof is now disclosed as a therapeutic agent for induction of lymphopoiesis, as well as for expansion, proliferation, activation and differentiation of lymphocytes.

According to one aspect, the present invention provides a method for treating an immunodeficiency disorder in a subject in need thereof, comprising administering a therapeutically effective amount of BAT monoclonal antibody to the subject.

According to a preferred embodiment, the subject in need thereof is a human subject.

The present invention is based in part on the unexpected finding that BAT exerts a significant lymphopoietic activity, *in vivo*, when injected into naïve or tumor-bearing nude mice, as disclosed in Hardy et al. (International Immunology, 17:615-619, March 31, 2005), which was published after the priority date of the present application and is incorporated herein in its entirety by reference. Moreover, the lymphopoietic effect of BAT is surprisingly significant not only in tumor-bearing mice but even in naïve mice that do not bear tumors. The present invention is also based on the unexpected finding that administration of humanized BAT (also termed hereinafter CT-011) to patients suffering from advanced stages of hematological malignancies that were previously treated with chemotherapy, irradiation therapy, transplantation of stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood or donor leukocyte infusion (DLI) resulted in significant increase in the percentage of peripheral CD4 T cells within about 24hr post administration of the humanized BAT.

According to another aspect, the present invention provides use of BAT in the preparation of a medicament for treating an immunodeficiency disorder. According to certain embodiments, the BAT monoclonal antibody comprises a light chain variable region comprising CDRs selected from the group consisting of: SEQ. ID NO. 13; SEQ.



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ID NO. 14 and SEQ. ID NO. 15. According to further embodiments, the BAT monoclonal antibody comprises a heavy chain variable region comprising CDRs selected from the group consisting of: SEQ. ID NO. 16; SEQ. ID NO. 17 and SEQ. ID NO. 18.

According to one embodiment, the immunodeficiency disorder comprises at least one of the disorders selected from the group consisting of: depletion of lymphocytes, reduction in lymphocyte number and malfunction of lymphocytes.

According to another embodiment, the lymphocytes include at least one population of cells selected from the group consisting of: NK-cells, NK-T cells, B cells, T-cells, $CD3^+$ cells, $CD4^+$ cells, $CD8^+$ cells, Thy1.2+ cells subpopulations thereof and a combination thereof.

According to yet another embodiment, the immunodeficiency disorder is congenital. According to yet another embodiment, the immunodeficiency disorder is acquired.

According to yet another embodiment, the immunodeficiency disorder is selected from the group consisting of: severe combined immunodeficiency disease, acquired immunodeficiency syndrome, X-linked agammaglobulinaemia, common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, Wiskott-Aldrich syndrome, DiGeorge anomaly, Ataxia Telangiectasia, adenosine deaminase deficiency and activation-induced cytidine deaminase deficiency.

According to yet another embodiment, the immunodeficiency disorder is related to viral infection, fungal infection or bacterial infection. According to yet another embodiment, the immunodeficiency disorder is associated with intoxication.

According to yet another embodiment, the method of the invention is used for treating anemia, particularly, aplastic anemia and Myelodysplastic syndromes (MDS), primarily for avoiding further complication of the anemia due to immunodeficiency disorders.

According to yet another embodiment, the immunodeficiency disorder is associated with any one of the treatments selected from: chemotherapy, irradiation, transplantation of stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood and donor leukocyte infusion. According to yet another embodiment the bone marrow transplantation is autologous, syngeneic or allogeneic.



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According to various specific embodiments, the BAT monoclonal antibody is selected from the group consisting of: full length monoclonal antibody, chimeric antibody, humanized antibody, IgG, IgM, IgD, IgA, IgE, diabody, bispecific antibody, linear antibody and fragments thereof.

According to yet another embodiment, the BAT monoclonal is a humanized antibody wherein the frame regions of the light chain variable region are derived from the light chain variable region of the human TEL9 antibody. According to yet another embodiment, said frame regions are selected from the group consisting of: SEQ. ID NO. 5; SEQ. ID NO. 6; SEQ. ID NO. 7 and SEQ. ID NO. 8.

According to yet another embodiment, the BAT monoclonal is a humanized antibody wherein the frame regions of the heavy chain variable region are derived from the heavy chain variable region of the human hsighv1295 antibody. According to yet another embodiment, said frame regions are selected from the group consisting of: SEQ. ID NO. 9; SEQ. ID NO. 10; SEQ. ID NO. 11 and SEQ. ID NO. 12.

According to yet another embodiment, the antibody fragment is selected from the group consisting of: Fab, Fab', $F(ab')_2$, Fv; single-chain antibody molecules and multi-specific antibodies formed from antibody fragments.

According to yet another embodiment, the method for treating an immunodeficiency disorder in a subject in need thereof, further comprises administering at least one additional therapeutic agent in combination with a therapeutically effective amount of BAT monoclonal antibody, the at least one additional therapeutic agent being selected from the group consisting of: anti-viral agents, antibiotics, cytokines, T-cell activators, hormones, growth factors (e.g. GM-CSF), cell vaccines, peptide vaccines, DNA vaccines, antibodies and fragments thereof and T-cell stimulatory antibodies.

According to yet another embodiment, the method further comprises administering at least one additional anti-cancer agent. According to yet another embodiment the at least one additional anti-cancer agent is selected from: anti-metabolic agent, anti-angiogenic agents, cytotoxic agents and anti-tumor therapeutic antibodies.

According to yet another embodiment, the T-cell activators are selected from the group consisting of: interleukin-1 (IL-1), interleukin-2 (IL-2) interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interferon-alpha (IFN$\alpha$), interferon-



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gamma (IFNγ), tumor necrosis factors such as TNFα, anti-CD3 antibodies (anti-CD3), anti-CD28 antibodies (anti-CD28), anti-CTLA4 antibodies, anti-TGF-beta antibodies, anti-4-1BB antibodies, cell-based vaccines peptide vaccines, DNA vaccines, growth factors, phytohemagglutinin, concanavalin-A and phorbol esters.

According to some embodiments, the lymphocyte activators are produced by any one of the methods selected from a group consisting of: derivation from a natural source, production by recombinant DNA technology and chemical synthesis.

According to yet another embodiment, said therapeutically effective amount of BAT monoclonal antibody and said at least one therapeutic agent are administered together or sequentially.

Other objects, features and advantages of the present invention will become clear from the following description and drawings.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** shows a FACS dot plot analysis of CD4 and CD8 T cell sub-populations (A-B and C-D, respectively) in blood of nude mice treated with mouse IgG3 (A and C) or BAT (B and D).

**Figure 2** demonstrates a FACS dot plot analysis of CD3/Thy-1.2 (A-B), CD4/Thy-1.2 (C-D) T cell sub-populations in blood of nude mice treated with mouse IgG3 (A and C) or BAT (B and D).

**Figure 3** presents histograms obtained from FACS analysis of CD3, CD4 and CD56 leukocytes (panels A-C, respectively) drawn from the blood of naïve nude mice 17 days following BAT administration (thin line), from the blood of naïve nude mice 17 days post control IgG3 administration (thick line) or from the blood of nude mice inoculated with HM7 tumor for 17 days and treated with BAT for 5 days (broken line)

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, by a first of its aspects, a method for the treatment of immunodeficiency disorders in a subject in need of such treatment comprising administering a therapeutically effective amount of BAT, so as to thereby treat the subject.



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As use herein, the term "BAT" is used in a broad sense and specifically covers a monoclonal antibody or an antigen binding fragment thereof, wherein the monoclonal antibody is secreted by the hybridoma cell line deposited at the Collection Nationale de Cultures de Microorganismes (CNCM), under Accession No. I-1397, or recognizes the same antigenic epitope as the antibody in the above, as fully disclosed in U.S. Patent No. 5,897,862 herein incorporated by reference in its entirety including supplements; A monoclonal antibody as fully described in U.S. Patent Application Publication No. 20030026800 (incorporated herein in its entirety by reference including supplements), A humanized monoclonal antibody, as fully described in WO03/099196 which is incorporated herein by reference in its entirety.

Thus, according to certain embodiments, the BAT monoclonal antibody is characterized as follows: an antibody having a heavy chain variable region encoded by the polynucleotide sequence set forth in SEQ ID NO. 1; an antibody having a heavy chain variable region as set forth in SEQ ID NO:2; an antibody having a light chain variable region encoded by the polynucleotide sequence set forth in SEQ ID NO. 3 and/or an antibody having a light chain variable region as set forth in SEQ ID NO:4, as disclosed in U.S. Patent Application Publication No. 20030026800.

According to other embodiments, the BAT monoclonal antibody is a humanized antibody having a light chain variable region characterized by the formula:

$FR_{L1}$-$CDR_{L1}$- $FR_{L2}$-$CDR_{L2}$- $FR_{L3}$-$CDR_{L3}$- $FR_{L4}$

wherein the FRs are derived from the light chain variable region of the human TEL9 antibody and selected from the group consisting of: $FR_{L1}$, [EIVLT QSPSS LSASV GDRVT ITC; SEQ. ID NO. 5]; $FR_{L2}$, [W (F or Y) QQKPG KAPKL (W or L) IY; SEQ. ID NO. 6]; $FR_{L3}$, [GVPSR FSGSG SGT (D or S) (Y or F) (C or T) LTINS LQPED FATYY C; SEQ. ID NO. 7]; $FR_{L4}$, [FGGGT KLEIK; SEQ. ID NO. 8]

and having a heavy chain variable region characterized by the formula:

$FR_{H1}$-$CDR_{H1}$- $FR_{H2}$-$CDR_{H2}$- $FR_{H3}$-$CDR_{H3}$- $FR_{H4}$

wherein the FRs are derived from the heavy chain variable region of the human hsigv1295 antibody and selected from the group consisting of: $FR_{H1}$, [Q (I or V) QLV QSGSE LKKPG ASVKI SCKAS GY (T or S) F (T or S); SEQ. ID NO. 9]; $FR_{H2}$, [WV (R or K) QAPGQ GL (Q or K) WMG; SEQ. ID NO. 10]; $FR_{H3}$, [RF (V or A) FSLDT SV (N or S) TAYLQ ITSL (T or N) AEDTG MYFC (V or A) (R or K); SEQ. ID NO. 11]; $FR_{H4}$, [WGQGT LVTVS S; SEQ. ID NO. 12]



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and wherein the CDRs are derived from the murine BAT-1 antibody (the subscripts "L" and "H" refer to light and heavy chain regions, respectively) and are selected from the group consisting of: $CDR_{L1}$ [SARSS VSYMH; SEQ. ID NO. 13]; $CDR_{L2}$ [RTSNL AS; SEQ. ID NO. 14]; $CDR_{L3}$ [QQRSS FPLT; SEQ. ID NO. 15]; $CDR_{H1}$ [NYGMN; SEQ. ID NO. 16]; $CDR_{H2}$ [WINTD SGEST YAEEF KG; SEQ. ID NO. 17]; $CDR_{H3}$ [VGYDA LDY; SEQ. ID NO. 18], as disclosed in International Patent Application, Publication No. WO03/099196.

Human TEL-9 antibody was identified in diverse libraries of immunoglobulin heavy (VH) and light (V kappa and V lambda) chain variable (V) genes prepared from peripheral blood lymphocytes of unimmunized donors (Marks et al. J Mol Biol. 1991, 222:581-97). This antibody was shown to bind specifically to the turkey egg-white lysozyme (TEL) antigen. Human hsiggv1295 antibody was isolated from stable hybridomas and Epstein-Barr virus-transformed B cell lines from the synovial fluid or peripheral blood of three patients with rheumatoid arthritis and one patient with systemic lupus erythematosus (Fang et al., J Exp Med. 1994, 179:1445-56).

According to particular embodiments, the light chain variable region of the humanized BAT monoclonal antibody is a selected from the group consisting of: $BATR\kappa_a$ (SEQ. ID NO. 19), $BATR\kappa_b$ (SEQ. ID NO. 20), $BATR\kappa_c$ (SEQ. ID NO. 21), $BATR\kappa_d$ (SEQ. ID NO. 22) an the heavy chain variable region is selected from the group consisting of: $BATRH_A$ (SEQ. ID NO. 23), $BATRH_B$ (SEQ. ID NO. 24), $BATRH_C$ (SEQ. ID NO. 25), $BATRH_D$ (SEQ. ID NO. 26) or $BATRH_E$ (SEQ. ID NO. 27).

According to some embodiments, the humanized monoclonal antibody comprises a variable region selected from the group consisting of: $BATRH_A/BATR\kappa_a$ (SEQ. ID NO. 23/SEQ. ID NO. 19), $BATRH_B/BATR\kappa_a$ (SEQ. ID NO. 24/SEQ. ID NO. 19), $BATRH_B/BATR\kappa_b$ (SEQ. ID NO. 24/SEQ. ID NO. 20), $BATRH_C/BATR\kappa_b$ (SEQ. ID NO. 25/SEQ. ID NO. 20), $BATRH_B/BATR\kappa_d$ (SEQ. ID NO. 24/SEQ. ID NO. 22), or $BATRH_C/BATR\kappa_d$ (SEQ. ID NO. 25/SEQ. ID NO. 22).

The term "antibody" is used in the broadest sense and specifically covers monoclonal antibodies (including full length monoclonal antibodies) of any of the classes IgG, IgM, IgD, IgA, IgE and antibody fragments so long as they exhibit the desired biological activity. "Antibody fragments" comprise a portion of a full-length antibody, generally the antigen binding or variable region thereof. Examples of antibody



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fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multi-specific antibodies formed from antibody fragments.

The term "monoclonal antibody" as used herein refers to antibodies that are highly specific, being directed against a single antigenic epitope. Alternatively, the term "monoclonal antibody" as used herein refers to an antibody produced from a single spleen cell clone. The monoclonal antibodies to be used in accordance with the present invention may be made by recombinant DNA methods (see, e.g., U.S. Patent Nos. 5,225,539 to Winter and 5,530,101 to Queen et al.).

In accordance with one embodiment of the invention, the monoclonal antibody is a chimeric human-mouse antibody, namely a mAb with a constant region derived from a human origin and a variable region derived from mouse. For this purpose, the Kappa light and heavy chain variable regions of the mAb of the invention were PCR cloned and their DNA sequenced.

In accordance with yet another embodiment of the invention the antibody is a fully humanized antibody, i.e. both its variable and constant region are derived from a human source.

In accordance with various specific embodiments, the BAT monoclonal antibody is selected from the group consisting of: full length monoclonal antibody, chimeric antibody, humanized antibody, IgG, IgM, IgD, IgA, IgE, diabody; linear antibody and fragments thereof.

In accordance with yet various specific embodiments, the antibody fragment is selected from the group consisting of: Fab, Fab', $F(ab')_2$, Fv; single-chain antibody molecules and multi-specific antibodies formed from antibody fragments.

The term “diabody” refers to a dimeric antibody fragment. In each polypeptide, a heavy-chain variable domain (VH) is linked to a light-chain variable domain (VL) but unlike single-chain Fv fragments, each antigen-binding site is formed by pairing of one VH and one VL domain from the two different polypeptides. Diabodies thus have two antigen-binding sites, and can be bispecific.

The term “bispecific antibody” refers to an antibody that is able to specifically bind to two different molecules. Binding of a bispecific antibody to a first molecule takes place with one F(ab’) binding arm, and binding to a second molecule, such as a



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tumor-specific antigen on a tumor cell, takes place with another F(ab') binding arm. A bispecific antibody may further bind an FcR via its Fc portion.

In accordance with one another embodiment of the invention, the provided method is used to treat any immunodeficiency disorder, resulting from intoxication or chemotherapy and/or irradiation and/or related to therapeutic procedures involving transplantation of stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood or donor leukocyte infusion that involves depletion, reduction in number, abnormal or malfunction of lymphocytes, including, but not limited to, T cells, NK cells, B cells, monocytes, macrophages or any combination thereof.

The term "T cell" as used herein refers to a lymphocyte that matures in the thymus and expresses a T-cell receptor, CD3, and CD4 or CD8 or Thy1.2 thymocytes. This term encompasses T cell subpopulations and combinations thereof.

The term "natural killer" or "NK" cell as used herein refers to a large, granular lymphocyte that has a cytotoxic ability but does not express antigen-binding receptors. The term "NK-T" as used herein refers to CD3 lymphocytes that present NK cell markers. The term "B cell" as used herein refers to antibody-producing lymphocyte lineage. The term "monocytes" as used herein refers to myeloid lineage cells. The term "macrophages" as used herein refers to differentiated monocytes.

In accordance with another embodiment of the invention, a method for treating congenital immunodeficiency disorder as well as acquired immunodeficiency disorder is provided. The immunodeficiency disorder includes, for example, a severe combined immunodeficiency disease (SCID), acquired immunodeficiency syndrome (AIDS), X-linked agammaglobulinaemia, common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, Wiskott-Aldrich syndrome, DiGeorge anomaly, Ataxia Telangiectasia (A-T), adenosine deaminase deficiency (ADA), activation-induced cytidine deaminase deficiency (AICDA or AID deficiency). The immunodeficiency disorder maybe associated with earlier or an ongoing treatment such as chemotherapy, irradiation, autologous, allogeneic or syngeneic transplantation of stem cells derived from the bone marrow, umbilical cord blood or peripheral blood and donor leukocyte infusion.

Although Ataxia Telangiectasia is not an immunodeficiency disorder *per se*, this disease is associated with variable immunologic diseases and immunologic deficits,



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which primarily lead to recurrent pneumonia, bronchiectases and chronic obstructive and restrictive pulmonary disease. Thus, including administration of BAT antibody in the treatment regimen of Ataxia Telangiectasia, is mostly directed to treat the immunologic deficits associated with Ataxia Telangiectasia.

In some other embodiments of the invention, the method is used for treating immune deficiency and/or malfunction due to any type of chemotherapy whether combined or not with radiation therapy. The method of the invention may be further used for treating immunodeficiency disorder related to viral infection, fungal infection or bacterial infection and for treating immunodeficiency disorders, which are associated with intoxication, including, but not limited to intoxication as a result of chemotherapy and chemical intoxication among others.

In yet other embodiments, the method for treating an immunodeficiency disorder in a subject in need thereof, further comprises administering at least one additional therapeutic agent in combination with a therapeutically effective amount of BAT monoclonal antibody, the at least one additional therapeutic agent being selected from the group consisting of: anti-viral agents, antibiotics, cytokines, T-cell activators, hormones, growth factors, cell vaccines, peptide vaccines, DNA vaccines, antibodies and fragments thereof and T-cell stimulatory antibodies.

In an alternative embodiment, the method of the invention further comprises administering at least one additional anti-cancer agent selected from: anti-metabolic agent, anti-angiogenic agents, cytotoxic agents and anti-tumor therapeutic antibodies.

In yet other embodiments of the invention, the method is used for treating immune deficiency and/or malfunction due to any type of bacterial, fungal or viral infection.

Immunodeficiency disorders may evolve from malfunction of the immune system, leading to the development of infections that recur frequently, are more severe, and last longer than usual. Immunodeficiency disorders impair the ability of the immune system to defend the body against invasions and attacks by foreign or abnormal cells (such as bacteria, viruses, fungi, and cancer cells). As a result, infections and cancers may develop.

Immunodeficiency disorders may be present at birth (congenital, or primary) or may develop later in life, often as a result of another disorder (acquired, or secondary). Congenital immunodeficiency disorders are usually hereditary. They typically become



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evident during infancy or childhood. There are more than 70 congenital immunodeficiency disorders; all are relatively rare. Acquired immunodeficiency disorders are much more common. Some immunodeficiency disorders shorten lifespan, others persist throughout life but do not affect lifespan, and a few resolve with or without treatment.

Immunodeficiency disorders are grouped by which part of the immune system is affected. They may involve problems with antibodies, T lymphocytes, both B and T lymphocytes, phagocytes, or complement proteins. The affected component of the immune system may be: depletion of T-cells, reduction in T-cell number and/or malfunction of T-cells.

Severe combined immunodeficiency disease (SCID) is considered as the most serious immunodeficiency disorder. It is a congenital immunodeficiency disorder resulting in low levels of antibodies and a low number and malfunction of T lymphocytes. SCID can be caused by several different genetic defects, most of which are hereditary. Most infants with severe combined immunodeficiency disease develop pneumonia, thrush, and diarrhea, usually by age 3 months. More serious infections, including pneumocystis pneumonia, can also develop. If not treated, these children usually die before age 2. The common treatment to date is by antibiotics and immune globulin or transplantation of stem cells from bone marrow or umbilical cord blood.

HIV infection is a viral infection that progressively destroys the white blood cells and causes acquired immunodeficiency syndrome (AIDS). The two human immunodeficiency viruses HIV-1 and HIV-2 progressively destroy lymphocytes, which are an important part of the body's immune defenses, thereby, turning the body much more susceptible to attack by many other infectious organisms. Many of the symptoms and complications of HIV infection, including death, are the result of these other infections and not of the HIV infection itself. HIV infection may lead to various troublesome infections with organisms that do not ordinarily infect healthy people (opportunistic infections).

Acquired immunodeficiency syndrome (AIDS) is considered as the most severe form of HIV infection. Because the number of $CD4^+$ lymphocytes in the blood helps determine the ability of the immune system to protect the body from infections, it is a good measure of the severity of the damage done by HIV infection. A healthy person has



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a $CD4^+$ lymphocyte count of roughly 800 to 1,300 cells per microliter of blood. Typically, 40 to 60% of $CD4^+$ lymphocytes are destroyed in the first few months of infection. After about 6 months, the $CD4^+$ count stops falling so quickly, but it continues to decline. If the $CD4^+$ count falls below about 200 cells per microliter of blood, the immune system becomes less able to fight certain infections. A count below about 50 cells per microliter of blood is particularly dangerous, because additional opportunistic infections that can rapidly cause severe weight loss, blindness, or death commonly occur.

AIDS has been directly linked to an increased incidence of malignancies. Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer are AIDS-defining illnesses in HIV-infected patients. Other neoplastic diseases associated with AIDS include Hodgkin's disease, anal cancer, testicular cancer, melanoma, nonmelanomatous skin cancers, lung cancer, and primary CNS lymphoma. Leiomyosarcoma has been reported as a rare complication of HIV infection in children.

In one embodiment, the immunodeficiency and/or malfunction or incompetence of the immune system is a consequence of chemotherapy and/or irradiation and/or intoxication. According to yet another embodiment the immunodeficiency and/or malfunction or incompetence of the immune system is associated with treatment procedures involving autologous and/or syngeneic and/or allogeneic transplantation of stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood and/or donor leukocyte infusion (DLI).

Cancer patients are frequently treated with chemotherapy and irradiation. For some malignant diseases, especially hematological malignancies, therapy includes also autologous or syngeneic or allogeneic bone marrow transplantation or donor leukocyte infusion (DLI). These therapeutic interventions may result in transient or persistant complete or partial immune deficiency or immune malfunction, turning the body much more susceptible to attacks by infectious organisms. Successful cell-based therapy frequently results in enhanced anti tumor immune response and reduced susceptibility to infections.

Cell-based therapy as used herein may include lymphocyte infusions (donor leukocyte infusions), transplantation of stem cells derived from the bone marrow,



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umbilical cord blood or peripheral blood (autologous, syngeneic or allogeneic), dendritic cell based therapies or T cell based therapies and any combination thereof.

The present invention is directed however to any of the aforementioned immunodeficiency disorders of the immune system including improper immune responses against invading microorganisms (immunodeficiency disorders) among others.

In one embodiment, the method of treatment also comprises administration of BAT antibody or a composition comprising thereof to a subject in parallel to, prior to, or following treatment with an additional active composition comprising cytokines, lymphocyte activators, growth factors, mitogenic factors and other antibodies, such as any T-cell stimulatory antibody.

The growth factors and lymphocyte activators may include, without limitation, one or more of the following agents: interleukin-1 (IL-1), interleukin-2 (IL-2) interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-6 (IL-6), interleukin-7 (IL-7), interlekin-11 (IL-11), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-15 (IL-15), interferon-alpha (IFN$\alpha$), interferon-gamma (IFN$\gamma$), tumor necrosis factors such as TNF$\alpha$, anti-CD3 antibodies (anti-CD3), anti-CD28 antibodies (anti-CD28), anti-CTLA4 antibodies, anti-TGF-beta antibodies, anti-4-1BB antibodies, cell-based vaccines comprising of inactivated or otherwise modified tumor or naive cells, peptide vaccines corresponding to cellular proteins whether tumor associated or not and any parts thereof, DNA vaccines encoding for cellular proteins whether tumor associated or not and any parts thereof, growth factors like erythropoietin or granulocyte-macrophage colony stimulating factor, mitogenic factors like phytohemagglutinin, concanavalin-A and phorbol esters. The lymphocyte activators, growth factors and mitogenic factors can be native factors obtained from natural sources, factors produced by recombinant DNA technology, chemically synthesized polypeptides or other molecules, or any derivative having the functional activity of the native factor.

In a currently preferred embodiment, the subject in need thereof is a human subject.

The present invention also provides use of BAT in the preparation of a medicament for therapy of an immunodeficiency disorder and/or malfunction or incompetence of the immune system. The immunodeficiency disorder may be any disorder that involves T-cell depletion, reduction in T-cell number, T-cell abnormalities and/or malfunction of T



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cell and/or NK cells and/or NK-T cells and/or B cells and/or monocytes and/or macrophages congenital or acquired and may include any disorder that mentioned above. Malfunction or incompetence of the immune system may be a consequence of chemotherapy, irradiation and/or intoxication.

In yet another preferred embodiment, the present invention also provides use of BAT in the preparation of a medicament for therapy in conjunction with procedures involving transplantation of stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood and/or donor leukocyte infusion.

The present invention also involves use of a pharmaceutical composition for treating an immunodeficiency disorder, wherein the pharmaceutical active ingredient is BAT in a therapeutically effective amount. The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier. Said composition may be in any pharmaceutical form suitable for administration to a patient, including but not limited to solutions, suspensions, lyophilized powders for reconstitution with a suitable vehicle or dilution prior to usage, capsules and tablets.

The administration of the compositions of the present invention can be typically achieved by means of parenteral administration, e.g., intravenously (i.v.) intraperitoneally (i.p.) subcutaneously (s.c.) or intramuscularly (i.m.) intradermally (i.d.). Methods of treatment may comprise pharmaceutical compositions of BAT according to the invention.

Preferably, the composition of the present invention has a form suitable for injections. The pharmaceutical composition disclosed in this invention may further comprise any pharmaceutically acceptable diluent or carrier to provide a physiologically acceptable conjugates comprising BAT with one or more therapeutic agents.

The pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, grinding, pulverizing, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Preferably, the pharmaceutical compositions of the present invention may be manufactured by processes that are particularly suitable for proteins, more particularly antibodies.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable



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carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations and that are pharmaceutically suitable. Proper formulation is dependent upon the route of administration chosen.

For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

Pharmaceutical compositions for parenteral administration include aqueous solutions of the active ingredients in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable natural or synthetic carriers are well known in the art. Optionally, the suspension may also contain suitable stabilizers or agents, which increase the solubility of the compounds, to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Pharmaceutical compositions for use in accordance with the present invention may be formulated for delivery via inhalation in a manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations and that are pharmaceutically suitable.

Pharmaceutical compositions suitable for use in context of the present invention include compositions wherein the active ingredient is contained in an amount effective to achieve the intended purpose. All formulations for administration should be in dosages suitable for the chosen route of administration. More specifically, a "therapeutically effective" dose means an amount of a compound effective to prevent, alleviate or ameliorate symptoms of a disease of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

Toxicity and therapeutic efficacy of the compositions described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the $IC_{50}$ (the concentration which provides 50% inhibition) and the maximal tolerated dose for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending *inter alia* upon the dosage



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form employed, the dosing regimen chosen, the composition of the agents used for the treatment and the route of administration utilized among other relevant factors. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. Depending on the severity and responsiveness of the condition to be treated, dosing can also be a single administration of a slow release composition, with course of treatment lasting from several days to several weeks or until cure is effected or diminution of the disease state is achieved. The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, and all other relevant factors.

In one embodiment of the invention, the effect of the composition may be the induction of lymphopoiesis and/or proliferation, activation or differentiation of cells, such as, T cells, NK cells, NK-T cells, Thy1.2 cells, B cells, monocytes, macrophages, transplanted stem cells derived from either the bone marrow, umbilical cord blood or peripheral blood or lymphocytes following donor leukocyte infusion.

In accordance with a certain embodiment, the BAT monoclonal antibody, being useful for a variety of therapeutic indications, is used for the treatment of immunodeficiency disorder.

In one embodiment, methods are provided for the use of a humanized BAT for the treatment of immunodeficiency disorder by administering to a subject an effective amount of the antibody of the invention. Since the antibodies used in such embodiment shall be used in an in vivo therapy, preferably antibodies or derivatives or fragments of human origin are used, or antibodies modified to be suitable for the use in humans (so-called "humanized antibodies") (see for example U.S. Patent Nos. 5,585,089 to Queen et al. and 5,225,539 to Winter)."

The term "effective amount" should be understood as meaning an amount of an antibody required to achieve a therapeutic effect. The effective amount required to achieve the therapeutic end result may depend on a number of factors including, for example, the specific type of the disorder and the severity of the patient's condition, and whether the antibody is co-administered together with another agent which acts together with the antibody in an additive or synergistic manner. BAT may be administered either



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following detection of a disorder in the subject or, as preventive therapy of a subject having a high risk of developing immunodeficiency disorder.

The dose of the composition to be administrated to a subject, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the subject over time, or to induce lymphopoiesis and/or proliferation, activation or differentiation of T cells, NK cells, NK-T cells, and B cells.

The dose will be determined by the activity of the therapeutic composition produced and the condition of the subject, as well as the body weight or surface area of the subject to be treated. The size of the dose and the dosing regiment also will be determined by the existence, nature, and extent of any adverse side effects that accompany the administration of a particular therapeutic composition in a particular subject. In determining the effective amount of the therapeutic composition to be administered, the physician needs to evaluate *inter alia* circulating plasma levels, toxicity, and progression of the disease.

Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

## EXAMPLES

## MATERIALS AND METHODS

### Molecular biology techniques and CDR grafting

Molecular biology techniques and CDR grafting protocols suitable to carrying out the invention as herein described are known to those skilled in the art. Suitable teachings are described in numerous manuals and primary publications, including *inter alia*, Sambrook et al., (Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989); Ausubel et al., (Protocols In Molecular Biology, Green Publishing Associates and Wiley-Interscience, John Wiley and Sons, New York 1987, 1988, 1989); US Patent Nos. 5,225,539 to Winter and 5,585,089 to Queen et al., which are herein incorporated by reference in their entirety including supplements.



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**PCR Technology**

The term "Polymerase Chain Reaction" ("PCR") refers to the methods disclosed in U.S. Patent Nos. 4,683,195; 4,683,202, and 4,965,188 and improvements thereto.

**BAT antibody**

BAT monoclonal antibodies were selected by binding to Daudi cells and by their ability to induce human peripheral blood mononuclear cell proliferation (Hardy, et al., 1994. Cancer Res. 54:5793; Hardy, et al., 1989. Cell. Immunol. 118:22). The BAT monoclonal antibody may be produced from either *in vitro* hybridoma cultures grown in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS) or from mice ascites, followed by purification on a protein G Sepharose column (Pharmacia, Uppsala, Sweden). Additionally, the BAT antibody may be obtained or produced in any method previously described by the inventors in U.S. Pat No. 5, 897,862; U.S. Pat. Application 20030026800; and WO03/099196 incorporated herein by reference in their entirety.

**Human tumor cell line**

HM7 is a sub-clone of the human CRC cell line LS174T, selected for its high mucin synthesis and metastatic potential (Bresalier, R. S., Niv, Y., Byrd, J. C., Duh, Q. Y., Toribara, N. W., Rockwell, R. W., Dahiya, R. and Kim, Y. S. 1991. Mucin production by human colonic carcinoma cells correlates with their metastatic potential in animal models of colon cancer metastasis. J. Clin. Invest. 87:1037). Cells were obtained from Professor Robert S. Breselier (MD Andersen, USA). The cells were grown in RPMI-1640 supplemented with 10% FCS, L-glutamine (2mM), Na-pyruvate (1nMol), penicillin (100 units/ml), streptomycin sulfate (0.1mg/ml) and nystatine (12.5u/ml). Cultures were maintained at 37°C in a humidified 5% $CO_2$ incubator.

**Human colon carcinoma tumor model in nude mice**

A liver metastases human colon carcinoma tumor model was used in nude mice (Bresalier, R. S., Niv, Y., Byrd, J. C., Duh, Q. Y., Toribara, N. W., Rockwell, R. W., Dahiya, R. and Kim, Y. S. 1991. Mucin production by human colonic carcinoma cells correlates with their metastatic potential in animal models of colon cancer metastasis. J. Clin. Invest. 87:1037). BALB/c nude mice were anesthetized and their spleens were exposed. HM7 ($2x10^6$) cells in 0.250 ml PBS were injected into the exposed spleen; after 1 minute, the spleens were removed and the excisions closed. HM7 cells colonize the



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liver as bulky nodules. Mice were divided into four groups: (1) Nude mice injected with BAT only (10μg/mouse in PBS); (2) Nude mice injected with the isotype control mouse IgG3; (3) Nude mice injected with tumor cells only; and (4) Nude mice inoculated with tumor cells and 12 days post-tumor inoculation injected intravenously with BAT antibodies at 10μg/mouse in PBS.

**Collecting blood samples of nude mice**

Two blood sampling periods, "first" and "second" sampling, were defined equivalently across all four groups detailed above, based on corresponding times after BAT (or BAT control) injection. Thus, blood from groups 1 and 2 of nude mice was collected on day 5 (first sampling) and 14 (second sampling) post-antibody and control IgG injections. Blood from group 3 and 4 was collected 17 (first sampling) and 26 (second sampling) days post-tumor inoculation, corresponding to 5 and 14 days post-BAT injection (BAT administration on day 12 post-tumor inoculation, plus either 5 or 14 days).

**Fluorocytometric Cell analysis of lymphocytes in blood**

Mononuclear cells were isolated from the blood by Ficoll-Hypaque centrifugation. Thereafter, $5x10^5$ fresh isolated leukocytes samples were suspended in 50 μl PBS containing 5% FCS and 0.1% Na-azide. Cells were stained with saturated amounts of the indicated antibodies for 45 minutes on ice: Rat anti mouse-CD3 Pycoerythrin (PE) labeled (clone number KT3), rat anti mouse-CD4 (clone number YTS 191.1), anti mouse CD56 antibody, rat anti mouse CD8 (clone number KT15) fluorescein labeled (serotec, Oxford, UK) and anti mouse Thy1.2 (CD90.2) labeled with biotin (clone number 30-H12, BioLegend, San Diego, USA) followed by streptavidin Cy5 coupled to R-phycoerytrin (DAKO Cytomation). Triple staining dot blot analysis was performed using a FACScan (Beckton Dickinson, USA).

PE-conjugated anti-NK1.1 (clone number PK136) antibodies were used in double staining with anti mouse CD3 labeled with FITC. Anti-mouse-kappa for detection of kappa positive B cells was labeled with biotin (Southern Biotechnology Associates, Birmingham, Alabama) and detected with streptavidin – FITC (Jackson Immuno-research, West Grove, Palo Alto, California).

Side-scatter and forward-scatter of dot plots were used to determine the gates of lymphocytes; PE or FITC labeled IgGs (Pharmingen, San Diego, CS, USA) served as



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isotope controls for PE or FITC labeled antibodies. FACS analysis was done using FACSCalibur flow cytometer (Becton Dickinson, Esembodegem, Belgium). Data were analyzed using CELLQuest (Becton Dickinson, Erembodegem, Belgium).

## EXAMPLE 1

**Effect of BAT injection to naive nude mice on lymphocyte populations in the blood.**

The proportion of lymphocyte sub-populations in blood of nude mice was followed 5 days after a single I.V. injection of 10 μg/mouse of BAT antibody. FACS analysis of a representative experiment (Table 1) determined the percent of CD3, CD4, CD8 T cells, the proportion of NK1.1 positive NK cells and the percent of Thy1.2, Thy1.2/CD3. and Thy1.2/CD4 cells. Study of lymphocytes obtained from blood of control nude mice demonstrated a low proportion of CD3 and CD4 positive T cells, which varied between 0.1-0.6% 5 days post-control IgG3 administration. However, 5 days after BAT injection, the proportion of CD3-positive cells increased to 24.5% and the proportion of CD4 cells increased to 20.8% ($p<0.05$). Double staining of CD3/CD4 populations increased to 19.3%. In contrast to CD4 cell propagation, CD8 T cells in the blood of the nude mice did not increase at any tested day following the injection of BAT antibodies and the values were as low as in the controls (0.3-0.6%).

The number of NK1.1 positive NK cells, increased from 7.3% in the control to 18.5% after 5 days following BAT administration. BAT administration did not induce an increase in the percentage of Thy1.2 cells. However, BAT induced an increase in the percentage of CD3/Thy1.2 from 0.4% to 24% and CD4/Thy1.2 from 0.1% to 21% (Table 1). FACS analysis of percent of CD3, CD4, CD8, Thy1.2 positive T cells and NK1.1 positive NK cells in blood of nude mice at different days post-injection of 10ug/mouse of BAT antibody or mouse IgG3 isotype control is shown in Table 1 below:



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**TABLE 1.** Percent of cells determined by FACS analysis

| | PERCENTAGE OF CELLS | |
|---|---|---|
| T-cell subtype | Control | BAT |
| CD3 | 0.8 | 24.5 |
| CD4 | 0.1 | 20.8 |
| CD3/CD4 | 0.1 | 19.3 |
| CD8 | 0.6 | 0.3 |
| CD3/CD8 | 0.3 | 0.3 |
| Thy1.2 | 29.6 | 30.2 |
| CD3/Thy1.2 | 0.4 | 24.0 |
| CD4/Thy1.2 | 0.1 | 20.9 |
| NK1.1 | 7.3 | 18.5 |

CD4 cells lymphopoiesis is induced 5 days post BAT administration, as depicted in Fig.1. Lymphocytes from nude mice that were treated with or without BAT for 5 days, were stained with PE-labeled anti mouse CD3 (demonstrated by FL2-H staining, A-D) and with either FITC-labeled anti mouse CD4 (A-B), or FITC-labeled anti mouse CD8 (C-D). Acquisition of 10:000 gated cells was confirmed by CD3-labeled cells. Results of double staining CD3/CD4 and CD3/CD8 lymphocyte subpopulations indicate that BAT induces lymphopoiesis of CD3/CD4 cells and not of CD3/CD8 cells following 5 days of treatment.

Increased lymphopoiesis of CD4 cells following BAT treatment is also demonstrated in Fig.2. Lymphocytes from nude mice that were treated with or without BAT for 5 days, were stained with anti mouse biotin-labeled Thy1.2 antibody followed by streptavidin-RPE-Cy5 (demonstrated by FL3-H staining, A-D) and with either anti-mouse CD3 PE-labeled antibody (A-B), or with anti CD4 FITC labeled antibody (C-D). The results demonstrate that BAT mAb administration induces a distinct increase in CD3/Thy1.2 and CD4/Thy1.2 cells following 5 days of treatment.

The proportion of lymphocyte sub-populations in blood of nude mice was followed 5 and 14 days after a single injection with 10 μg/mouse of BAT antibody. FACS analysis determined the percent of CD3, CD4, CD8 T cells and proportion of CD56 positive cells NK. Lymphocytes in blood of control nude mice tested at the 2 time points maintained a low proportion of CD3 and CD4 positive T cells, which varied between 0.6 to 3 percent. However, 5 days after BAT injection, CD3 cells increased to



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12 percent and reached 19 percent on day 14. CD4 cells increased after 5 days to 18.8% ($p<0.05$) and at 14 days settled at 14.6 percent. In contrast to CD4 cell propagation, CD8 T cells in the blood of the nude mice did not increase at any tested day following the injection of BAT antibodies and the values were as low as in the controls (0.1-1.1%)

The number of CD56 positive NK cells, increased from 2.6% in control to 25% 5 days post BAT administration and remained 24.2% 14 days post BAT treatment.

FACS analysis of percent of CD3, CD4, CD8 positive T cells and CD56 positive NK cells in blood of nude mice at different days post-injection of 10ug/mouse of BAT antibody or mouse IgG3 isotype control is shown in Table 2 below:

**TABLE 2.** Percent of cells determined by FACS analysis

| T-cell subtype | Time post treatment | | | |
|---|---|---|---|---|
| | Day 5 | | Day 14 | |
| | Control | BAT | Control | BAT |
| CD3 | 1. 2 | 12.0 | 3.0 | 19.0 |
| CD4 | 0.6 | 18.8 | 11.1 | 14.6 |
| CD8 | 0.0 | 1.1 | 0.0 | 0.0 |
| CD56 | 2.6 | 25.0 | 0.3 | 24.2 |

## EXAMPLE 2

**Effect of BAT treatment on peripheral blood leukocytes in nude mice engrafted with human colon carcinoma.**

A. Effect of HM7 human colon carcinoma engraftment of nude mice on lymphocyte populations in blood

Percent of lymphocyte sub-populations in blood of nude mice engrafted with tumor was followed on the first (17 days post tumor inoculation) and second (26 days post tumor inoculation) samplings. The effect of tumor on blood lymphocytes



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determined by FACS analysis is presented in Table 3. As can be seen the percent of CD3, CD4, CD8 T cells was low and not significantly changed by tumor implantation: 1.2 to 3.5 percent for CD3, 1.1 and 2.7 for CD4 and 0.3 and 1.1 for CD8 cells. The number of anti-kappa positive B cells increased with time. NK cells were 7.4 on first sampling and 0.3 percent on second sampling.

Effect of human colon carcinoma HM7 administration on the percent of CD3, CD4, CD8 positive T cells, CD56 positive NK cells and B kappa positive B cells in the blood of nude mice is shown in Table 3 below:

**TABLE 3.** Percent of lymphocyte sub-populations in blood of nude mice engrafted with tumors

| Lymphocyte sub-population | Days post-tumor administration | |
|---|---|---|
| | 17 days | 26 days |
| CD3 | 1.2 | 3.5 |
| CD4 | 1.1 | 2.7 |
| CD8 | 0.3 | 1.1 |
| anti-kappa | 52.7 | 87.4 |
| CD56 | 7.4 | 0.3 |

B. Effect of BAT treatment of human colon carcinoma of nude mice on peripheral blood leukocytes.

Treatment of HM7 tumor bearing mice with a single administration of BAT (10ug/mouse) 12 days post-tumor administration induced a remarkable anti-tumor activity, manifested as prevention of liver metastases. Blood analysis (Table 4) tested on the first sampling (5 days post-BAT injection) demonstrated a significant 33.6% increase in CD3 cells ($p<0.05$) and 20.8% in CD4 positive cells ($p<0.05$). A similar effect of BAT treatment was also seen in increased number of NK cells on the first sampling (22.1%) and CD8 cells (9.7%). B cells bearing kappa-light chain were present in all groups of mice and were not significantly affected by BAT treatment (52.8%). On second sampling (14 days after BAT treatment, 26 days after tumor inoculation), CD3,



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CD4 and CD8 and NK cell subpopulations decreased to the control nude mice values in the blood.

As can be seen in the FACS analysis shown in Fig.3, (and also in table 2 and 4), the effect of BAT in tumor bearing mice is further enhanced compared to BAT stimulation of CD3 and CD4 in the non tumor bearing mice. The percentage of NK cells is enormously enhanced already 14 days after BAT treatment.

**TABLE 4.** Percent of lymphocytes in blood of nude mice injected with BAT antibody post-human colon tumor in nude mice

| Lymphocyte subtypes | 17 days after tumor inoculation and 5 days after BAT injection | 26 days after tumor inoculation and 14 days after BAT injection |
|---|---|---|
| CD3 | 33.6 | 3.6 |
| CD4 | 20.8 | 9.2 |
| CD8 | 9.7 | 2.9 |
| Anti-kappa | 52.8 | 59.8 |
| CD56 | 22.1 | 0.7 |

## EXAMPLE 3

### Treatment of patients suffering from hematological malignancies with humanized BAT (CT-011 antibody) results in significant increase in peripheral CD4 T cells

Phase I clinical study was conducted for evaluating the safety of escalating doses of the humanized BAT (CT-011) administered to patients suffering from advanced stages of a variety of hematological malignancies i.e., AML (Acute myeloid leukemia), HD (Hodgkin's disease), NHL (Non Hodgkin's lymphoma), and CLL (Chronic lymphocytic leukemia). Medical history of these patients included chemotherapy and/or irradiation and/or autologous or allogeneic bone marrow transplantation and/or donor leukocyte infusion (DLI). Changes in blood lymphocytes were monitored by staining of



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peripheral blood lymphocytes drawn from said patients before and 24 hours after administration of 0.6 or 3 mg/kg CT-011 with labeled-anti human CD4 antibody followed by FACS analysis.

The results indicate significant increases in the percentage of peripheral CD4 T cells 24 hours post antibody administration from 22% to 34% ($p$=0.02) in patients treated with 0.6mg/kg of CT-011 and from 33% to 42% ($p$=0.005) in patients treated with 3mg/kg of CT-011 (Table 5).

**TABLE 5**: Effect of CT-011 on the percentage of CD4 T cells in patients with advanced stage hematological malignancies

| Phase of Treatment | % of CD4 T cells (Mean±SDV) | |
|---|---|---|
| | **CT-011 Dose (mg/kg)** | |
| | **0.6[1]** | **3.0[2]** |
| Pre-treatment | 22±11 | 33±7 |
| 24 hrs post administration | 34±14 | 42±10 |
| $p$ | 0.02 | 0.005 |

$p$ = significance by paired t-test;
[1] Number of patients =6;
[2] Number of patients = 3.

## EXAMPLE 4

### BAT antibody treatment in conjunction with Stem Cell Transplantation or Donor Leukocyte Infusion – Case study

Stem cell transplantation (SCT) is a special therapy for patients with cancer or other diseases, which affect the bone marrow. Currently, the major sources of stem cells for transplantation include bone marrow, peripheral blood, and cord blood derived from a variety of donors including the recipient itself (i.e. autologous source) or a donor other than the recipient (i.e. allogeneic source). The three types of allogeneic donors are: syngeneic – in the case where the donor and recipient are identical twins, related – in cases where the donor and recipient are relatives, and unrelated - where the donor is identified through a donor registry or from a cord blood bank. The goal of SCT is to transfuse healthy bone marrow cells into a person after their own unhealthy or dysfunctional bone marrow has been eliminated.



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Establishment and repopulation of a normal functioning immune system after transplantation of the new or reinfused cells to the body is a long process. Particularly, the an immune-competent T cell population recovers within 6 to 12 months post transplantation. The time frame for the recovery of an immune response in patients who develop graft versus host disease (GVHD), a common side effect of SCT, is considerably longer. During this time the body is at greater risk for bacterial viral and fungal infections. In addition, the desired therapeutic effect, e.g., anti tumor activity, may be substantially compromised during this recovery period.

Another form of therapy which usually follows SCT failure is donor leukocyte infusion (also termed: DLI) which involves infusion of lymphocytes obtained from blood donated by the original donor. These donated white blood cells contain cells of the immune system that can recognize and destroy cancer cells. The goal of this therapy is to induce a remission of the cancer disease by a process called the graft-versus-tumor effect (GVT). The donor T-cells can attack and control the growth of residual cancer cells providing the GVT effect. Approximately 20 percent of patients treated with DLI develop pancytopenia, a deficiency of all types of blood cells.

BAT antibody treatment is utilized in the aforementioned clinical conditions to promote the recovery of the body's immune system and enhance its return to normal function following SCT or DLI. Administration of BAT concomitant with or following SCT or DLI enhances the generation of disease specific immune cells, in particular NK, T and B cells.

A patient suffering stage IV Hodgkin's lymphoma patient who underwent autologous bone marrow transplantation, received a single dose of humanized BAT antibody (0.6 mg/kg) 4 months after the autologous transplantation. An increase of 80% in the percentage of CD4 T cells 24 hours post humanized BAT antibody treatment was observed. Despite of the patient's advanced condition, stabilization of the disease has been observed for approximately 8 months post treatment with the humanized BAT antibody.



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**Example 5**
**BAT antibody treatment in conjunction with Chemotherapy and Irradiation – Case study**

Chemotherapy in combination with irradiation is commonly used for the treatment of cancer diseases.

A patient at stage III Chronic Lymphocytic Leukemia received chemotherapy (ESHAP: etoposide, methylprednisolone, cytarabine, and cisplatin). Approximately 1 month after the chemotherapy the patient was further treated by irradiation and was then treated with a single dose of humanized BAT antibody (0.6 mg/kg). A 40% increase in the percentage of CD4 T cells 24 hours post humanized BAT antibody treatment was observed in this patient. Despite of the patient's advanced condition, stabilization of the disease has been observed for approximately 8 months post humanized BAT antibody treatment.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention.



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## CLAIMS

1. A method for the treatment of an immunodeficiency disorder in a subject in need thereof, the method comprising administering a therapeutically effective amount of BAT monoclonal antibody to said subject.

2. The method of claim 1, wherein the immunodeficiency disorder comprises at least one disorder, symptom or abnormality selected from the group consisting of: depletion of lymphocytes, attenuation in the count of lymphocytes, malfunction of lymphocytes and combinations thereof.

3. The method of claim 1, wherein said immunodeficiency disorder is congenital.

4. The method of claim 1, wherein said immunodeficiency disorder is acquired.

5. The method of claim 1, wherein said immunodeficiency disorder is selected from the group consisting of: severe combined immunodeficiency disease, aplastic anemia, acquired immunodeficiency syndrome, X-linked agammaglobulinaemia, common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, Wiskott-Aldrich syndrome, DiGeorge anomaly, Ataxia Telangiectasia, adenosine deaminase deficiency and activation-induced cytidine deaminase deficiency.

6. The method of claim 1, wherein the immunodeficiency disorder is related to viral infection, fungal infection or bacterial infection.

7. The method of claim 1, wherein said immunodeficiency is associated with at least one treatment selected from: chemotherapy, irradiation, transplantation of stem cells and donor leukocyte infusion.

8. The method of claim 1, wherein the immunodeficiency disorder is associated with intoxication.

9. The method of claim 1, wherein the immunodeficiency disorder is associated with aplastic anemia or Myelodysplastic syndromes



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10. The method of claim 7, wherein the stem cells are derived from a source selected from the group consisting of: bone marrow, umbilical cord blood and peripheral blood.

11. The method of claim 1, wherein the BAT monoclonal antibody comprises a light chain variable region comprising CDRs selected from the group consisting of: SEQ. ID NO. 13; SEQ. ID NO. 14 and SEQ. ID NO. 15.

12. The method of claim 1, wherein the BAT monoclonal antibody comprises a heavy chain variable region comprising CDRs selected from the group consisting of: SEQ. ID NO. 16; SEQ. ID NO. 17 and SEQ. ID NO. 18.

13. The method of claim 1, wherein the BAT monoclonal antibody is selected from the group consisting of: full length monoclonal antibody, chimeric antibody, humanized antibody, IgG, IgM, IgD, IgA, IgE, diabody, bispecific antibody, linear antibody and fragments thereof.

14. The method of claim 1, wherein the BAT monoclonal antibody is selected from the group of antibody fragments consisting of: Fab, Fab', $F(ab')_2$, Fv; single-chain antibody molecules and multi-specific antibodies formed from antibody fragments.

15. The method of claim 13, wherein the BAT monoclonal antibody is a humanized antibody and wherein the frame regions of the light chain variable region are derived from the light chain variable region of the human TEL9 antibody.

16. The method of claim 15, wherein said frame regions are selected from the group consisting of: SEQ. ID NO. 5; SEQ. ID NO. 6; SEQ. ID NO. 7 and SEQ. ID NO. 8.

17. The method of claim 13, wherein the BAT monoclonal antibody is a humanized antibody and wherein the frame regions of the heavy chain variable region are derived from the heavy chain variable region of the human hsighv1295 antibody.

18. The method of claim 17, wherein said frame regions are selected from the group consisting of: SEQ. ID NO. 9; SEQ. ID NO. 10; SEQ. ID NO. 11 and SEQ. ID NO. 12.



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19. The method of claim 2, wherein the immunodeficiency disorder relates to lymphocytes selected from the group consisting of: $CD3^+$ cells, $CD4^+$ cells, $CD8^+$ cells, Thy1.2+ cells, NK cells, NK-T cells, B cells, monocytes and macrophages.

20. The method of claim 1, further comprising administering at least one additional therapeutic agent in combination with a therapeutically effective amount of BAT monoclonal antibody, the at least one additional therapeutic agent being selected from the group consisting of: anti-viral agents, antibiotics, cytokines, T-cell activators, hormones, growth factors, cell vaccines, peptide vaccines, DNA vaccines, antibodies and fragments thereof, T-cell stimulatory antibodies, cell-based therapies, stem cells derived from either the bone marrow, umbilical cord blood, peripheral blood, donor leukocyte infusion, .

21. The method of claim 20, wherein the T-cell activator is selected from the group consisting of interleukin-1, interleukin-2, interleukin-4, interleukin-5, interleukin-6, interleukin-7, interleukin-11, interleukin-12, interleukin-13, interleukin-15, interferon-alpha, interferon-gamma, tumor necrosis factors, anti-CD3 antibodies, anti-CD28 antibodies, anti-CTLA4 antibodies, anti-TGF-beta antibodies, anti-4-1BB antibodies, cell-based vaccines peptide vaccines, DNA vaccines, growth factors, phytohemagglutinin, concanavalin-A and phorbol esters.

22. The method of claim 20, wherein said therapeutically effective amount of BAT monoclonal antibody and said at least one therapeutic agent are administered together or sequentially.

23. The method of claim 1, further comprising administering at least one additional anti-cancer agent selected from: anti-metabolic agent, anti-angiogenic agents, cytotoxic agents and anti-tumor therapeutic antibodies and cell based therapies.

24. The method according to claim 1, wherein the subject in need thereof is a human subject.



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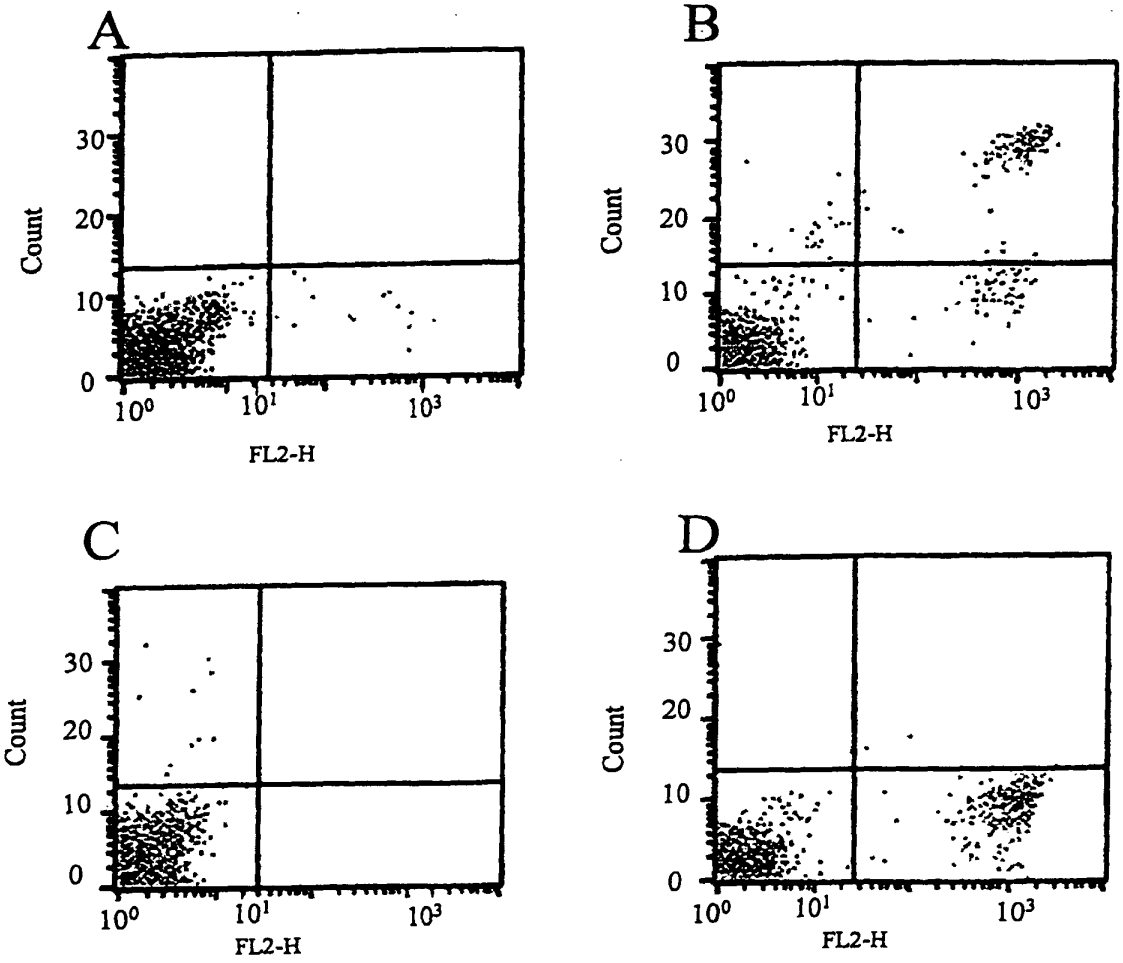



Figure 1

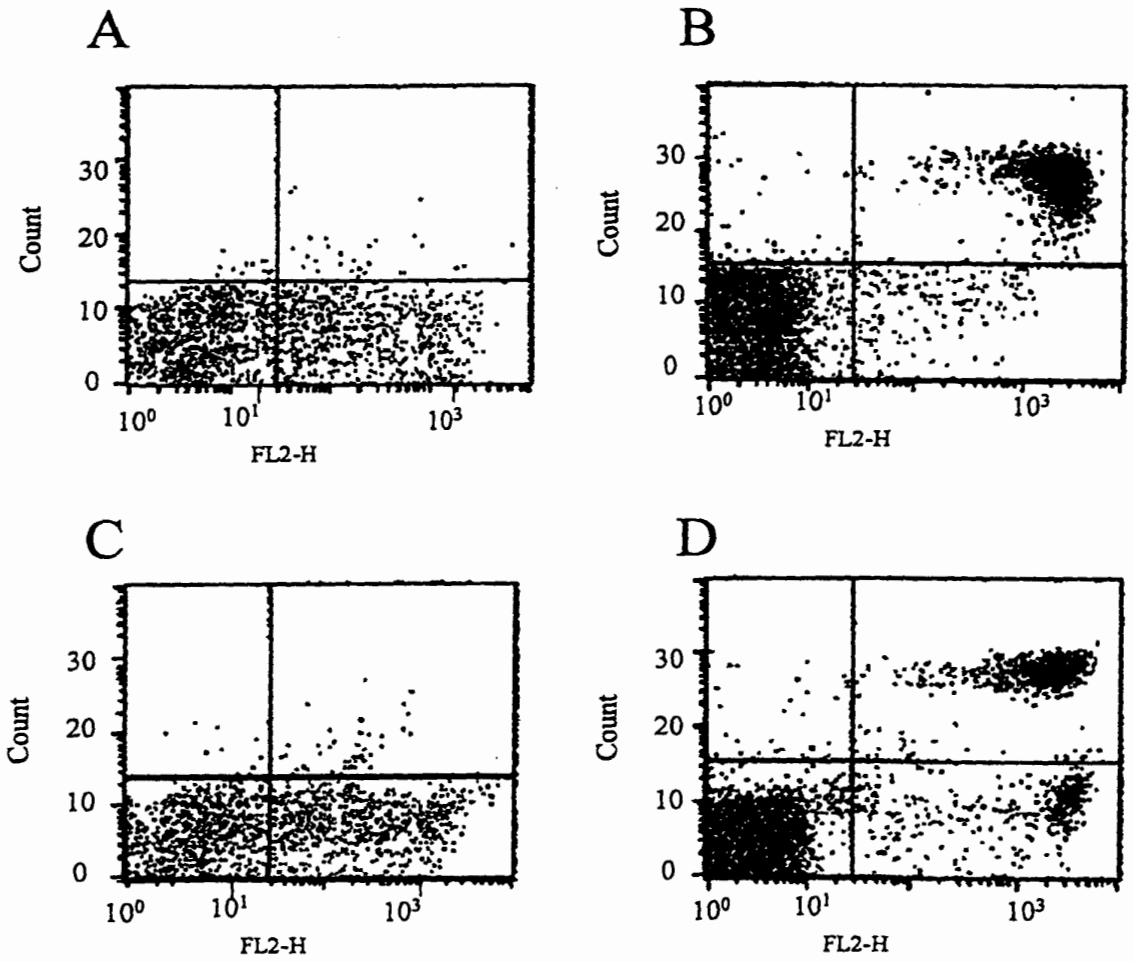



Figure 2

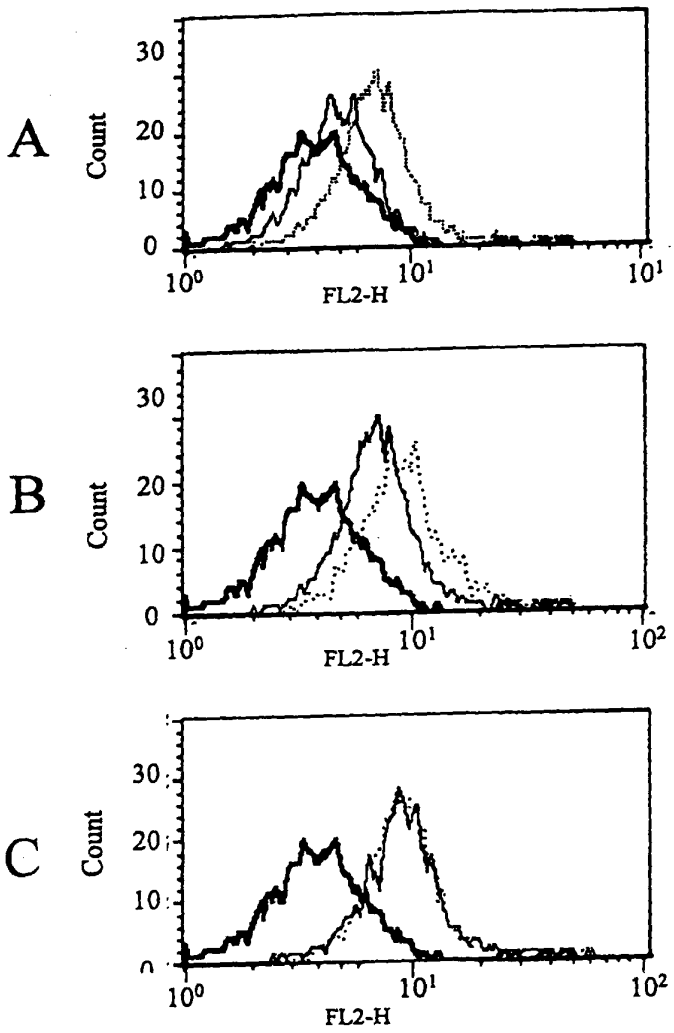



Figure 3

SEQUENCE LISTING

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cagatcaaca acctcaacaa tgaggacacg gctacatatt tctgtgtgag agtcggctac 360

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Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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Lys Trp Met Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala
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Glu Glu Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Asn
85 90 95



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Met Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Arg
35 40 45

Ser Ser Val Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser
50 55 60

Pro Lys Leu Trp Ile Tyr Arg Thr Ser Asn Leu Ala Ser Gly Val Pro
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Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile
85 90 95

Ser Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg
100 105 110



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20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
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Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
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Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60



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Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
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Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
        35                  40                  45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30
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Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
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            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
    50                  55                  60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
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Val Thr Val Ser Ser
        115
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35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
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35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe



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65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
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Val Thr Val Ser Ser
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20 25 30

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35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Asn Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
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Val Thr Val Ser Ser
115



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20 25 30

Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Asn Tyr Gly Met Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu
50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala
65 70 75 80

Glu Glu Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Asn
85 90 95



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1 5 10 15

Val Ile Met Ser Arg Gly Gln Ile Val Leu Thr Gln Ser Pro Ala Ile
20 25 30

Met Ser Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Ser Ala Arg
35 40 45

Ser Ser Val Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Thr Ser
50 55 60

Pro Lys Leu Trp Ile Tyr Arg Thr Ser Asn Leu Ala Ser Gly Val Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile
85 90 95

Ser Arg Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg
100 105 110



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Ser Ser Phe Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
115 120 125

<210> 5
<211> 23
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<220>
<223> Frame region L1, derived from human TEL9 antibody

<400> 5

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1 5 10 15

Asp Arg Val Thr Ile Thr Cys
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<210> 6
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<220>
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<223> Xaa = Phe or Tyr

<220>
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<223> Xaa = Trp or Leu

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<210> 7
<211> 32
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<220>
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<220>
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<222> (15)..(15)
<223> Xaa = Tyr or Phe

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<222> (16)..(16)
<223> Xaa = Cys or Thr

<400> 7

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Xaa Xaa Xaa
1 5 10 15

Leu Thr Ile Asn Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 8
<211> 10
<212> PRT
<213> artificial sequence

<220>
<223> Frame region L4, derived from human TEL9 antibody

<400> 8

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
1 5 10

<210> 9
<211> 30
<212> PRT
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<220>
<223> Frame region H1, derived from human hsighv1295 antibody

<220>
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<223> Xaa = Ile or Val

<220>
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<223> Xaa = Thr or ser

<220>
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<223> Xaa = Thr or Ser

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20 25 30

<210> 10
<211> 14
<212> PRT
<213> artificial sequence

<220>
<223> Frame region H2, derived from human hsighv1295 antibody



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<210> 11
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<220>
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<220>
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<223> Xaa = Val or Ala

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<223> Xaa = Arg or Lys

<400> 11

Arg Phe Xaa Phe Ser Leu Asp Thr Ser Val Xaa Thr Ala Tyr Leu Gln
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Ile Thr Ser Leu Xaa Ala Glu Asp Thr Gly Met Tyr Phe Cys Xaa Xaa
20 25 30

<210> 12
<211> 11
<212> PRT
<213> artificial sequence

<220>



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Dana-Farber v. BMS, IPR2023-00501
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<223> Frame region H4, derived from human hsighv1295 antibody

<400> 12

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 13
<211> 10
<212> PRT
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<220>
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<400> 13

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1 5 10

<210> 14
<211> 7
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<220>
<223> Synthetic peptide derived from murine BAT antibody

<400> 14

Arg Thr Ser Asn Leu Ala Ser
1 5

<210> 15
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide derived from murine BAT antibody

<400> 15

Gln Gln Arg Ser Ser Phe Pro Leu Thr
1 5

<210> 16
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide derived from the CDR of the heavy cahin variable region of murine BAT antibody

<400> 16

Asn Tyr Gly Met Asn
1 5

<210> 17
<211> 17
<212> PRT



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<213> Artificial Sequence

<220>
<223> Synthetic peptide derived from the CDR of the heavy cahin variable region of murine BAT antibody

<400> 17

Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe Lys
1 5 10 15

Gly

<210> 18
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide derived from the CDR of the heavy cahin variable region of murine BAT antibody

<400> 18

Val Gly Tyr Asp Ala Leu Asp Tyr
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<210> 19
<211> 106
<212> PRT
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<220>
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<400> 19

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
65 70 75 80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105



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<210> 20
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
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<400> 20

Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu
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<210> 21
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1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
35 40 45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60



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Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
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<210> 22
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the light chain variable region of humanized BAT

<400> 22

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Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
        35                  40                  45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Asp Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
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<210> 23
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the heavy chain variable region of humanized BAT

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Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Ser Asn Tyr
            20                  25                  30
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Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
    50                  55                  60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
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<210> 24
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the heavy chain variable region of humanized BAT

<400> 24

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1               5                   10                  15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
    50                  55                  60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
                85                  90                  95

Ala Lys Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 25
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the heavy chain variable region of humanized BAT

<400> 25

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 26
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the heavy chain variable region of humanized BAT

<400> 26

Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe



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50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 27
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide corresponding to one alternative of the heavy chain variable region of humanized BAT

<400> 27

Gln Ile Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
65 70 75 80

Leu Gln Ile Thr Ser Leu Asn Ala Glu Asp Thr Gly Met Tyr Phe Cys
85 90 95

Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115



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(74) Agents: **WEBB, Cynthia** et al.; WEBB & ASSOCIATES, P.O. Box 2189, 76121 Rehovot (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: USE OF BAT MONOCLONAL ANTIBODY FOR IMMUNOTHERAPY

(57) Abstract: The present invention relates to immunotherapy and more specifically concerns the use of immunostimulatory BAT monoclonal antibodies for treatment of a variety of immunodeficiency related diseases and disorders and malfunction or incompetence of the immune system.

WO 2006/021955 A3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL05/00909

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **A61K 39/395**( 2006.01);**C07K 16/44**( 2006.01)

USPC: 424/141.1;530/387.3;530/388.15
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/141.1;530/387.3;530/388.15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Sequence search of commercial amino acid databases for SEQ ID NOS: 5-18.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2005/0180969 A1 (HARDY et al.) 18 August 2005 (18.08.2005), see [0015, 0025-0028, 0031, 0061-0062, 0103, 0174, 0177, 0180]. | 1-7 and 11-24 |
| Y | Hardy et al. SEQ ID NOS: 13-18, Application #US 20050180969A1, see sequence alignment. (see also comments supra on form PCT/ISA/237) | 1-7 and 11-24 |
| Y | HUNT et al. Orthotopic Human Lung Carcinoma Xenografts in BALB/c Mice Immunosuppressed with Anti-CD4 Monoclonal Antibodies and Chromic Alchohol Consumption. Cancer. 2000, Vol. 88, pages 468-479, see entire document, especially the abstract. | 8 |
| Y | WELTE et al. Defective Interleukin 2 Production in Patients After bone Marrow Transplantation and In Vitro Restoration of Defective T Lymphocyte Proliferation by Highly Purified Interleukin 2. Blood, August 1984, Vol. 64, No. 2, pages 380-385, see abstract, and Figures 1 and 3. | 9 and 10 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search
03 October 2006 (03.10.2006)

Date of mailing of the international search report
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Commissioner for Patents
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Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Lynn Bristol
Telephone No. 571-272-6883

Form PCT/ISA/210 (second sheet) (April 2005)

Continuation of B. FIELDS SEARCHED Item 3:
Electronic databases searched: PubMed, STN (caplus, bioeng, biotechno, biotechds, esbiobase), DIALOG (155, 159, 10, 203, 35, 5, 467, 73, 434, 34) and WEST.

Search terms: BAT or BAT-1 or BAT1 and monoclonal and immunodeficiency and T cell or lymphocyte



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(19) Europäisches Patentamt
European Patent Office
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(11) EP 0 742 795 B1

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(51) Int Cl.[6]: **C07K 16/28**, C12N 5/20, A61K 39/395, C07K 14/705

(86) International application number:
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(54) **IMMUNO-STIMULATORY MONOCLONAL ANTIBODIES**

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(73) Proprietor: **MOR RESEARCH APPLICATIONS LTD.**
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**Postfach 86 07 67**
**81634 München (DE)**

(56) References cited:
- **CELLULAR IMMUNOLOGY, vol. 118,no. 1, January 1989 NEW YORK, NY, USA, pages 22-29, B. HARDY ET AL. 'A monoclonal antibody to human B lymphoblastoid cells activates human and murine T lymphocytes.' cited in the application**
- **CANCER RESEARCH, vol. 54,no. 22, 15 November 1994 BALTIMORE, MD, USA, pages 5793-5796, B. HARDY ET AL. 'A monoclonal antibody against a human B lymphoblastoid cell line induces tumor regression in mice.'**

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EP 0 742 795 B1

## Description

The present invention is generally in the field of immunotherapy and concerns monoclonal antibodies useful within the framework of such a therapy for a variety of indication, e.g., in the treatment of cancer.

The following is a list of prior art references considered to be pertinent for the subsequent description:

1. Clark, E.A., and Ledbetter, J.A., Amplification of the immune response by agonistic antibodies, *Imunol.*Today, 7:267-270, 1986.

2. Meuer, S.C., Huspey, R.E., Cantrell, D.A., Hodgdon, J.C., Schlomman, S.F., Smith, K.A. and Reinberg, E.L., Triggering of the T3-T1 antigen-receptor complex results in clonal T cell proliferation through an interleukin-2 dependent autocrine pathway, *Proc. Natl. Acad. Sci.* (USA), 31:1509-1513, 1984.

3. Van Wauve, J.P., De Mey, J.R., and Gooser, J.G., OKT3: a monoclonal anti-human T lymphocyte antibody and potent mitogenic properties, *J. Immunol.* 124:2708-2713, 1980.

4. Jung, G., Martin, D.E., and Muller-Eberhard, J.H., Induction of cytotoxicity in human peripheral blood mononuclear cells by monoclonal antibody OKT3, *J. Immunol.*, 139:639-644, 1987.

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The acknowledgement herein of any of the above references is to allow the reader to gain appreciation of the prior art. The acknowledgement should, however, not be construed as an indication that these references are in any way relevant to the issue of patentability of the invention as defined in the appended claims.

Acknowledgement of the above references will be made by indicating the number from the above list.

Cancer in its different forms is a major cause of death in humans. One-third of all individuals in the United State develop cancer and 20% die from cancer (494,000 in 1988).



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The most widely used therapeutic treatments of cancer are surgery, radiation and chemotherapy. In recent years, another therapeutic treatment based on use of biological response modifiers (BRM) has also been proposed. The BRMs used include mainly cytokines (e.g., Interleukin-2 (IL-2) and Interferon-α (INF-α)), activated mononuclear cells (e.g., lymphokine activated killer cells (LAK)) and antibodies. The BRMs act both directly on tumors and indirectly by enhancing non-specific or specific immunological and cytotoxic mechanisms.

To date, no substantial clinical success has been obtained using BRMs, mainly due to their toxicity and side effects. Active immunization against tumor cancer has also been proposed but found ineffective. Furthermore, several monoclonal antibodies (mAbs) were evaluated for use in diagnosis and therapy of cancer but no mAb has yet proven to be effective within a standard therapeutic procedure in cancer patients.

Various mAbs capable of binding to determinants on the surface of T cells have been found to induce proliferation, activation or differentiation of these cells[1]. Binding of mAbs directed against the CD3/TCR complex on T cells[2-4], binding of mAbs directed at the CD2[5] receptor antigen on T cells as well as binding of both above kinds of antibodies to T cells, have been demonstrated to bring about T cell proliferation, IL-2 receptor expression and IL-2 production in T cells resulting in the enhancement of the cytolytic process in these cells. The anti CD3 mAb was shown to initiate an anti tumor activity *in vivo* in an animal model[6-7].

Various other mAbs directed against T-lymphocyte antigens have also been reported which, after binding to the cells, cause their activation such as mAbs directed against CD5[5], against CD69[9] and against CD28[10,11]. Anti-CD28 mAbs were reported to have decreased the rate of growth of a murine melanoma although they were not successful in completely eliminating the tumors in the mice[12].

A mAb directed against a human B lymphoblastoid cell line termed "*Daudi*" was shown to stimulate murine lymphocytes and human peripheral T cells[13].

The invention concerns a monoclonal antibody or an antigen binding fragment thereof wherein the monoclonal antibody is secreted by the hybridoma cell line deposited at the Collection Nationale de Culture de Microorganismes (CNCM) under Accession no. 1-1397 or binds to an antigen to which the above antibody binds. The invention further concerns an immortalized cell line secreting the antibody of the invention, pharmaceutical compositions containing the antibody of the invention and a proteinaceous substance to which the antibody of the invention specifically binds.)

The monoclonal antibody of the present invention in an immuno-stimulatory antibody, which binds to B lymphoblastoid cells and induces proliferation and activation of peripheral blood lymphocytes, the monoclonal antibody being characterized in that when injected into a tumor-bearing animal, it elicits an anti-tumor effect.

An anti-tumor effect is a biological effect which can be manifested by a decrease in tumor size, a decrease in the number of metastases, an increase in life expectancy, or amelioration of various physiological symptoms associated with the cancerous condition. An anti-tumor effect can also be manifested by the ability of the mAb in prevention of the occurrence of tumor in the first place. Given its properties, the mAb of the invention can be used for the preperation of a pharmaceutical composition for both the treatment of acute cancer as well as in cancer prophylaxis.

The monoclonal antibodies of the invention can be obtained by first immunizing an animal with an immunogen, being B lymphoblastoid cells, lysed B lymphoblastoid cells or membrane preparations thereof. Following immunization and the development of an immune reaction in the immunized animals, B-lymphocytes are withdrawn from the animal, lines are grown and selected for such which secrete antibodies which bind to the immunogen. The selected mAbs are then subjected to a further selection for such capable of inducing proliferation and activation of peripheral blood lymphocytes.

In order to obtain the mAbs of the invention, the antibodies selected as above, are then subjected to a still further selection for such capable of eliciting an anti-tumor effect. In order to select such antibodies, typically an animal model of cancer can be used. At times the effect may also be tested in various *in vivo* models. Such a model may, for example, be any laboratory animal in which cancer has been induced. Specifically relevant, particularly for choosing a mouse for studying the therapeutic use in humans, are models allowed to develop human-originated tumors. Examples of animal models of the latter type are immuno compromised mice, e.g. a SCID mouse or a nude mouse, which have been injected or implanted with tumor cells or tissue obtained from human cancer patients. In such selection, the ability of the mAb to reduce the tumor size, increase survival time, etc., is determined as compared to control (a similar tumor-bearing animal not treated with the mAb or treated with a non relevant mAb).

The selection may also involve testing in an appropriate model of the mAb's ability in preventing the occurrence of cancer. For example, animals having a genetic predisposition for developing cancer may be injected with the mAb and then the tumor incidence and the survival in the group treated with the mAb can be compared to a control group, otherwise treated and maintained in the same manner. Rather than using animals having a genetic predisposition, the ability of the mAb to prevent cancer can be tested in various other animals treated with the mAb prior to experimental administration of malignant cells in the animal.

The mAb of the invention is formulated in a pharmaceutical composition in an amount effective to achieve such an anti-tumor effect. The term *"effective amount"* should be understood as meaning an amount of a mAb required to achieve a therapeutic effect. The effective amount required to achieve the therapeutic result may depend on a number



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of factors including, for example, the tumor type and the severity of the patient's condition (i.e. the cancerous state), and whether the mAb is for co-administration together with another agent which acts together with the mAb in an additive or synergistic manner (regarding such co-administration, see below).

The obtaining of an immortalized cell line secreting mAbs of the invention can be performed by a number of means known *per se*, such as by fusion with an immortalized cell line to yield a hybridoma; by EBV transformation; by genetically engineering a cell line, e.g. a CHO cell line, which can be achieved by a variety of means known *per se*; etc. In general, the manner of obtaining immortalized monoclonal antibody secreting cell lines is today a routine procedure known to the artisan and the description thereof goes beyong the present writing.

Typically, where the mAb is intended to be formulated in a pharmaceutical composition, for treatment in a human, the immunogen will be of a human origin. However, at times there is an inter-species cross reactivity and it is also possible, occasionally, to use in humans mAbs obtained following immunization with a non-human derived immunogen, as the e.g., primate derived.

The antibodies of the invention should be understood as encompassing monoclonal antibodies, which may be IgG or IgM antibodies, may be Fab fragments of such antibodies, $F(ab')_2$ fragments, single chain antibodies, and the like. In addition, antibodies derived from a non-human origin, e.g. murine, may be *"humanize"* by various genetic engineering means (a *"humanized"* antibody is an antibody in which major portions have been replaced with portions of a human origin).

Antibodies in accordance with the invention, while being useful for a variety of therapeutic indications, are used, in accordance with a preferred embodiment of the invention, for the preparation of a pharmaceutical composition for the treatment of cancer. It has been found that a monoclonal antibody in accordance with the invention is active in reducing tumorigenicity of a variety of tumors.

The hybridoma cell line in accordance with the present invention was deposited at the Collection Nationale de Cultures de Microorganismes (CNCM), Institute pasteur, 25, Rue du Docteur Roux, 75724, Paris, Cedex 15, under Deposit Accession No. 1-1397, on January 28, 1994. The cells of this line are referred to herein at times as *"BAT-1 cells"*, and the respective monoclonal antibody is referred to herein at times as "*BAT-1 mAb*".

The invention is directed to the use of a monoclonal antibody having the characteristics of the BAT-1 mAb, specifically the BAT-1 mAb itself.

The BAT-1 monoclonal antibody was selected on the basis of its binding to cells of the Daudi human B lymphoblastoid line. The BAT-1 mAb was found to bind to a proteinaceous substance (termed below as *"BAT-1 binding protein"*) having an apparent molecular weight of 48-50K Daltons, as determined by SDS-PAGE.

The BAT-1 binding protein forms another aspect of the present invention. The BAT-1 binding protein may be isolated, by various means known *per se* by using the mAbs of the invention. The BAT-1 binding protein may then be used for immunization of animals from which mAbs of the invention may then be derived.

The present invention also provides a pharmaceutical composition comprising, as an active ingredient, an effective amount of an mAb of the invention, and a physiologically acceptable carrier.

A further aspect of the invention is the use of the mAb of the invention for the preparation of a pharmaceutical composition for the treatment of a disease or disorder, particularly cancer, whereby the mAb is for administration to a subject in need in an effective amount. The administration of the mAb is typically by means of paranteral administration, e.g., intravenously (i.v.) intraperitoneally (i.p.) of intramuscularly (i.m.). The carrier for administration may be any one of such known *per se*, e.g., a saline solution or any other suitable physiological solution.

The mAb of the invention was found, as already noted above, to be active in reducing tumorigenicity of a variety of tumors. The efficacy of the mAb of the invention in reducing tumorigenicity is correlated with its ability to induce cytotoxic activity of lymphocytes. In order to boost up this activity, it is at times advantageous to formulate the mAb of the invention together with other agents which can act in an additive or synergistic manner with the mAb. Examples include various cytokines such as IL-1 (Interleuken-1), IL-2, IL-6 and IFN-$\alpha$ (Interferon-$\alpha$).

The mAb of the invention may be useful in the therapy of a variety of diseases other than cancer where activation or other effects of the mAb on the immune system's cytotoxic activity may have a therapeutic effect, such as, for example, in early stages of HIV infection (the causative virus of acquired immuno deficiency - AIDS), in various autoimmune disorders, or in some cases of genetic or acquired immune deficiencies.

In the treatment of cancer the antibody may be formulated in a pharmaceutical composition for administration either following detection of primary or secondary tumors in the subject or, in preventive therapies of subject having a high risk of developing cancers, such as an individual exposed to radiation or such having a genetic disposition. Similarly, in AIDS patients, the mAb may be formulated in a pharmaceutical composition for administration, to infected individuals, which have not yet developed any symptoms of the disease, or in individuals at early stages of the HIV infection process.

In the following, the invention will be illustrated by various examples describing experiments demonstrating the anti-cancer therapeutic activity. It should, however, be undestrood that this is meant for illustration purposes only and is not to be considered limiting.



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**Fig. 1** shows flow cytometry analysis of binding of BAT monoclonal antibodies (mAbs) to human purified T-lymphocytes. Binding of the BAT antibodies was assessed by a second antibody carrying a fluorescent marker, FITC-goat anti-mouse antibody.

**Fig. 1a** - background reading without BAT antibody;
**Fig. 1b** - anti-CD3 antibody;
**Fig. 1c** - BAT-1;
**Fig. 1d** - BAT-5;
**Fig. 1e** - BAT-2;
**Fig. 1f** - BAT-4.
**Fig. 2** shows a flow cytometry analysis of human peripheral blood monocytes (PBM) (left plate) and of Jurkat T cells (right plate) double labeled with primary antibody being either a BAT mAb or an anti CD3 mAb and a second FITC conjugated anti-mouse IgG antibody,
**Fig. 2A** - ungated cells;
**Fig. 2A(a)** - PBM cells treated with BAT mAb;
**Fig. 2A(b)** - PBM cells treated with anti-CD3 mAb;
**Fig. 2A(c)** - Jurkat T cells treated with BAT mAb;
**Fig. 2A(d)** - Jurkat T cells treated with anti-CD3;
**Fig. 2B** - gated cells;
**Fig. 2B(a)** - PBM cells gated to small (R1) and large cells (R2);
**Fig. 2B(b)** - (R1) cells treated with BAT mAb;
**Fig. 2B(c)** - (R1) cells treated with anti-CD3;
**Fig. 2B(d)** - (R2) cells treated with BAT mAb;
**Fig. 2B(e)** - (R2) cells treated with anti-CD3.
**Fig. 3** shows a flow cytometry analysis of surface expression of BAT binding protein and CD3 on human PBM double labeled with FITC-conjugated BAT mAb and PE-conjugated anti-CD3.
**Fig. 3A** - ungated cells;
**Fig. 3A(a)** - Becton-Dickinson simultest control, used as a negative control;
**Fig. 3A(b)** - PE-anti-CD3 alone;
**Fig. 3A(c)** - FITC-BAT mAb alone;
**Fig. 3A(d)** - Double labelling with both FITC-BAT mAb and PE-anti-CD3 antibody;
**Fig. 3B -** Gated cells;
**Fig. 3B(a)** - PBM cells gated to small (R1) and large cells (R2);
**Fig. 3B(b)** - (R1) cells double labeled with FITC-BAT mAb and PE-anti CD3;
**Fig. 3B(c)** - R2) cells double labeled with FITC-BAT mAb and PE-anti CD3.
**Fig. 4** shows Western Blot analysis of the binding of BAT-1 antibodies to different lysates of Daudi cells.
**Fig. 4(1)** - lysates from Daudi cells (untreated);
**Fig. 4(2)** - lysates treated with neuraminidase (0.2 u/ml);
**Fig. 4(3)** - lysates treated with neuraminidase (0.4 u/ml);
**Fig. 4(4)** - lysates treated with Endo Hf (100u/μg).
**Fig. 5** is a graphical representation of results of [$^3$H]Thymidine incorporation in cells cultured for six days in the presence of increasing concentrations of a panel of BAT Mabs: BAT-1 (- ▲ -), BAT-2 (- X -), BAT-3 (- ● -), BAT-5 (- ★ -), BAT-6 (- ♦ -), BAT-7 (- ■ -).
Fig. 6 is a graphical representation of an experiment in which the induction of cytotoxic activity was tested in PBM cultured for various time intervals with 2.5 μg/ml BAT mAbs. HT-29 (left) or RC 29 (right) cells were used as target cells. Effector to target ratio was 20:1. Control (- 0 -, BAT-1 (- ● -), BAT-2 (- X -) BAT-3 (- ▲ -).
**Fig. 7** shows lungs from C57BL mice inoculated with B-16 melanoma cells: Upper row shows lungs of mice inoculated with cells only, 24 days after inoculation; lower row shows lungs of mice inoculated with B-16 cells as above followed 14 days later by I.V. injection of 10 μg f BAT-1 mAbs, 24 days after inoculation.
**Fig. 8** is a graphical representation of a summary of experiments of the kind shown in Fig. 7, showing the number of metastasis in lungs of mice which were inoculated with tumor cells being either B-16 melanoma cells, 3LL Lewis lung carcinoma cells or MCA 105 fibrosarcoma cells, one month after inoculation. The results summarize 3-4 experiments carried out with each kind of tumor. Mice untreated (-) or treated (+) with BAT-1 (10 μg/mouse) 2 weeks after tumor administration. Metastasis (●); no metastasis (O).
**Fig. 9** shows lungs from mice inoculated with 3LL Lewis lung carcinoma cells. Similarly as in Fig. 7, the upper row shows lung inoculated with tumor cells only and the lower row shows lungs of mice inoculated I.V, 14 days later with 10 μg of BAT-1 mAbs.
**Fig. 10** shows a similar experiment as that shown in Fig. 9 where the tumor cells are MCA 105 fibroblastoma cells.



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Production of monoclonal antibodies

BALB/c mice were immunized with membrane preparation of Daudi cells. Membranes from Daudi cells were prepared by the glycerol load-hypotonic shock method (Jett, M., Seed, T.M., and Jamieson. G.A., *J. Biol. Chem.*, 252: 2134, (1977)). 50-80x$10^6$ cells suspended in PBS and incubated at 37°C were gradually loaded with 30% glycerol. Afer 5 mins. incubation on ice, they were centrifuged and resuspended in cold Tris lysate buffer (containing 10 mM Tris-HCl, 1 mM $MgCl_2$, 1 mM $CaCl_2$, pH 7.4) mixed for 5 mins. at 4°C and centrifuged at 700 g. Supermatants were removed and centrifuged at 3300 g (10 mins. 4°C). The pellet was washed again and the two supernatants containing membrane fraction were pooled, 260 µl of membrane preparation (3 mg/ml) were emulsified with 260 µl of complete Freund adjuvant and injected i.p. into BALB/c mice. Three weeks later the spleens of mice were removed. Spicnocytes were fused with the mycloma cell line NS-0 at a ratio of 10:1. Fusion was performed using polyethylene glycol and the hybridomas were grown in selective media according to Köhler and Milstein (Köhler, G., and Milstein, C., *Nature*, (London) 256:495, (1975)).

A cell bound enzyme linked immunosorbent assay (ELISA) was used to screen supernatants from growing hybridomas (Glassy, M.C. and Surh, C.D., *J. Immunal. Method*, 81:115 (1985)) which bind to Daudi cells. Positive hybridoma supernatants were then further selected by their ability to induce proliferation of human PBM using [$^3$H]Thymidine uptake assay. Positive clones were subcloned by limited dilution, repeatedly tested, expanded and grown in culture.

mAbs were purified from culture medium by 50% ammonium sulfate precipitation, followed by extensive dialysis against PBS. Further purification was performed by affinity chromatography on Sepharose (a trademark of Pharmacia, Sweden) bound anti-mouse antibody columns.

**Culture medium**

All cells were suspended in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS), Na-pyruvate (1.1 mg/ml), L-glutamine (0.3 mg/ml) and antibiotics (Penicillin 200 u/ml and streptomycin 10 µg/ml) and incubated in 5% $CO_2$ humid incubator.

IL-2 units used are Cetus units (1 Cetus unit equals 3 International units).

**Cell preparations**

Human peripheral blood mononuclear cells (PBM) were obtained from healthy adult donors by ficoll-hypaque density centrifugation (Histopaque, a trademark of Sigma, St. Louis, Missouri, U.S.A.). PBM were depleted of monocytes by Sephadex (a trademark of Pharmacia, Sweden) G10 columns. T cells were separated by SRBC rosetting method. Depletion of CD3 positive and Leu19 positive cells was performed by immunomagnetic technique. Cultures of PBM incubated for 5-6 days with BAT mAbs or control were washed three times with PBS. Unconjugated antibodies to either CD3 or Leu19 (CD56) were added to the cells in complete RPMI medium and incubated for one hour at 4°C. Magnetic beads coated with antimouse antibody were added for 30 mins. The cells attached to the beads were removed with the magnet and the unattached cells were analyzed for cytotoxic activity and stained by flow cytometry.

**Cytotoxicity assay**

Cytotoxicity assays were done as follows: 2-4x$10^6$ target cells were mixed with 200 µCi of $^{51}$Cr-chromate for 1 hour in serum free medium. They were washed three times with complete medium and finally resuspended in RPMI-10% FCS and plated at $10^4$ cells per well. Effector cells were cultured, lymphocytes prepared from normal peripheral blood incubated for various time periods with the different mAbs, isotypic control IgG or with IL-2. Prior to the assay the cells were washed three times in RPMI medium, stained for viability cells using 1% Trypan blue, mixed with target cells at various effector-target ratios in round bottom microtiter plates and incubated for 3 hours 15 37°C in a 5% $CO_2$. The culture supernatants were harvested and counted in a β-scintillation counter. Maximum isotope release (MR) is produced by incubation of the target cells with Triton (a trademark of Sigma, St. Louis, Missouri, U.S.A.) x-100. Spontaneous release (SR) is measured by incubation of the targets with medium alone. Percentage of cell lysis is calculated by (ER-SR/MR-SR)x100, where ER is the experimental effector release.

**Induction of cytotoxity in human lymphocyte subpopulations**

PBM cells (4.$10^6$/ml) were cultured for 6 days in the presence of BAT mAbs. Thereafter the cells were washed three times and were depleted of CD3 and Leu19 cells by magnetic beads coated with anti-mouse f(ab')$^2$ and tested for cytotoxicity against K562 and Daudi cells.



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**Flow cytometry**

Cell surface antigens were detected by flow cytometry using a FACS 440 (Becton-Dickinson), For each analysis $10^6$ cells were used. The cells were stained by sequential incubation with an optimal concentration of murine mAb to human CD3, IL-2 receptor, or the mAb BAT 1-9 that were produced. FITC-conjugated goat anti-mouse $F(ab')_2$ was used as a second antibody in this indirect straining. Each incubation was carried in PBS pH 7.4 containing 1% BSA and 0.5% Na-azide for 30 mins. at 4°C and was followed by three washings with the same buffers, $10^4$ stained cells were analyzed.

**Detection of BAT mAb binding determinant(s)**

Detection of BAT mAb binding determinant(s) on Daudi B lymphoblastoid cell lysates, was done using Western Blot technique. Brietly, $50x10^6$ cells/ml suspended in PBS was gradually loaded with 30% glycerol and membranes were separated by sequential centrifugations.

Samples of the membrane preparations were separated by SDS-PAGE (12%) and then transferred to nitrocellulose blots which were immersed in 1% low fat milk in PBS. Detection of the BAT mAb binding protein in the nitrocellulose blots was done by incubating the blots with BAT mAb for 2 hours at room temperature, followed by 30 mins. incubation with peroxidase-horscradish-conjugated antibody 70 anti-mouse IgG $(Fab')_2$. The cells were then rinsed and bands were detected with 0-dianizidine substrate.

**Mouse tumor models**

Three mouse tumor models were used: B16 melanoma, Lewis lung carcinoma (3LL) and methylcholanthrene induced fibrosarcoma (MCA 105). $50\text{-}200x10^6$ cells were injected i.v. to C57BL mice (8 weeks of age). Two weeks later, BAT-1 was injected (i.v.), 1-10 µg/mouse and 10 days later mice were sacrificed and established lung metastases were counted.

**Example 1**

a. Binding characteristics

Nine manoclonal antibodies (mAbs) designated BAT 1-9. obtained by immunization with B lymphoblastoid cells, were selected first for binding to Daudi cells and then for inducing human peripheral blood lymphocytes proliferation. The isotypes of BAT mAbs were determined by both ELISA and Ochterlony, assays. BAT 1,2,3,6,7 and 9 were found to be of IgG1 class whereas BAT 4 and 5 were of the IgM class. BAT 8 was IgG2a.

Binding of the above Mabs to purified peripheral human T cells was analyzed by FACS analysis using indirect immunofluorescence staining. Fig. 1 demonstrates FACS analysis of such an experiment. As can be seen, BAT mAbs bind to peripheral blood CD3+ T cells. The extent of binding varied from BAT-2 44% BAT-5 38%, BAT-1 32% to a somewhat weaker binding of BAT-4 (13%). Purified peripheral blood B lymphocytes from the same blood donors, did not bind these mAbs (data not shown).

b. Binding of BAT-1 mAb to human lymphocyte subpopulations

As seen in Fig. 2, further FACS analysis showed that BAT-1 binds CD3+ human PBM as well as cells of the Jurkat T-cell line. The finding that BAT-1 binds to CD3+ PBM cells was even further corroborated using FACS analysis of double labeled cells (Fig. 3).

As seen in Table 1 below, BAT-1, in addition to its binding to CD3 bearing cells, binds also to Leu 19/NK cells.



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## Table 1

**Binding of BAT-1 mAb to human lymphoid subpopulations**

| | Positive cells (%) | |
|---|---|---|
| | Subpopulation of cells enriched for: | |
| mAb | CD3+ | Leu 19+ |
| CD3 | 66.4 (100%) | - |
| Leu 19 | - | 59.5 (100%) |
| BAT-1 | 19.8 (30%) | 42.2 (70%) |

c. Binding of BAT mAbs to various cell types

Binding of BAT mAbs to various cell types was determined. As can be seen in Table 2 below, BAT mAbs bind to K562, an erythroleukemia cell line, and MCF7, a human mammary carcinoma cell line, in addition to their binding to PBL, Daudi and the Jurkat T cell line. The extent of binding varied among the BAT mAbs and cell types tested. mAbs 2-9 bound to the mouse renal carcinoma (MR28) only with very low affinity. Only BAT-8 bound to MEL (murine erythroleukemia) cells, also at a very low affinity.



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## Table 2

### Binding of BAT mAbs to various cell types

| | BAT mAb | | | | | |
|---|---|---|---|---|---|---|
| **Cells** | 1 | 2 | 4 | 5 | 8 | 9 |
| **Human** | | | | | | |
| Daudi | +++ | ++ | ++ | +++ | ± | +++ |
| Jurkat | + | ± | +++ | +++ | – | +++ |
| PBL | +++ | ± | + | + | ± | ± |
| K562 | +++ | + | + | +++ | ± | +++ |
| MCF7 | ± | ++ | +++ | +++ | + | +++ |
| **Mouse** | | | | | | |
| MR28 | – | ± | + | + | ± | ± |
| MEL | – | – | – | – | ± | – |

Binding was assayed by ELISA and is expressed as:
+ (0.1–0.2 OD)
++ (0.2–0.3 OD)
+++ (over 0.3 OD)

**Example 2**

**Analysis of BAT mAb binding site and purification of the BAT-1 binding protein**

In order to determine the molecular weight of the membrane protein that interacts with the BAT-1 mAbs, a membrane preparation of Daudi cells was solubilized and the protein was separated by SDS-PAGE. Nitrocellulose transferred blots were incubated with BAT-1 mAb and bands were detected by further incubation with horseradish-peroxidase-conjugated antibody to anti-mouse IgG $(fab')_2$ and detection using 0-dianizidine substrate. The molecular size of the BAT-1 binding protein was found to be about 48-50 KDa (Fig. 4).

The BAT mAb binding protein was purified using BAT mAb conjugated to Sepharose (a trademark of Pharmacia, Sweden). This binding protein can also be prepared by cloning using molecular biology techniques. Administration of BAT-1 *in vivo* to mice in the induction of BAT antibodies.

**Example 3**

**Functional characteristic of BAT mAbs**

a. BAT mAbs induced thymidine incorporation

Human peripheral blood cells were cultured for 6 days in the presence of increasing concentrations of a panel of



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BAT mAbs and pulsed with [$^3$H]Thymidine 20 hours prior to harvesting.

As seen in Fig. 5, a gradual increase in concentrations of BAT mAbs resulted in a modest but significant increase in [$^3$H]Thymidine incorporation in the PMB cells. However, a high dose of antibody caused a decrease in uptake by the cells. In control experiments, isotype matched antibodies did not increase the [$^3$H]Thymidine in PBL cells indicating that the agonistic effect of the BAT mAbs was dependent on their binding specific properties. For example, mAb of the IgG1 isotype, that was raised in our laboratory against ovarian carcinoma cells, caused no increase in [$^3$H]Thymidine uptake in contrast to BAT 1,2,3,6,7 and 9 mAbs which also belong to the IgG1 class.

b. BAT mAbs induce cytotoxicity in human PBM

Cultures of human peripheral blood mononuclear cells incubated with BAT mAbs for various time periods, were tested for their ability to lyse tumor cell lines.

As seen in Table 3 below, human PBM cells incubated for one week with a panel of BAT mAbs were cytotoxic against K562, human crythroleukemia (NK sensitive) and RC-29, renal carcinoma cell line (NK resistant) cells.

The kinetics of the increase in cytotoxic activity of human PBM that were stimulated with BAT mAbs was investigated. As seen in Fig. 6, maximal cytotoxicity toward human colon carcinoma (HT-29) and renal cell carcinoma (RC-29) was attained after 7 day incubation of human PBM with BAT mAbs.

**Table 3**

**BAT mAbs induce cytotoxicity in human PBM**

| | Specific $^{51}$Cr release (%) | |
|---|---|---|
| **mAb** | **K562** | **RC-29** |
| Nonc | 11.0* | 9.1 |
| BAT-1 | 25.1 | 45.4 |
| 2 | 29.0 | 23.2 |
| 3 | 26.3 | 32.3 |
| 4 | 30.6 | 40.7 |
| 5 | 32.3 | 34.3 |
| 6 | 15.2 | 13.8 |
| 7 | 17.8 | 16.7 |
| 8 | 17.8 | 19.2 |
| IL2 1000 u/ml | 57.6 | 36.9 |

* Percent lysis of target cells using effector: target ratio of 5:1

c. Characterization of lumphocyte subpopulation involved in BAT-induced cytotoxicity

In order to assess whether the increase in cytotoxic activity of human PBM induced by BAT mAbs, is due to activation of NK cells, T cells or both, NK and T cells were purified and their cytotoxicity induced by BAT was determined. For purification of the NK and T cells Leu19 and anti CD3 monoclonal antibodies were incubated with the human PBM cells, followed by incubation with anti-mouse IgG coated magnetic beads. This led to depletion of the subpopulations of cells which bind to the corresponding antibody. As can be seen in Table 4 below, the number of lytic units increased



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in both the CD3 depleted and Leu19 depleted cell cultures. BAT 6 and 8 were used in these experiments and the targets were human erythroleukemia (K562) and human lymphoma (Daudi).

## Table 4

### BAT mAbs induce cytotoxicity in human lymphocyte subpopulations

| | Lytic Units | | | |
|---|---|---|---|---|
| | Target cells: | | | |
| | K562 | | Daudi | |
| | effector cells depleted of: | | | |
| | CD3 | Leu 19 | CD3 | Leu 19 |
| Control | 8 | 4 | 10 | 3.8 |
| BAT 6 | 25 | 10 | 20 | 13 |
| BAT 8 | 28 | 12.5 | 26 | 20 |

**Example 4**

**Synergism between BAT mAb and IL-2 in the induction of cytotoxicity**

Induction of cytotoxicity in human PBM was studied upon incubation of the PBM cells with BAT mAb in combination with IL-2. IL-2 at suboptimal concentrations (1U/ml) was added together with increasing concentrations of BAT-2 mAb. Cytotoxicity was tested after one week in culture against K562 and HT29 tumor cell lines. As shown in Table 5 below, low concentration of BAT-2 synergized with IL-2 in the induction of cytotoxicity of the PBM cells against both kinds of target cells.

INF-$\alpha$ was previously shown to enhance the expression of MHC-I class antigens.Therefore, administration of INF-$\alpha$ is likely to potentiate the anti-tumor effect of BAT which is mediated by cytotoxic cells directed against various tumor cells (Bearing MHC class I antigens).



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## Table 5

**Synergistic effect of BAT-2 mAb and IL2 in the induction of cytotoxicity in human PBL**

| | Specific $^{51}Cr$ release (%) | | | |
|---|---|---|---|---|
| | Target cells | | | |
| BAT | HT29 | | K562 | |
| (μg/ml) | IL-2 (1 U/ml) | | | |
| | - | + | - | + |
| 0 | 5.8±0.1 | 7.5±0.3 | 3.7±0.1 | 6.9±0.4 |
| 2 | 14.8±1.3 | 37.6±2.0 | 12.1±0.4 | 29.6±1.6 |
| 4 | 16.7±0.6 | 27.3±1.0 | 13.3±0.6 | 18.5±1.2 |
| 8 | 22.0±1.0 | 15.1±0.6 | 19.9±0.7 | 12.5±0.4 |

**Example 5**

**Immune stimulatory effects of BAT-1 mice:**

a. *In vitro* studies

The mAb BAT-1 demonstrates stimulatory properties in murine splenocytes similar to those seen in human PBL. They include:

(i) Increased splenocyte proliferation *in vitro* as measured by $^{3}H$Thymidine incorporation (Table 6);
(ii) Synergistic stimulatory effect by incubation of splenocytes with a combination of BAT-1 and IL-2 (Table 6);



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Table 6

| | cpm [$^3$H]Thmidine x $10^3$ | | |
|---|---|---|---|
| **BAT-1** | **IL2** | | |
| **(μg/ml)** | **-** | **1 U/ml** | **10 u/ml** |
| - | 1.5±0.07 | 16.0±0.9 | 67.5± 1.6 |
| 10 | 11.0±0.4 | 32.1±1.5 | 241.6±17.1 |
| 1 | 12.9±0.8 | 35.9±3.3 | 247.8± 1.9 |
| 0.1 | 18.1±0.9 | 51.0±7.3 | 255.1±18.0 |
| 0.001 | 10.5±0.1 | 34.1±0.5 | 215.1±20.8 |
| 0.0001 | 2.6±0.1 | 13.2±0.9 | 73.3± 5.6 |

C57BL murine splenocytes incubated for 5 days *in vitro* with various concentrations of BAT-1 and in combination with interleukin-2 (lu and 10 u per ml)

(iii) Increased cytotoxicity in murine splenocytes cultures in the presence of BAT-1 and further increase in cytotoxicity upon incubation in the presence of IL-2 (Table 7).



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**Table 7**

| | Specific $^{51}Cr$ release (%)[a] | | |
|---|---|---|---|
| **BAT-1** | **Interleukin-2** | | |
| **(ng/ml)** | **-** | **1 u/ml** | **10 u/ml** |
| - | 7.4 | 10.0 | 31.1 |
| 100 | 24.9 | 31.3 | 52.4 |
| 10 | 17.4 | 26.7 | 52.8 |
| 1 | 12.3 | 23.9 | 46.8 |
| 0.1 | 12.2 | 21.7 | 45.5 |

Induction of cytotoxicity in C57BL splenocytes cultures for 5 days *in vitro* in the presence of various BAT-1 concentrations and in combinations with low does IL-2.

[a] B16 melanoma cells were used as a target. Effector to target cell ratio was 50:1

Murine tumor target cells that were susceptible to the killing effect by BAT-1 activated splenocytes included: B16 melanoma, Lewis lung carcinoma (3LL), fibrosarcoma (MCA 105), renal cell carcinoma (MR 28) and lymphoma (YAC) (Table 8).



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## Table 8

### BAT-1 induced cytotoxicity in splenocytes against mouse tumor cells

(In *in vitro* study)

| Mouse strain | Tumor target | Specific $^{51}Cr$ release %[a] BAT-1 | |
|---|---|---|---|
| | cells | - | + |
| C57BL | B16 melanoma | 5.4 | 13.6 |
| | Lewis lung carcinoma (3LL) | 11.2 | 24.0 |
| | Fibrosarcoma (MCA 105) | 27.0 | 45.0 |
| BALB/C | Lymphoma (YAC) | 8 | 12.2 |
| | Renal cell carcinoma (MR28) | 0.1 | 5.2 |

[a] Splenocytes were cultured, *in vitro*, for 5 days, in the absence of BAT-1 mAb (1 μg/ml).

Cytotoxicity was determined at an effector/target ratio of 60:1.

b. *In vivo* studies

As seen in Table 9 below, BAT-1 manifested immune-stimulatory effects upon administration *in vivo*. They included:

(i) Stimulation of [$^3$H]Thymidine incorporation in splenocytes from mice injected 10 clays earlier with BAT-1 (Table 9A). Maximal stimulation (10 fold) was attained upon administration of BAT at closes of 10 μg/mouse.
(ii) Induction of cytotoxicity in splenocytes from mice injected with BAT-1 (Table 9B). BAT-1 administered at different doses 10 days prior to the cytotoxicity assay induced cytotoxicity towards murine melanoma (B16-F10) cells, renal cell carcinoma (MR-28) cells and lymphoma (YAC) cells. Maximal effect was attained upon administration of BAT at a dose of 10 μg/mouse.



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## Table 9

### Proliferation and cytotoxicity of splenocytes from mice injected with BAT mAb

| A [$^3$H]Thymidine incorporation | | B Specific $^{51}$Cr release (% ± SEM) | | |
|---|---|---|---|---|
| cpm x $10^{-3}$ ± SEM | | Cell Target | | |
| | BAT (μg/mouse) | B16 | MR-28 | YAC |
| 9.9 ± 1.5 (n=16) | 0 | 3.9 ± 1.4 (n=10) | 16.0 ± 2.7 (n=8) | 3.3 ± 0.4 (n=6) |
| 15.3 ± 2.3 (n=12) p < 0.1 | 1 | 13.2 ± 1.4 (n=6) p < 0.001 | 31.7 ± 2.8 (n=8) p < 0.01 | 16.7 ± 1.6 (n=6) p < 0.001 |
| 20.0 ± 4.0 (n=14) p < 0.05 | 10 | 14.0 ± 1.2 (n=6) p < 0.001 | 25.2 ± 2.1 (n=8) p < 0.02 | 19.0 ± 2.6 (n=6) p < 0.001 |

Mice C57BL and BALB/c were inject I.V. with BAT mAb at different concentrations. 10 days later cytotoxity and [$^3$H]Thymidine incorporation was determined in isolated splenocytes. Splenocytes from C57BL mice were tested on B16 melanoma target cells and from BALB/c mice were tested on MR-29 and YAC cells (effector: target ration 50:1). Each group contained between 6-16 mice in 3-4 separate experiments. Cytotoxicity and [$^3$H]Thymidine incorporation for each mouse was done in triplicates and the mean calculated. results are expressed at mean ± standard error of n mice, p-values for the differences between the control and the BAT treated animals are given.

**Example 6**

**Immunotherapeutic effect of BAT-1 against mouse tumors**

As seen in Table 10, administration of BAT-1 to melanoma-inoculated mice 14 days after inoculation of the tumor cells, reduced the number of lung metastases in lungs of mice bearing B16, 3LL and MCA tumors:

a1. BAT-1 abolishes lung metastases in B16 melanoma-inoculated mice, using an established lung metastases model

C57BL mice were injected (i.v.) with 50x$10^3$ B16 melanoma cells (Table 10). 24 days after injection numerous metastases developed in the lungs (practically reached confluency) as seen in Fig. 7, upper row.

Against this, as seen in Fig. 7, lower row, lung of mice that were injected with BAT-1 (10 μg/mouse) two weeks



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after inoculation with the B16 melanoma were practically free of metastases.

Fig. 8 summarizes the results of six separate experiments done under similar conditions as above.

## Table 10

### Anti tumor effect of BAT mAB

### BAT-induced reduction in lung metastases

| | Tumors[a] | | | | | |
|---|---|---|---|---|---|---|
| | B16 | | 3LL | | MCA | |
| No. of mets.[c] | BAT treatment[b] | | | | | |
| | − (n=24)[d] | + (n=27) | − (n=11) | + (n=11) | − (n=8) | + (n=9) |
| None | 0 | 25 | 0 | 6 | 0 | 4 |
| 1-10 | 0 | 2 | 0 | 4 | 0 | 5 |
| 11-50 | 8 | 0 | 3 | 1 | 5 | 0 |
| >250 | 16 | 0 | 8 | 0 | 3 | 0 |
| Lung weight (gr) | 0.803[e] ± 0.26 | 0.315 ± 0.66 | 1.014 ± 0.21 | 0.364 ± 0.06 | 0.836 ± 0.31 | 0.328 ± 0.06 |

[a] Tumor was inoculated at day 0

[b] BAT mAb (10 μg/mouse) was injected i.v. at day fourteen

[c] Lung metastases were scored 24 days post tumor inoculation using a Zeiss stereomicroscope

[d] Number of mice

[e] Mean ± SD of lungs weight from (n) mice

a2. Anti-tumor effect of BAT-1 mAb injected at different times in relation to B16 tumo inoculation

As seen in Table 11, mice given injections of the melanoma cells and treated 10-14 days later by BAT-1 mAb administration were found to be free of metastases and have normal lung weights. A marked decrease in the number of metastases in the lungs of the mice, although not complete, was noticed 5 days after tumor inoculation and as late as 19 days post-tumor administration. Injection of BAT-1 on the same day as inoculation of tumor cells had no thereapeutic effect.



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Table 11

| BAT administration at different times in relation to B16 melanoma inoculation | | | |
|---|---|---|---|
| Day[†] | No. of Mice | No. of Mets. | lungs weight (gr) |
| None | 10 | 155.0±28 | 0.892±0.19 |
| -6 | 3 | 61.0±0.8 | 0.983±.01 |
| 0 | 7 | 148.0±36 | 0.425±0.05 |
| 5 | 4 | 0.8±0.5 | 0.243±0.07 |
| 10 | 4 | 0.0±0.0 | 0.240±0.08 |
| 14 | 7 | 0.0±0.0 | 0.286±0.03 |
| 19 | 4 | 2.2±1.3 | 0.338±0.01 |
| 23 | 4 | 75.4±44 | 0.840±0.24 |

[†] Day of BAT mAb administration relative to tumor inoculation at day zero.

b. BAT-1 abolishes lung metastases in Lewis lung carcinoma (3LL)- inoculated mice using an established lung metastases model

Experimental conditions were similar to those described for B16 melanoma (see above) except that $2x10^5$ 3LL cells were injected. Fig. 9, upper row, shows lungs from 3LL-inoculated mice with numerous metastases. Fig. 9, lower row shows lungs from mice that had been inoculated with the tumor cells followed 14 days later by BAT-1 treatment which as seen, are almost free of metastasis.

c. BAT abolishes lung metastases in MCA fibrosarcoma (MCA 105)- inoculated mice using an established lung metastases model

Experimental conditions were similar to those described for the 3LL Lewis lung carcinoma model. Fig. 10, upper row, shows lungs from MCA 105 inoculated mice with numerous metastases. Fig. 10, lower row shows lungs from mice that had been inoculated with the tumor followed by BAT- 1 treatment which, as seen, are almost free of metastases.

**Example 7**

**BAT-1 cures mice bearing B16 and 3LL tumors**

Mice inoculated with B16 melanoma cells or with 3LL cells as described above die within 25-35 days after tumor inoculation. Against this, as seen in Fig. 11, all mice that were injected with BAT-1 (10 μg/mouse) 14 days after tumor inoculation survived over 100 days. The majority of the animals which were followed up for months showed no signs of illness and were free of metastasis upon pathological examination.

**Example 8**

**Adoptive transfer of splenocytes from mice treated with BAT-1 mAb**

Splenocytes from mice that had been treated with BAT-1 mAb alone or first given injections of B16 melanoma cells and then treated with BAT-1 mAb, were transferred into recipient mice. The recipient mice were inoculated either with B16 melanoma cells or with 3LL tumor cells. As seen in Table 12 below, adoptive transfer of splenocytes from the BAT-1 mAb injected mice, induced tumor regression in the tumor bearing mice receiving the transferred splenocytes. The most effective treatment was obtained when $10^8$ splenocytes of mice which were both inoculated with B16 melanoma cells and 14 days later injected with BAT-1 were adoptively transferred to recipient tumor bearing mice. As seen in Table 12, in this case, there was complete elimination of melanoma tumor cells in B16 tumor bearing recipients and pronounced tumor regression in 3LL tumor bearing recipients, as presented in the number of metastases as well as in the lung weight.



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**Table 12**

**Adoptive transfer induced tumor retression[a]**

| | Tumor inoculated mice (Recipients) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | B16 | | | | 3LL | | | |
| | No. of splenocytes transferred | | | | | | | |
| **Donor Group** | $10^7$ | | $10^8$ | | $10^7$ | | $10^8$ | |
| | No. Mets. | Lung Wt. | No. Mets. | Lung Wt. | No. Mets. | Lung Wt. | No. Mets. | Lung Wt. |
| A. untreated | >250 | 1.09±0.9[e] | >250 | 1.12±0.04 | >250 | 1.05±0.16 | >250 | 1.12±0.16 |
| B. BAT-treated[b] | 89±10[d] | 0.67±0.04 | 28±4.3 | 0.41±0.19 | 134±15 | 0.87±0.29 | 134±19 | 0.77±0.31 |
| C. B16 injected[c] and BAT treated | 4±4 | 0.32±0.01 | 0±0.0 | 0.31±0.01 | 3.6±2.9 | 0.34±0.06 | 2.6±1.1 | 0.36±0.03 |

[a] Splenocytes from three groups of mice (A, B, C) were injected i.v. into recipient mice, 14 days post tumor inoculation.
[b] Splenocytes were transferred from mice 20 days after i.v. injection of BAT (10 μg/mouse).
[c] Conditions as in [b] except that mice were inoculated with B16 melanoma 14 days prior to BAT administration.
[d] Mean number of lung metastases ±SD from three mice.
[e] Mean number of lungs weight (gr) ±SD from three mice.



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These results indicated that splenocytes alone from B16 inoculated and BAT-1 treated mice exhibited anti-tumor effect against both B16 and 3LL tumors. Therefore, it seems that BAT-1 enhances non-specific cellular effector mechanisms. Furthermore, the presence of tumors potentiated the enhancement of BAT-1 induced generation of such effector cells.

## Claims

1. A monoclonal antibody or an antigen binding fragment thereof, the monoclonal antibody being

   i. a monoclonal antibody secreted by the hybridoma cell line deposited at the Collection Nationale de Cultures de Microorganismes (CNCM), under Accession No. I-1397, or
   ii. a monoclonal antibody which binds to an antigen to which the antibody under (i) binds.

2. An immortalized cell line secreting an antibody of claim 1.

3. The immortalized cell line of claim 2, being a hybridoma cell line.

4. The hybridoma cell line of claim 3, being the hybridoma cell line CNCM I-1397.

5. A pharmaceutical composition comprising, as an active ingredient, a monoclonal antibody according to claim 1, and a physiologically acceptable carrier.

6. The pharmaceutical composition of claim 5, comprising also an agent other than said antibody, capable of enhancing the activity of the cytotoxic lymphocytes, in an additive or synergistic manner to that of said antibody.

7. A proteinaceous substance to which the antibody of claim 1 specifically binds.

8. The substance of claim 7, having an apparent molecular weight, as established by gel electrophoresis, of about 48-50 kD.

9. Use of an antibody of claim 1 for the preparation of a pharmaceutical composition for the treatment of cancer.

10. Use of an antibody of claim 1 for the preparation of a pharmaceutical composition for the stimulation of the cytotoxic activity of the immune system.

## Patentansprüche

1. Monoclonaler Antikörper oder Antigenbindefragment davon, wobei der monoclonale Antikörper

   (i) ein monoclonaler Antikörper ist, der von der Hybridomzellinie sezemiert wird, die bei der Collection Nationale de Culture de Microorganismes (CNCM) unter der Hinterlegungsnummer 1-1397 hinterlegt ist, oder
   (ii) ein monoclonaler Antikörper ist, der an ein Antigen bindet, an welches der Antikörper von (i) bindet.

2. Immortalisierte Zellinie, die einen Antikörper nach Anspruch 1 sezerniert.

3. Immortalisierte Zellinie nach Anspruch 2, die eine Hybridomzellinie ist.

4. Hybridomzellinie nach Anspruch 3, die die Hybridomzellinie CNCM 1-1397 ist.

5. Arzneimittel, das als Wirkstoff einen monoclonalen Antikörper nach Anspruch 1 und einen physiologisch verträglichen Träger umfaßt.

6. Arzneimittel nach Anspruch 5, das ferner ein anderes Agens als den Antikörper umfaßt, das fähig ist, die Aktivität der cytotoxischen Lymphocyten in einer additiven oder synergistischen Weise zu jener des Antikörpers zu verstärken.



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7. Proteinartige Substanz, an die der Antikörper nach Anspruch 1 spezifisch bindet.

8. Substanz nach Anspruch 7, die ein offenbares, durch Gelelektrophorese bestimmtes Molekulargewicht von etwa 48 bis 50 kD hat.

9. Verwendung eines Antikörpers nach Anspruch 1 zur Herstellung eines Arzneimittels zur Behandlung von Krebs.

10. Verwendung eines Antikörpers nach Anspruch 1 zur Herstellung eines Arzneimittels zur Stimulierung der cytotoxischen Aktivität des Immunsystems.

**Revendications**

1. Anticorps monoclonal ou fragment de celui-ci se liant à un antigène, l'anticorps monoclonal étant

   i) un anticorps monoclonal sécrété par une lignée cellulaire d'hybridome déposée à la Collection Nationale de Cultures de Microorganismes (CNCM), sous le numéro d'enregistrement I-1397, ou
   ii) un anticorps monoclonal qui se lie à un antigène auquel se lie l'anticorps défini en (i) ci-dessus.

2. Lignée cellulaire immortalisée sécrétant un anticorps selon la revendication 1.

3. Lignée cellulaire immortalisée selon la revendication 2 qui est une lignée cellulaire d'hybridome.

4. Lignée cellulaire d'hybridome selon la revendication 3, qui est la lignée cellulaire d'hybridome I-1397 de la Collection CNCM.

5. Composition pharmaceutique comprenant, en tant que principe actif, un anticorps monoclonal selon la revendication 1, et un véhicule physiologiquement acceptable.

6. Composition pharmaceutique selon la revendication 5, comprenant en outre un agent distinct dudit anticorps capable d'augmenter l'activité des lymphocytes cytotoxiques de façon additive ou synergique par rapport à celle dudit anticorps.

7. Substance protéinique à laquelle l'anticorps de la revendication 1 se lie de façon spécifique.

8. Substance selon la revendication 7 présentant un poids moléculaire apparent tel que mesuré par gel d'électrophorèse d'environ 48-50 kD.

9. Utilisation d'un anticorps selon la revendication 1 pour la préparation d'une composition pharmaceutique pour le traitement du cancer.

10. Utilisation d'un anticorps selon la revendication 1 pour la préparation d'une composition pharmaceutique pour la stimulation de l'activité cytotoxique du système immunitaire.



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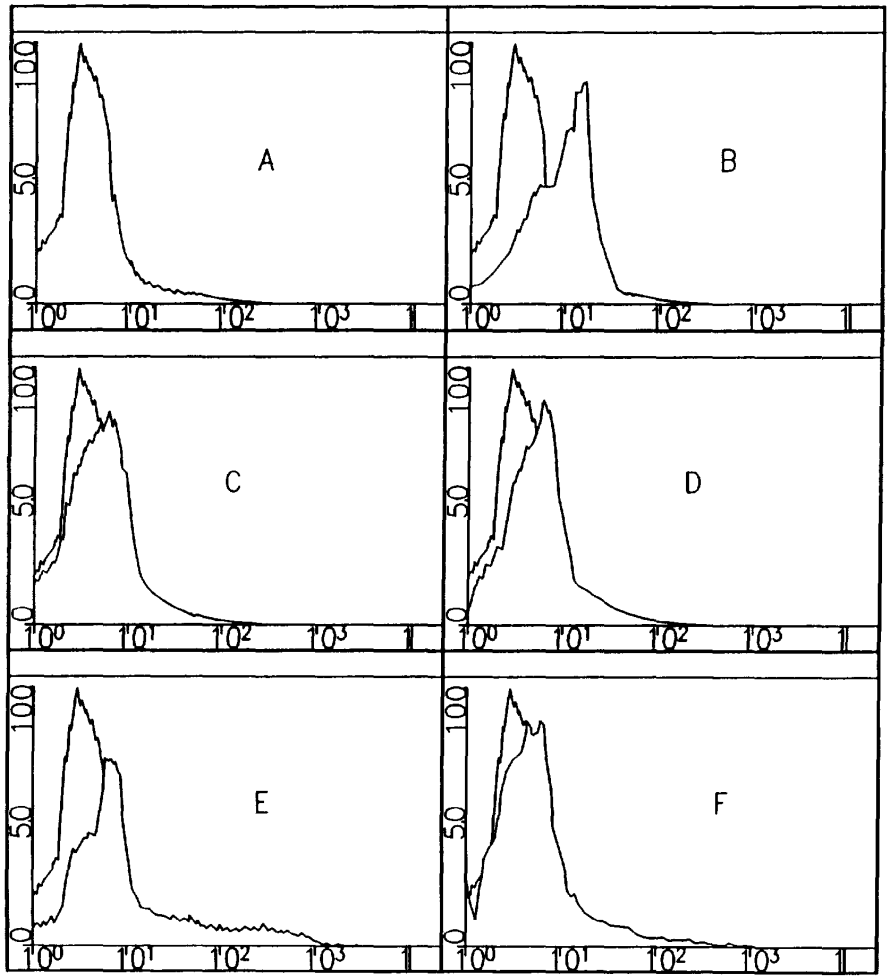



FIG. 1



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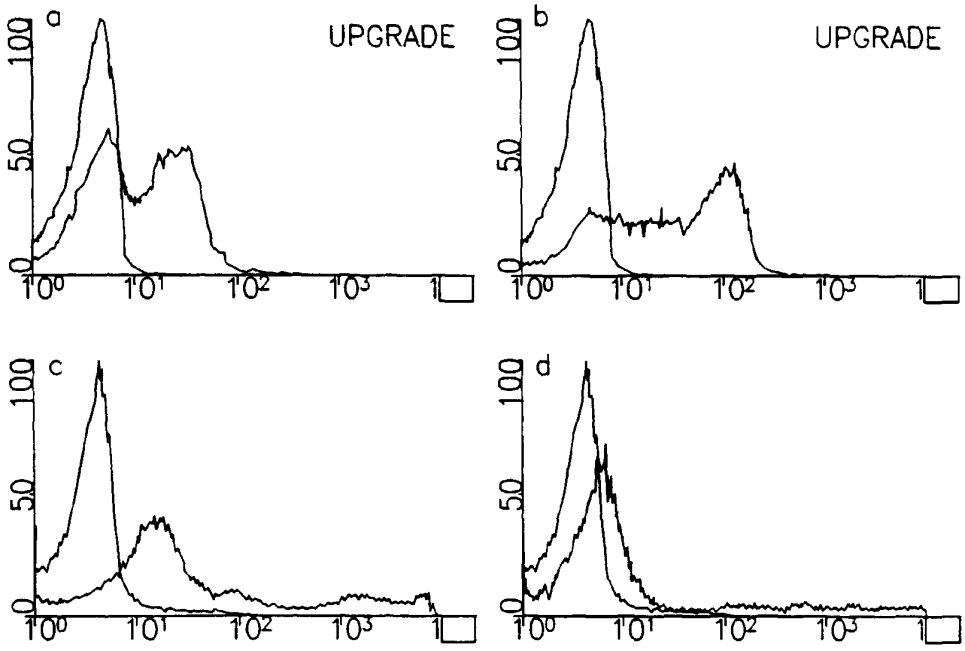



FIG.2A



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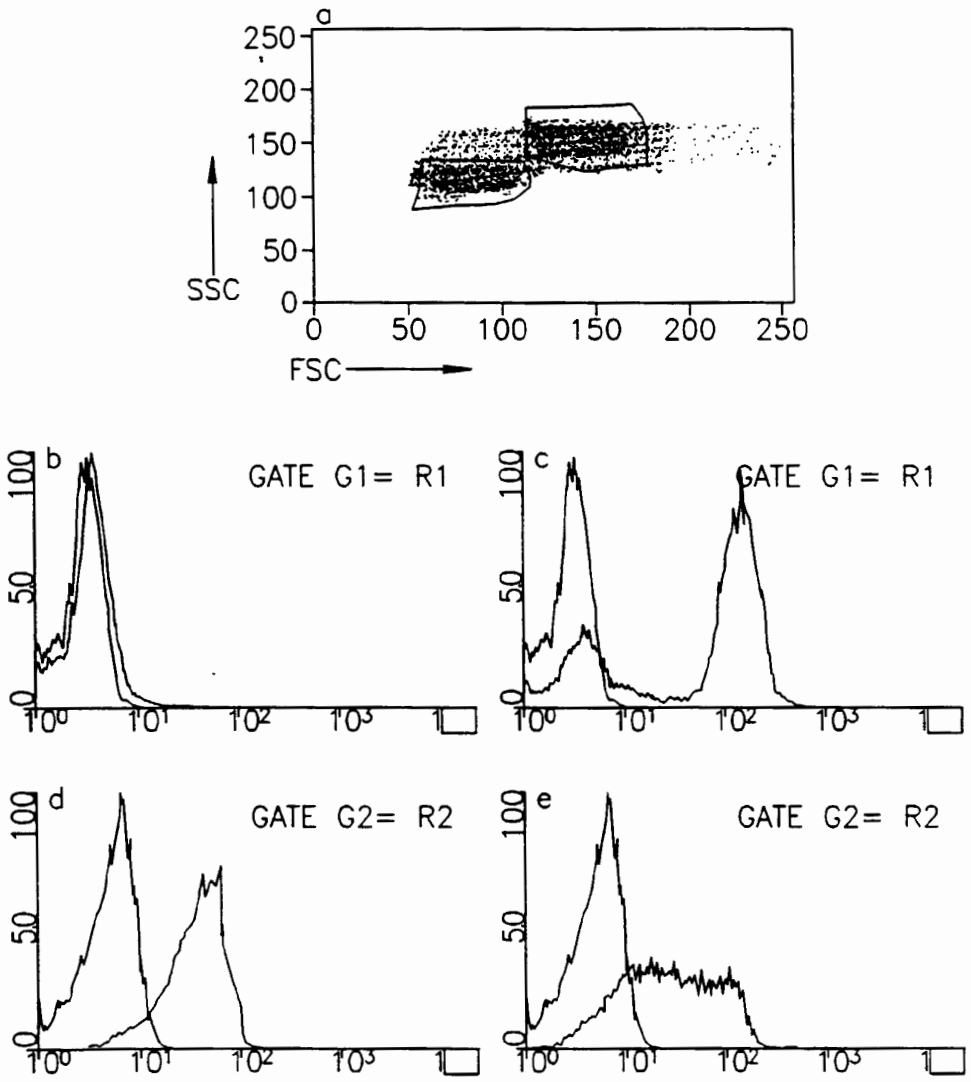



FIG.2B



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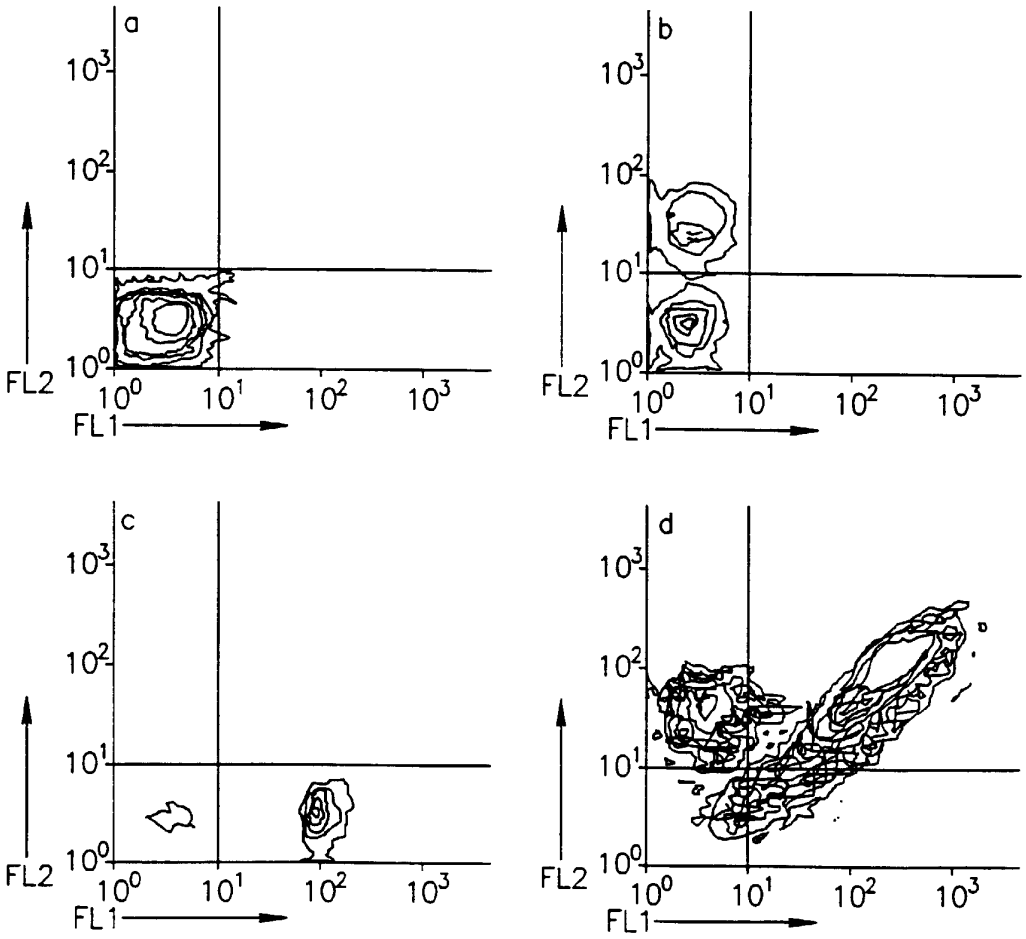



FIG.3A



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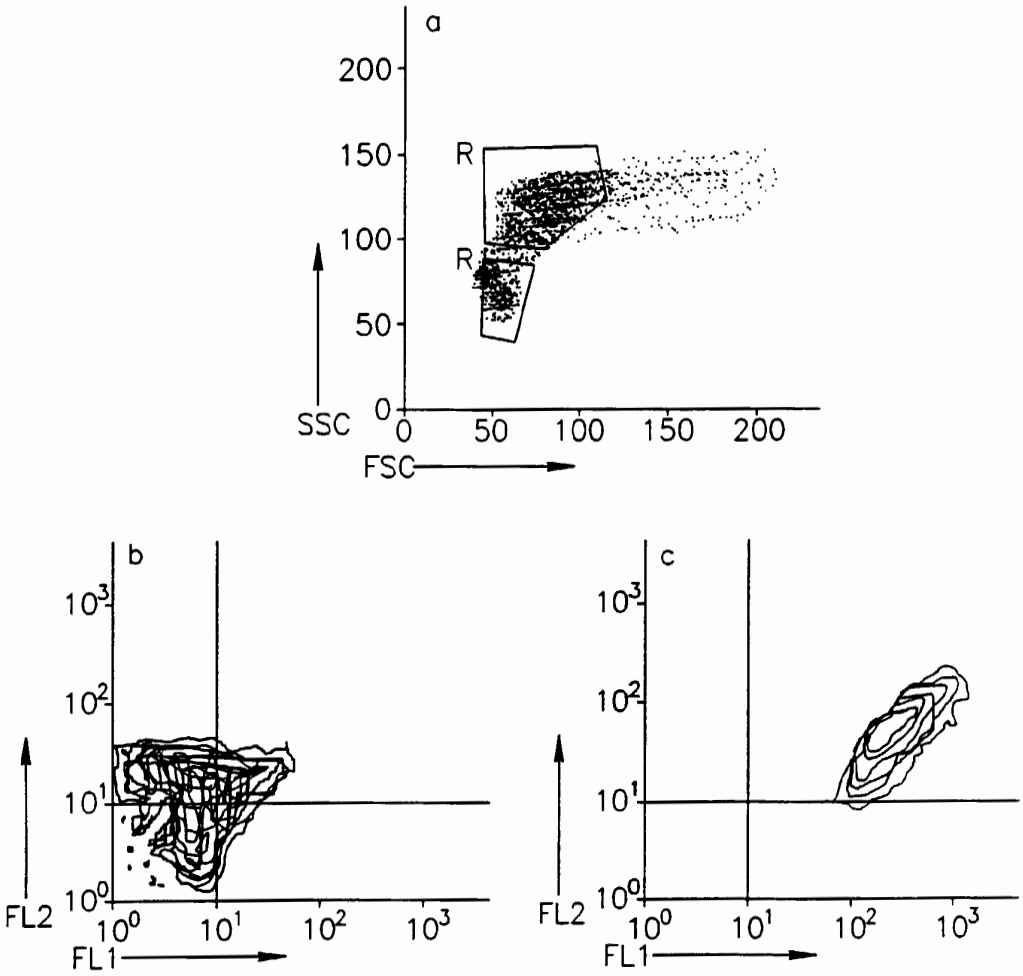



FIG.3B



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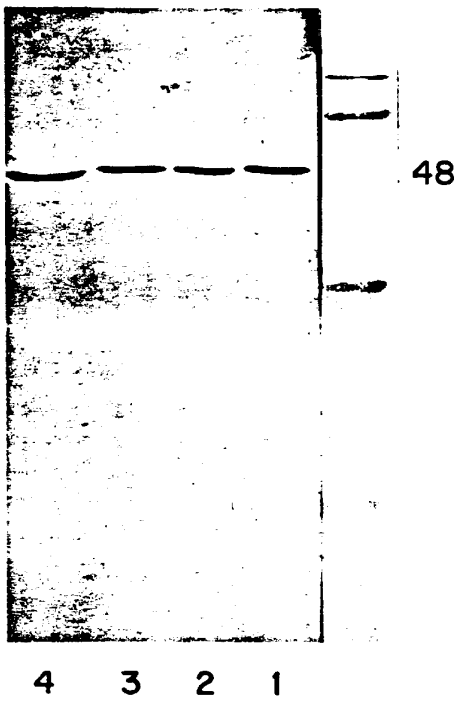



Fig. 4



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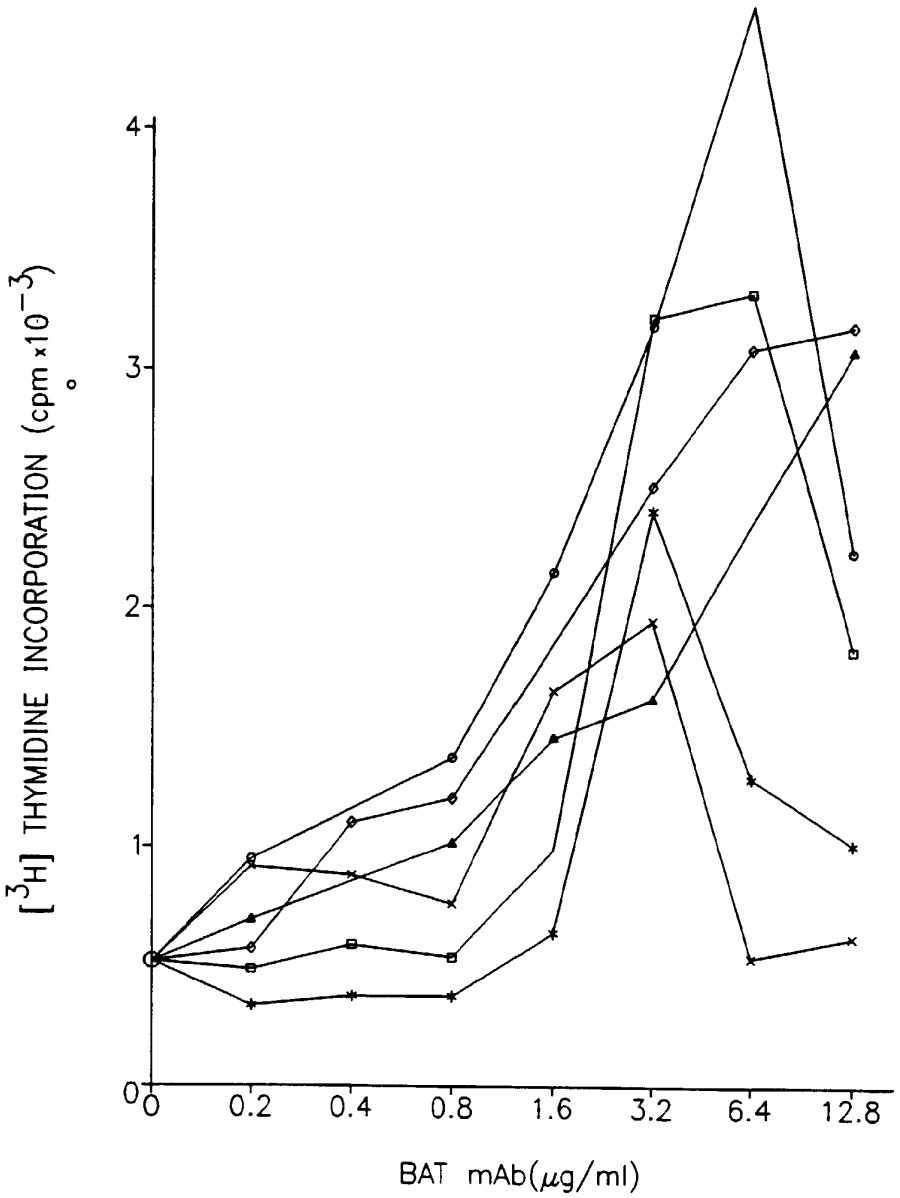



FIG.5



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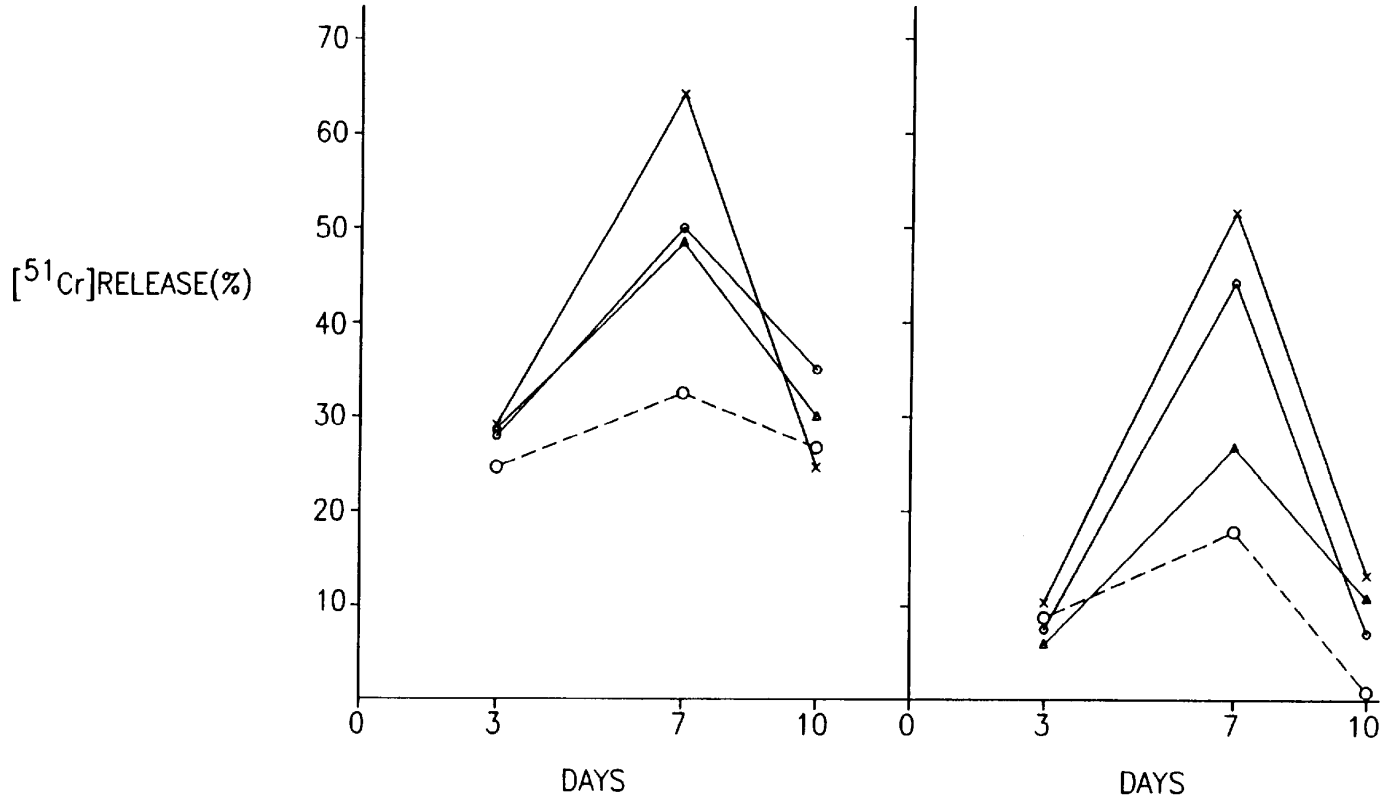



FIG.6



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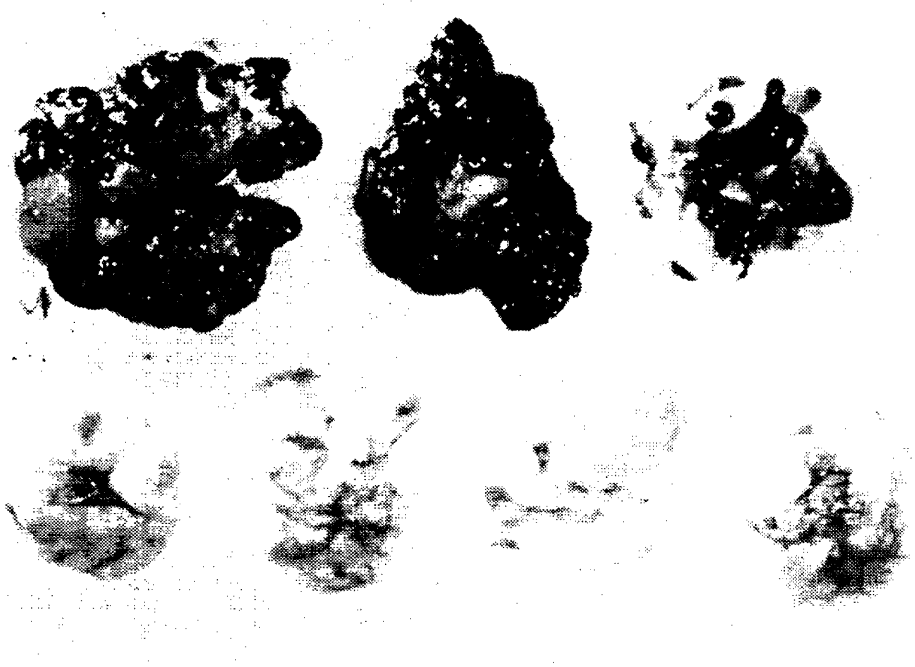


Fig. 7



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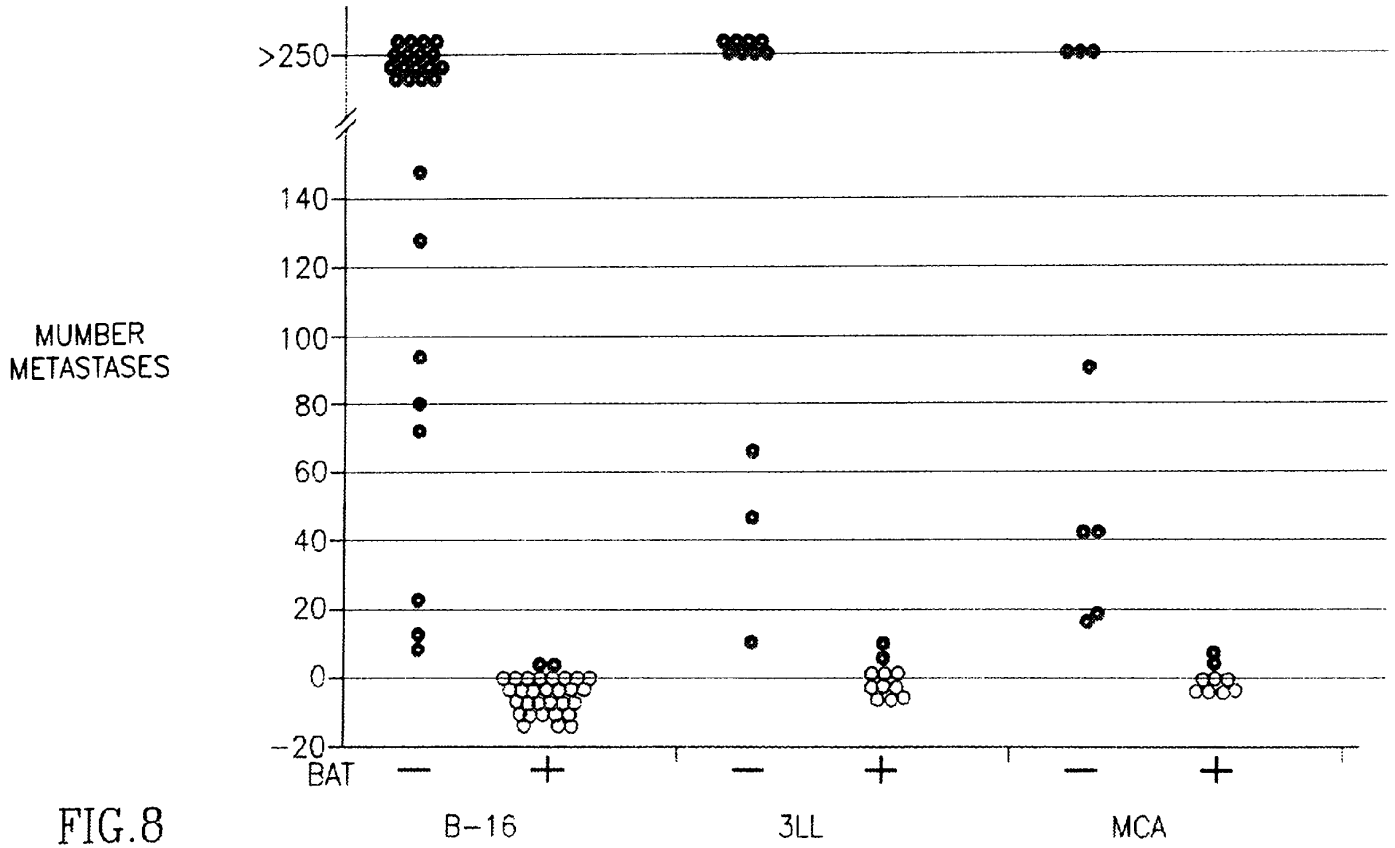



FIG.8



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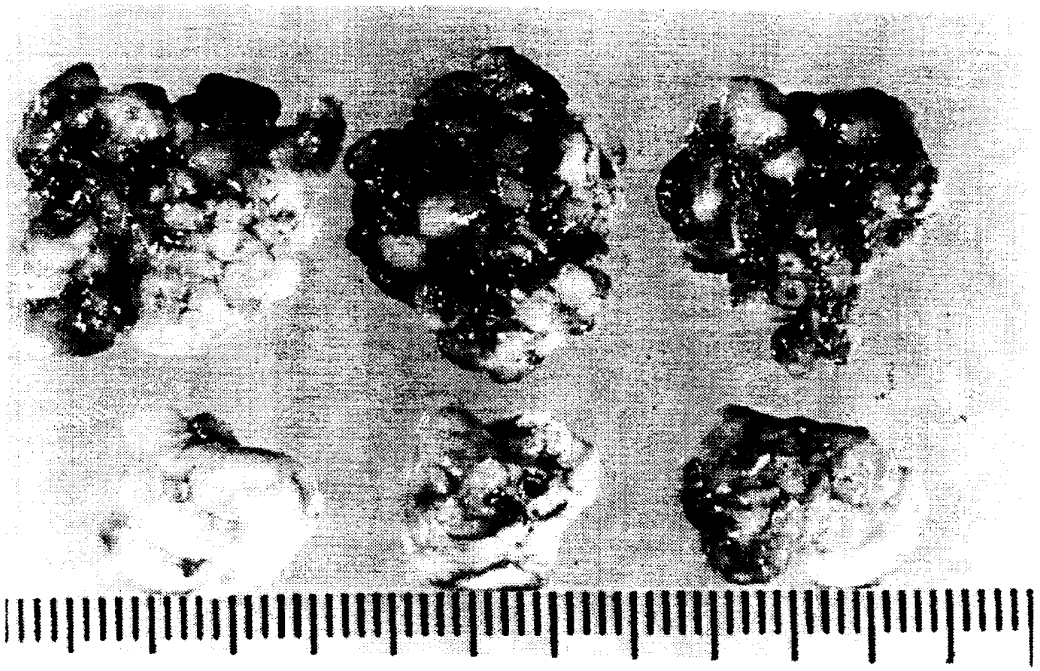


Fig. 9



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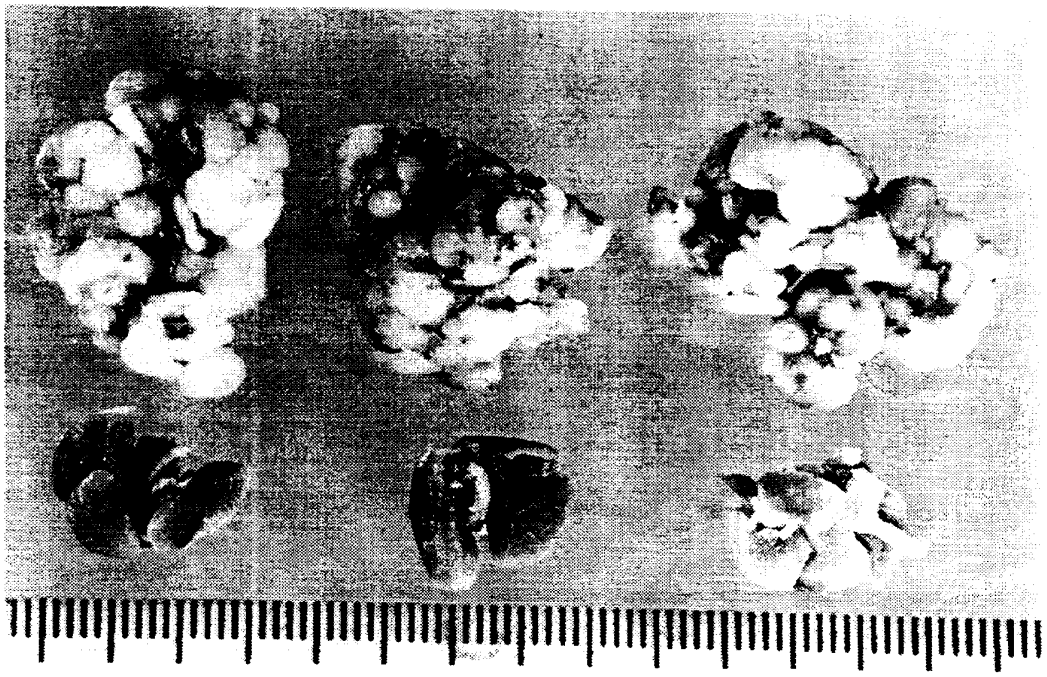


Fig. 10



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# (54) IMMUNOPOTENTIATING COMPOSITIONS

(57) Compositions for cancer or infection treatment via immunopotentiation caused by inhibition of immunosuppressive signal induced by PD-1, PD-L1, or PD-L2 and therapies using them, immunopotentiative substrates included as the active ingredient, screening methods of the substrates for cancer or infection treatment, cell lines used for the screening methods, evaluation methods that selects the substrates for cancer treatment, and carcinoma cell transplanted mammals used for the evaluation methods.

The compositions of the present invention that inhibits the function of PD-1, PD-L1, or PD-L2 are useful for cancer or infection treatment.

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## Description

### TECHNICAL FIELD

**[0001]** The present invention relates to immunopotentiation characterized by inhibiting immunosuppressive signals induced by PD-1, PD-L1 or PD-L2, compositions for cancer or infection treatment, and therapies that use them.

**[0002]** More specifically, the present invention relates to the compositions for cancer or infection treatment through an immunopotentiation caused by inhibition of immunosuppressive signals induced by PD-1, PD-L1 or PD-L2, the therapies that use them, screening methods of immunopotentiative substances, or substances for cancer treatment or for infection treatment that are contained in the composition as an active ingredient, cell lines used for those screening methods, an evaluation that selects the substances for cancer treatment, and carcinoma cells transplanted mammals used for the evaluation.

### BACKGROUND ART

**[0003]** Immunotherapies can reduce side reactions that can't be avoided easily in most chemotherapies, and is expected as a therapy with extremely high specificity. The Immunotherapies can be executed in the purpose to recover patient's QOL by activating the immune reaction that human originally has by an extrinsic method and subrogating a part of the load by medication.

**[0004]** Immunopotentiation can be executed by methods of activating immune reaction of T lymphocytes. It is said that not only stimulation through antigen receptors (TCR) but also an additionally stimulative inducement through conjugated stimulative molecular groups (for example, CD28) could be necessary for the activation of T cells. However, it is reported that as the molecular groups with homologous structures to the conjugated stimulative molecular groups, CTLA-4 and PD-1 were discovered recently and give signals that suppress signals of antigen receptors (TCR). It is thought that a method of activating T cells could be an effective mean to suprress the function of those conjugated control molecules.

**[0005]** PD-1 was cloned as 55kD of I type membrane protein that belong to an immunoglobulin family (The EMBO Journal (1992), vol.11, issue 11, p.3887-3895, JP5336973, JP7291996). Human PD-1 cDNA is composed of the base sequence shown in EMBUGenBank Acc.No.NM_005018 and mouse PD-1 cDNA is composed of the base sequence shown in Acc.No.X67914, and those expression are observed when thymus cells differentiate from CD4-CD8- cell into CD4+CD8+ cell (International Immunology (1996), vol.18, issue 5, p. 773-780., Journal of Experimental Medicine (2000), vol. 191, issue5, p.891-898.). It is reported that PD-1 expression in periphery is observed in myeloid cells including T cells or B lymphocytes activated by stimulation from antigen receptors, or activated macrophages (*International Immunology* (1996), vol.18, issue 5, p.765-772.).

**[0006]** In an intracellular domain of PD-1, there are ITIM motifs (Immunoreceptor Tyrosine-based Inhibitory Motif) that could been thought to be a repression domain to immune reaction. Since PD-1-deficient mice develop lupus-like autoimmune disease such as glomerular nephritis and arthritis (for C57BL/6 gene background.) (*International Immunology* (1998), vol.10, issue10, p. 1563-1572., Immunity (1999), vol. 11, issue2, p. 141-151.) and a disease like dilated cardiomyopathy (for BALB/c gene background.)(Science (2001), vol.291, issue5502, p.319-332.), it has been suggested that PD-1 could be a control factor of development of autoimmune disease, especially the peripheral self-tolerance.

**[0007]** PD-L1 (human PD-L1 cDNA is composed of the base sequence shown by EMBUGenBank Acc. No. AF233516 and mouse PD-L1 cDNA is composed of the base sequence shown by NM_021893.) that is a ligand of PD-1 is expressed in so-called antigen-presenting cells such as activated monocytes and dendritic cells (*Journal of Experimental Medicine* (2000), vol.19, issue7, p.1027-1034.). These cells present interaction molecules that induce a variety of immuno-inductive signals to T lymphocytes, and PD-L1 is one of these molecules that induce the inhibitory signal by PD-1. It has been revealed that PD-L1 ligand stimulation suppressed the activation (cellular proliferation and induction of various cytokine production) of PD-1 expressing T lymphocytes. PD-L1 expression has been confirmed in not only immunocompetent cells but also a certain kind of tumor cell lines (cell lines derived from monocytic leukemia, cell lines derived from mast cells, cell lines derived from hepatic carcinomas, cell lines derived from neuroblasts, and cell lines derived from breast carcinomas) (*Nature Immunology* (2001), vol.2, issue3, p. 261-267.).

**[0008]** Though PD-L2 (human PD-L2 cDNA is composed of the base sequence shown by EMBUGenBank Acc.No.NM_025239 and mouse PD-L2 cDNA is composed of the base sequence shown by NM_021896.) had been identified as a second ligand of PD-1, it has been reported that the expression and function are almost same as PD-L1 (*Nature Immunology* (2001), vol. 2, issue3, p.261-267.).

**[0009]** It has been thought that the inhibitory signals from the conjugated suppressive molecules represented by PD-1 could control abnormal immune reaction to autoantigen and immunological tolerance in lymphocyte generation or maturation by a mechanism that appropriately controls positive signals with antigen receptors (TCR) and conjugated stimulation molecules. It has been thought that a certain kind of tumour and virus could use those conjugated suppressive molecules to intercepte the activation and proliferation of T cells and weaken the host immunity reaction to oneself by a direct



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or indirect mechanism (Cell (1992), vol.71, issue7, p. 1093-1102, Science(1993), vol.259, issue5093, p. 368-370.). It has been thought that those conjugated suppressive molecules could have caused the impairment of T cells in a part of disease thought to originate in impairment of T cells.

DISCLOSURE OF THE INVENTION

**[0010]** A problem of the present invention is to provide compositions to activate immunity by inhibiting the inhibitory signals of PD-1, PD-L1 or PD-L2 and compositions for cancer or infection treatment through this mechanism.

**[0011]** The present inventors paid attention to PD-1, PD-L1, or PD-L2 as a new target in cancer or infection treatment and found that substances that inhibit the inhibitory signals of PD-1, PD-L1 or PD-L2 inhibit cancer proliferation through the mechanism of the recovery and activation of immune function. Further, they found that PD-1 signal, concretely, an interaction of PD-1 and PD-L1 or PD-1 and PD-L2 took part in the exclusion of infectious virus. According to those facts, they found the substances that could inhibit the inhibitory signals of PD-1, PD-L1 or PD-L2 having therapeutic potential for cancer or infection and completed the present invention.

**[0012]** That is, the present invention relates to

1. an immunopotentiative composition containing an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
2. a composition for cancer treatment containing the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
3. the composition for cancer treatment of the subsection 2, which is a composition that suppresses cancer metastasis,
4. a composition for infection treatment containing an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
5. the composition for cancer treatment of the subsection 2 or 3, which is characterized by acting through immunopotentiation,
6. the composition for infection treatment of the subsection 4, which are characterized by acting through immunopotentiation,
7. the composition of either of the subsection 1 to 6, which the immunosuppressive signal inhibitor is/are one or more selected from an interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, an intracellular signaling inhibitor of PD-1, and an inhibitory substance of PD-1, PD-L1 or PD-L2 production,
8. the composition of the subsection 7, which is/are one or more of the interaction inhibitor(s) of PD-1 and PD-L1 selected from PD-1 antibody, PD-L1 antibody, soluble PD-1, and soluble PD-L1,
9. the composition of the subsection 8, which is PD-1 antibody selected from anti-human PD-1 antibody of which hybridomas identified by International Trust Number FERM BP-8392 product, anti-PD-1 antibody humanized from non-human antibody, and human type anti-human PD-1 antibody,
10. the composition of either of the subsection 1 to 6, which the immunosuppressive signal inhibitor is a lymphocyte of which PD-1 expression is inhibited by gene-recombination,
11. the composition of the subsection 7, which the interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, an intracellular signaling inhibitor of PD-1, or the inhibitory substance of PD-1, PD-L1 or PD-L2 production is one or more of substance(s) selected from protein, polypeptide or peptide, polynucleotide or polynucleoside, antibody or the derivative, organic synthesis compound, inorganic compound, and natural product,
12. an immunopotentiative method containing a method of administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
13. a method for cancer treatment containing a method of administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
14. the method of cancer treatment of the subsection 13, which is a method of suppressing cancer metastasis,
15. a method for infection treatment containing a method of administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2,
16. the method for cancer treatment of the subsection 13 or 14, which is characterized by acting through immunopotentiation,
17. the method for infection treatment of the subsection 15, which is characterized by acting through immunopotentiation,
18. the method of either of the subsection 12 to 17, which the immunosuppressive signal inhibitor is/are one or more selected from the interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, the intracellular signaling inhibitor of PD-1, and the inhibitory substance of PD-1, PD-L1 or PD-L2 production,
19. the method of the subsection 18, which the interaction inhibitor is/are one or more selected from PD-1 antibody, PD-L1 antibody, soluble PD-1, and soluble PD-L1,
20. the method of the subsection 19, which PD-1 antibody is an antibody selected from anti-human PD-1 antibody of which hybridomas identified by international trust number FERM BP-8392 product, anti-PD-1 antibody humanized from non-human antibody, and human type anti-human PD-1 antibody,
21. the method of either of the subsection 12 to 17, which the immunosuppressive signal inhibitor is a lymphocyte of which PD-1 expression is inhibited by gene-recombination,
22. the method of the subsection 18, which the interaction inhibitor of PD-1 and PD-L1 or PD-1 and



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PD-L2, the intracellular signaling inhibitor of PD-1, or the inhibitory substance of PD-1, PD-L1 or PD-L2 production are one or more of substance(s) selected from protein, polypeptide or peptide, polynucleotide or polynucleoside, antibody or the derivative, organic synthesis compound, inorganic compound, and natural product,

23. use of the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 to manufacture the immunopotentiative composition,

24. use of the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 to manufacture the composition for cancer treatment,

25. use of the substance of the subsection 24, which the composition for cancer treatment is the composition for suppression of cancer metastasis,

26. use of the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 to manufacture the composition for infection treatment,

27. carcinoma cell lines for screening, which are transformed to express PD-L1 or PD-L2,

28. a screening method for the immunopotentiative substance characterized by touching the cells of the subsection 27 to lymphocytes and a subject substance, followed by evaluating the enhancement of the subject substance for immune reaction of lymphocytes to the cells of the subsection 27,

29. a screening method for a substance for cancer treatment characterized by touching the carcinoma cells of the subsection 27 to lymphocytes and a subject substance, followed by evaluating the enhancement of the subject substance for immune reaction of lymphocytes to carcinoma cells and inhibitory effect on the subject substance for carcinoma cells proliferation,

30. a screening method for a substance for infection treatment characterized by touching the infected cells of the subsection 27 to lymphocytes and a subject substance, followed by evaluating the enhancement of the subject substance for immune reaction of lymphocytes to the infected cells and inhibitory effect on the subject substances for pathogens proliferation,

31. a mammal created by transplant the carcinoma cell lines of the subsection 27, and

32. a screening method for a substance for cancer treatment characterized by administering the subject substance to the mammal of of the subsection 31, followed by evaluating the inhibitory ratio of the subject substance for the transplanted carcinoma cells proliferation.

**[0013]** PD-1, PD-L1, or PD-L2 of the present invention includes each one derived from mammal, for example, mouse, rat, hamster, guinea pig, dog, pig, ape, or primate including human. They are suitable to be human PD-L1, PD-1, and PD-L2, respectively.

**[0014]** The immunosuppressive signal of PD-1, PD-L1, or PD-L2 in the present invention is at least composed of the interaction of PD-1 and PD-L1 or PD-1 and PD-L2, and the intracellular signalings of PD-1. Production of PD-1, PD-L1 or PD-L2 itself is included in them.

**[0015]** The immunosuppressive signal of PD-1, PD-L1, or PD-L2 in the present invention is inhibited by direct or indirect inhibition of the interaction of PD-L1 or PD-1 and PD-L2 or the intracellular signalings of PD-1. A substance that selectively binds to PD-1, PD-L1, or PD-L2 respectively is included as a substance with those inhibitory activities. For example, it is suitable to be protein, polypeptide or peptide, polynucleotide or polynucleoside, antibody or the derivative, organic synthesis compound, inorganic compound, or natural product. Especially, an antibody to PD-1, PD-L1 or PD-L2 is enumerated as an excellent substance in specificity.

**[0016]** The immunosuppressive signals are inhibited by inhibiting production of PD-1, PD-L1 or PD-L2 itself.

**[0017]** As an antibody to PD-1, PD-L1 or PD-L2, all antibodies derived from human, mouse, rat, rabbit, or goat which can inhibit the immunosuppressive signals by PD-1, PD-L1, or PD-L2, those polyclonal or monoclonal antibodies, complete or shorten (for example, F (ab') 2, Fab', Fab, or Fv fragment) antibodies, chimeric antibodies, humanized antibodies, or completely humanized antibodies will be acceptable.

**[0018]** Such antibodies can be manufactured using a partial protein of the extracellular region of PD-1, PD-L1, or PD-L2 as an antigen according to well-known production methods of antibody or antiserum. The partial protein of the extracellular region can be prepared by well-known protein expression and purification techniques.

**[0019]** The polyclonal antibodies can be manufactured according to well-known methods. For example, they can be manufactured by separation and refinement of the antibody of which a mixture of an antigen and a carrier protein is immunized to suitable animal, and an antibody inclusion to the antigen is gathered from the immunized animal. As such animal, mouse, rat, sheep, goat, rabbit, and guinea pig are generally enumerated. To improve the antibody producibility, Freund's complete adjuvant or Freund's incomplete adjuvant can be administered with the antigen. The administering is usually executed once every two weeks about 3-10 times in total. The polyclonal antibody can be gathered from the immunized animal's blood and peritoneal fluid, etc. by the above method. The measurement of the polyclonal antibody's titer in antiserum can be measured by ELISA. The separation and refinement of the polyclonal antibody can be executed by refining techniques that use active adsorbents such as antigen binding solid phase, protein A, or protein G, etc., salting-out, alcohol precipitation, isoelectric precipitation, electrophoresis, adsorption and desorption with ion exchanger, ultracentrifugation, or separation and refinement of immunoglobulins such as gel filtration technique, etc.

**[0020]** As an antibody preparation, the monoclonal antibody or the modifier is more suitable.



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**[0021]** The monoclonal antibody producing cells can be prepared as hybridomas to be possible to subculture which produce the monoclonal antibody by selecting the individual of which the antibody titre is confirmed in an antigen immunized animals, gathering the spleen or the lymph node on day 2-5 after the final immunization, and fusing the antibody producting cells included in them with homogeneous or heterozoic myeloma cells. The antigen itself or with the carrier and the diluent is administered to the part in which the antibody production is possible. To improve the antibody producibility, Freund's complete adjuvant or Freund's incomplete adjuvant can be administered with the antigen. According to the method of calling "DNA immunization", animals are immunized. This method is a method using a phenomenon in which antigen-expressing vectors are introduced into the part and are taken into myocytes on the process of tissue repair, and expresses the antigenic protein (*Nature Immunology* (2001), vol.2, issue 3, p.261-267) after Cardiotoxin is treated to immune animal's tibialis anterior muscle of hind leg.

**[0022]** As an immune animal, mouse, rat, sheep, goat, rabbit, or guinea pig can be used, mouse and rat are suitable. The fusion operation can be executed by the method (*Nature* (1975), vol. 256, issue 5517, p. 495-497.) of Kohler and Milstein, and as fusion accelerants, polyethylene glycol (PEG) and Sendai virus, etc. are used. As those myeloma cells, myeloma cells such as P3U1, NS1, SP2/0, and AP1 can be used, P3U1 are often used usually. The monoclonal antibody producing cells can be selected by detecting by ELISA, etc. executed by adding hybridoma culture supernatant to solid phase in which antigenic proteins are adsorbed direct or with carrier perhaps. Hybridoma culture supernatant's antibody titre can be measured by ELISA. The separation and refinement of the monoclonal antibody can be executed according to the separation refining method similar to the separation and refinement of immunoglobulin for the above polyclonal antibody. Concretely, it is anti-mouse PD-L1 antibody producted by hybridomas identified by International Trust Number FERM BP-8396 or anti-human PD-1 antibody producted by a hybridoma identified by International Trust Number FERM BP-8392.

**[0023]** The hybridomas identified by International Trust Number FERM BP-8392 had been deposited as Trust Number FERM P-19162 to National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary in Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan (ZIP code 305-8566) at Dec 19, 2002, and had been transferred to International Deposit at June 5, 2003. The hybridomas identified by International Trust Number FERM BP-8396 had been deposited as Trust Number FERM P-18908 at June 25, 2002, and had been transferred to International Deposit at June 11, 2003.

**[0024]** The antibody fragment means $F(ab')_2$, Fab', Fab, or scFv antibody fragment and can be prepared by reducing optionally after processing with protease enzyme.

**[0025]** $F(ab')_2$ antibody fragments can be purified by either method of affinity chromatography such as ion-exchange chromatography, gel filtration, or protein A or protein G column, etc. after the purified monoclonal antibody is completely digested by pepsin. Because digestive time by pepsin is different depending on Ig subtype, it is necessary to prepare it suitably. Fab' antibody fragment can be prepared by reducing $F(ab')_2$ by 2-mercaptoethylamine partly. Fab antibody fragment can be prepared by the direct digestion under the presence of cysteine by the digestive enzyme papain followed by refining.

**[0026]** Further, the monoclonal antibody is prepared as a rearrangement antibody and a hybrid antibody modified by gene recombination technology using DNA sequence that codes the amino acid sequence of antibody isolated from the hybridomas. For example, it can be prepared as a single-chain antibody but not a usual complete type antibody. scFv antibody (single chain Fv) can be prepared by the method of Jost (*Journal of Biological Chemistry* (1994), vol. 269, issue 42, p. 26267-26273.). The single-chain antibody with the characteristic and the affinity of an original antibody can be prepared by making expression an expression vector including a fused DNA of which DNA fragments respectively coding a variable region of the heavy chain and the light chain had been connected with a spacer coding neurtal amino acids (glycine or serine) in suitable host cells.

**[0027]** When non-human antibody is used to treat for human, it is indispensable to decrease the antigenicity of the antibody. Since the immune reaction to patient's antibody often shortens an effective treatment period, the process of decreasing the antigenicity of the antibody by making the antibody humanize or completely human type is necessary. The humanized antibody modified to be acceptable for administering to human is the antibody which is modified so that the decrease of antigenicity or the blood movement may improve to extent that can be allowed in pharmacology when the antibody is administered to human.

**[0028]** Human PD-1 antibody or human PD-L1 antibody in specification of the present invention includes the humanized or the complete human type antibody, too.

**[0029]** The humanized antibody can be prepared by substituting a part of non-human antibody which was prepared by being immunized to mammals other than human for a part of human antibody. Concretely, it has been known to be able to be prepared by constructing a chimera with a gene coding a constant region of the human antibody (*Proc.Natl.Acad.Sci.* (USA) (1987), vol. 84, p.3439-3443, *Journal of Immunology* (1987), vol. 139, issue 1, p.3521.). The DNA sequence of the human constant region has been described to a prior art and the constant region gene can be easily obtained from



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an already-known clone. Then, the DNA sequence coding the variable region of the antibody can be fused to the human constant region. An isotype of the human constant region can be selected due to desire effective function or antibody dependent cytotoxicity. A suitable isotype is IgG1, IgG3, and IgG4. Both human light-chain constant region, κ chain, and λ chain can be used. It is possible to make this humanized chimeric antibody expression by a routine method.

**[0030]** The complete human type antibody can be prepared by using mice (XenoMouse (*Chemical Biology* (2000), vol.7, issue8, p.R185-6.), HuMAb-Mouse (*Infection and Immunity* (2002), vol.70, issue2, p.612-9.), TC mouse (*Biotechnology and Genetics Enginnering Revew* (2002),vol.19, p.73-82.), and KM mouse (*Cloning Stem Cells* (2002), vol.4, issue1, p.91-102.)) of which a constant region gene of human immunoglobulin have been transferred, and a target antibody can be mass-produced by making the antibody production lymphocytes separated from mice to hybridomas. It can be prepared by phage display method (*FEBS Letter* (1998), vol.441, p.20-24.). In this method, by using phages of which the human antibody gene have been incorporated into a cyclic single strand DNA, the human type antibody can be expressed on the surface of the phage as a form fused with coat protein of the phages.

**[0031]** Polypeptides or the derivatives that bind to PD-1, PD-L1, or PD-L2 include each partial proteins of PD-1, PD-L1 or PD-L2 of which the immunosuppressive signal is not induced. The presence of PD-1 in the neighborhood of the antigen receptors is indispensable for the inducement of the immunosuppressive signal of PD-1, for that purpose it is necessary to be restrained by the interaction with PD-L1 or PD-L2 in antigen-presenting cells, tumours, or carcinoma cells. Therefore, soluble PD-L1 or soluble PD-L2 with a part which is only extracellular domains and interacts with PD-1 can inhibit the immunosuppressive signal of PD-1. On the other hand, soluble PD-1 with a part which has a similar structure and can interact with PD-L1 or PD-L2 can inhibit the immunosuppressive signal. These soluble proteins have only to include an extracellular region which is necessary and sufficient to bind to PD-1, PD-L1, or PD-L2 and can be prepared by a well-known expression and refining technique.

**[0032]** If an interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2 is a protein or a polypeptide and an essential area for the interaction is composed by only consecutive polypeptide, such a polypeptide fragment can become a mutual antagonist. Further, an antagonist with stronger activity can be identified from molecular groups of which this polypeptide fragment is chemically modified, or designed by computer based on the spatial structure of the polypeptide fragment. Also, the best antagonist can be more efficiently selected from molecular groups designed by computer based on protein stereoanalysis data of the interaction area.

**[0033]** A substance that inhibits the interaction of PD-1 and PD-L1, or PD-1 and PD-L2 can be screened directly. Such a substance can be identified from each libraries of protein, polypeptide or peptide, polynucleotide or polynucleoside, non-peptide compound, organic synthesis compound, or natural product (for example, fermentational product, cell extract, plant extract, and animal tissue extract.).

**[0034]** Since the inhibitory signals of PD-1 intracellular domain are caused by contacting dephosphorylation enzymes (for example, SHP-1 and 2 (Sathish JG, *Journal of Immunology* (2001), vol.166, issue 3, p.1763-70.)) that bind to ITIM in PD-1 intracellular domain with an intracellular complex including an antigen receptor complex, they are generally inhibited by inhibiting the contact between the antigen receptor complex and PD-1. The substance that inhibits the inhibitory signals includes a substance that directly inhibits the activity of dephosphorylation enzymes, a substance that inhibit phosphorylation of tyrosine residue in ITIM, a substance that inhibits bonds of dephosphorylation enzymes to ITIM, or a substance that directly inhibits activity of dephosphorylation enzymes, etc. The antigen receptor complex includes T cell receptor complex or B cell receptor complex.

**[0035]** The production of PD-1, PD-L1, or PD-L2 is inhibited by specific polynucleotide or polynucleoside, organic synthesis compound, inorganic compound, or natural product, etc. Especially, the suitable polynucleotide or polynucleoside includes antisense nucleotide derivative so-called ribozyme. This uses a mechanism of which the expressed mRNA is destroyed by which the polynucleotide derivative that is complement to mRNA of PD-1, PD-L1, or PD-L2 is transferred into subject cells. Further, the vector can be used for the gene manipulation to lymphocyte stem cells gathered from a patient so that it inhibits the expression of PD-1, and the manipulated cells can be used for cell medical treatment of which the cells will be proliferated, differentiated, activated, and administered to the patient again. Especially, in immunotherapy for cancer, more specific and clonal lymphocytes to target cells can be prepared by adding a specific antigen of the target cells on the process of the maturation and activation of lymphocyte stem cells.

**[0036]** The screening method of the present invention can be executed by a method of measuring cell function. The carcinoma cell lines for screening of which PD-L1 or PD-L2 used by the method is transformed to be expressed includes carcinoma cell lines transformed transitory or stably after expression vectors constructed to express PD-L1 or PD-L2 have been introduced to the cells by well-known methods. As the carcinoma cell lines used, ape COS-1 cells, COS-7 cells, Vero, chinese hamster CHO cells (hereafter, abbreviated with CHO cells.), dhfr gene deficient chinese hamster CHO cells (hereafter, abbreviated with CHO (dhfr-) cells.), mouse L cells, mouse AtT-20, mouse myeloma cells, rat GH3, HEK293 T cells, and human FL cells, etc. are used. Especially, the transformation of animal cells can be exe-



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cuted according to methods described in, for example, *Cell Tehcnology* separate volume 8, *New Experimental Protocol of Cell Technology* (1995), vol. 263, published by SHUJUNSHA Co., Ltd., and Virology (1973), vol.52, issue 456.

**[0037]** Cells naturally expressing PD-L1 or PD-L2 can be also used. Such cells include leukocyte, suitablely, monocytes, macrophages or antigen-presenting cells, epithelial cells, tumor cells, carcinoma cells, or those cell lines, etc. As tumor cells or carcinoma cells, for example, P38D1 cells, P815 cells, NB41A3 cells, MDA-231 cells, SKBR-3 cells, MCF-7 cells, BT474 cells, J558L cells, P3U1 cells, PAI cells, X63 cells, or SP2/0 cells can be used. Cells infected with pathogens, which express PD-L1 or PD-L2 naturally or compellingly, can be used. Infectious pathogens include human hepatitis virus (hepatitis B, hepatitis C, and hepatitis A) or hepatitis E), human retrovirus, human immunodeficiency virus (HIV1 and HIV2), human T cell leukemia virus, human T lymphocytic virus (HTLV1 and HTLV2), simple herpes virus type 1 or 2, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, human herpesvirus including human herpesvirus 6, poliovirus, measles virus, rubella virus, Japanese encephalitis virus, mumps virus, influenza virus, adenovirus, enterovirus, rhinovirus, virus developing severely acute respiratory syndrome (SARS), Ebola virus, West Nile virus, or these virus modified artificially. Other pathogens include, for example, pathogenesis protozoan (for example, trypanosome, malaria, and toxoplasma), bacillus (for example, mycobacterium, salmonella, and listeria) or fungus (for example, candida), etc.

**[0038]** The lymphocytes used in the screening method of the present invention are T or B lymphocytes, and suitably cytotoxic T lymphocytes (CTL). The immune reaction of lymphocytes in the screening method of the present invention includes citotoxic response (for example, tumor immunity reaction), mixed lymphocyte reaction, production of cytokines, antibodies, complements or other cell surface antigens, or cellular proliferation, etc.

**[0039]** In the present invention, the screening method of an active ingredient contained in the composition for immunopotentiation or cancer treatment can be executed by measuring cytotoxic activity of cytotoxic T lymphocytes against subject cells followed by measuring an effect of a subject substance against the activity. This method is an assay of recovery and reinforcement of cytotoxic activity by adding the subject substance to a culture mixed cytotoxic T lymphocytes (CTL) naturally expressing PD-1 or cell lines (for example, 2C cells) with cells naturally or compulsorily expressing PD-L1 or PD-L2 which are derived from syngeneic mouse. Since the cytotoxic activity against PD-L1 or PD-L2 expressing cells is lower than that against PD-L1 or PD-L2 non-expressing cells, this method has a feature of which the recovery of cytotoxic activity (rising part) due to the subject substance can be measured more clearly. The recovery of cytotoxicity due to the subject substance can be evaluated as an equivalent to inhibition of suppression of cytotoxicity. Further, it is preferable that the the cytotoxicity due to the subject substance is arbitrarily measured. As these cells, tumor cell lines or carcinoma cell lines naturally expressing PD-L1 or PD-L2 (*Nature Immunology* (2001), vol. 2, issue 3, p.261-267.), for example, P38D1 cells, P815 cells, NB41A3 cells, MDA-231 cells, SKBR-3 cells, MCF-7 cells, BT474 cells, J558 L cells, P3U1 cells, PAI cells, X63 cells, or SP2/0 cells can be used, and tumor cell lines or carcinoma cell lines transformed so as to stably or transiently express PD-L1 or PD-L2 can be also used.

**[0040]** On the other hand, it is preferable that the cytotoxic lymphocytes are PD-1 expressing cells derived from syngeneic animal to targeted cells.

**[0041]** In the present invention, the screening method of an active ingredient contained in the composition for infection treatment is an assay of enhancement effect on immune reaction of lymphocytes to infected cells or inhibitory effect on proliferation activity of pathogen or virus by adding the subject substance to a culture mixed cytotoxic T lymphocytes (CTL) or cell lines (for example, 2C cells) naturally expressing PD-1 with cells naturally or compulsorily expressing PD-L1 or PD-L2 which are derived from syngeneic mouse and was infected with pathogen or virus.

**[0042]** Further, in evaluations using a similar principle, a mammal created by transplanting the above carcinoma cell lines for screening which are transformed so as to express PD-L1 or PD-L2 or cells naturally expressing PD-L1 or PD-L2 to a syngeneic mammal can be used. To a manufacture method of the mammal, a process of transplanting cells and a process of breeding the mammal until becoming appropriate for the evaluation is indispensable. This evaluation is characterized in evaluating proliferation of the transplant cells and the amount of production of various cytokines or cell surface antigens, especially, in case of carcinoma cells, proliferation, permeation, or histological analysis of metastasis of the cells, or survival rates of the transplanted mammal. The cellular proliferation can be evaluated as the number of carcinoma cells per unit capacity in case of ascites tumors or blood cancers, or the size or the weight after removing in case of solid cancer. The effect of the subject substance for cancer treatment in this method can be evaluated as an equivalent to effect due to inhibition of suppression of cytotoxicity caused in PD-L1 or PD-L2. As such cells, syngeneic cells to a mammal for transplant, with good proliferation are more suitable. The mammal include s primates except human, mouse, rat, hamster, guinea pig, dog, pig, and ape.

## INDUSTRIAL AVAILABILITY

**[0043]** As a substance that demonstrates remarkable suppression of cancer proliferation and life prolongation of an individual by administering to the carcinoma cells-



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transplanted animal model, the present inventors invented each specific antibody (anti-PD-1 antibody and anti-PD-L1 antibody) that inhibited PD-1 and PD-L1 function respectively. These antibodies showed actions that recover or reinforce cytotoxic activity that has relatively decreased by presenting PD-L1 ligand to PD-1-expressing CTL (cytotoxic T lymphocyte) (example 1 and figure.1.). This suggests that the cytotoxic activity to carcinoma cells by CTL could be reinforced by administering these antibodies. In the carcinoma cells-transplanted animal model (*Protein, Nucleic acid, and Enzyme* (1981), vol.26, issue 3, p.208-22.) which uses syngeneic mouse of which cell lines artificially expressing PD-L1 derived from mastocytomas have been imported, administration of anti-PD-L1 antibody presented suppression of proliferation, invasion, and metastasis of carcinoma cells, and life prolongation of an individual (figure 2 and 3.). It was suggested that inhibition of PD-1 function or production could achieve an effect similar to the effect on inhibition of PD-L1 function by this antibody. This is based on non-proliferation of imported carcinoma cells in the cancer imported model using PD-1-deficient mice, and presents that inhibition of PD-1 function or production could be effective on cancer treatment (Example 5 and figure.3.).

**[0044]** Actually, it had been proven that administration of anti-PD-1 antibody significantly suppressed metastasis of imported carcinoma cells to liver in the cancer imported animal model (Example 13).

**[0045]** The inventors presented that the substance that inhibits the immunosuppressive signal induced by PD-1, PD-L1 or PD-L2 was useful for infection treatment (Example 11, figure.15 and 16).

**[0046]** These results experimentally presented by the present inventors prove that only PD-1 antibody or PD-L1 antibody don't presents aforementioned effect, but also any substance that can inhibit the immunosuppressive signal from PD-1, PD-L1, or PD-L2 present almost similar effect. The substances with such effects include, for example, anti-PD-L2 antibody, soluble PD-1, soluble PD-L1, soluble PD-L2, PD-1 antagonists, PD-L1 antagonists, PD-L2 antagonists, substances that inhibits interaction between PD-1 and PD-L1 or PD-1 and PD-L2, PD-1 production inhibitors, PD-L1 production inhibitors, PD-L2 production inhibitors, and intracellular inhibitory signal inhibitors by PD-1.

**[0047]** Cancer or tumour of which the therapeutic potential could be expected by administration of the composition for cancer treatment of the present invention include, for example, carcinoma, squamous carcinoma (for example, cervical canal, eyelid, tunica conjunctiva, vagina, lung, oral cavity, skin, urinary bladder, tongue, larynx, and gullet), and adenocarcinoma (for example, prostate, small intestine, endometrium, cervical canal, large intestine, lung, pancreas, gullet, intestinum rectum, uterus, stomach, mammary gland, and ovary). Further, they include sarcomata (for example, myogenic sarcoma), leukosis, neuroma, melanoma, and lymphoma.

**[0048]** The effect on the ones that remarkably express PD-L1 or PD-L2 in these cancers or tumours is remarkable. PD-L1 or PD-L2 expression can be identified by checking up surgically excised cancer, tumour mass, or lesioned part gathered outside of the body as a sample. Administration of the composition of the present invention will become an efficient and available method as a treatment after surgery for tumour or cancer patient that PD-L1 or PD-L2 is remarkably expressed. PD-L1 or PD-L2 expression can be identified by, for example, immunochemical method using PD-L1 antibody or PD-L2 antibody, RT-PCR, or DNA array.

**[0049]** A side reaction violently decreasing lymphocytes proliferation in chemotherapy and radiotherapy for cancer is inevitable. Administration of the composition of the present invention presents an effect on stimulating and proliferating the decreased lymphocytes and can suppress a fierce side reaction accompanied by usual chemotherapy to minimum. Further, it is similar as to radiotherapy. Concomitant use with the composition of the present invention can greatly decrease the dose of chemotherapy drug or the exposure dose of irradiation from the dose or the exposure dose used usually.

**[0050]** The composition for cancer treatment of the present invention can be used together with existing chemotherapy drugs or be made as a mixture with them. Such a chemotherapy drug include, for example, alkylating agents, nitrosourea agents, antimetabolites, antitumor antibiotics, alkaloids derived from plant, topoisomerase inhibitors, hormone therapy medicines, hormone antagonists, aromatase inhibitors, P-glycoprotein inhibitors, platinum complex derivatives, other immunotherapeutic drugs, and other anticancer agents. Further, they can be used together with hypoleukocytosis (neutrophil) medicines that are cancer treatment adjuvant, thrombopenia medicines, antiemetic drugs, and cancer pain medicines for patient's QOL recovery or be made as a mixture with them.

**[0051]** The composition for cancer treatment of the present invention can be used together with immunopotentiative substances or be made as a mixture with them. Such immunopotentiative substances include, for example, various cytokines and a tumor antigen, etc. Cytokines that stimulate immune reactions include, for example, GM-CSF, M-CSF, G-CSF, interferon-$\alpha$, $\beta$, $\gamma$, IL-1, IL-2, IL-3, and IL-12, etc. B7 ligand derivatives, anti-CD3 antibodies and anti-CD28 antibodies, and anti-CTLA-4 antibodies can also improve the immune reactions.

**[0052]** Administration of the tumor antigen can also improve a specific immune reaction against T lymphocytes against carcinoma cells and additionally or synergistically reinforce by using together with the composition for cancer treatment of the present invention. The tumor antigen can be prepared as a purified protein in case of an already-known gene, or as a lysate of carcinoma cells in case of an unknown gene.



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**[0053]** Such the tumor antigen includes, for example, HLA-A1 and HLA-A2 restrictive peptides of malignant melanoma MAGE-1 or MAGE-3, MART-1, and gp100. Further, they include HER2/neu peptide of mammary carcinomas and ovarian carcinomas, MUC-1 peptide of adenocarcinoma, and NY-ESO-1 of metastatic carcinomas.

**[0054]** It has been thought that viruses could use conjugate suppressive factors of T lymphocytes as one of methods to escape from host's immune-protection, It is thought that a part of virus infection could attribute the escape function of such viruses and administration of the composition of the present invention could improve the immune reaction of T lymphocytes to viruses.

**[0055]** Administration of the composition for infection treatment of the present invention is effective on treatment for, for example, human hepatitis virus (hepatitis B, Hepatitis C, hepatitis A, or hepatitis E), human retrovirus, human immunodeficiency virus(HIV1, HIV2), human T leukemia virus (HTLV1, HTLV2), or human lymphocytic cell type virus. Further, it is thought to be effective on treatment for simple herpes virus type 1 or 2, epstein-barr virus, cytomegalovirus, varicella-zoster virus, human herpesvirus including human herpesvirus 6, poliovirus, measles virus, rubella virus, Japanese encephalitis virus, mumps virus, influenza virus, adenovirus, enterovirus, rhinovirus, virus developing severely acute respiratory syndrome (SARS), ebola virus, west nile virus, or these virus modified artificially.

**[0056]** It is thought to be also effective on infection treatment for other pathogens such as, for example, pathogenesis protozoan (for example, trypanosome, malaria, and toxoplasma), bacillus (for example, mycobacterium, salmonella, and listeria) or fungus (for example, candida), etc.

**[0057]** The composition for infection treatment of the present invention can be used together with existing anti-HIV drugs, antiviral agents, antibiotic agents, antimicrobial agents, or visceral mycosis medicines or be made as a mixture with them. The anti-HIV drugs include, for example, reverse transcriptase inhibitors (for example, AZT, ddI, 3TC, and d4T), protease inhibitors (for example, saquinavir mesylate, ritonavir, nelfinavir mesylate, amprenavir, delavirdine mesylate, saquinavir, and lopinavir/ritonavir) or CCR5 receptor antagonists. The antiviral agents include, for example, anti-herpesvirus agents, anti-influenza virus agents, interferon-$\alpha$ and $\beta$, or various immunoglobulins.

**[0058]** The composition for infection treatment of the present invention can be used together with vaccines of virus or pathogen or be made as a formulation with them. Such vaccines include, for example, poliovaccine, measles vaccine, Japanese encephalitis vaccine, BCG vaccine, triple vaccine, mumps virus vaccine, varicella virus vaccine, influenza vaccine, hepatitis A vaccine, hepatitis B vaccine, and cholera vaccine.

**[0059]** The composition of the present invention is usually administered systemically or locally, and orally or parenterally.

**[0060]** The dosage is determined depending on medicines used for the present invention, age, body weight, symptom, therapeutic effect, administration route, and duration of the treatment, etc. For oral administration, generally, the dosage range from 1$\mu$g to 100mg per an adult is orally administered once to several times per day, or the dosage range from 0.1ng to 10mg per an adult is administered once to several times per day parenterally, suitably intravenously, and is intravenously administered for 1 to 24 hours per day continuously.

**[0061]** Since the dosage changes depending on various conditions as described above, there are cases in which doses lower or greater than the above dosage may be used.

**[0062]** When a concomitant drug of the composition of the present invention and other medicines is administered, it is used as solid medicines for internal use, and injections, external preparations, suppositoriums, inhalant, pernasal preparation, etc. for parenteral administration.

**[0063]** The solid medicines for oral administration include compressed tablets, pills, capsules, dispersing powders, granules, etc. The capsules include hard capsules and soft capsules. The tablets include sublingual tablets, intraoral strapping tablets, and intraoral speed disintegrators, etc.

**[0064]** As to such the solid medicines, one or more active compound(s) may be pharmaceutically manufactured as itself/themselves or a formulation with excipients (lactose, mannitol, glucose, microcrystal cellulose, and starch, etc.), binders (hydroxypropylcellulose, polyvinyl pyrrolidone, and magnesium metasilicate aluminate, etc.), disintegrators (cellulose calcium glycolate, etc.), lubricants (magnesium stearate etc.), stabilizers, or solubilizers (glutamate and aspartic acid, etc.), etc. according to usual methods. Further, they may be optionally coated by coatings (sucrose, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, etc.) or coated in the layer of two or more. Further, capsules of absorbable materials such as gelatin may be included.

**[0065]** The sublingual tablets are manufactured according to a well-known method. For example, they may be pharmaceutically manufactured as a mixture one or more active compound(s) with excipients (lactose, mannitol, glucose, microcrystal cellulose, colloidal silica, and starch, etc.), binders (hydroxypropylcellulose, polyvinylpyrrolidone, and magnesium metasilicate aluminate, etc.), disintegrator (starch, L-hydroxypropylcellulose, carboxymethylcellulose, crosscarmellose sodium, and cellulose calcium glycolate, etc.), lubricants (magnesium stearate etc.), swelling agents (hydroxypropylcellulose, hydroxypropylmethylcellulose, carbopole, carboxymethylcellulose, polyvinyl alcohol, xanthan gum, and Cyamoposis Gum, etc.), swelling adjuvants (glucose, fructose, mannitol, xylitol, erythritol, maltose, trehalose, phosphate salt, citrate, silicate, glycine,



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glutamate, and arginine, etc.), stabilizers, solubilizers (polyethylene glycol, propylene glycol, glutamate, and aspartic acid, etc.), or spices (orange, strawberry, mint, lemon, and vanilla, etc.), etc. according to usual methods. Further, they may be optionally coated by coatings (sucrose, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, etc.) or coated in the layer of two or more. Additives such as preservatives, anti-oxidants, coloring agents, and sweeteners used regularly may be optionally added.

**[0066]** The intraoral strapping tablets are manufactured according to a well-known method. For example, they may be pharmaceutically manufactured as a mixture one or more active compound(s) with excipients (lactose, mannitol, glucose, microcrystal cellulose, colloidal silica, and starch, etc.), binders (hydroxypropylcellulose, polyvinylpyrrolidone, and magnesium metasilicate aluminate, etc.), disintegrator (starch, L-hydroxypropylcellulose, carboxymethylcellulose, crosscarmellose sodium, and cellulose calcium glycolate, etc.), lubricants (magnesium stearate etc.), swelling agents (hydroxypropylcellulose, hydroxypropylmethylcellulose, carbopole, carboxymethylcellulose, polyvinyl alcohol, xanthan gum, and Cyamoposis Gum, etc.), swelling adjuvants (glucose, fructose, mannitol, xylitol, erythritol, maltose, trehalose, phosphate salt, citrate, silicate, glycine, glutamate, and arginine, etc.), stabilizers, solubilizers (polyethylene glycol, propylene glycol, glutamate, and aspartic acid, etc.), or spices (orange, strawberry, mint, lemon, and vanilla, etc.), etc. according to usual methods. Further, they may be optionally coated by coatings (sucrose, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, etc.) or coated in the layer of two or more. Additives such as preservatives, anti-oxidants, coloring agents, and sweeteners used regularly may be optionally added.

**[0067]** The intraoral speed disintegrators are manufactured according to a well-known method. For example, they may be pharmaceutically manufactured as one or more active compound(s) itself/themselves or a mixture bulk or granulated bulk particle with suitable coatings (ethyl cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and acrylic acid methacrylate copolymer, etc.), plasticizers (polyethylene glycol and triethyl citrate, etc.), excipients (lactose, mannitol, glucose, crystallite cellulose, colloidal silica, and starch, etc.), binders (hydroxypropylcellulose, polyvinyl pyrrolidone, and magnesium metasilicate aluminate, etc.), disintegrators (starch, L-hydroxypropylcellulose, carboxymethylcellulose, crosscarmellose sodium, and cellulose calcium glycolate, etc.), lubricants (magnesium stearate etc.), dispersant adjuvants (glucose, fructose, mannitol, xylitol, erythritol, maltose, trehalose, phosphate salt, citrate, silicate, glycine, glutamate, and arginine, etc.), stabilizers, solubilizer (polyethylene glycol, propylene glycol, glutamate, and aspartic acid, etc.), spices (orange, Strawberry, Mint, lemon, and vanilla, etc.) etc. according to usual methods. Further, they may be optionally coated by coatings (sucrose, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, etc.) or coated in the layer of two or more. Additives such as preservatives, anti-oxidants, coloring agents, and sweeteners used regularly may be optionally added.

**[0068]** The liquid compositions for oral administration include pharmaceutically acceptable waters, suspensions, emulsions, syrups, and elixirs, etc. As to such liquid medicines, one or more active compound(s) may be dissolved, suspended, or emulsified to generally used diluent (purified water, ethanol or those mixing liquids, etc.). Further, those liquid medicines may contain humectants, suspending agents, emulsifying agents, sweeteners, flavor agents, flavoring agents, preservatives, and buffers, *etc.*

**[0069]** The external preparations for parenteral administration include, for example, ointments, gels, creams, fomentations, patchs, embrocations, aerosols, inhalants, sprays, aerosols, eye drops, and nasal drops, etc. These include one or more activator(s) and are manufactured by a well-known method or the formula usually used.

**[0070]** The ointments include one or more activator(s) and are manufactured by a well-known method or the formula usually used. For example, they are manufactured by levigating and melting one or more activator(s) to basis.

**[0071]** The ointment bases are chosen from a well-known or the one usually used. They are used mixing one or two or more kinds chosen from, for example, higher fatty acid or higher fatty acid ester (adipic acid, myristic acid, palmitic acid, stearic acid, oleic acid, adipic acid ester, myristic acid ester, palmitate, stearic acid ester, and oleic acid ester, *etc.*), rows (yellow wax, spermaceti, and ceresin, *etc.*), surfactants (polyoxyethylene alkyl ether phosphate etc.), higher alcohols (cetanol, stearyl alcohol, and cetostearyl alcohol, *etc.*), silicone oils (dimethylpolysiloxane *etc.*), hydrocarbons (hydrophilic petrolatum, white petrolatum, purified lanolin, and liquid paraffin, *etc.*), glycols (ethylene glycol, diethylene glycol, propylene glycol, polyethylene glycol, and macrogol, *etc.*), vegetable oils (castor oil, olive oil, sesame oil, and oil of turpentine, *etc.*), animal oils (mink oil, yolk oil, squalane, and squalene, *etc.*), water, absorption enhancer, and poisoned inhibitor. Further, they may include moisturizing agents, preservatives, stabilizing agents, anti-oxidants, and flavors, *etc.*

**[0072]** The gels are manufactured by a well-known method or a formula usually used. For example, they are manufactured by levigating and melting one or more activator(s) to a basis. The base is chosen from a well-known or the one usually used. It is used mixing one or two or more kinds chosen from, for example, lower alcohols (ethanol and isopropyl alcohol, etc.), gelatinizers (carboxymethylcellulose, hydroxyethyl cellulose, hydroxypropylcellulose, and ethyl cellulose, etc.), neutralizers (triethanolamine and diisopropanolamine, etc.),



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surfactants (mono-stearic acid polyethylene glycol, etc.), gums, water, absorption enhancers, and poisoned inhibitors. Further, they may include preservatives, anti-oxidants, and flavors, etc.

**[0073]** The creams are manufactured by a well-known method or a formula usually used. For example, they are manufactured by levigating one or more activator(s) to a basis and spreading and rolling on the support after kneading. The base is chosen from a well-known or the one usually used. It is used mixing one or two or more kinds chosen from, for example, higher fatty acid esters, lower alcohols, hydrocarbons, polyhydric alcohols (propylene glycol, 1, 3-butylene glycol, *etc.*), higher alcohols (2-hexyl decanol and cetanol, *etc.*), and emulsifiers (polyoxyethylene alkyl ethers and fatty acid esters, *etc.*), water, absorption enhancers, and poisoned inhibitors. Further, they may include preservatives, anti-oxidants, and flavors, *etc.*

**[0074]** The fomentations are manufactured by a well-known method or a formula usually used. For example, they are manufactured by levigating one or more activator(s) to a basis and spreading and rolling on the support after kneading. The base is chosen from a well-known or the one usually used. It is used mixing one or two or more kinds chosen from, for example, thickeners (polyacrylic acid, polyvinyl pyrrolidone, arabic gum, starch, gelatin, and methyl cellulose, *etc.*), humectants (urea, glycerin, and propylene glycol, *etc.*), and fillers (china clay, flower of zinc, talc, calcium, and magnesium, *etc.*), water, absorption enhancers, and poisoned inhibitors. Further, they may include preservatives, anti-oxidants, and flavors, *etc.*

**[0075]** The patchs are manufactured by a well-known method or a formula usually used. For example, they are manufactured by levigating one or more activator(s) to a basis and spreading and rolling on the support after kneading. The base for the pacth is chosen from a well-known or the one usually used. It is used mixing one or two or more kinds chosen from, for example, high molecular basis, oils, fats, higher fatty acids, tackifiers, and poisoned inhibitors. Further, they include preservatives, anti-oxidants, and flavors, *etc.*

**[0076]** The liniments are manufactured by a well-known method or a formula usually used. For example, they are manufactured by dissolving, suspending, or emulsifying one or more activator(s) to one or two or more kinds chosen from water, alcohols (ethanol and polyethylene glycol, *etc.*), higher fatty acids, glycerins, soaps, emulsifiers, suspending agents, etc. Further, they may include preservatives, anti-oxidants, and flavors, *etc.*

**[0077]** The aerosols, the inhalants, and the sprays may contain stabilizers such as sodium hydrogen sulfite besides the diluent generally used, buffers giving isotonicity, and isotonic agents such as, for example, sodium chloride, sodium citrate, and citrates.

**[0078]** The injections for parenteral administration include solid shots that are dissolved or suspended to solution, suspension, emulsion, or time of use solvent. The injections are used by dissolving, levigating and melting one or more activator(s) to the solvent. As the solvent, for example, water for injection, distilled saline, vegetable oil, propylene glycol, polyethylene glycol, alcohols such as ethanol, *etc.*, and these combination are used. Further, this injection may include stabilizers, solubilizers (glutamate, aspartic acid, and polysorbate 80 (registered trademark), *etc.*), suspending agents, emulsifying agents, soothing agents, buffers, and preservatives, *etc.* These are sterilize in the final process or are manufactured from the aseptic manipulation. Aseptic solid medicines may be manufactured as a freeze-drying product and may be used by making to be aseptic or dissolving to aseptic distilled water for injection or other solvents before use.

**[0079]** The inhalant for parenteral administration includes aerosols, inhalant powders, or inhalant solutions, which may be used by making to dissolve or suspend to water or other suitable media at the time of use.

**[0080]** These inhalants are manufactured according to a well-known method.

**[0081]** For example, the inhalant solutions are prepared by properly selecting from preservatives (benzalkonium chloride and paraben, *etc.*), coloring agent, buffers (sodium phosphate and sodium acetate, *etc.*), tonicity agents (sodium chloride and concentrated glycerin, *etc.*), thickeners (carboxyvinyl polymer, *etc.*), and absorption enhancers, *etc.*, optionally.

**[0082]** The inhalant powders are prepared by properly selecting from lubricants (stearic acid and the salt, *etc.*), binders (starch and dextrin, *etc.*), excipients (lactose and cellulose, *etc.*), coloring agents, preservatives (benzalkonium chloride and paraben, *etc.*), and absorption enhancers, *etc.*, optionally.

**[0083]** When the inhalant solution is administered, a sprayer (atomizer and nebulizer) is usually used. When the inhalant powder is administered, an inhalation administering machine for powder is usually used.

**[0084]** Other compositions for parenteral administration contain one or more activator(s) and include suppository for intrarectal administration which is prescribed according to a routine procedure and pessary, *etc.* for intravaginal administering.

**[0085]** The sprays may contain a stabilizer such as sodium hydrogen sulfite besides the diluent generally used, a buffer giving isotonicity, and an isotonic medicine such as, for example, sodium chloride, sodium citrate, or citrates. Production methods of the sprays have been described in, for example, U.S. patent 2,868,691 specification and U.S. patent 3,095,355 specification in detail.

## BRIEF DESCRIPTION OF DRAWINGS

**[0086]**

Figure. 1 (A) shows a flow cytometry that presents



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PD-1 expression in H-2L$^d$-specific 2C CTL clone and PD-L1 expression of P815 (cell line derived from mastocytoma) stable transfectant clone, and (B) shows a cytotoxic activity of 2C CTL cell line to PD-L1-expressing P815 cell lines and the effect on the cytotoxic activity of anti-PD-L1 antibody (anti-PD-L1 F(ab')$_2$ IgG).

Figure.2 shows tumor growth and infiltrating of PD-L1-expressing P815 cell lines transplanted into syngeneic mouse. (A) shows the tumour volume (upper) of the transplanted PD-L1-expressing P815 tumours and the survival rate (under) after the transplant, (B) shows the tissue staining view of the transplanted PD-L1-expressing P815 tumour mass in syngeneic DBA/2 mouse (a shows a view (x40) that presents invasion of tumor cells across the abdominal wall and the peritoneum, b shows the same view (x400), c shows the view of invasion into spleen, and d shows the view of invasion into liver.).

Figure.3 shows in vivo effect of anti-PD-L1 antibody for the tumor growth of the transplanted PD-L1-expressing P815 cell lines in syngeneic mice. (A) shows in vivo effect of anti-PD-L1 antibody for IFN-γ production from the tumor-specific CD8+ T cells in mice, (B) shows in vivo effect of anti-PD-L1 antibody for the tumour volume (upper) and the survival rate (under) of the transplanted PD-L1-expressing P815 tumors in mice (squares show control group (rat IgG administrated group) and circles show anti-PD-L1 antibody (anti-PD-L1 F(ab')$_2$ IgG) administrated group in the figure.).

Figure.4 shows proliferation suppression of PD-L1-expressing B16 melanomas in homo-deficient syngeneic mice (PD-1 -/-).

Figure.5 shows in vivo effect of anti-PD-L1 antibody to tumor growth of transplanted myeloma cell lines in syngeneic mouse (BALB/c) and the involvement of PD-1. (A) shows a flow cytometry that shows PD-L1 expression in various myeloma cell lines, (B) shows in vivo effect of anti-PD-L1 antibody for tumor growth of J558L tumors transplanted in the above mouse, and (C) shows comparison of tumor growth of J558L tumors transplanted in wild type and PD-1 gene deficient (PD-1-/-) syngeneic mice.

Figure.6 shows PD-L1 expression in capillary endothelium. (A) shows PD-L1 and PD-L2 expression in vascular endothelial cells of mice heart. (B) shows tissue staining of PD-L1 expression in each tissue of mice. Each PD-L1 expression in (a): eyeball, (b): submandibular gland, (c): heart, (d): lungs, (e): liver, (f): kidney is shown. In the figure, Ch means choroidea, CV means middle cardiac vein, Gl means glomerule, and Re means retina. Each arrow shows vascular endothelial cells. Each staining image is enlargement view (x40).

Figure.7 shows PD-L1 expression in liver non-parenchymal cells.

Figure.8 shows cell surface molecule phenotype in Kupffer cells and liver sinusoidal endothelial cells (LSECs).

Figure.9 shows cell surface molecule phenotype in CD4 positive T cells of PD-1 gene homo-deficient mice (PD-1 -/-) or wild type mice (wt).

Figure.10 shows cell surface molecule phenotype in CD8 positive T cells of PD-1 gene homo-deficient mice (PD-1 -/-) or wild type mice (wt).

Figure.11 shows the effect of PD-L1 on T-cell proliferation in LNPC. (A) shows cellular proliferation when stimulating each naive T cells of PD-1 -/- mice and wt mice. (B) shows the effect of anti-PD-L1 antibody on cellular proliferation in the co-culture of T cells that has already been activated and derived from PD-1 -/- mice or wt mice and LNPC.

Figure. 12 shows the effect of PD-L1 on cytokine production in LNPC. (A) shows cytokine production when stimulating each naive T cell of PD-1 -/- mice and wt mice. (B) shows the effect of anti-PD-L1 antibody on cytokine production in the co-culture of T cells that has already been activated and derived from PD-1 -/- mice or wt mice and LNPC. (C) shows cell division of the activated T cells from PD-1 -/- mice or wt mice in the co-culture with LNPC.

Figure.13 shows the involvement of PD-1 in T lymphocytes proliferation in virus infected mouse liver. Cellular proliferation of CD19- and CD3-positive lymphoid cells in liver and spleen of PD-1 -/- mice or wt mice on (A) day 0 and (B) day 7 after adenovirus infection are shown.

Figure.14 shows the involvement of PD-1 to cellular proliferation of T lymphocytes in virus infected mouse liver. (A) shows cellular proliferation of CD4- and CD8-positive lymphoid cells in liver of PD-1 -/- mice or wt mice on day 7 after adenovirus infection. (B) shows the ratio of various proliferative lymphocytes on day 7 after the infection.

Figure.15 shows the involvement of PD-1 in virus infection. In this figure, (a) - (d) show tissue staining images that presents each cellular proliferation in liver of PD-1 -/- mice and wt mice on day 0 and day 7 after adenovirus infection. (e) and (f) show cellular proliferation of CD4- and CD8-positive T cells in PD-1 -/- mice on day 7 after adenovirus infection.

Figure.16 shows the involvement of PD-1 to virus infection. In this figure, (g) - (n) show hematoxylin & eosin tissue staining images in liver of PD-1 -/- mice and wt mice on day 0 and day 7 after adenovirus infection. (o) - (r) show X-gal tissue staining images in liver of PD-1 -/- mice and wt mice on day 0 and day 7 after adenovirus infection.

Figure.17 shows the enhancement of each material to cytotoxic activity. In this figure, (a) the enhancement of anti-mouse PD-1 antibody, (b) the enhancement of anti-mouse PD-L1 antibody, (c) the enhancement of mouse PD-1 Fc, and (d) the enhancement of human PD-1 Fc are shown.



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## BEST MODE FOR CARRYING OUT INVENTION

**[0087]** The following example explains the present invention more concretely, but do not limit the range of the present invention.

Example 1

**[0088]** A mouse PD-L1 expression vector was constructed by being inserted and ligated mouse PD-L1 cDNA (Journal of Experimental Medicine (2000), vol.19, issue7, p.1027-1034.) digested with restriction enzyme EcoRI to pApuroXS expression vector (*The EMBO Joumal* (1994), vol.13, issue6, p.1341-1349.). The expression vector pApuroXS-PD-L1 was transfected into P815 cells by electroporation (360V, 500μF). The P815 cells were cultured in RPMI-1640 medium including FCS (10%), 2-mercaptoethanol ($10^{-5}$M), and various antibiotics. The P815 cell lines which stably expressed mouse PD-L1 can be cloned by subculturing as resistant cells under medium including antibiotic puromycin (3μg/ml). PD-L1 expression can be confirmed by flow cytometric analysis. Figure 1(A) shows flow cytometries presenting (i) PD-1 expression of H-2L$^d$-specific 2C CTL clones and (ii) PD-L1 expression in PD-L1 expressing stable transformant of P815 (cell line derived from mastocytoma). Transformed B16 cell lines (B16/PD-L1) stably expressing PD-L1 were cloned by a similar method (figure. 1(A) (iii)-(v)). pEFBOSneo-PD-L1 (Nucleic Acid Research (1990), vol. 18, issue17, p.5322.) constructed as a expression vector by a similar method was used, and G418 (0.5mg/ml) was used for selective culture of the cell lines.

**[0089]** cDNA coding protein to connect tandem 6xhis peptide tag (His-Tag) to 3' end side of total length mouse PD-L1 cDNA was inserted in expression vector pVL1393 (the trade name: purchase from Clonetech) after being digested by restriction enzyme EcoRI and NotI. Then, this expression vector was continuously introduced to SF9 insect cells (purchased from Invitrogen), and the inclusion body was collected. This inclusion body virus was infected to HiFive insect cells (purchased from Invitrogen) by culturing for 2 days at 27°C. The purified PD-L1 protein that are used as antigen was obtained by processing cell lysate dissolved with buffer solution (Tris-HCl (50mM, pH7, and 1% TritonX-100), EDTA (10mM), and NaCl (150mM), various protease inhibitors) with Ni-sepharose column chromatography.

**[0090]** The dialyzed PD-L1 protein was immunized to female wister rat at 8 weeks age (purchased from SLC Japan) with a complete Freund adjuvant (purchased from Amersham) and after several days, $2\times10^8$ of cells collected from peripheral lymph node were fused with the same number of SP2/0 cells using PEG1500. Further, the fused cells were selected by culturing in RPM11640 medium (HAT (purchased from Sigma), Origen (10%, purchased from Igen), and FCS (10%), 2-mercaptoethanol ($10^{-5}$M), and various antibiotics), and the presence of the antibody production was confirmed by flow cytometric analysis. The monoclonal antibody (1-111) to PD-L1 was obtained by purification of the collected peritoneal fluid with protein G sepharose column chromatography after transfering the established hybridoma (hybridomas recognized with International Trust Number: FERM BP-8396) to Balb/C nu/nu mice. As antibodies used by flow cytometry, etc., biotinated antibodies using Sulfo-NHS-LC-biotin (the trade name: purchased from Pierce) can be used.

**[0091]** Further, anti-human PD-1 antibody (the monoclonal antibody producted from hybridomas recognized with International Trust Number: FERM BP-8392) was prepared according to a similar method.

**[0092]** Cytotoxicity assay was executed by $^{51}$Cr (chromium) separation assay.

**[0093]** 2C cells (*Journal of Immunology* (1996), vol. 157, issue2, p.670-678.) are (H-2L)$^d$ alloreactive cytotoxic T-cells derived from 2C transgenic B6 mice. After mixing 2C cells (E: effector) together with $^{51}$Cr-labeled P815 cells (T: target) (circle), three kinds of PD-L1-expressing P815 cells (P815/PD-L1) (square, diamond, and triangle) respectively, or further under the presence of 10mg/ml rat anti-PD-L1 F(ab')$_2$ IgG (filled triangle), a result of measuring separated $^{51}$Cr for 4 hours with various E/T ratio is shown in figure.1 (B).

**[0094]** Anti-PD-L1 antibody (anti-PD-L1 F(ab')$_2$) recovered the decreased cytotoxic activity of cytotoxic T lymphocytes. Those results suggested that inhibition of PD-1 and PD-L1 signal by inhibiting PD-L1 function could reinforce cytotoxic activity to carcinoma cells.

Example 2

**[0095]** The tumor growth and the survival rate of mice was evaluated by hypodermically transfering $1\times10^6$ of P815 cells (n=6) or P815/PD-L1 cells (n=6) to syngeneic DBA/2 mice respectively. The result is shown in figure. 2 (A). In this figure, circles show P815 cell lines transplanted group, and squares and triangles show PD-L1-expressing P815 cell lines transplanted group respectively. Further, histological analysis of P815/PD-L1 cells transferred group was executed. Figure.2(B) shows staining images dyed with hematoxylin & eosin after being fixed by 10% formaldehyde and embedded into paraffin. In this figure, a shows a view (x40) that presents invasion of tumor cells across the abdominal wall and the peritoneum, b shows the same view (x400), c shows the view of invasion into spleen, and d shows the view of invasion into liver.

**[0096]** In the P815 cells transplanted group, P815 cells proliferation was suppressed and 30 percent of mice in this group lived by 6-7 weeks, while in PD-L1-expressing P815 cells (P815/PD-L1) transplanted group, carcinoma cells proliferation was remarkable and all mice died by 2-4 weeks (figure.2(A)). P815/PD-L1 cells were observed to permeate across the peritoneal cavity and the abdominal cavity, and further those metastases



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to liver and spleen (figure. 2(B) a-d).

Example 3

**[0097]** After co-culturing $2x10^6$ of 2C cells togather with $5x10^6$ of P815 cells or P815/PD-L1 cells only, or P815/PD-L1 cells under the presence of 10mg/ml rat anti-PD-L1 $F(ab')_2$ IgG respectively, IFN-γ in culture supernatant at 24 hours was measured with ELISA kit (purchased from Bioscience). The result is shown in figure. 3 (A).

**[0098]** Figure.3 (B) shows the result of evaluating of the tumor growth and the survival rate of mice of which anti-rat IgG (square) or anti-PD-L1 $F(ab')_2$ IgG (0.1mg/mouse) (circle) was intraperitoneally administered to syngeneic DBA/2 mice(n=10) to which $3x10^6$ of P815/PD-L1 cells had been hypodermically transferred on day 1, 3, 5, and 7 after the cell-transfer.

**[0099]** Anti-PD-L1 antibody restored IFN-γ production from cytotoxic T lymphocytes which had been suppressed by P815/PD-L1 (figure. 3(A)). Administration of anti-PD-L1 antibody suppressed carcinoma cell growth, and showed the clear survival effect (figure. 3(B)). This result presents that administration of anti-PD-L1 antibody is effective on cancer treatment.

Example 4

**[0100]** $1\times10^6$ of B16 melanomas (n=6) or B16/PD-L1cells (n=6) were hypodermically transferred to B6 mice (n=6) respectively, and the same number of B16/PD-L1 cells were transferred to PD-1 transgenic B6 mice (n=5) and PD-1 gene homo-deficient B6 mice (PD-1/-(n=4)) (*Science*(2001), vol. 291, issue5502, p. 319-332.), each tumor growth was measured by 25 days thereafter. Figure.4 shows the result.

Example 5

**[0101]** Tumor growth of which (n=9) anti-rat IgG or anti-PD-L1 $F(ab')_2$ IgG (0.1mg/mouse) was intraperitoneally administered to syngeneic Balb/C mice to which $2.5\times10^8$ of J558 myeloma cells had been hypodermically transferred on day 3, 5, and 7 after the cell-transfer was evaluated. Each tumor growth in PD-1 gene homo-deficient Balb/C mice and Balb/C mice (n=4) to which J558 myeloma cells had been hypodermically transferred were compared (figure 5(B)).

**[0102]** Administration of anti-PD-L1 antibody suppressed PD-L1-expressing J558 carcinoma cells proliferation (flow cytometries of PD-L1 expression in various myeloma cell lines are shown in figure. 5(A))(figure.5 (B)). The transplanted tumor cells proliferation was completely inhibited in PD-1-deficient mice to which J558 cells had been transplanted (figure. 5(c)). These results present that inhibition of PD-L1 or PD-1 is effective on cancer treatment.

Example 6

**[0103]** Vascular endothelial cells (hereafter, abbreviated as ECs) was gathered from mouse heart by the method of Marelli-Berg (*Journal of immunological methods* (2000), vol. 244, issuel-2, p.205-215.). Concretely, heart tissue digested by collagenase was pre-cultured followed by being pre-cultured with mouse Ig and co-cultured together with FITC-modified anti-CD3 antibody, the same modified anti-CD105 antibody, the same modified anti-isolectin B4 antibody, and anti-FITC bead. These vascular endothelial cells were purified by positive selection using Magnetic-activated cell-sorting separation columns (the trade name: purchased from Miltenyi Biotec).

**[0104]** PD-L1 and PD-L2 expressions in the gathered vascular endothelial cells were confirmed by flow cytometry. The cell labelling was executed using anti-PD-L1 antibody (the antibody name: 1-111), anti-PD-L2 antibody (the antibody name: #122), and fluorescent labelling second antibody (figure. 6(A)). The analysis was executed 10,000 events with Facscalibur (the equipment name: purchased from Becton Dickinson) using CellQuest software (purchased from Dickinson). PD-L1 or PD-L2 expression is shown as shedding curve, and control Ig is shown as filling curve.

**[0105]** PD-L1 expression in each mouse tissue was confirmed by tissue staining. Before 1 hour each tissue sampling, 100μl of PBS which 100μg of biotin-labelling anti-PD-L1 antibody (1-111) had been dissolved was intravenously administered to mouse. Then, 5μm frozen section was fixed by 4% paraformaldehyde (PFA), and dyed with Streptavidin-FITC. Each section was countered staining by Phalloidin(Figure. 6(B) shows PD-L1 expression in (a) eyeball, (b) submaxillary gland, (c) heart, (d) lung, (e) liver, (f) kidney. In this figure, Ch presents choroid, CV presents vena centralis, Gl presents glomerule, and Re presents retina. Each arrow presents vascular endothelial cells. Each staining figure is 40 x enlargement view.). PD-L1 expression was observed in capillary endothelium of heart, lung, kidney, stomach, small intestine, submandibular gland, eyeball, and liver. The expression in liver was localized in liver sinusoidal capillary.

Example 7

**[0106]** PD-L1 expression in liver non-parenchymal cells (hereafter, abbreviated with LNPCs) was confirmed by tissue staining (figure. 7(A)) and flow cytometry (figure. 7(B)). In the tissue staining, 5μm liver frozen section fixed with 3% of PFA was preprocessed by rat serum followed by being reacted for 1 hour at room temperature using biotin-labeled anti-PD-L1 antibody (1-111) or biotin-labeled anti-ICAM-1 antibody (the trade name: purchased from BD Pharmingen), and then the biotin antibodies were visualized by tyramide signal amplification (TSA) fluorescence system (the equipment



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name: purchased from PerkinElmer Life Sciences) (figure. 7(A) shows ICAM-1 expression, figure. 7(B) shows PD-L1 expression, and CV presents vena centralis. Each staining figure is 40 x enlargement view.).

**[0107]** LNPCs were isolated from mouse liver according to the pronaseE method (*Experimental Cell Research* (1976, vol. 99, p.444-449.). Concretely, LNPCs obtained by which liver is circulated with pronaseE solution (Merck) were cultured and were separated by density gradient centrifugation. Relative distribution of Kupffer cells (CD54+, CD11bhigh) in the cell suspension is 20-25%, and that of liver perisinusoidal space endothelial cells (hereafter, abbreviated with LSECs.) (CD54+, CD11bhigh) is 75-80%. Kupffer cells and LSECs were doubly stained using FITC-labeled anti-CD11b antibody, each biotinated monoclonal antibody to ICAM-1, PD-L1, B7-1, and B7-2, and PE-labeled Streptavidin, respectively. Kupffer cells and LSECs were gate as CD11b high and CD11b low cell, respectively (figure. 8).

**[0108]** PD-L1 expressed together with ICAM-1, B7-1, and B7-2 in Kupffer cells, while the expression was weak in LSECs (figure. 8).

Example 8

**[0109]** Native T cells were refined (refining degree 90% or more) from spleen and lymphoid of PD-1 gene homo-deficient mice (PD-1 -/-) or wild type C57BL/6 mice (wt) by a negative selection using T-cell enrichment column (the trade name: purchased from Genzyme). The cells cultured for 48 hours with 10μg/ml of anti-CD3 monoclonal antibody (2C11) were activated. The naive T cells activated by the above method were doubly stained using FITC-labeled anti-CD4 antibody or APC-labeled anti-CD8 antibody, PE-labeled anti-CD25 antibody, PE-labeled anti-CD4 antibody, PE-labeled anti-CD69 antibody, or PE-labeled anti-CTLA-4 antibody, biotin-labeled anti-B7-1 (CD80) antibody or biotin-labeled anti-87-2 (CD86) antibody, and anti-PD-1 antibody (the antibody name: J43, monoclonal antibody producted from hybridomas recognized by International Trust Number FERM BP-8118) or anti-PD-L1 antibody (1-111), and each molecule expressions were analyzed by flow cytometry (figure. 9 and 10).

**[0110]** The hybridomas identified by International Trust Number FERM BP-8118 had been deposited as Trust Number FERM P-18356 to National Institute of Advanced Industrial Science and Technology, International Patent Organism Depositary in Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan (ZIP code 305-8566) at May 30, 2001, and was transferred to International Deposit at July 16, 2002.

Example 9

**[0111]** The naive T cells activation of PD-1 gene homo-deficient mice (PD-1 -/-) or wild type mice (wt) was executed by the method described in example 8. Proliferation of these activated cells was measured by BrdU incorporation method (figure. 11(A)). The proliferation was measured by adding BrdU at the last 6 hours of 48 hours to label the cells and measuring using Proliferation ELISA kit (the trade name: Purchased from Roche). The amount of IFN-γ production at this time was measured in ELISA Kit (the trade name: purchased from Genzyme) (figure. 12(A)).

**[0112]** T cells derived from PD-1 gene homo-deficient mice (PD-1 -/-) or wild type mice (wt) was beforehand activated by the method described in example 8. The activated T cells were respectively cultured for 60 hours under the presence or the absence of Mitomycin C-processed LNPCs of wild type mice and under the presence or the absence of 30μg/ml of anti-PD-L1 antibody (1-111) (rat IgG as control) and 20μg/ml of CTLA4-Ig (Genzyme) (human IgG as control), and the cells proliferation for the last 12 hours was measured by BrdU incorporation method (figure. 11(B)). Further, the amount of IFN-γ production at 48 hours was measured (figure. 12(B)).

**[0113]** As to the amount of IFN-γ production when naive T cells were activated, a significant difference between PD-1 -/- and wild type mice was not observed. On the other hand, in the activated T cells, the amount of IFN-γ production of T cells derived from wild type mice was significantly lower than that derived from PD-1 -/- (figure. 12). Therefore, it was suggested that the effect of PD-1 inhibitory action on the activated T cells could be higher than the effect on naive T cells activation.

**[0114]** In co-culture of the activated T cells derived from wild type mice and LNPCs, a significant difference in the cellular proliferation and the amount of IFN-γ production of these T cells was not observed, while in the co-culture of the activated T cells derived from PD-1-/- mice and LNPCs, a significant increase in the cellular proliferation of these T cells was observed (figure. 11 (B), figure. 12(B)). In adding anti-PD-L1 antibody to the co-culture of the activated T cells derived from wild type mice and LNPCs, an increase in the cellular proliferation of these T cells was observed (figure. 11(B)). These results suggest that PD-1 or PD-L1 of LNPCs could take part in suppression of T cells activation and lack of PD-1 or inhibition of interaction between PD-1 and PD-L1 could activate T cells.

**[0115]** The activated T cells of PD-1 gene homo-deficient mice (PD-1 -/-) or wild type mice (wt) was labeled by 5μM CFSE (5-(6)-carboxy-fluorescein diacetate succinimidyl diester) (the trade name: purchased from Molecular probes) and was co-cultured together with LNPCs for 48 hours. Cell division at this time was decided by CFSE activity measurement using FACS (figure. 12(C)).

**[0116]** It was suggested that the cellular proliferation suppression of the activation T cells could cause in cytostasis suppression and PD-1 signal could suppress cell division of T cells (figure. 12(C)).



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Example 10

**[0117]** PD-1 gene homo-deficient mice (PD-1-/-) or wild type mice (wt) (3 per a group) were infected in adenoviruses by intravenous administration of $10^9$-$10^{10}$ PFU (plaque-forming units) of Ad-lacZ. Ad-lacZ used here, which are 5 type adenovirus with lacZ gene; lacks E1 and E 3 region and can be purified by cesium chloride density-gradient centrifugation (*Nucleic Acid Research* (1995), vol. 234,issue19, p.3816-3821.) after proliferating them in 293 cells. On day 0 or 7 after infection, spleen cells and intrahepatic lymphocytes that had been gathered after intravenous administration of 0.5mg of BrdU (the trade name: purchased from Sigma) to the mice at 1 hour before slaughtering were doubly labeled by anti-BrdU antibody and anti-CD19 antibody, or anti-CD3 antibody (figure. 13).

**[0118]** The cells on day 7 after infection were doubly labeled by anti-BrdU antibody, anti-CD19 antibody, anti-CD3 antibody, anti-CD4 antibody, and anti-CD8 antibody (figure. 14(B), each bar graph shows the ratio of BrdU-positive cells.).

**[0119]** In adenovirus infected PD-1-/- mice liver, the ratio of each proliferative (BrdU positive) lymphocyte (CD19 positive, CD3 positive, CD4 positive, or CD8 positive) had increased compared to that in similarly infected wild type mice liver. On the other hand, since such a phenomenon in spleen was not observed, it was suggested that PD-1 could inhibit T cells proliferation in inflammatory tissues (figure. 14(B)).

Example 11

**[0120]** On day 0 or 7 after $10^9$-$10^{10}$ PFU of Ad-lacZ had been intravenously administered to PD-1 gene homo-deficient mice (PD-1-/-) or wild type mice (wt) (3 per a group), liver slices that had been gathered after intravenous administration of 0.5mg of BrdU (the trade name: purchased from Sigma) to the mice at 1 hour before slaughtering were doubly labeled by anti-BrdU antibody (figure. 15(a)-(d), 20x enlargement view.). Liver slices of PD-1 gene homo-deficient mice (PD-1-/-) on day 7 after infection were doubly labeled by anti-BrdU antibody, anti-CD19 antibody, anti-CD3 antibody, anti-CD4 antibody, and anti-CD8 antibody (figure. 15(e), (f), 40 x enlargement view.).

**[0121]** In wild type mice liver on day 30 after infection, the locally and medium cell invasion to sinusoidal capillary and non-parenchymal region was observed, but in PD-1-/- mice, hepatitis symptom was not observed (figure. 16(h), (i) and (i), (n)).

**[0122]** Liver slices of PD-1 gene homo-deficient mice (PD-1-/-) or wild type mice (wt) on day 7 or 30 after infection were stained by hematoxylin & eosin (figure. 16 (g)-(j), 20 x enlargement view, (k)-(n), 40 x enlargement view.) and X-gal (figure. 16 (o)-(r), 40 x enlargement view.). These results presented that PD-1 signal could take part in the exclusion of viruses by which the proliferation of effector T cells in virus infected tissue could be induced.

Example 12

**[0123]** P-815/PD-L1 cells compellingly expressing mouse PD-L1 were sown into culture flask and were cultured in usual medium including 5μg/mL of puromycin (purchased from Sigma)(hereafter, abbreviated as selective medium) at 37°C under 5% $CO_2$/95% air until to be 50%-90% confluent. Mouse cytotoxic T lymphocyte 2C cells were subcultured for several days in usual medium together with P-815 cells processed by MMC (Mitomycin C) and culture supernatant of ConA-stimulated rat splenic cells. The collected P-815/PD-L1 cells were cultured for 15 minutes after adding 3μL of BATDA Reagent of DELFIA EuTDA Cytotoxicity Reagents (purchased from PerkinElmer). Then, they were washed with PBS. 2C cells subcultured for 5-8 days after adding P-815 cells were used.

**[0124]** As subject substrates, 20μL(10ng/mL) of anti-mouse PD-1 antibody (figure. 17, anti-mPD-1Ab(J43)), anti-mouse PD-L1 antibody (anti-mPD-L1Ab(1-111) in this figure), mouse PD-1 Fc (mPD-1Fc in this figure), human PD-1Fc (hPD-1Fc in this figure), mouse IgG2ak (Control Ig in this figure), or PBS were dispensed into 96 well plate, and then 50μL of P-815/PD-L1 cells or usual medium were added. Further, 50μL of 2 C cells, usual medium, or usual medium including 1% Triton x 100 were added. 50μL of supernatants in wells which the usual medium were added were collected for background and other supernatants were preserved at 37°C until being collected. The residual cells were cultured for 4 hours. The 96 well plates were centrifuged and the supernatants were collected. 200μL of DELFIA Europium Solution of Cytotoxicity Reagents (purchased from PerkinElmer) were added to the collected supernatants, and were shaken for 15 minutes. After shaking, time resolved fluorescence measurement was executed with ARVOsx multi-label counter (WALLAC). The supernatants in wells that the usual medium including 1% Triton x 100 was added were used as a high control, and the one in wells that the usual medium were used as a low control.

**[0125]** The evaluated group is composed of a subject substrate, P-815/PD-L1 cells, and 2C cells, the high control group is composed of PBS, P-815/PD-L1 cells, and usual medium including 1% Triton x 100, and the low control group is composed of PBS, P-815/PD-L1 cells, and usual medium, the 2C cell control group is composed of PBS, usual medium, and 2C cells, and the background group is composed of PBS, P-815/PD-L1 cells, and usual medium. CTL activity (%) was calculated by the following formula. All values are the one that had been subtracted by the average of the background.

**[0126]** CTL activity (%) = ([the measurement of the evaluation group] - [the measurement of the 2C cell control group] - [the measurement of the low control group])



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/ ([the measurement of the high control group] - [the measurement of the low control group]) x 100

**[0127]** Anti-PD-1 antibody, anti-PD-L1 antibody, and PD-1 Fc have significantly reinforced CTL activity (figure.17 (a)-(d), E: T ratio presents the mixing ratio of 2C cells and PD-L1/P815 cells.).

Example 13

**[0128]** The inhibiting effect of anti-PD-1 antibody on cancer metastasis was evaluated by intraperitoneal administration of anti-mouse PD-1 monoclonal antibody to C57BL/6 mice to which B16 melanoma cells had been transferred at intervals of 2 days followed by measuring the liver weight on day 18 after transfer.

**[0129]** The increase in the liver weight of anti-PD-1 antibody administrated group was significantly suppressed than that in control IgG administrated control group (liver weight/carcinoma cell non-transferred group: 1.3g, decrease from control group: 6.8g to anti-PD-1 antibody administrated group: 3.5g.). The suppression of the increase in this weight presents that the metastasis of B16 melanoma cells is suppressed.

## Claims

1. An immunopotentiative composition comprising an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

2. A composition for treatment of cancer comprising the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

3. The composition for treatment of cancer according to claim 2, which is a composition that suppresses cancer metastasis.

4. A composition for treatment of infection comprising an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

5. The composition for treatment of cancer according to claim 2 or 3, which acts through immunopotentiation.

6. The composition for treatment of infection according to claim 4, which acts through immunopotentiation.

7. The composition according to any one of claims 1 to 6, wherein the immunosuppressive signal inhibitor is one or more selected from an interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, an intracellular signaling inhibitor of PD-1, and a production inhibitor of PD-1, PD-L1 or PD-L2.

8. The composition according to claim 7, wherein the interaction inhibitor of PD-1 and PD-L1 is one or more selected from a PD-1 antibody, a PD-L1 antibody, soluble PD-1, and soluble PD-L1.

9. The composition according to claim 8, wherein the PD-1 antibody is selected from an anti-human PD-1 antibody produced by a hybridoma internationally deposited as FERM BP-8392, a humanized anti-PD-1 antibody of a non-human antibody, and a human anti-human PD-1 antibody.

10. The composition according to any one of claims 1 to 6, wherein the immunosuppressive signal inhibitor is a lymphocyte in which PD-1 expression is inhibited by gene-recombination.

11. The composition according to claim 7, wherein the interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, the intracellular signaling inhibitor of PD-1, or the production inhibitor of PD-1, PD-L1 or PD-L2 is one or more substances selected from a protein, a polypeptide, a peptide, a polynucleotide, a polynucleoside, an antibody or a derivative thereof, an organic synthesis compound, an inorganic compound, and a natural product.

12. An immunopotentiative method, which comprises administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

13. A method for treatment of cancer, which comprises administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

14. The method for treatment of cancer according to claim 13, which suppresses cancer metastasis.

15. A method for treatment of infection, which comprises administering the immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2.

16. The method for treatment of cancer according to claim 13 or 14, which is acted through immunopotentiation.

17. The method for treatment of infection according to claim 15, which is acted through immunopotentiation.

18. The method according to any one of claims 12 to 17, wherein the immunosuppressive signal inhibitor is one or more selected from an interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, an intracellular signaling inhibitor of PD-1, and a production inhibitor of PD-1, PD-L1 or PD-L2.

19. The method according to claim 18, wherein the in-



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teraction inhibitor is one or more selected from a PD-1 antibody, a PD-L1 antibody, soluble PD-1, and soluble PD-L1.

**20.** The method according to claim 19, wherein the PD-1 antibody is an antibody selected from an anti-human PD-1 antibody produced by a hybridoma internationally deposited as FERM BP-8392, a humanized anti-PD-1 antibody of a non-human antibody, and a human anti-human PD-1 antibody.

**21.** The method according to any one of claims 12 to 17, wherein the immunosuppressive signal inhibitor is a lymphocyte in which PD-1 expression is inhibited by gene-recombination.

**22.** The method according to claim 18, wherein the interaction inhibitor of PD-1 and PD-L1 or PD-1 and PD-L2, the intracellular signaling inhibitor of PD-1, or the production inhibitor of PD-1, PD-L1 or PD-L2 is one or more substances selected from a protein, a polypeptide, a peptide, a polynucleotide, a polynucleoside, an antibody, a derivative thereof, an organic synthesis compound, an inorganic compound, and a natural product.

**23.** Use of an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 for the manufacture of an immunopotentiative composition.

**24.** Use of an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 for the manufacture of a composition for treatment of cancer.

**25.** The use according to claim 24, wherein the composition for treatment of cancer is a composition for suppression of cancer metastasis.

**26.** Use of an immunosuppressive signal inhibitor of PD-1, PD-L1 or PD-L2 for manufacture of the composition for treatment of infection.

**27.** A carcinoma cell line for screening, which is transformed to thereby express PD-L1 or PD-L2.

**28.** A screening method for an immunopotentiative substance, which comprises allowing a test substance to contact with the cells according to claim 27 and a lymphocyte to evaluate enhancement of the test substance for immune reaction of the lymphocyte to the cells according to claim 27.

**29.** A screening method for a substance for treatment of cancer, which comprises allowing a test substance to contact with the cell according to claim 27 which is a carcinoma cell and a lymphocyte to evaluate enhancement of the test substance for immune reaction of the lymphocyte to the carcinoma cell and inhibitory effect of test substance for carcinoma cell proliferation.

**30.** A screening method for a substance for treatment of infection, which comprises allowing a test substance to contact with the cell according to claim 27 which is infected with a pathogen and a lymphocyte to evaluate enhancement of the test substance for immune reaction of the lymphocyte to the infected cell and inhibitory effect of test substance for pathogen proliferation.

**31.** A mammal prepared by transplanting the cell line according to claim 27 which is a carcinoma cell.

**32.** A screening method for a substance for treatment of cancer, which comprises administering a test substance to the mammal according to claim 31 to evaluate an inhibitory ratio of the test substance for transplanted carcinoma cell proliferation or a survival rate of the mammal which is transplanted.



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FIG. 1 (A)

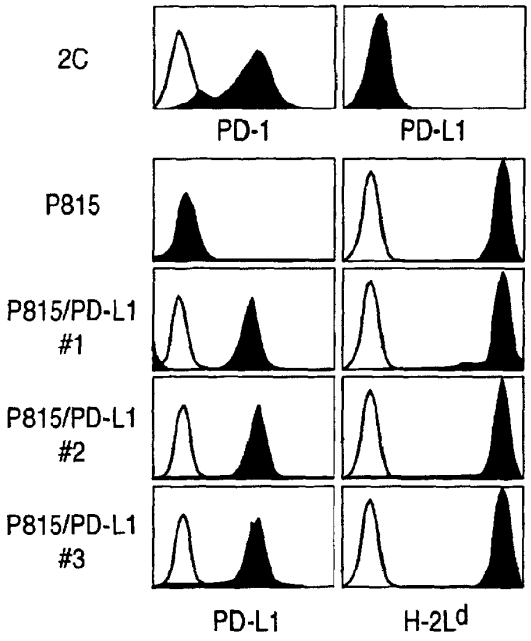
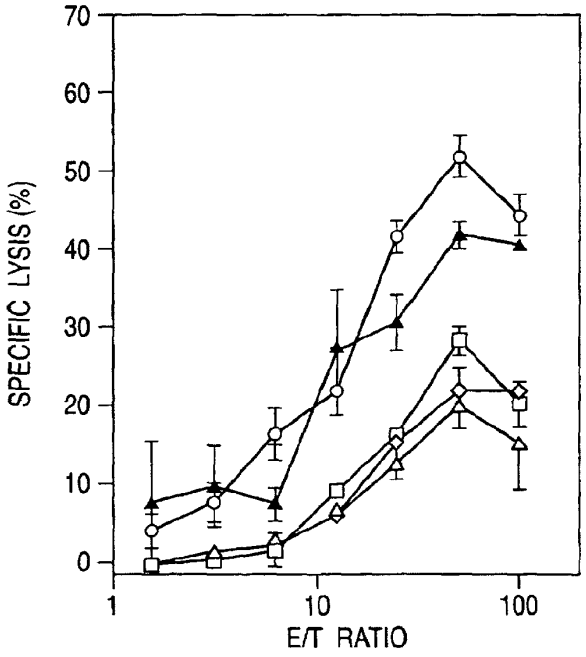



FIG. 1 (B)






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FIG. 2 (A)

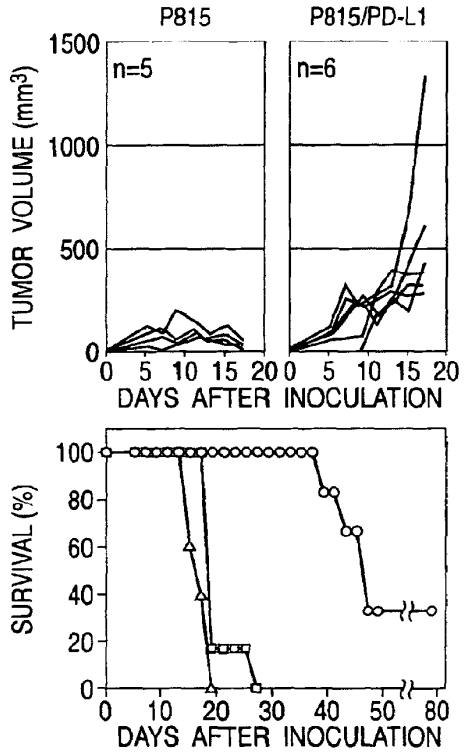
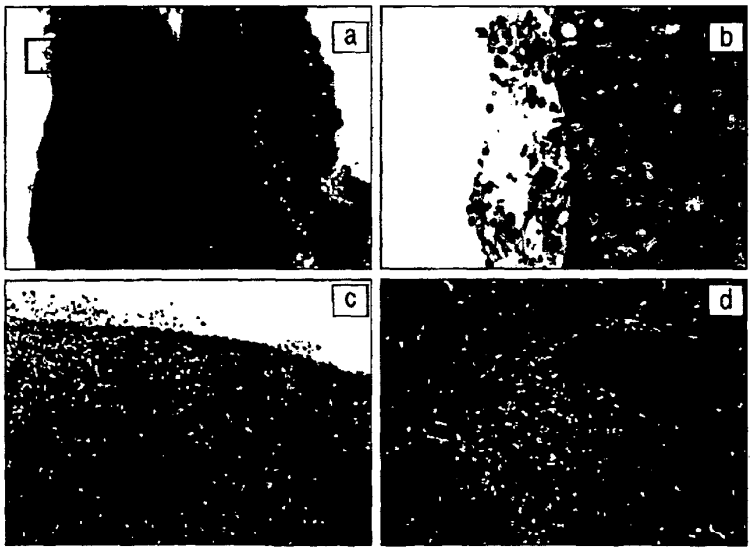



FIG. 2 (B)






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FIG. 3 (A)

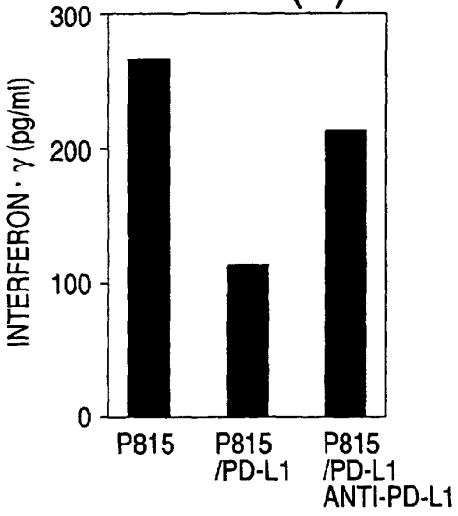
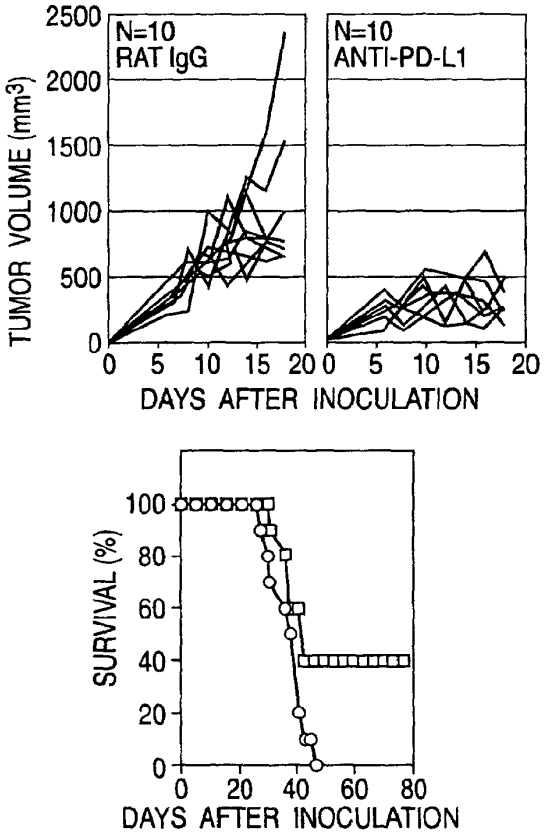


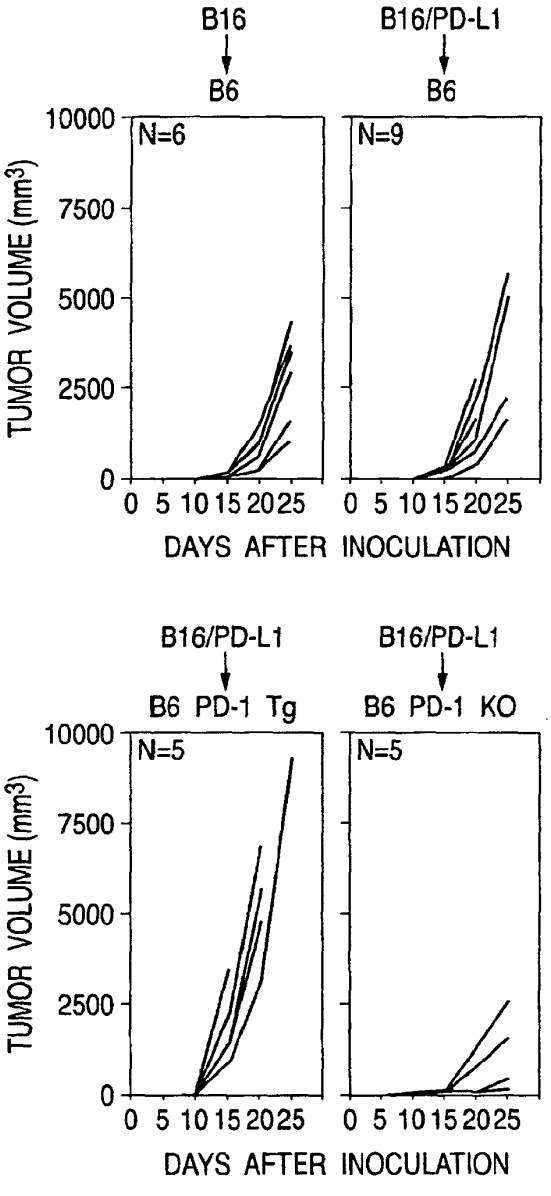

FIG. 3 (B)






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FIG. 4






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FIG. 5 (A)

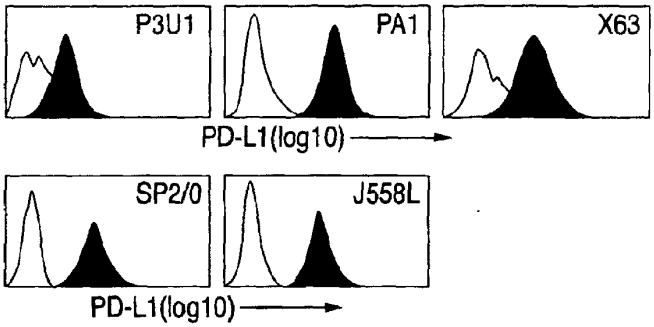



FIG. 5 (B)

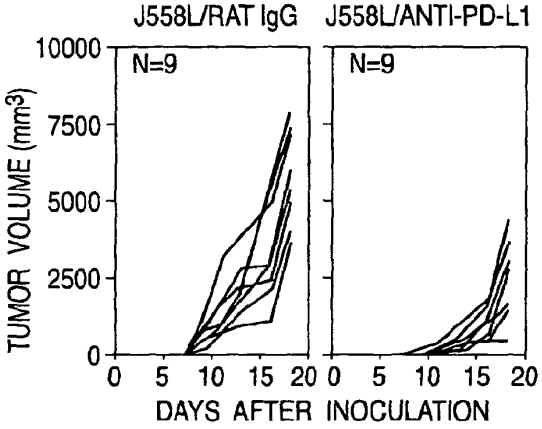
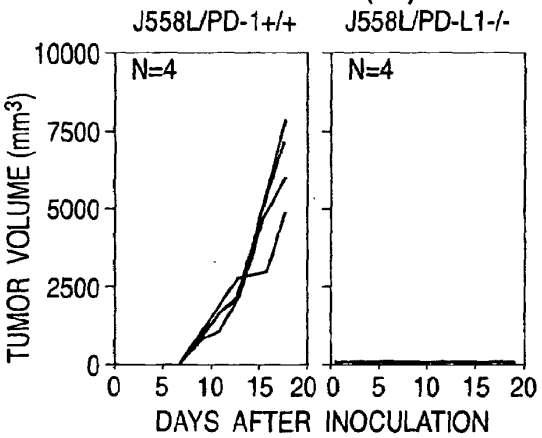



FIG. 5 (C)






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FIG. 6 (A)

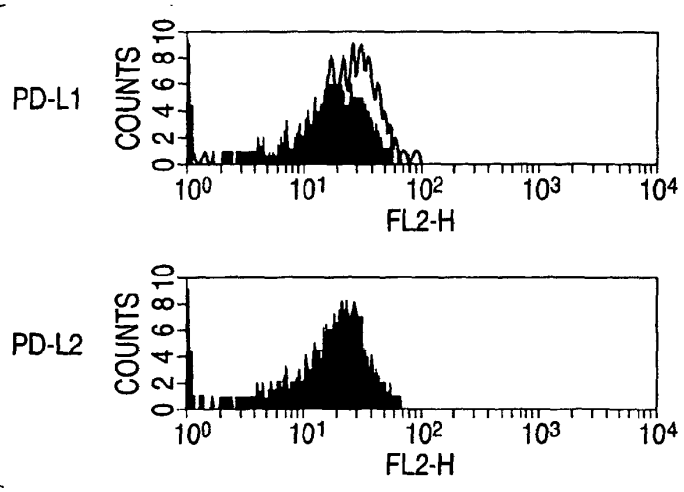
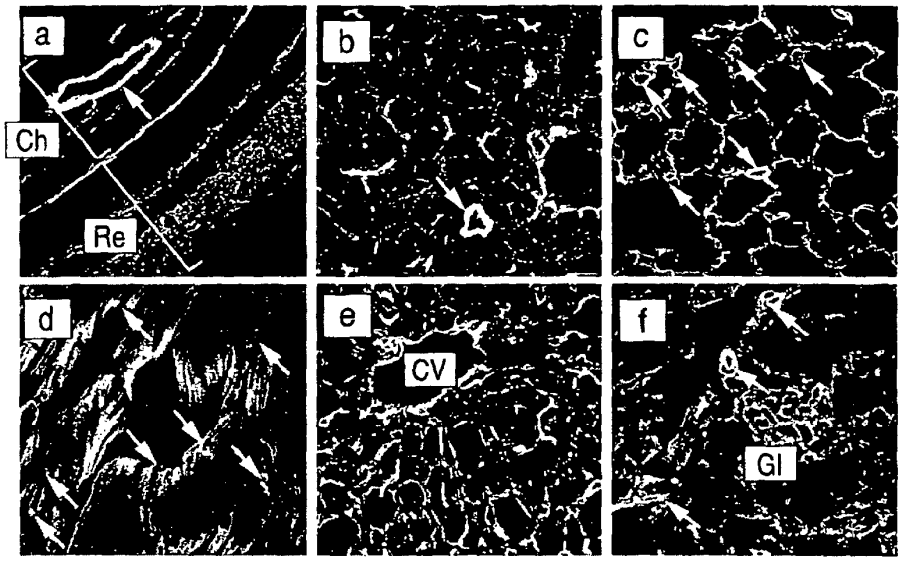



FIG. 6 (B)






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FIG. 7 (A)

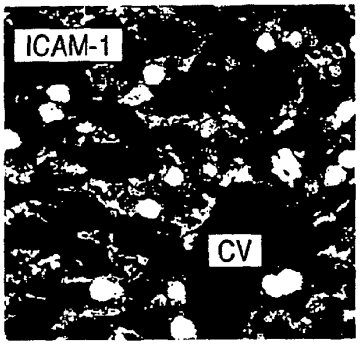
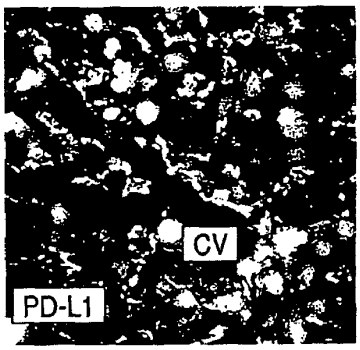



FIG. 7 (B)

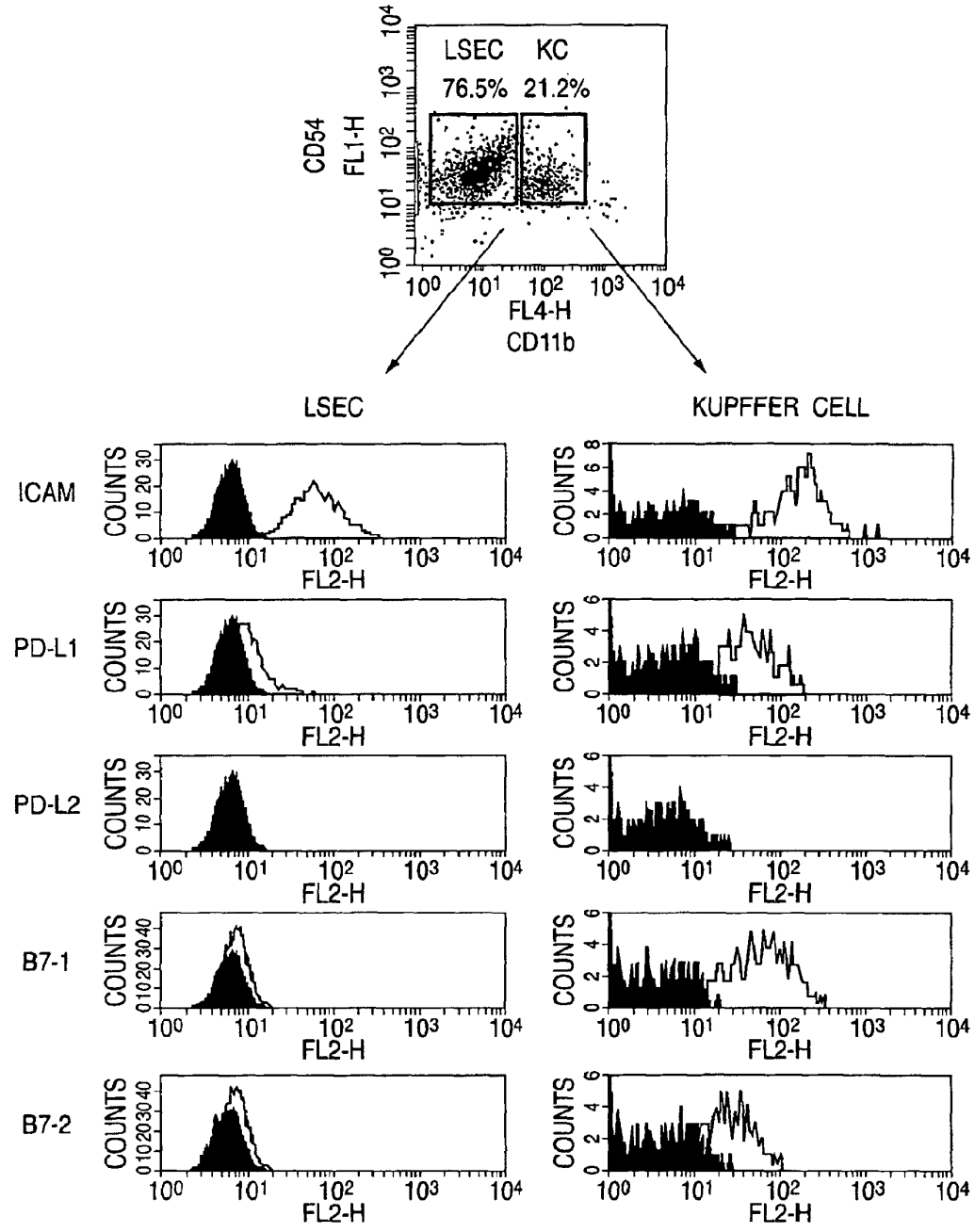



x 40



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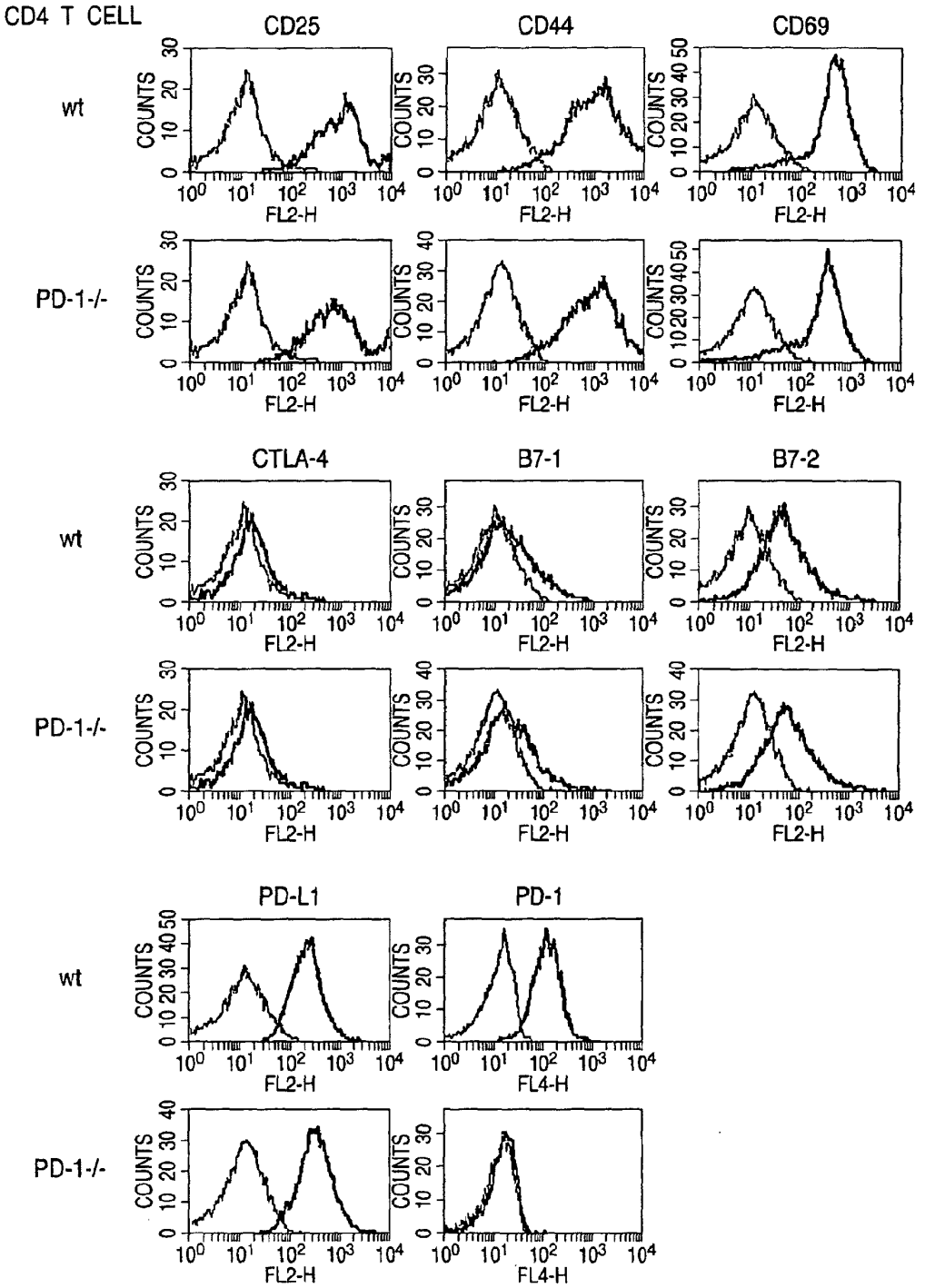
FIG. 8






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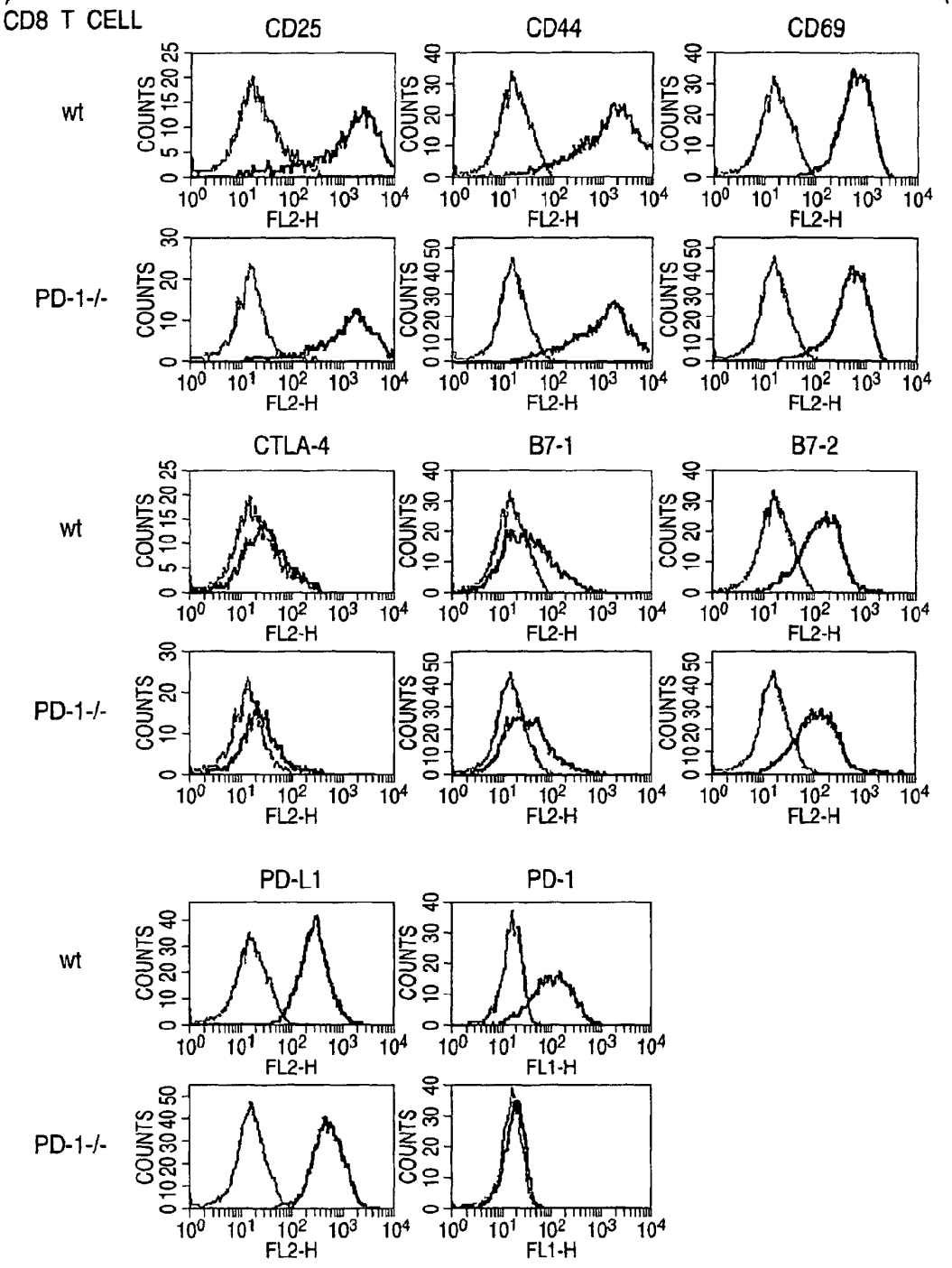
FIG. 9






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FIG. 10






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FIG. 11 (A)

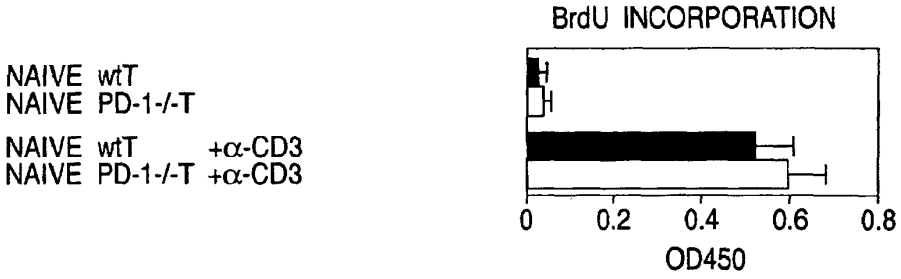
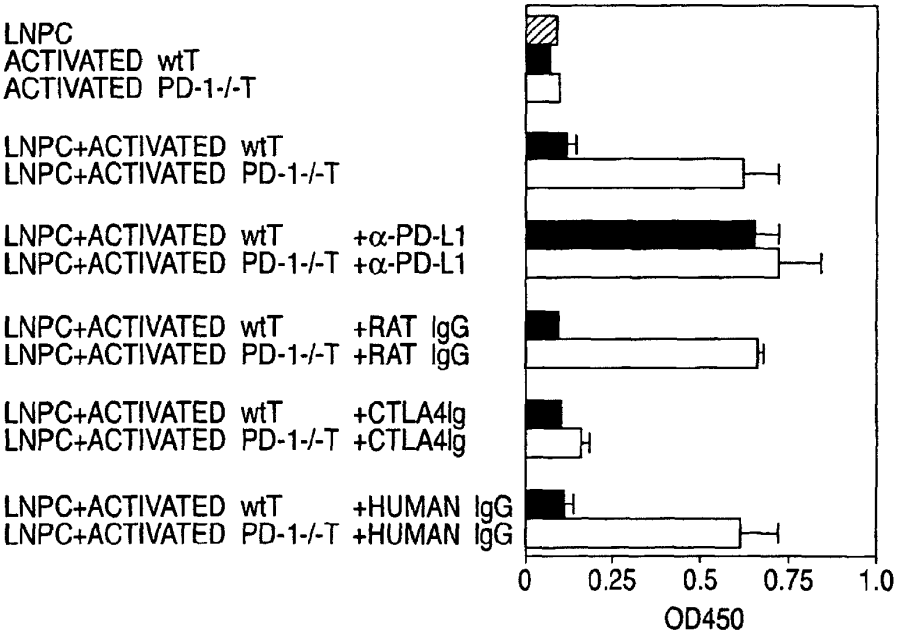



FIG. 11 (B)






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FIG. 12 (A)

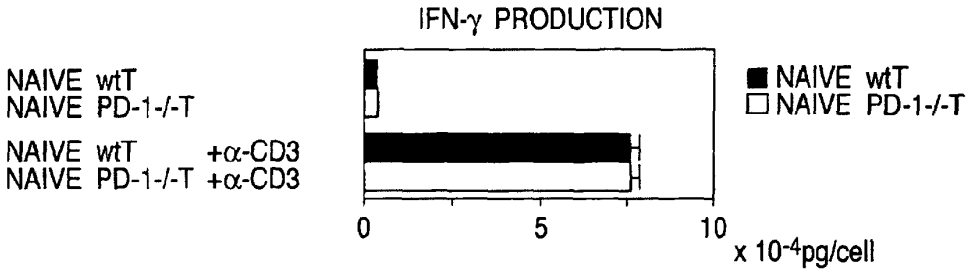



FIG. 12 (B)

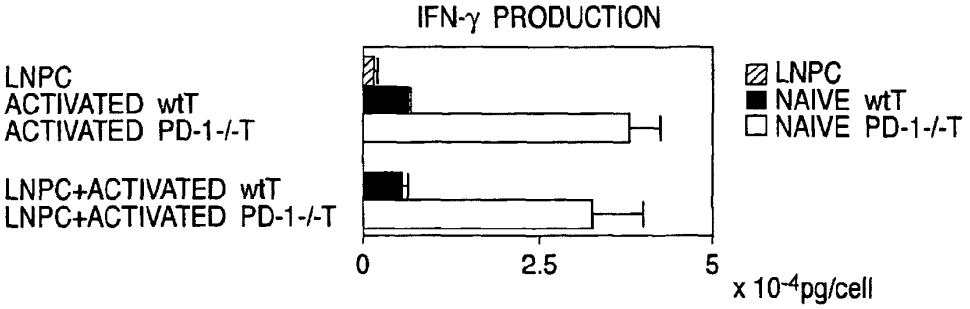
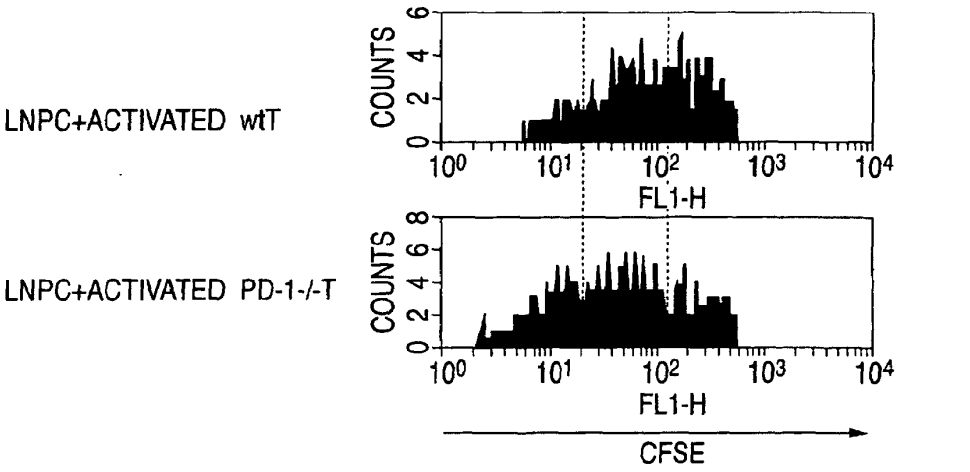



FIG. 12 (C)






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FIG. 13 (A)

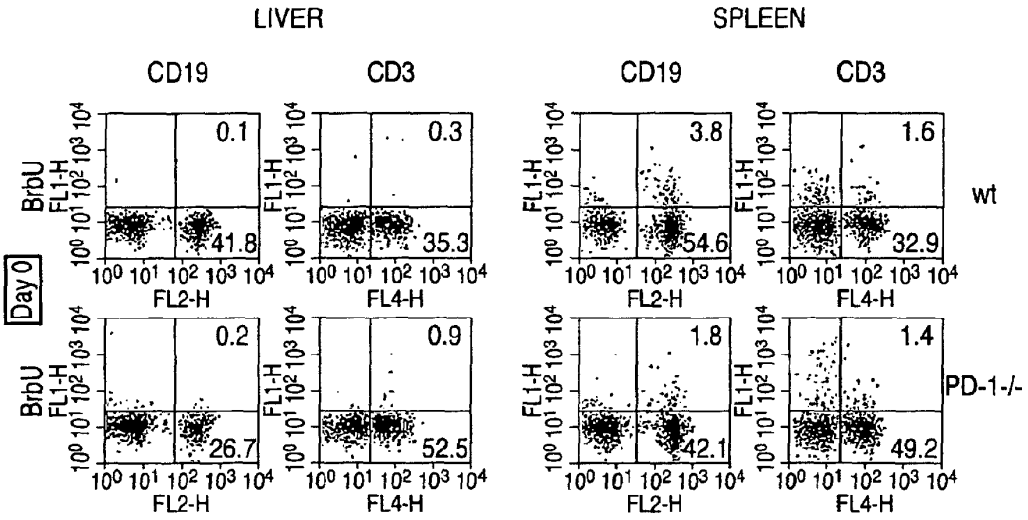
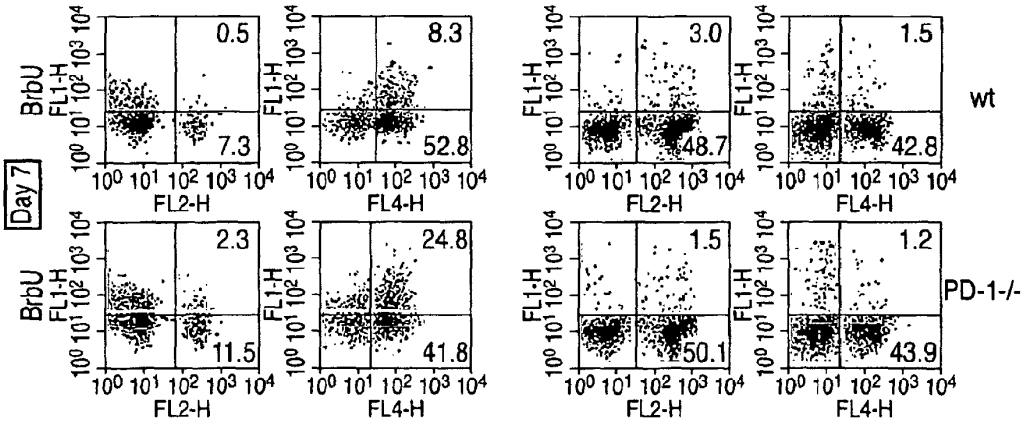



FIG. 13 (B)






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FIG. 14 (A)

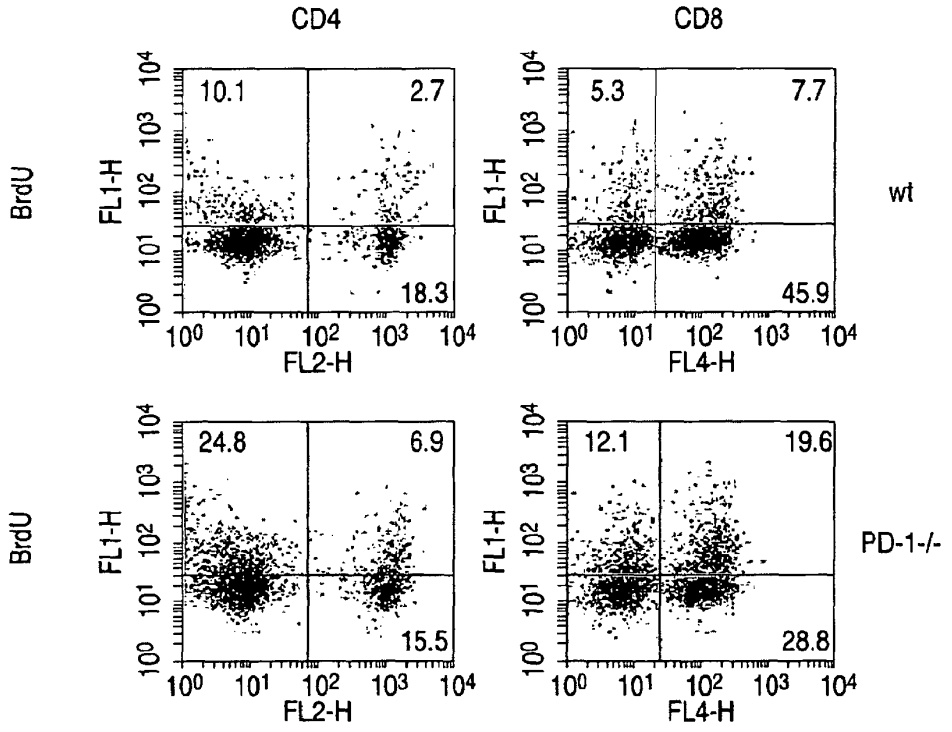
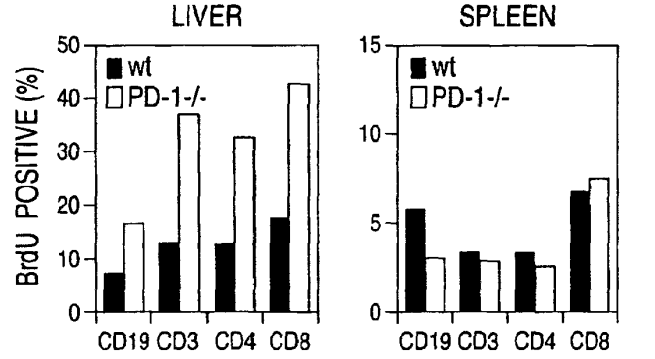


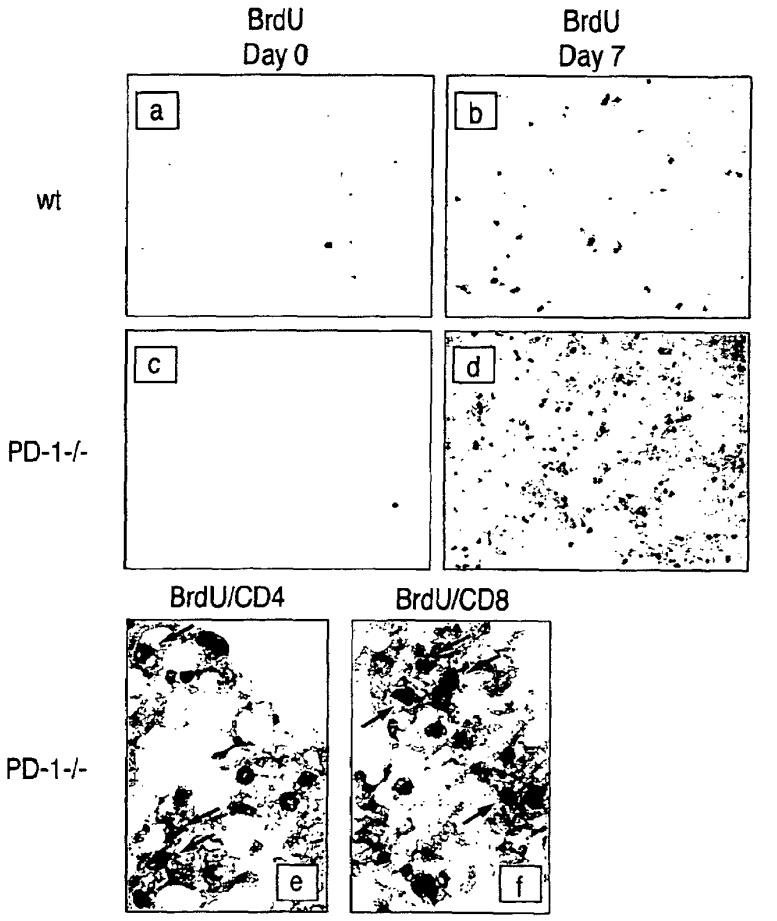

FIG. 14 (B)






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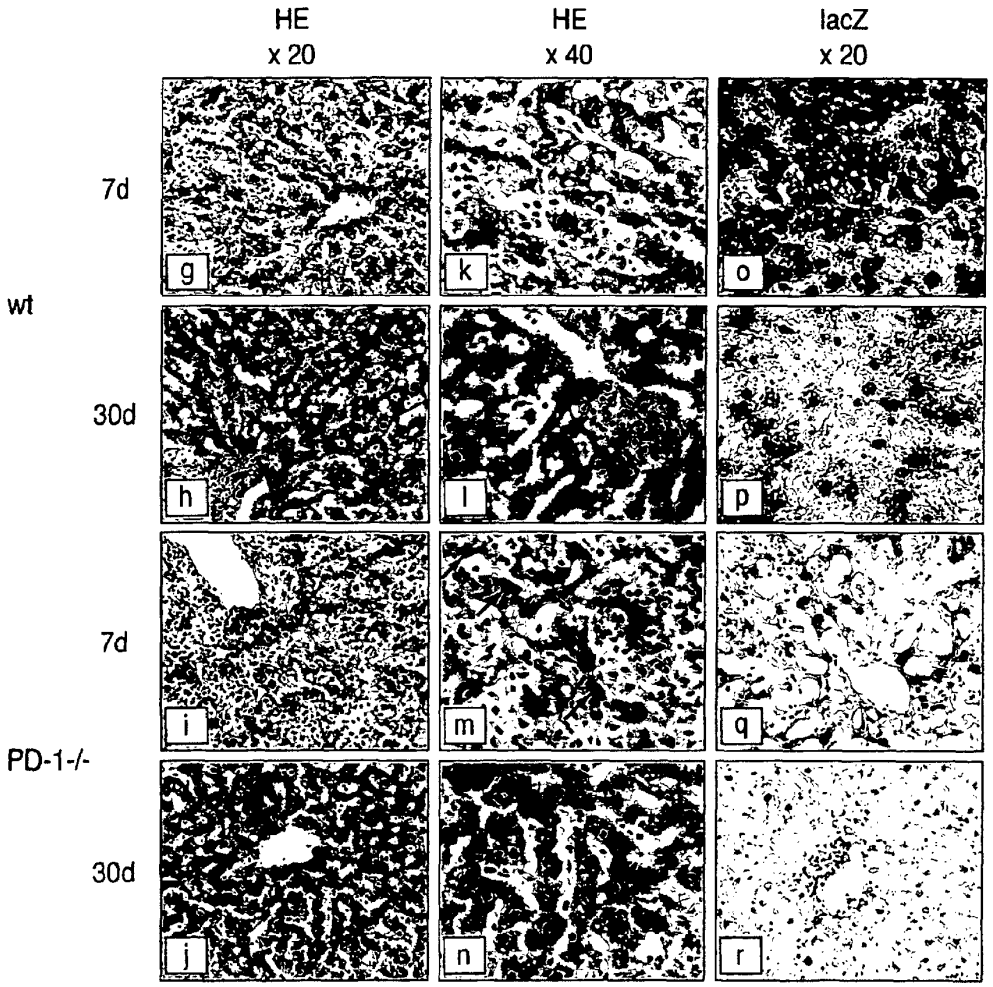
FIG. 15






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FIG. 16






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FIG. 17 (a)

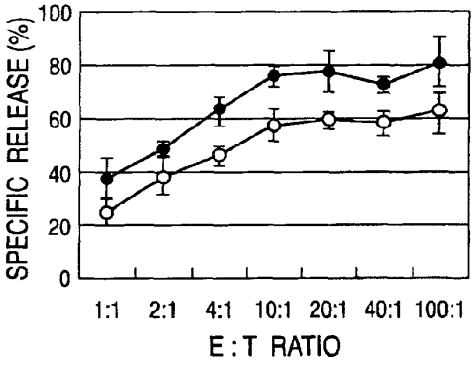



FIG. 17 (b)

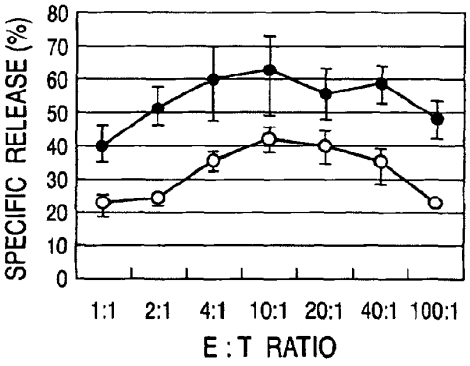



FIG. 17 (c)

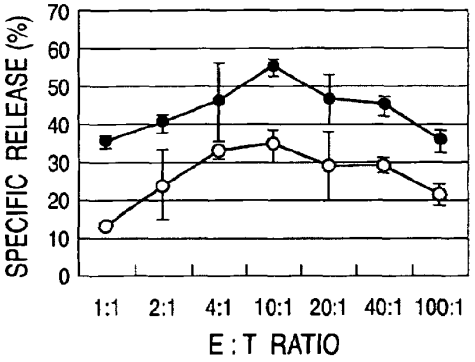
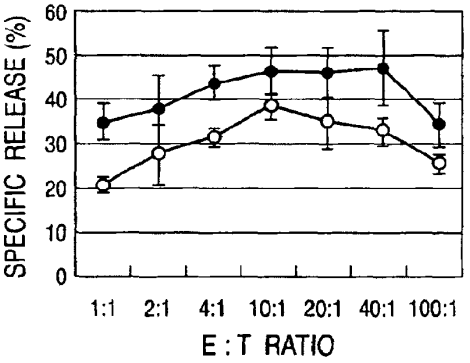
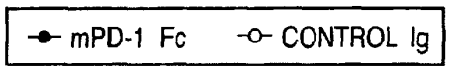
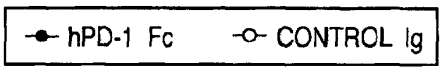



FIG. 17 (d)






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## INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/08420

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K45/00, 38/17, 39/395, 31/7088, A61P31/00, 35/00, 35/04, 37/04, C12N5/10, C12Q1/02, G01N33/50, A01K6//027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K45/00, 38/17, 39/395, 31/7088, A61P31/00, 35/00, 35/04, 37/04, C12N5/10, C12Q1/02, G01N33/50, A01K6//027

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), MEDLINE(STN), EMBASE(STN), BIOSIS(STN), JICST(JOIS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 01/14557 A1 (DANA-FARBER CANCER INSTITUTE, INC.), 01 March, 2001 (01.03.01), Particularly, abstract; Claims; page 82, line 8 to page 86, line 10 & EP 1210428 A1 & US 2002/102651 A1 & US 2002/160000 A1 & BR 2000013581 A & NO 2002000859 A | 1-11,23-33 |
| X | WO 02/00730 A2 (GENETICS INSTITUTE, INC.), 03 January, 2002 (03.01.02), Particularly, abstract; Claims; page 104, line 9 to page 108, line 13 & WO 02/00730 A3 & WO 02/00730 C2 & EP 1297135 A2 & US 2002/110836 A1 & US 2002/164600 A1 & AU 2001071731 A5 | 1-11,23-33 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 04 October, 2003 (04.10.03) | 21 October, 2003 (21.10.03) |
| Name and mailing address of the ISA/ Japanese Patent Office | Authorized officer |
| Facsimile No. | Telephone No. |

Form PCT/ISA/210 (second sheet) (July 1998)



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## INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/08420

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/00692 A2 (GENETICS INSTITUTE, INC.), 03 January, 2002 (03.01.02), Particularly, abstract; Claims; page 104, line 9 to page 108, line 13 & WO 02/00692 A3 & WO 02/00692 C2 & EP 1320599 A2 & US 2002/110836 A1 & US 2002/164600 A1 | 1-11,23-33 |
| X | EP 670369 A2 (ONO PHARMACEUTICAL CO., LTD.), 06 September, 1995 (06.09.95), Particularly, abstract; Claims; page 5, line 52 to page 6, line 6 & EP 670369 A3 & US 5629204 A & US 5698520 A & JP 7-291996 A & JP 2003-230395 A & CA 2143491 A & CN 1113518 A & CN 1080311 B | 1-11,23-33 |
| X | BROWN, Julia A. et al., Blockade of PD-1 Ligands on dendritic cells enhances T cell activation and cytokine production., FASEB Journal, March 2002, Vol.16, No.4, pp.A710,517.4 | 1-11,23-33 |
| P,X | WO 03/042402 A2 (DANA-FARBER CANCER INSTITUTE, INC.), 22 May, 2003 (22.05.03), Particularly, abstract; Claims; page 56 line 21 to page 59, line 2 (Family: none) | 1-11,23-33 |
| P,X | WO 03/011911 A1 (ONO PHARMACEUTICAL CO., LTD.), 13 February, 2003 (13.02.03), Particularly, abstract; Claims; page 14, lines 17 to 19 (Family: none) | 1-11,23-33 |
| P,X | WO 02/078731 A1 (WYETH), 10 October, 2002 (10.10.02), Particularly, abstract; Claims; page 74, line 27 to page 77, line 29 (Family: none) | 1-11,23-33 |
| P,X | BROWN, Julia A. et al., Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production., The Journal of Immunology., February 2003, Vol.170, No.3, 1257-66 | 1-11,23-33 |

Form PCT/ISA/210 (continuation of second sheet) (July 1998)



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**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/JP03/08420

**Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-22

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 12-22 pertain to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. [ ] Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1643 of 2058

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 5664437 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Perry Moy |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 08-JUL-2009 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 15:23:03 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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 | Request for Corrected Filing Receipt | 0773750499RequestCorrectedFilingReceipt.PDF | 222258<br>a96971191b4aeb40dd2e7985bc24e1630e8003cd | no | 5 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Information Disclosure Statement (IDS) Filed (SB/08) | 0773750499IDS.PDF | 175750<br>30b2125261b4bea225d78325bd21ae38fe671274 | no | 4 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| This is not an USPTO supplied IDS fillable form | | | | | |
| 3 | Foreign Reference | WO2003033644.pdf | 1257691<br>3975c4b0acae6711d0351f17addb60bf76824f8c | no | 52 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | WO2006021955.pdf | 2309042<br>f477c25b7f1258097e3fbc721991cc4d47e8c108 | no | 62 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | EP0742795B1.pdf | 608903<br>35abee0340fa777d6d51f41dbc2531350ce13ef9 | no | 33 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 6 | Foreign Reference | EP1537878.pdf | 2317918<br>cb2f5b1b2bb36de1be98a5893fa509266a43a4ef | no | 38 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 7 | NPL Documents | BergerEtAl.pdf | 138724<br>4fc4c64b08403b1ff6a3ecefc4b106099e07dfb2 | no | 8 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 8 | NPL Documents | BlankEtAl2004.pdf | 1238091<br>0759a7a49495bf8bba6bb17fafb3482f0d2edfc1 | no | 6 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 9 | NPL Documents | CoxEtAl1994.pdf | 1410112<br>cf63d66dfb1ca06f0e56ae8b3957ba9c276362ae | no | 10 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 10 | NPL Documents | KogaEtAl2004.pdf | 1248296<br>8d9d95a13474162126d1d6460a85fa71ef23893b | no | 6 |

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|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 11 | NPL Documents | TomlinsonEtAl1992.pdf | 2963028<br>c6f955ae08c6ffd470157280f3a8ab30e1ed859f | no | 23 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | | **Total Files Size (in bytes):** | 13889813 | |

**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.**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman, *et al.* | Customer No. | : 63367 |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| Filed | : 10/31/2007 | Group Art Unit | : 1632 |
| Examiner | : TBD | | |
| For | : Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics | | |

**REQUEST FOR A CORRECTED FILING RECEIPT**

**FILED VIA EFS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

On the Official Filing Receipt dated May 21, 2009, we noted an error in the Applicants's information. Please correct the Applicants's information as follows:

**Changyu Wang, ~~Fremont~~, CA** should read **Changyu Wang, Union City, CA**.

**~~Bing~~ Chen, Alameda, CA** should read **Bingliang Chen, Alameda, CA**.

A copy of the Official Filing Receipt with the correction noted is enclosed.

Applicant hereby respectfully requests the issuance of a corrected Official Filing Receipt.



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Applicant does not believe that this submission requires a fee. However, if for any reason a fee is due, the Commissioner is hereby authorized to charge payment of any fees required in connection with this submission to Deposit Account No. 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

July 8, 2009
Date

/Lisa D. Tyner/
Lisa D. Tyner
Patent Office Reg. No. 51,619

30 Rockefeller Plaza
45th Floor
New York, NY 10112-4498
Attorney for Applicant(s)
212-408-2500



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1648 of 2058

UNITED STATES PATENT AND TRADEMARK OFFICE

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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 |
|---|---|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | 1656 | 2980 | 077375.0499 | 31 | 7 |

**CONFIRMATION NO. 1207**

**FILING RECEIPT**

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

*OC000000036016738*

Date Mailed: 05/21/2009

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

**Applicant(s)**

Alan J. Korman, Piedmont, CA;
Mohan Srinivasan, San Jose, CA;
Changyu Wang, Fremont, CA; s/b Union City
Mark J. Selby, San Francisco, CA;
Bing Chen, Alameda, CA; s/b Ringliang
Josephine M. Cardarelli, San Carlos, CA;

**Assignment For Published Patent Application**

MEDAREX, INC, Princeton, NJ

**Power of Attorney:** The patent practitioners associated with Customer Number 63367

**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/JP2006/309606 05/02/2006
which claims benefit of 60/679,466 05/09/2005
and claims benefit of 60/738,434 11/21/2005
and claims benefit of 60/748,919 12/08/2005

**Foreign Applications**

**If Required, Foreign Filing License Granted:** 05/15/2009

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/913,217**

**Projected Publication Date:** 08/27/2009

**Non-Publication Request:** No

**Early Publication Request:** No

**Title**

Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics

**Preliminary Class**

435

## 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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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 (1-866-999-4158).

## LICENSE FOR FOREIGN FILING UNDER

## Title 35, United States Code, Section 184

## Title 37, Code of Federal Regulations, 5.11 & 5.15

**GRANTED**

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where

the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

**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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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 |

CONFIRMATION NO. 1207

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

PUBLICATION NOTICE

*OC000000037544819*

**Title:**Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics

**Publication No.**US-2009-0217401-A1
**Publication Date:**08/27/2009

## 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 Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, 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 http://pair.uspto.gov/. 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.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

63367 7590 08/09/2010

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| EXAMINER | |
|---|---|
| OUSPENSKI, ILIA I | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 08/09/2010 | 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):

DLNYDOCKET@BAKERBOTTS.COM



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1653 of 2058

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/913,217 | KORMAN ET AL. | |
| | Examiner | Art Unit | |
| | ILIA OUSPENSKI | 1644 | |

*-- 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 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *13 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,8,27,35,43,44,50,52-57,62,64,65,67-72,79,80,84,88,89,96,97,101 and 105.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1,8,27,35,43,44,50,52-57,62,64,65,67-72,79,80,84,88,89,96,97,101 and 105.



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Dana-Farber v. BMS, IPR2023-00501
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## DETAILED ACTION

1. Applicant's preliminary amendment filed on 10/13/2007 is acknowledged.

Claims 1, 8, 27, 35, 43, 44, 50, 52-57, 62, 64, 65, 67-72, 79, 80, 84, 88, 89, 96, 97, 101 and 105 are pending.

### *Restriction Requirement*

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

I. Claims 1, 8, 27, 35, 43, 44 and 50, drawn to an antibody to PD-1, and to compositions and immunoconjugates of said antibody.

II. Claims 52 – 54, drawn to a nucleic acid encoding an anti-PD-1 antibody, and to a vector and host cell comprising said nucleic acid.

III. Claim 55, drawn to a transgenic mouse expressing an anti-PD-1 antibody.

IV. Claim 56, drawn to a hybridoma which produces an anti-PD-1 antibody.

V. Claims 57, 62, 64, 67-72, 79, 80, 84, 88, 89, 96, 97 and 101, drawn to a method of treating a hyperproliferative disorder comprising administering to the subject an anti-PD-1 antibody.

VI. Claims 57, 65, 67 and 68, drawn to a method of treating an infectious disease comprising administering to the subject an anti-PD-1 antibody.

VII. Claim 105, drawn to a method for preparing an anti-PD-1 antibody.

In accordance with 37 CFR 1.499, Applicant is required, in response to this action, to elect a single invention to which the claims must be restricted. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

3. The inventions listed as Groups I – VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I - VII are deemed to have no special technical feature that defines the contribution over the prior art of Wood et al. (US Patent No. 6,808,710; of record – cited on IDS of 10/07/2008; see entire document).

The technical feature linking Groups I – VII is deemed to be a human monoclonal anti-PD-1 antibody with at least one of the properties recited in claim 1.

Wood et al. teach human monoclonal antibodies to PD-1 (e.g. Examples 9 and 10 at columns 80 – 81). The claimed and referenced antibodies appear to have equivalent binding specificities. The Office is not in a position to test the antibody described in the prior art for the functional properties recited in the instant claims. The burden is on the applicant to establish a patentable distinction between the claimed and

referenced antibodies. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Therefore, the teachings of the prior art anticipate the technical feature linking Groups I – VII, and as such, the claimed inventions do not contribute a special technical feature when viewed over the prior art. Thus they do not have a single general inventive concept and so lack unity of invention.

***Species Election***

4. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Applicant is required to elect a species of single antibody from those recited in a) through g) of claim 8.

These species do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features, for the same reason as set forth in section 3 above.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on 571-272-0735. 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 http://pair-direct.uspto.gov. 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.

/ILIA OUSPENSKI/
ILIA OUSPENSKI, Ph.D.
Primary Examiner
Art Unit 1644

August 4, 2010

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | | |
|---|---|---|---|---|---|
| Applicant(s) | : | Korman et al. | Confirmation No. | : | 1207 |
| Serial No. | : | 11/913,217 | Examiner | : | OUSPENSKI, ILIA I |
| Filed | : | January 29, 2009 | Group Art Unit | : | 1644 |
| For | : | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS | | | |

**Mail Stop AMENDMENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**PRELIMINARY AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT**

Sir:

In response to the Restriction Requirement of August 9, 2010, please consider the following remarks.

**Amendments to the claims** begin on page 2 of this paper.

**Remarks** begin on page 13 of this paper.



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## AMENDMENTS TO THE CLAIMS

The listing of claims provided below will replace all prior versions, and listings, of claims in the application.

**Listing of claims**

1. - 7. **(Canceled)**

8. **(Currently Amended)** An isolated human monoclonal antibody, or an antigen-binding portion thereof [[;]] , wherein the antibody cross-competes for binding to PD-1 with a reference antibody, and wherein the reference antibody is selected from the group consisting of:

a) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;

b) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;

c) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

d) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

e) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5 and the human light chain variable region comprising the amino acid sequence of SEQ ID NO: 12;

f) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6 and the human light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and



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g) an antibody comprising a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 14.

9. - 26. **(Canceled)**

27. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, wherein the antibody is selected from the group consisting of:

a) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 15;
a heavy chain variable region CDR2 comprising SEQ ID NO: 22;
a heavy chain variable region CDR3 comprising SEQ ID NO: 29;
a light chain variable region CDR1 comprising SEQ ID NO: 36;
a light chain variable region CDR2 comprising SEQ ID NO: 43; and
a light chain variable region CDR3 comprising SEQ ID NO: 50;

b) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 16;
a heavy chain variable region CDR2 comprising SEQ ID NO: 23;
a heavy chain variable region CDR3 comprising SEQ ID NO:30;
a light chain variable region CDR1 comprising SEQ ID NO: 37;
a light chain variable region CDR2 comprising SEQ ID NO: 44; and
a light chain variable region CDR3 comprising SEQ ID NO: 51;

c) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 17;
a heavy chain variable region CDR2 comprising SEQ ID NO: 24;
a heavy chain variable region CDR3 comprising SEQ ID NO: 31;
a light chain variable region CDR1 comprising SEQ ID NO: 38;
a light chain variable region CDR2 comprising SEQ ID NO: 45; and
a light chain variable region CDR3 comprising SEQ ID NO: 52;

d) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 18;



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a heavy chain variable region CDR2 comprising SEQ ID NO: 25;
a heavy chain variable region CDR3 comprising SEQ ID NO: 32;
a light chain variable region CDR1 comprising SEQ ID NO: 39;
a light chain variable region CDR2 comprising SEQ ID NO: 46; and
a light chain variable region CDR3 comprising SEQ ID NO: 53

e) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 19;
a heavy chain variable region CDR2 comprising SEQ ID NO: 26;
a heavy chain variable region CDR3 comprising SEQ ID NO: 33;
a light chain variable region CDR1 comprising SEQ ID NO: 40;
a light chain variable region CDR2 comprising SEQ ID NO: 47; and
a light chain variable region CDR3 comprising SEQ ID NO: 54

f) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 20;
a heavy chain variable region CDR2 comprising SEQ ID NO: 27;
a heavy chain variable region CDR3 comprising SEQ ID NO: 34;
a light chain variable region CDR1 comprising SEQ ID NO: 41;
a light chain variable region CDR2 comprising SEQ ID NO: 48; and
a light chain variable region CDR3 comprising SEQ ID NO: 55; and

g) an antibody comprising
a heavy chain variable region CDR1 comprising SEQ ID NO: 21;
a heavy chain variable region CDR2 comprising SEQ ID NO: 28;
a heavy chain variable region CDR3 comprising SEQ ID NO: 35;
a light chain variable region CDR1 comprising SEQ ID NO: 42;
a light chain variable region CDR2 comprising SEQ ID NO: 49; and
a light chain variable region CDR3 comprising SEQ ID NO: 56,

wherein the antibody specifically binds to PD-1.

28. - 34. **(Canceled)**



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35. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, wherein the antibody is selected from the group consisting of:

a) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;

b) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;

c) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

d) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

e) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12; or

f) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and

g) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14,

wherein the antibody specifically binds to PD-1.

36. - 42. **(Canceled)**

43. **(Currently Amended)** A composition comprising the antibody, or antigen-binding portion thereof, of claim [[1]] 8, and a pharmaceutically acceptable carrier.



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44. **(Currently Amended)** An immunoconjugate comprising the antibody, or antigen-binding portion thereof, of claim [[1]] 8, linked to a therapeutic agent.

45. - 49. **(Canceled)**

50. **(Currently Amended)** A bispecific molecule comprising the antibody, or antigen-binding portion thereof, of claim [[1]] 8, linked to a second functional moiety having a different binding specificity than said antibody, or antigen-binding portion thereof.

51. - 56. **(Canceled)**

57. **(Currently Amended)** A method of modulating an immune response in a subject comprising administering to the subject the antibody, or antigen-binding portion thereof, of claim [[1]] 8 such that the immune response in the subject is modulated.

58. - 61. **(Canceled)**

62. **(Previously Presented)** The method of claim 64, wherein the tumor cells are of a cancer selected from the group consisting of melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer.

63. **(Canceled)**

64. **(Currently Amended)** A method of inhibiting growth of tumor cells in a subject, comprising administering to a subject the antibody, or antigen-binding portion thereof, of claim [[1]] 8 in an amount effective to inhibit growth of the tumor cells.

65. **(Currently Amended)** A method of treating an infectious disease in a subject comprising administering to the subject the antibody, or antigen-binding portion thereof, of claim [[1]] 8 such that the subject is treated for the infectious disease.

66. **(Canceled)**

67. **(Currently Amended)** A method of enhancing an immune response to an antigen in a subject, comprising administering to the subject: (i) the antigen; and (ii) the antibody, or



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antigen-binding portion thereof, of claim [[1]] 8 such that an immune response to the antigen in the subject is enhanced.

68. **(Original)** The method of claim 67, wherein the antigen is a tumor antigen, a viral antigen, a bacterial antigen or an antigen from a pathogen.

69. **(Currently Amended)** A method for treating a hyperproliferative disease, which method comprises:

(a) administering [[a]] an anti-PD-1 antibody of claim 8 to a subject, and

(b) administering [[a]] an anti-CTLA-4 antibody to the subject.

70. **(Original)** The method of claim 69, wherein the anti-PD-1 antibody is administered at a subtherapeutic dose.

71. **(Original)** The method of claim 69, wherein the anti-CTLA-4 antibody is administered at a subtherapeutic dose.

72. **(Original)** The method of claim 69, wherein the anti-PD-1 antibody and the anti-CTLA-4 antibody are each administered at a subtherapeutic dose.

73. - 78. **(Canceled)**

79. **(Previously Presented)** The method of claim 69 wherein the hyperproliferative disease is cancer.

80. **(Original)** The method of claim 79 wherein the cancer is colon cancer.

81. - 83. **(Canceled)**

84. **(Previously Presented)** The method of claim 69, wherein the anti-PD-1 human sequence monoclonal antibody is selected from the group consisting of:

a) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;



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b) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;

c) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

d) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

e) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12; or

f) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and

g) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14.

85. -87. **(Canceled)**

88. **(Currently Amended)** A method for altering an adverse event associated with treatment of a hyperproliferative disease with an immunostimulatory agent, which method comprises:

(a) administering an anti-PD-1 antibody of claim 8 to a subject, and

(b) administering a subtherapeutic dose of anti-CTLA-4 antibody to the subject.

89. **(Original)** The method of claim 86 wherein the anti-PD-1 antibody is administered in a subtherapeutic dose.

90. - 95. **(Canceled)**



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96. **(Previously Presented)** The method of claim 88, wherein the hyperproliferative disease is cancer.

97. **(Original)** The method of claim 96 wherein the cancer is colon cancer.

98. -100. **(Canceled)**

101. **(Previously Presented)** The method of claim 88 wherein the anti-PD-1 human sequence monoclonal antibody is selected from the group consisting of:

a) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;

b) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;

c) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

d) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

e) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12; or

f) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and

g) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14.

102. - 104. **(Canceled)**



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105. **(Original)** A method for preparing an anti-PD-1 antibody comprising:

(a) providing: (i) a heavy chain variable region antibody sequence comprising a CDR1 sequence that is selected from the group consisting of SEQ ID NOs: 15, 16, 17, 18, 19, 20 and 21, a CDR2 sequence that is selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27 and 28; and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 29, 30, 31, 32, 33, 34 and 35; or (ii) a light chain variable region antibody sequence comprising a CDR1 sequence that is selected from the group consisting of SEQ ID NOs: 36, 37, 38, 39, 40, 41 and 42, a CDR2 sequence that is selected from the group consisting of SEQ ID NOs: 43, 44, 45, 46, 47, 48 and 49, and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 50, 51, 52, 53, 54, 55 and 56;

(b) altering at least one amino acid residue within at least one variable region antibody sequence, said sequence being selected from the heavy chain variable region antibody sequence and the light chain variable region antibody sequence, to create at least one altered antibody sequence; and

(c) expressing the altered antibody sequence as a protein.

106. (**New**) An isolated monoclonal antibody, or antigen-binding portion thereof, wherein the antibody is selected from the group consisting of:

a) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to an amino acid sequence encoded by a human $V_H$ 3-33 gene; and

b) a light chain variable region comprising an amino acid sequence that is at least 90% identical to an amino acid sequence encoded by a human $V_K$ L6 gene;
wherein the antibody specifically binds to PD-1.

107. (**New**) An isolated monoclonal antibody, or antigen-binding portion thereof, wherein the antibody is selected from the group consisting of:

a) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to an amino acid sequence encoded by a human $V_H$ 4-39 gene; and

b) a light chain variable region comprising an amino acid sequence that is at least 90% identical to an amino acid sequence encoded by a human $V_K$ L15 gene;
wherein the antibody specifically binds to PD-1.



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108. (**New**) An isolated monoclonal antibody, or antigen-binding portion thereof, comprising a heavy chain variable region that comprises CDR1, CDR2, and CDR3 sequences; and a light chain variable region that comprises CDR1, CDR2, and CDR3 sequences, wherein:

a) the heavy chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 30, 31, 32, 33, 34 and 35, and conservative modifications thereof;

b) the light chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 51, 52, 53, 54, 55 and 56, and conservative modifications thereof; and c) the antibody specifically binds to PD-1.

109. (**New**) The antibody of claim 108, wherein the heavy chain variable region CDR2 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 22, 23, 24, 25, 26, 27 and 28, and conservative modifications thereof; and the light chain variable region CDR2 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 43, 44, 45, 46, 47, 48 and 49, and conservative modifications thereof.

110. (**New**) The antibody of claim 109, wherein the heavy chain variable region CDR1 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 15, 16, 17, 18, 19, 20 and 21, and conservative modifications thereof; and the light chain variable region CDR1 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 36, 37, 38, 39, 40, 41 and 42, and conservative modifications thereof.

111. (**New**) An isolated monoclonal antibody, or antigen-binding portion thereof, comprising a heavy chain variable region and a light chain variable region, wherein:

a) the heavy chain variable region comprises an amino acid sequence that is at least 95% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6 and 7;



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b) the light chain variable region comprises an amino acid sequence that is at least 95% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 9, 10, 11, 12, 13 and 14;

c) the antibody binds to human PD-1 with a $K_D$ of 1 x $10^{-7}$M or less; and

d) the antibody does not substantially bind to human CD28, CTLA-4 or ICOS.

112. (**New**) The antibody of claim 111, wherein the antibody further comprises at least one of the following properties:

a) the antibody increases T-cell proliferation in a Mixed Lymphocyte Reaction (MLR) assay;

b) the antibody increases interferon-gamma production in a MLR assay; or

c) the antibody increases interleukin-2 (IL-2) secretion in a MLR assay.

113. (**New**) The antibody of claims 8, wherein the antibody inhibits the suppression of CD4+ CD25- T cells by regulatory T cells.

114. (**New**) The antibody of claim 8, wherein the antibody enhances the antigen specific-memory response to a tumor or a pathogen.

115. (**New**) The antibody of claim 8, wherein the antibody confers a persistent immunity to tumor relapse.

116. (**New**) The antibody of claim 8, wherein the antibody is an IgG4 isotype.

117. (**New**) The antibody of claim 116, wherein the antibody has neither ADCC activity nor CDC activity.



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## REMARKS

Claims 1, 8, 27, 35, 43-44, 50, 52-57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105 were pending in this application. Upon entry of this amendment, claims 1, and 52-56 were cancelled without prejudice, claims 8, 27, 35, 43-44, 50, 57, 64-65, 67, 69, and 88 were amended, and new claims 106-117 were added. Accordingly, claims 8, 27, 35, 43-44, 50, 57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105-117 will remain pending. Support for the new claims can be found throughout the specification and claims as originally filed. In particular, support for new claims 106-107 can be found at ¶ [0155] to ¶ [0159], ¶ [0307], and Figures 8-12 of the instant specification. Support for new claim 113 can be found at Example 21 at ¶ [0613] and ¶ [0614] of the instant specification. Support for new claim 114 can be found at ¶ [0315], ¶ [0467], ¶ [0484], ¶ [0494] and Example 22 at ¶ [0615] of the instant specification. Support for new claim 115 can be found at ¶ [0611] of the instant specification. Support for new claims 116-117 can be found at Examples 23-24 at ¶ [0616] and ¶ [0617] of the instant specification. *No new matter has been added.*

Consideration of the above-identified application, in view of the following remarks, is respectfully requested.

***Restriction Requirement***

The Examiner has required restriction to one of the following groups under 35 U.S.C. §121:

> **Group I:** Claims 1, 8, 27, 35, 43, 44 and 50, drawn to an antibody to PD-1, and to compositions and immunoconjugates of said antibody;
>
> **Group II:** Claims 52-54, drawn to a nucleic acid encoding an anti-PD-1 antibody, and to a vector and host cell comprising said nucleic acid;
>
> **Group III**: Claim 55, drawn to a transgenic mouse expressing an anti-PD-1 antibody;
>
> **Group IV**: Claim 56, drawn to a hybridoma which produces an anti-PD-1 antibody;



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**Group V**: Claims 57, 62, 64, 67-72, 79-80, 84, 88, 89, 96-97, and 101, drawn to a method of treating a hyperproliferative disorder comprising administering to the subject an anti-PD-1 antibody;

**Group VI**: Claims 57, 65, and 67-68, drawn to a method of treating an infectious disease comprising administering to the subject to an anti-PD-1 antibody; and

**Group VII**: Claim 105, drawn to a method for preparing an anti-PD-1 antibody.

***Traversal of Restriction Requirement***

Applicants respectfully traverse the restriction requirement set forth by the Examiner. MPEP § 1.475 states that a national stage application containing claims to different categories of inventions will be considered to have unity of invention if the claims are drawn to a product, a process specially adapted for the manufacture of the said product, and a use of said product. Therefore, the instant application containing claims identified at least in Groups I, V, VI, and VII should be considered to have unity of invention as they all directed to anti-PD-1 antibodies, use of these antibodies in methods of treatment, and methods for manufacture of these antibodies. Applicant respectfully requests reconsideration and withdrawal of the restriction set forth by the Examiner.

***Election to Restriction Requirement***

If the Examiner maintains the restriction requirement between Groups I, II, III, IV, V, VI, and VII, as defined, then Applicant hereby elects, with traverse, to prosecute the claims of Group I (claims 8, 27, 35, and 106-115) drawn to an antibody to PD-1, and to compositions and immunoconjugates of said antibody. Although Applicant makes the above election to be fully responsive to the Restriction Requirement, Applicant reserves the right to petition under 37 C.F.R. § 1.144.

***Species Election***

The Examiner has stated that the application contains claims directed to the following seven patentably distinct species:



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**Species a:** an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8;

**Species b**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9;

**Species c**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 3; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 10;

**Species d**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 4; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 11;

**Species e**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 5; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12;

**Species f**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 6; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 13; and

**Species g**: an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7; and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 14,

In response to the requirement for election of a single species, Applicants hereby elect the species d.

Under 35 U.S.C. §121, if an election of a single species for prosecution on the merits in required, the claims will be restricted if no generic claim is finally held allowable. At least claims 8, 27, 35, 106-108, and 111 are generic claims. Upon allowance of a generic claim, it is Applicants understanding that Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. 1.141 *et seq.*

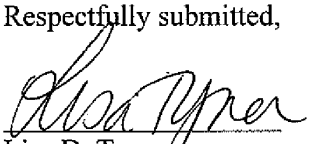


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## CONCLUSION

It is believed that this paper is fully responsive to the outstanding Restriction Requirement. Accordingly, consideration of these remarks is respectfully requested.

Respectfully submitted,



**September 9, 2010**

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# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Lisa Tyner/Lillian Garcia |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| Claims in excess of 20 | 1615 | 6 | 52 | 312 |
| Independent claims in excess of 3 | 1614 | 1 | 220 | 220 |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **532** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8384247 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Lillian Garcia |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 09-SEP-2010 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 15:00:25 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

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|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $532 |
| RAM confirmation Number | 1262 |
| Deposit Account | 024377 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 077375_0499_Preliminary_Amendment_Restriction.pdf | 514842<br>446ba22ded89ac098e739b343e743348b47c848b | yes | 18 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Miscellaneous Incoming Letter | 1 | 2 |
| Response to Election / Restriction Filed | 3 | 3 |
| Claims | 4 | 14 |
| Applicant Arguments/Remarks Made in an Amendment | 15 | 18 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (PTO-875) | fee-info.pdf | 31817<br>95ebe2c23ae5d58f0ded222655cdb2e1ced35ff5 | no | 2 |

**Warnings:**

**Information:**

| **Total Files Size (in bytes):** | 546659 |
|---|---|

**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.**

**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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/SB/21 (10-07)
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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Alan J. Korman et al. |
| Art Unit | 1644 |
| Examiner Name | Ilia I. Ouspenski |
| Attorney Docket Number | 077375.0499 |

## ENCLOSURES *(Check all that apply)*

- ☑ Fee Transmittal Form
  - ☑ Fee Attached
- ☑ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature |  | | |
| Printed name | Lisa D. Tyner | | |
| Date | 09/09/2010 | Reg. No. | 51,619 |

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

| | | | |
|---|---|---|---|
| Signature | | | |
| Typed or printed name | | Date | |

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# FEE TRANSMITTAL for FY 2007

| Complete if Known | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Alan J. Korman et al. |
| Examiner Name | Ilia I. Ouspenski |
| Art Unit | 1644 |
| Attorney Docket No. | 077375.0499 |

☐ Applicant claims small entity status. See 37 CFR 1.27

| TOTAL AMOUNT OF PAYMENT | ($) 532 |
|---|---|

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

| Deposit Account Number | 02-4377 |
|---|---|
| Deposit Account Name | Baker Botts L.L.P. |

**The Director is authorized to:** *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

## FEE CALCULATION

### Extra Claim Fees

| | Extra Claims | | Fee | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | 6 | x | 52 | = | $312 |
| Independent Claims | 1 | x | 220 | = | $220 |
| Multiple Dependent | | | | = | $0 |

SUBTOTAL $532

| Fee Description | Large Entity | Small Entity |
|---|---|---|
| Claims in excess of 20 | 52 | 26 |
| Independent claims in excess of 3 | 220 | 110 |
| Multiple dependent claim, if not paid | 390 | 195 |

## FEE CALCULATION (continued)

### ADDITIONAL FEES

| | |
|---|---|
| ☐ Surcharge - late oath or filing fee | |
| ☐ Non-English Specification | |
| ☐ Extension for reply within first month | |
| ☐ Extension for reply within second month | |
| ☐ Extension for reply within third month | |
| ☐ Extension for reply within fourth month | |
| ☐ Extension for reply within fifth month | |
| ☐ Notice of Appeal | |
| ☐ Filing a brief in support of an appeal | |
| ☐ Petition to revive - unavoidable | |
| ☐ Petition to revive - unintentional | |
| ☐ Utility Issue Fee | |
| ☐ Design Issue Fee | |
| ☐ Publication Fee | |
| ☐ Petitions to the Commissioner | |
| ☐ Request for Continued Examination (RCE) | |
| ☐ Information Disclosure Statement (IDS) | |
| Other fee - | |

SUBTOTAL ($) 0

**SUBMITTED BY** (Complete *(if applicable)*)

| Name (Print/Type) | Lisa D. Tyner | Registration No. (Attorney/Agent) | 51,619 | Telephone | 212-408-2500 |
|---|---|---|---|---|---|
| Signature | | | | Date | 09/09/2010 |

**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 1.17 and 1.27. 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.**

PTO/SB/06 (07-06)
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# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

| Application or Docket Number | Filing Date | ☐ To be Mailed |
|---|---|---|
| 11/913,217 | 01/29/2009 | |

## APPLICATION AS FILED – PART I

| | (Column 1) | (Column 2) | SMALL ENTITY ☐ | | OR | OTHER THAN SMALL ENTITY | |
|---|---|---|---|---|---|---|---|
| FOR | NUMBER FILED | NUMBER EXTRA | RATE ($) | FEE ($) | | RATE ($) | FEE ($) |
| ☐ BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| | | (Column 1) | | (Column 2) | (Column 3) | SMALL ENTITY | | OR | OTHER THAN SMALL ENTITY | |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT | 09/09/2010 | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
| | Total (37 CFR 1.16(i)) | * 36 | Minus | ** 30 | = 6 | X $ = | | OR | X $52= | 312 |
| | Independent (37 CFR 1.16(h)) | * 8 | Minus | ***7 | = 1 | X $ = | | OR | X $220= | 220 |
| | ☐ 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 | 532 |

| | | (Column 1) | | (Column 2) | (Column 3) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT | | CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
| | 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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
//REGINA D. BALTIMORE//

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Document code: WFEE

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Sales Receipt for Accounting Date: 02/01/2011

EWARREN SALE #00000001 Mailroom Dt: 09/09/2010 024377 11913217
01 FC : 1201 220.00 DA

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

63367 7590 10/25/2010

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| EXAMINER | |
|---|---|
| OUSPENSKI, ILIA I | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 10/25/2010 | 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):

DLNYDOCKET@BAKERBOTTS.COM

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 11/913,217 | KORMAN ET AL. | |
| | Examiner | Art Unit | |
| | ILIA OUSPENSKI | 1644 | |

*-- 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 *09 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ 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**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *57,62,64,65,67-72,79,80,84,88,89,96,97,101 and 105* is/are withdrawn from consideration.

5)☒ Claim(s) *8,27,35,43,44,50 and 113-117* is/are allowed.

6)☒ Claim(s) *106-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2007* 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).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**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).

a)☐ All b)☐ Some * c)☐ None of:

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) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/08;4/24/09;7/8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 8,27,35,43,44,50,57,62,64,65,67-72,79,80,84,88,89,96,97,101 and 105-117.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1686 of 2058

## DETAILED ACTION

1. Applicant's amendment and remarks filed on 09/09/2010 are acknowledged.

Claims 8, 27, 35, 43-44, 50, 57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105-117 are pending.

2. Applicant's election with traverse of Group I in the reply filed on 09/09/2010 is acknowledged.

The traversal is on the grounds that, according to Applicant, a national stage application containing claims to different categories of inventions should be considered to have unity of invention if the claims are drawn to a product, a process specially adapted for the manufacture of the said product, and a use of said product.

This is not found persuasive because, as addressed in the previous Office Action, the claimed inventions do not contribute a special technical feature when viewed over the prior art, thus they do not have a single general inventive concept and so lack unity of invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 8, 27, 35, 43-44, 50 and 106-117 are presently under consideration.

3. Applicant further elected Species “d” in the reply filed on 09/09/2010.

In the interest of compact prosecution, examination has been extended to include all species of the elected invention.

4. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 108 – 112 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for an antibody wherein the sequences of the six CDRs are from the same monoclonal antibody disclosed in the specification, and wherein the sequences of the heavy chain variable region and the light chain variable region are from the same monoclonal antibody disclosed in the specification, does not reasonably provide enablement for an antibody wherein the sequences of recited CDRs are from different antibodies, or wherein the sequences of the heavy chain variable region and the light chain variable region are from different antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

One of skill in the art is aware that combining a light chain of an antibody with a heavy chain from a different antibody usually results in a non-functional combination. Likewise, combining CDRs from different antibodies usually results in a non-functional antibody. Therefore, in the absence of sufficient guidance in the instant specification as to which specific variable region or CDR sequences can be combined to produce functional antibodies one of skill in the art is not enabled to make and use the claimed antibodies.

6. Claims 106 – 112 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for an antibody wherein the sequences of the six CDRs are defined, and for an antibody that specifically binds to PD-1 wherein the sequence of at least the heavy chain CDR3 is defined, does not reasonably provide enablement for an antibody wherein the sequences of fewer than six CDRs are defined, or for an antibody that that specifically binds to PD-1 wherein the sequence of the heavy chain CDR3 is not defined, or for an antibody wherein the sequence of any CDR is qualified by the “conservative modifications” language, or for an antibody wherein the sequence of any variable region is qualified by the “percent homology” language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

An ability of the claimed antibody to bind to a specific antigen is considered to be an essential feature of the claimed invention. However, it is well established in the art that the formation of an intact antigen-binding site generally requires all six CDRs. Specific interaction with the antigen requires the association of the complete heavy and light chain variable regions of the antibody, each of which consists of three CDRs, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce an antibody having antigen-binding function, and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function, as evidenced by numerous references (e.g. Rudikoff et al. 1982, Proc. Natl. Acad. Sci. USA, , 79: 1979 – 1983; see entire document, in particular, e.g. the Abstract; Adair et al., 2003, US Patent No. 6,632,927; see entire document, in particular, e.g. columns 2 – 3, bridging paragraph; and Panka et al., 1988, Proc. Natl. Acad. Sci. USA, 85: 3080 – 3084; see entire document, in particular, e.g. the Abstract), which all teach that alteration of a single amino acid in an antibody results in the loss or a major change of the antigen-binding function.

Therefore, it is unpredictable whether antibodies as defined by the claims, which may contain less than the full complement of CDRs from the heavy and light chain variable regions, have the antigen-binding function. The specification provides insufficient direction or guidance regarding how to produce functional antibodies broadly defined by the claims. Undue experimentation would be required to make and use the invention commensurate with the scope of the claims from the written disclosure alone.

7. Claims 106 and 107 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not provide a sufficient enabling description of an isolated monoclonal antibody comprising variable regions encoded by the specified genes, wherein the antibody specifically binds to PD-L1.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

It is acknowledged that one of skill in the art is enabled to make monoclonal antibodies that specifically bind to PD-L1, and then determine the identity of the gene encoding the respective heavy and light chain variable regions. However, given the large number of genes encoding the variable regions, it is unpredictable which, if any, monoclonal antibodies would have the specific combinations or genes recited in the instant claims, and thus the experimentation left to those skilled in the art, is unnecessarily, and improperly, extensive and undue.

***8. Conclusion: claims 8, 27, 35, 43-44, 50 and 113-117 are allowable.***

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on 571-272-0735. 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 http://pair-direct.uspto.gov. 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.

/ILIA OUSPENSKI/
ILIA OUSPENSKI, Ph.D.
Primary Examiner
Art Unit 1644

October 19, 2010

| Notice of References Cited | Application/Control No. 11/913,217 | Applicant(s)/Patent Under Reexamination KORMAN ET AL. | |
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| | Examiner ILIA OUSPENSKI | Art Unit 1644 | Page 1 of 1 |

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| | C | US- | | | |
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| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
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| | L | US- | | | |
| | M | US- | | | |

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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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# BIB DATA SHEET

**CONFIRMATION NO. 1207**

| SERIAL NUMBER | FILING or 371(c) DATE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009<br>RULE | 435 | 1644 | 077375.0499 |

**APPLICANTS**

Alan J. Korman, Piedmont, CA;
Mohan Srinivasan, San Jose, CA;
Changyu Wang, Fremont, CA;
Mark J. Selby, San Francisco, CA;
Bing Chen, Alameda, CA;
Josephine M. Cardarelli, San Carlos, CA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/JP2006/309606 05/02/2006
which claims benefit of 60/679,466 05/09/2005
and claims benefit of 60/738,434 11/21/2005
and claims benefit of 60/748,919 12/08/2005

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

05/15/2009

| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☑ No<br>Verified and Acknowledged /ILIA I OUSPENSKI/ Examiner's Signature | ☐ Met after Allowance<br>Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | CA | 58 | 31 | 7 |

**ADDRESS**

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498
UNITED STATES

**TITLE**

Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics

| FILING FEE RECEIVED | FEES: Authority has been given in Paper | |
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BIB (Rev. 05/07).

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|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

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* Examiner: Initial citation 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.

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, *et al.* |
| | Art Unit | 1632 |
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| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, *et al.* |
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| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | Examiner | Art Unit |
| | ILIA OUSPENSKI | 1644 |

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| SEARCH NOTES | | |
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| Search Notes | Date | Examiner |
| Priority documents | 10/19/2010 | /I.O./ |
| Sequence search: in SCORE | 10/19/2010 | /I.O./ |
| WEST: attached | 10/19/2010 | /I.O./ |
| Dialog: same as WEST | 10/19/2010 | /I.O./ |
| Inventor search | 10/19/2010 | /I.O./ |

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|---|---|---|
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| | Filing Date | TBD |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
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END OF SEARCH HISTORY



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Dana-Farber v. BMS, IPR2023-00501
Page 1704 of 2058

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : KORMAN *et al.* | Examiner | : OUSPENSKI, ILIA I |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| Filed | : 10/31/2007 | Group Art Unit | 1644 |
| For | : HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS | | |

**INFORMATION DISCLOSURE STATEMENT**

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

Sir:

Enclosed herewith are patents and/or publications for consideration by the Patent and Trademark Office in regard to the invention claimed in the above-identified application. In compliance with 37 C.F.R. §1.56, such documents are listed on the enclosed Form PTO-1449.

This Information Disclosure Statement is submitted according to the following selected paragraph(s):

☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(b) (1) within three months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. § 1.53(d); (2) within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application; (3) before the mailing of a first Office action on the merits; or (4) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.



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Dana-Farber v. BMS, IPR2023-00501
Page 1705 of 2058

☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(c) prior to either a final action or a notice of allowance. Payment for the fee required by 37 C.F.R. §1.17(p) is hereby authorized to be charged to Deposit Account No. 02-4377.

☒ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(c), with a statement under, 37 C.F.R. §1.97(e) prior to either a final action or a notice of allowance. The undersigned hereby states that (check one):

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☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(d), with a statement under 37 C.F.R. §1.97(e), after a final action or a notice of allowance but prior to payment of the issue fee. Payment for the fee required by 37 C.F.R. §1.17(p) is hereby authorized to be charged to Deposit Account No. 02-4377. The undersigned hereby petitions that this Information Disclosure Statement be considered prior to issuance of the patent. The undersigned hereby states that (check one):

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- ☐ no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information



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disclosure statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the information disclosure statement.

☐ The references listed on the accompanying PTO-1449 were either cited by the Examiner or previously submitted in co-pending application U.S. Serial No. _____, filed _____. Pursuant to 37 C.F.R. § 1.98(d), the references are not required if the earlier application is identified and relied upon for an effective filing date under 35 U.S.C. § 120 and therefore are not enclosed herewith.

**Co-Pending Application Disclosure**

☐ Applicants would like to bring to the attention of the Examiner the following co-pending patent applications, which are also listed on the accompanying PTO-1449:

| Serial No. | Filing Date |
|---|---|
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| | |

**Disclosure of Office Actions and Responses in Co-Pending Applications**

☐ Applicants would like to bring to the attention of the Examiner the following Office Actions issued in co-pending patent applications and Responses to Office Actions filed in such applications, which are also listed on the accompanying PTO-1449:

| Serial No. | Date of Office Action or Response |
|---|---|
| | |
| | |

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed documents are material or constitute "prior art." If the Examiner applies the documents as prior art against any claim in the application and applicants determine that the cited documents do not constitute "prior art" under United States law, applicants reserve the right to present to the Office the relevant facts and law regarding the appropriate status of the documents.



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Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the documents be applied against the claims of the present application.

Applicants believe no additional fee is due in connection with this submission. However, if any additional fee is due, or if any overpayment has been made, the Commissioner is authorized to charge any such fee or credit any overpayment to our Deposit Account No. 02-4377.

Respectfully submitted,

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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
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(54) Title: ANTIBODIES AGAINST PD-1 AND USES THEREFOR

(57) Abstract: This disclosure provides antibodies and antigen-binding fragments that can act as agonists and/or antagonists of PD-1 (Programmed Death 1), thereby modulating immune responses in general, and those mediated by TcR and CD28, in particular. The disclosed compositions and methods may be used for example, in treating autoimmune diseases, inflammatory disorders, allergies, transplant rejection, cancer, and other immune system disorders.

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# ANTIBODIES AGAINST PD-1 AND USES THEREFOR

## DESCRIPTION OF THE INVENTION

### Field of the Invention

[001] The technical field relates to modulation of immune responses regulated by the Programmed Death 1 (PD-1) receptor.

### Background of the Invention

[002] An adaptive immune response involves activation, selection, and clonal proliferation of two major classes of lymphocytes termed T cells and B cells. After encountering an antigen, T cells proliferate and differentiate into antigen-specific effector cells, while B cells proliferate and differentiate into antibody-secreting cells.

[003] T cell activation is a multi-step process requiring several signaling events between the T cell and an antigen-presenting cell (APC). For T cell activation to occur, two types of signals must be delivered to a resting T cell. The first type is mediated by the antigen-specific T cell receptor (TcR), and confers specificity to the immune response. The second, costimulatory, type regulates the magnitude of the response and is delivered through accessory receptors on the T cell.

[004] A primary costimulatory signal is delivered through the activating CD28 receptor upon engagement of its ligands B7-1 or B7-2. In contrast, engagement of the inhibitory CTLA-4 receptor by the same B7-1 or B7-2 ligands results in attenuation of T cell response. Thus, CTLA-4 signals antagonize costimulation mediated by CD28. At high antigen concentrations, CD28 costimulation overrides the CTLA-4 inhibitory effect. Temporal regulation of the CD28 and CTLA-4 expression maintains a balance between activating and inhibitory signals and ensures the development of an effective immune response, while safeguarding against the development of autoimmunity.



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[005] Molecular homologues of CD28 and CTLA-4 and their B-7 like ligands have been recently identified. ICOS is a CD28-like costimulatory receptor. PD-1 (Programmed Death 1) is an inhibitory receptor and a counterpart of CTLA-4. This disclosure relates to modulation of immune responses mediated by the PD-1 receptor.

[006] PD-1 is a 50-55 kDa type I transmembrane receptor that was originally identified in a T cell line undergoing activation-induced apoptosis. PD-1 is expressed on T cells, B cells, and macrophages. The ligands for PD-1 are the B7 family members PD-L1 (B7-H1) and PD-L2 (B7-DC).

[007] PD-1 is a member of the immunoglobulin (Ig) superfamily that contains a single Ig V–like domain in its extracellular region. The PD-1 cytoplasmic domain contains two tyrosines, with the most membrane-proximal tyrosine (VAYEEL in mouse PD-1) located within an ITIM (immuno-receptor tyrosine-based inhibitory motif). The presence of an ITIM on PD-1 indicates that this molecule functions to attenuate antigen receptor signaling by recruitment of cytoplasmic phosphatases. Human and murine PD-1 proteins share about 60% amino acid identity with conservation of four potential N-glycosylation sites, and residues that define the Ig-V domain. The ITIM in the cytoplasmic region and the ITIM-like motif surrounding the carboxy-terminal tyrosine (TEYATI in human and mouse) are also conserved between human and murine orthologues.

[008] PD-1 is expressed on activated T cells, B cells, and monocytes. Experimental data implicates the interactions of PD-1 with its ligands in downregulation of central and peripheral immune responses. In particular, proliferation in wild-type T cells but not in PD-1-deficient T cells is inhibited in the presence of PD-L1. Additionally, PD-1-deficient mice exhibit an autoimmune phenotype. PD-1 deficiency in the C57BL/6 mice results in chronic progressive lupus-like glomerulonephritis and arthritis. In Balb/c mice, PD-1 deficiency leads to severe cardiomyopathy due to the presence of heart-tissue-specific self-reacting antibodies.



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[009] In general, a need exists to provide safe and effective therapeutic methods for immune disorders such as, for example, autoimmune diseases, inflammatory disorders, allergies, transplant rejection, cancer, immune deficiency, and other immune system-related disorders. Modulation of the immune responses involved in these disorders can be accomplished by manipulation of the PD-1 pathway.

## SUMMARY OF THE INVENTION

[010] The present disclosure provides antibodies that can act as agonists and/or antagonists of PD-1, thereby modulating immune responses regulated by PD-1. The disclosure further provides anti-PD-1 antibodies that comprise novel antigen-binding fragments. Anti-PD-1 antibodies of the invention are capable of (a) specifically binding to PD-1, including human PD-1; (b) blocking PD-1 interactions with its natural ligand(s); or (c) performing both functions. Furthermore, the antibodies may possess immunomodulatory properties, i.e., they may be effective in modulating the PD-1-associated downregulation of immune responses. Depending on the method of use and the desired effect, the antibodies may be used to either enhance or inhibit immune responses.

[011] Nonlimiting illustrative embodiments of the antibodies are referred to as PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2. Other embodiments comprise a $V_H$ and/or $V_L$ domain of the Fv fragment of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2. Further embodiments comprise one or more complementarity determining regions (CDRs) of any of these $V_H$ and $V_L$ domains. Other embodiments comprise an H3 fragment of the $V_H$ domain of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2.

[012] The disclosure also provides compositions comprising PD-1 antibodies, and their use in methods of modulating immune response, including methods of treating humans or animals. In particular embodiments, anti-PD-1 antibodies are used to treat or prevent immune disorders by virtue of increasing or reducing the T cell response mediated by TcR/CD28.



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Disorders susceptible to treatment with compositions of the invention include but are not limited to rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosis, type I diabetes, transplant rejection, graft-versus-host disease, hyperproliferative immune disorders, cancer, and infectious diseases.

[013] Additionally, anti-PD-1 antibodies may be used diagnostically to detect PD-1 or its fragments in a biological sample. The amount of PD-1 detected may be correlated with the expression level of PD-1, which, in turn, is correlated with the activation status of immune cells (e.g., activated T cells, B cells, and monocytes) in the subject.

[014] The disclosure also provides isolated nucleic acids, which comprise a sequence encoding a $V_H$ or $V_L$ domain from the Fv fragment of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2. Also provided are isolated nucleic acids, which comprise a sequence encoding one or more CDRs from any of the presently disclosed $V_H$ and $V_L$ domains. The disclosure also provides vectors and host cells comprising such nucleic acids.

[015] The disclosure further provides a method of producing new $V_H$ and $V_L$ domains and/or functional antibodies comprising all or a portion of such domains derived from the $V_H$ or $V_L$ domains of PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2.

[016] Additional aspects of the disclosure will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practicing the invention. The invention is set forth and particularly pointed out in the appended claims, and the present disclosure should not be construed as limiting the scope of the claims in any way. The following detailed description includes exemplary representations of various embodiments of the invention, which are not restrictive of the invention, as claimed. The accompanying figures constitute a part of this specification and, together with the description, serve only to illustrate various embodiments and not limit the invention. Citation of references is not an admission that these references are prior art to the invention.



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## BRIEF DESCRIPTION OF THE FIGURES

[017] Figures 1A and 1B show reactivity of scFv antibodies with human PD-1 as determined by phage ELISA.

[018] Figures 2A-2C show reactivity of IgG-converted antibodies with human or mouse PD-1 as determined by ELISA.

[019] Figure 3 shows results of an ELISA demonstrating that selected PD-1 antibodies inhibit binding of PD-L1 to PD-1.

[020] Figure 4 shows results of an ELISA demonstrating that immunomodulatory PD-1 antibodies bind to distinct sites on PD-1 as determined by cross-blocking ELISA assays.

[021] Figure 5 shows results of T-cell proliferation assays demonstrating that co-engagement by TcR and anti-PD-1 antibody PD1-17 or PD-L1.Fc reduces proliferation. Co-engagement by TcR and anti-PD-1 J110 has no effect on proliferation.

[022] Figure 6 demonstrates enhanced proliferation of primary T cells by PD1-17 in a soluble form.

## DETAILED DESCRIPTION

### Definitions

[023] The term "antibody," as used in this disclosure, refers to an immunoglobulin or a fragment or a derivative thereof, and encompasses any polypeptide comprising an antigen-binding site, regardless whether it is produced in vitro or in vivo. The term includes, but is not limited to, polyclonal, monoclonal, monospecific, polyspecific, non-specific, humanized, single-chain, chimeric, synthetic, recombinant, hybrid, mutated, and grafted antibodies. Unless otherwise modified by the term "intact," as in "intact antibodies," for the purposes of this disclosure, the term "antibody" also includes antibody fragments such as Fab, $F(ab')_2$, Fv, scFv, Fd, dAb, and other antibody fragments that retain antigen-binding function, i.e., the ability to



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bind PD-1 specifically. Typically, such fragments would comprise an antigen-binding domain.

[024] The terms "antigen-binding domain," "antigen-binding fragment," and "binding fragment" refer to a part of an antibody molecule that comprises amino acids responsible for the specific binding between the antibody and the antigen. In instances, where an antigen is large, the antigen-binding domain may only bind to a part of the antigen. A portion of the antigen molecule that is responsible for specific interactions with the antigen-binding domain is referred to as "epitope" or "antigenic determinant."

[025] An antigen-binding domain typically comprises an antibody light chain variable region ($V_L$) and an antibody heavy chain variable region ($V_H$), however, it does not necessarily have to comprise both. For example, a so-called Fd antibody fragment consists only of a $V_H$ domain, but still retains some antigen-binding function of the intact antibody.

[026] The term "repertoire" refers to a genetically diverse collection of nucleotides derived wholly or partially from sequences that encode expressed immunoglobulins. The sequences are generated by in vivo rearrangement of, e.g., V, D, and J segments for H chains and, e.g., V and J segment for L chains. Alternatively, the sequences may be generated from a cell line by in vitro stimulation, in response to which the rearrangement occurs. Alternatively, part or all of the sequences may be obtained by combining, e.g., unrearranged V segments with D and J segments, by nucleotide synthesis, randomised mutagenesis, and other methods, e.g., as disclosed in U.S. Patent No. 5,565,332.

[027] The terms "specific interaction" and "specific binding" refer to two molecules forming a complex that is relatively stable under physiologic conditions. Specific binding is characterized by a high affinity and a low to moderate capacity as distinguished from nonspecific binding which usually has a low affinity with a moderate to high capacity. Typically, binding is considered specific when the affinity constant $K_A$ is higher than $10^6\ M^{-1}$, or more preferably higher than $10^8\ M^{-1}$. If necessary, non-specific binding can be



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reduced without substantially affecting specific binding by varying the binding conditions. The appropriate binding conditions such as concentration of antibodies, ionic strength of the solution, temperature, time allowed for binding, concentration of a blocking agent (e.g., serum albumin, milk casein), etc., may be optimized by a skilled artisan using routine techniques. Illustrative conditions are set forth in Examples 1, 2, 4, 6, and 7.

[028] The phrase "substantially as set out" means that the relevant CDR, $V_H$, or $V_L$ domain of the invention will be either identical to or have only insubstantial differences in the specified regions (e.g., a CDR), the sequence of which is set out. Insubstantial differences include minor amino acid changes, such as substitutions of 1 or 2 out of any 5 amino acids in the sequence of a specified region.

[029] The term "PD-1 activity" refers to one or more immunoregulatory activities associated with PD-1. For example, PD-1 is a negative regulator of the TcR/CD28-mediated immune response. Procedures for assessing the PD-1 activity in vivo and in vitro are described in Examples 8, 9, and 10.

[030] The terms "modulate," "immunomodulatory," and their cognates refer to a reduction or an increase in the activity of PD-1 associated with downregulation of T cell responses due to its interaction with an anti-PD-1 antibody, wherein the reduction or increase is relative to the activity of PD-1 in the absence of the same antibody. A reduction or an increase in activity is preferably at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more. When PD-1 activity is reduced, the terms "modulatory" and "modulate" are interchangeable with the terms "inhibitory" and "inhibit." When PD-1 activity is increased, the terms "modulatory" and "modulate" are interchangeable with the terms "activating" and "activate." The activity of PD-1 can be determined quantitatively using T cell proliferation assays as described in Examples 8 and 9.

[031] The terms "treatment" and "therapeutic method" refer to both therapeutic treatment and prophylactic/preventative measures. Those in need of treatment may include individuals already having a particular medical



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disorder as well as those who may ultimately acquire the disorder (i.e., those needing preventative measures).

[032] The term "effective amount" refers to a dosage or amount that is sufficient to reduce the activity of PD-1 to result in amelioration of symptoms in a patient or to achieve a desired biological outcome, e.g., increased cytolytic activity of T cells, induction of immune tolerance, reduction or increase of the PD-1 activity associated with the negative regulation of T-cell mediated immune response, etc.

[033] The term "isolated" refers to a molecule that is substantially free of its natural environment. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it is derived. The term "isolated" also refers to preparations where the isolated protein is sufficiently pure to be administered as a pharmaceutical composition, or at least 70-80% (w/w) pure, more preferably, at least 80-90% (w/w) pure, even more preferably, 90-95% pure; and, most preferably, at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

Anti-PD-1 Antibodies

[034] The disclosure provides anti-PD-1 antibodies that comprise novel antigen-binding fragments.

[035] In general, antibodies can be made, for example, using traditional hybridoma techniques (Kohler and Milstein (1975) Nature, 256: 495-499), recombinant DNA methods (U.S. Patent No. 4,816,567), or phage display performed with antibody libraries (Clackson et al. (1991) Nature, 352: 624-628; Marks et al. (1991) J. Mol. Biol., 222: 581-597). For other antibody production techniques, see also Antibodies: A Laboratory Manual, eds. Harlow et al., Cold Spring Harbor Laboratory, 1988. The invention is not limited to any particular source, species of origin, method of production.

[036] Intact antibodies, also known as immunoglobulins, are typically tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each and two heavy (H) chains of approximately 50 kDa each. Two types of light chain, designated as the λ chain and the κ



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chain, are found in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins can be assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), e.g., $IgG_1$, $IgG_2$, $IgG_3$, $IgG_4$, $IgA_1$, and $IgA_2$.

[037] The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of antibody structure, see Harlow et al., supra. Briefly, each light chain is composed of an N-terminal variable domain ($V_L$) and a constant domain ($C_L$). Each heavy chain is composed of an N-terminal variable domain ($V_H$), three or four constant domains ($C_H$), and a hinge region. The $C_H$ domain most proximal to $V_H$ is designated as $C_H1$. The $V_H$ and $V_L$ domains consist of four regions of relatively conserved sequence called framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequence called complementarity determining regions (CDRs). The CDRs contain most of the residues responsible for specific interactions with the antigen. The three CDRs are referred to as CDR1, CDR2, and CDR3. CDR constituents on the heavy chain are referred to as H1, H2, and H3, while CDR constituents on the light chain are referred to as L1, L2, and L3, accordingly. CDR3 and, particularly H3, are the greatest source of molecular diversity within the antigen-binding domain. H3, for example, can be as short as two amino acid residues or greater than 26.

[038] The Fab fragment (**F**ragment **a**ntigen-**b**inding) consists of the $V_H$-$C_H1$ and $V_L$-$C_L$ domains covalently linked by a disulfide bond between the constant regions. To overcome the tendency of non-covalently linked $V_H$ and $V_L$ domains in the Fv to dissociate when co-expressed in a host cell, a so-called single chain (sc) Fv fragment (scFv) can be constructed. In a scFv, a flexible and adequately long polypeptide links either the C-terminus of the $V_H$ to the N-terminus of the $V_L$ or the C-terminus of the $V_L$ to the N-terminus of the $V_H$. Most commonly, a 15-residue $(Gly_4Ser)_3$ peptide is used as a linker but other linkers are also known in the art.



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[039] Antibody diversity is a result of combinatorial assembly of multiple germline genes encoding variable regions and a variety of somatic events. The somatic events include recombination of variable gene segments with diversity (D) and joining (J) gene segments to make a complete $V_H$ region and the recombination of variable and joining gene segments to make a complete $V_L$ region. The recombination process itself is imprecise, resulting in the loss or addition of amino acids at the V(D)J junctions. These mechanisms of diversity occur in the developing B cell prior to antigen exposure. After antigenic stimulation, the expressed antibody genes in B cells undergo somatic mutation.

[040] Based on the estimated number of germline gene segments, the random recombination of these segments, and random $V_H$-$V_L$ pairing, up to $1.6 \times 10^7$ different antibodies could be produced (Fundamental Immunology, 3rd ed., ed. Paul, Raven Press, New York, NY, 1993). When other processes which contribute to antibody diversity (such as somatic mutation) are taken into account, it is thought that upwards of $1 \times 10^{10}$ different antibodies could be potentially generated (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995). Because of the many processes involved in antibody diversity, it is highly unlikely that independently generated antibodies will have identical or even substantially similar amino acid sequences in the CDRs.

[041] The disclosure provides novel CDRs derived from human immunoglobulin gene libraries. The structure for carrying a CDR will generally be an antibody heavy or light chain or a portion thereof, in which the CDR is located at a location corresponding to the CDR of naturally occurring $V_H$ and $V_L$. The structures and locations of immunoglobulin variable domains may be determined, for example, as described in Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, MD, 1991.

[042] DNA and amino acid sequences of anti-PD-1 antibodies, their scFv fragment, $V_H$ and $V_L$ domains, and CDRs are set forth in the Sequence



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Listing and are enumerated as listed in Table 1. Particular nonlimiting illustrative embodiments of the antibodies are referred to as PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2. The positions for each CDR within the $V_H$ and $V_L$ domains of the illustrative embodiments are listed in Tables 2 and 3.

Table 1: DNA and Amino Acid (AA) Sequences of $V_H$ and $V_L$ Domains and CDRs

| Sequence | PD1-17 | PD1-28 | PD1-33 | PD1-35 | PD1-F2 |
|---|---|---|---|---|---|
| $V_H$ DNA | SEQ ID NO:1 | SEQ ID NO:5 | SEQ ID NO:9 | SEQ ID NO:13 | SEQ ID NO:46 |
| $V_H$ AA | SEQ ID NO:2 | SEQ ID NO:6 | SEQ ID NO:10 | SEQ ID NO:14 | SEQ ID NO:47 |
| $V_L$ DNA | SEQ ID NO:3 | SEQ ID NO:7 | SEQ ID NO:11 | SEQ ID NO:15 | SEQ ID NO:48 |
| $V_L$ AA | SEQ ID NO:4 | SEQ ID NO:8 | SEQ ID NO:12 | SEQ ID NO:16 | SEQ ID NO:49 |
| H1 AA | SEQ ID NO:17 | SEQ ID NO:23 | SEQ ID NO:29 | SEQ ID NO:35 | SEQ ID NO:50 |
| H2 AA | SEQ ID NO:18 | SEQ ID NO:24 | SEQ ID NO:30 | SEQ ID NO:36 | SEQ ID NO:51 |
| H3 AA | SEQ ID NO:19 | SEQ ID NO:25 | SEQ ID NO:31 | SEQ ID NO:37 | SEQ ID NO:52 |
| L1 AA | SEQ ID NO:20 | SEQ ID NO:26 | SEQ ID NO:32 | SEQ ID NO:38 | SEQ ID NO:53 |
| L2 AA | SEQ ID NO:21 | SEQ ID NO:27 | SEQ ID NO:33 | SEQ ID NO:39 | SEQ ID NO:54 |
| L3 AA | SEQ ID NO:22 | SEQ ID NO:28 | SEQ ID NO:34 | SEQ ID NO:40 | SEQ ID NO:55 |

Table 2: Positions of Heavy Chain CDRs

| CDR | PD1-17 SEQ ID NO:2 | PD1-28 SEQ ID NO:6 | PD1-33 SEQ ID NO:10 | PD1-35 SEQ ID NO:14 | PD1-F2 SEQ ID NO:47 |
|---|---|---|---|---|---|
| H1 | 31-42 | 31-35 | 31-35 | 31-37 | 34-42 |
| H2 | 57-72 | 50-66 | 50-66 | 52-67 | 57-73 |
| H3 | 105-117 | 99-108 | 99-108 | 100-116 | 106-114 |



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Table 3: Positions of Light Chain CDRs

| CDR | PD1-17 SEQ ID NO:4 | PD1-28 SEQ ID NO:8 | PD1-33 SEQ ID NO:12 | PD1-35 SEQ ID NO:16 | PD1-F2 SEQ ID NO:49 |
|---|---|---|---|---|---|
| L1 | 23-35 | 23-33 | 23-36 | 23-35 | 28-35 |
| L2 | 51-57 | 49-55 | 52-58 | 51-57 | 54-61 |
| L3 | 92-100 | 88-98 | 91-102 | 90-100 | 94-101 |

[043] Anti-PD-1 antibodies may optionally comprise antibody constant regions or parts thereof. For example, a $V_L$ domain may have attached, at its C terminus, antibody light chain constant domains including human Cκ or Cλ chains. Similarly, a specific antigen-binding domain based on a $V_H$ domain may have attached all or part of an immunoglobulin heavy chain derived from any antibody isotope, e.g., IgG, IgA, IgE, and IgM and any of the isotope sub-classes, which include but are not limited to, $IgG_1$ and $IgG_4$. In the exemplary embodiments, PD1-17, PD1-28, PD1-33, and PD1-35, antibodies comprise C-terminal fragments of heavy and light chains of human $IgG_{1\lambda}$, while PD1-F2 comprises C-terminal fragments of heavy and light chains of human $IgG_{1\kappa}$. The DNA and amino acid sequences for the C-terminal fragment of are well known in the art (see, e.g, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, MD, 1991). Nonlimiting exemplary sequences are set forth in Table 4.

Table 4

| C-Terminal Region | DNA | Amino acid |
|---|---|---|
| **IgG1 heavy chain** | SEQ ID NO:44 | SEQ ID NO:45 |
| **λ light chain** | SEQ ID NO:42 | SEQ ID NO:43 |
| **κ light chain** | SEQ ID NO:57 | SEQ ID NO:58 |



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[044] Certain embodiments comprise a $V_H$ and/or $V_L$ domain of an Fv fragment from PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2. Further embodiments comprise at least one CDR of any of these $V_H$ and $V_L$ domains. Antibodies, comprising at least one of the CDR sequences set out in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NOs:16-40, SEQ ID NO:47, or SEQ ID NO:49 are encompassed within the scope of this invention. An embodiment, for example, comprises an H3 fragment of the $V_H$ domain of antibodies chosen from at least one of PD1-17, PD1-28, PD1-33, PD1-35, and PD1-F2.

[045] In certain embodiments, the $V_H$ and/or $V_L$ domains may be germlined, i.e., the framework regions (FRs) of these domains are mutated using conventional molecular biology techniques to match those produced by the germline cells. In other embodiments, the framework sequences remain diverged from the consensus germline sequences.

[046] In certain embodiments, the antibodies specifically bind an epitope within the extracellular domain of human PD-1. The predicted extracellular domain consists of a sequence from about amino acid 21 to about amino acid 170 of SEQ ID NO:41 (Swissport Accession No. Q15116). In certain other embodiments, the antibodies specifically bind an epitope within the extracellular domain of mouse PD-1, with an affinity of more than $10^7$ $M^{-1}$, and preferably more than $10^8$ $M^{-1}$. The amino acid sequence of mouse PD-1 is set out in SEQ ID NO:56 (Accession No. NM_008798) and is as a whole about 60% identical to its human counterpart. In further embodiments, antibodies of the invention bind to the PD-L-binding domain of PD-1.

[047] It is contemplated that antibodies of the invention may also bind with other proteins, including, for example, recombinant proteins comprising all or a portion of the PD-1 extracellular domain.

[048] One of ordinary skill in the art will recognize that the antibodies of this invention may be used to detect, measure, and inhibit proteins that differ somewhat from PD-1. The antibodies are expected to retain the



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specificity of binding so long as the target protein comprises a sequence which is at least about 60%, 70%, 80%, 90%, 95%, or more identical to any sequence of at least 100, 80, 60, 40, or 20 of contiguous amino acids in the sequence set forth SEQ ID NO:41. The percent identity is determined by standard alignment algorithms such as, for example, Basic Local Alignment Tool (BLAST) described in Altshul et al. (1990) J. Mol. Biol., 215: 403-410, the algorithm of Needleman et al. (1970) J. Mol. Biol., 48: 444-453, or the algorithm of Meyers et al. (1988) Comput. Appl. Biosci., 4: 11-17.

[049] In addition to the sequence homology analyses, epitope mapping (see, e.g., Epitope Mapping Protocols, ed. Morris, Humana Press, 1996) and secondary and tertiary structure analyses can be carried out to identify specific 3D structures assumed by the disclosed antibodies and their complexes with antigens. Such methods include, but are not limited to, X-ray crystallography (Engstom (1974) Biochem. Exp. Biol., 11:7-13) and computer modeling of virtual representations of the presently disclosed antibodies (Fletterick et al. (1986) Computer Graphics and Molecular Modeling, in Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

Derivatives

[050] This disclosure also provides a method for obtaining an antibody specific for PD-1. CDRs in such antibodies are not limited to the specific sequences of $V_H$ and $V_L$ identified in Table 1 and may include variants of these sequences that retain the ability to specifically bind PD-1. Such variants may be derived from the sequences listed in Table 1 by a skilled artisan using techniques well known in the art. For example, amino acid substitutions, deletions, or additions, can be made in the FRs and/or in the CDRs. While changes in the FRs are usually designed to improve stability and immunogenicity of the antibody, changes in the CDRs are typically designed to increase affinity of the antibody for its target. Variants of FRs also include naturally occurring immunoglobulin allotypes. Such affinity-increasing changes may be determined empirically by routine



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techniques that involve altering the CDR and testing the affinity antibody for its target. For example, conservative amino acid substitutions can made within any one of the disclosed CDRs. Various alterations can be made according to the methods described in Antibody Engineering, 2nd ed., Oxford University Press, ed. Borrebaeck, 1995. These include but are not limited to nucleotide sequences that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a "silent" change. For example, the nonpolar amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine, and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs (see Table 5). Furthermore, any native residue in the polypeptide may also be substituted with alanine (see, e.g., MacLennan et al. (1998) Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al. (1998) Adv. Biophys. 35:1-24).

[051] Derivatives and analogs of antibodies of the invention can be produced by various techniques well known in the art, including recombinant and synthetic methods (Maniatis (1990) Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, and Bodansky et al. (1995) The Practice of Peptide Synthesis, 2nd ed., Spring Verlag, Berlin, Germany).



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Table 5

| Original Residues | Exemplary Substitutions | Typical Substitutions |
|---|---|---|
| Ala (A) | Val, Leu, Ile | Val |
| Arg (R) | Lys, Gln, Asn | Lys |
| Asn (N) | Gln | Gln |
| Asp (D) | Glu | Glu |
| Cys (C) | Ser, Ala | Ser |
| Gln (Q) | Asn | Asn |
| Gly (G) | Pro, Ala | Ala |
| His (H) | Asn, Gln, Lys, Arg | Arg |
| Ile (I) | Leu, Val, Met, Ala, Phe, Norleucine | Leu |
| Leu (L) | Norleucine, Ile, Val, Met, Ala, Phe | Ile |
| Lys (K) | Arg, 1,4-Diamino-butyric Acid, Gln, Asn | Arg |
| Met (M) | Leu, Phe, Ile | Leu |
| Phe (F) | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro (P) | Ala | Gly |
| Ser (S) | Thr, Ala, Cys | Thr |
| Thr (T) | Ser | Ser |
| Trp (W) | Tyr, Phe | Tyr |
| Tyr (Y) | Trp, Phe, Thr, Ser | Phe |
| Val (V) | Ile, Met, Leu, Phe, Ala, Norleucine | Leu |

[052] In one embodiment, a method for making a $V_H$ domain which is an amino acid sequence variant of a $V_H$ domain of the invention comprises a step of adding, deleting, substituting, or inserting one or more amino acids in the amino acid sequence of the presently disclosed $V_H$ domain, optionally combining the $V_H$ domain thus provided with one or more $V_L$ domains, and testing the $V_H$ domain or $V_H/V_L$ combination or combinations for a specific binding to PD-1 or and, optionally, testing the ability of such antigen-binding domain to modulate PD-1 activity. The $V_L$ domain may have an amino acid sequence that is identical or is substantially as set out according to Table 1.



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[053] An analogous method can be employed in which one or more sequence variants of a $V_L$ domain disclosed herein are combined with one or more $V_H$ domains.

[054] A further aspect of the disclosure provides a method of preparing antigen-binding fragment that specifically binds with PD-1. The method comprises:

(a) providing a starting repertoire of nucleic acids encoding a $V_H$ domain that either includes a CDR3 to be replaced or lacks a CDR3 encoding region;

(b) combining the repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out herein for a $V_H$ CDR3 (i.e., H3) such that the donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a $V_H$ domain;

(c) expressing the nucleic acids of the product repertoire;

(d) selecting a binding fragment specific for PD-1; and

(e) recovering the specific binding fragment or nucleic acid encoding it.

[055] Again, an analogous method may be employed in which a $V_L$ CDR3 (i.e., L3) of the invention is combined with a repertoire of nucleic acids encoding a $V_L$ domain, which either include a CDR3 to be replaced or lack a CDR3 encoding region. The donor nucleic acid may be selected from nucleic acids encoding an amino acid sequence substantially as set out in SEQ ID NO:17-40 or SEQ ID NO:50-55.

[056] A sequence encoding a CDR of the invention (e.g., CDR3) may be introduced into a repertoire of variable domains lacking the respective CDR (e.g., CDR3), using recombinant DNA technology, for example, using methodology described by Marks et al. (Bio/Technology (1992) 10: 779-783). In particular, consensus primers directed at or adjacent to the 5' end of the variable domain area can be used in conjunction with consensus primers to the third framework region of human $V_H$ genes to provide a repertoire of $V_H$



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variable domains lacking a CDR3. The repertoire may be combined with a CDR3 of a particular antibody. Using analogous techniques, the CDR3-derived sequences may be shuffled with repertoires of $V_H$ or $V_L$ domains lacking a CDR3, and the shuffled complete $V_H$ or $V_L$ domains combined with a cognate $V_L$ or $V_H$ domain to make the PD-1-specific antibodies of the invention. The repertoire may then be displayed in a suitable host system such as the phage display system such as described in WO92/01047 so that suitable antigen-binding fragments can be selected.

[057] Analogous shuffling or combinatorial techniques are also disclosed by Stemmer (Nature (1994) 370: 389-391), who describes the technique in relation to a β-lactamase gene but observes that the approach may be used for the generation of antibodies.

[058] In further embodiments, one may generate novel $V_H$ or $V_L$ regions carrying one or more sequences derived from the sequences disclosed herein using random mutagenesis of one or more selected $V_H$ and/or $V_L$ genes. One such technique, error-prone PCR, is described by Gram et al. (Proc. Nat. Acad. Sci. U.S.A. (1992) 89: 3576-3580).

[059] Another method that may be used is to direct mutagenesis to CDRs of $V_H$ or $V_L$ genes. Such techniques are disclosed by Barbas et al. (Proc. Nat. Acad. Sci. U.S.A. (1994) 91: 3809-3813) and Schier et al. (J. Mol. Biol. (1996) 263: 551-567).

[060] Similarly, one or more, or all three CDRs may be grafted into a repertoire of $V_H$ or $V_L$ domains, which are then screened for an antigen-binding fragment specific for PD-1.

[061] A portion of an immunoglobulin variable domain will comprise at least one of the CDRs substantially as set out herein and, optionally, intervening framework regions from the $scF_V$ fragments as set out herein. The portion may include at least about 50% of either or both of FR1 and FR4, the 50% being the C-terminal 50% of FR1 and the N-terminal 50% of FR4. Additional residues at the N-terminal or C-terminal end of the substantial part of the variable domain may be those not normally associated with naturally



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occurring variable domain regions. For example, construction of antibodies by recombinant DNA techniques may result in the introduction of N- or C-terminal residues encoded by linkers introduced to facilitate cloning or other manipulation steps. Other manipulation steps include the introduction of linkers to join variable domains to further protein sequences including immunoglobulin heavy chain constant regions, other variable domains (for example, in the production of diabodies), or proteinaceous labels as discussed in further detail below.

[062] Although the embodiments illustrated in the Examples comprise a "matching" pair of $V_H$ and $V_L$ domains, a skilled artisan will recognize that alternative embodiments may comprise antigen-binding fragments containing only a single CDR from either $V_L$ or $V_H$ domain. Either one of the single chain specific binding domains can be used to screen for complementary domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to PD-1. The screening may be accomplished by phage display screening methods using the so-called hierarchical dual combinatorial approach disclosed in WO92/01047, in which an individual colony containing either an H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H) and the resulting two-chain specific binding domain is selected in accordance with phage display techniques as described.

[063] Anti-PD1 antibodies described herein can be linked to another functional molecule, e.g., another peptide or protein (albumin, another antibody, etc.), toxin, radioisotope, cytotoxic or cytostatic agents. For example, the antibodies can be linked by chemical cross-linking or by recombinant methods. The antibodies may also be linked to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337. The antibodies can be chemically modified by covalent conjugation to a polymer, for example, to increase their circulating half-life. Exemplary polymers and methods to



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attach them are also shown in U.S. Patent Nos. 4,766,106; 4,179,337; 4,495,285; and 4,609,546.

[064] The disclosed antibodies may also be altered to have a glycosylation pattern that differs from the native pattern. For example, one or more carbohydrate moieties can be deleted and/or one or more glycosylation sites added to the original antibody. Addition of glycosylation sites to the presently disclosed antibodies may be accomplished by altering the amino acid sequence to contain glycosylation site consensus sequences known in the art. Another means of increasing the number of carbohydrate moieties on the antibodies is by chemical or enzymatic coupling of glycosides to the amino acid residues of the antibody. Such methods are described in WO 87/05330 and in Aplin et al. (1981) CRC Crit. Rev. Biochem., 22: 259-306. Removal of any carbohydrate moieties from the antibodies may be accomplished chemically or enzymatically, for example, as described by Hakimuddin et al. (1987) Arch. Biochem. Biophys., 259: 52; and Edge et al. (1981) Anal. Biochem., 118: 131 and by Thotakura et al. (1987) Meth. Enzymol., 138: 350. The antibodies may also be tagged with a detectable, or functional, label. Detectable labels include radiolabels such as $^{131}I$ or $^{99}Tc$, which may also be attached to antibodies using conventional chemistry. Detectable labels also include enzyme labels such as horseradish peroxidase or alkaline phosphatase. Detectable labels further include chemical moieties such as biotin, which may be detected via binding to a specific cognate detectable moiety, e.g., labeled avidin.

[065] Antibodies, in which CDR sequences differ only insubstantially from those set out in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NOs:16-40, SEQ ID NO:47, or SEQ ID NO:49 are encompassed within the scope of this invention. Typically, an amino acid is substituted by a related amino acid having similar charge, hydrophobic, or stereochemical characteristics. Such substitutions would be within the ordinary skills of an artisan. Unlike in CDRs, more substantial changes can be made in FRs without adversely affecting the



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binding properties of an antibody. Changes to FRs include, but are not limited to, humanizing a non-human derived or engineering certain framework residues that are important for antigen contact or for stabilizing the binding site, e.g., changing the class or subclass of the constant region, changing specific amino acid residues which might alter the effector function such as Fc receptor binding, e.g., as described in U.S. Patent Nos. 5,624,821 and 5,648,260 and Lund et al. (1991) J. Immun. 147: 2657-2662 and Morgan et al. (1995) Immunology 86: 319-324, or changing the species from which the constant region is derived.

[066] One of skill in the art will appreciate that the modifications described above are not all-exhaustive, and that many other modifications would obvious to a skilled artisan in light of the teachings of the present disclosure.

Nucleic Acids, Cloning and Expression Systems

[067] The present disclosure further provides isolated nucleic acids encoding the disclosed antibodies. The nucleic acids may comprise DNA or RNA and may be wholly or partially synthetic or recombinant. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

[068] The nucleic acids provided herein comprise a coding sequence for a CDR, a $V_H$ domain, and/or a $V_L$ domain disclosed herein.

[069] The present disclosure also provides constructs in the form of plasmids, vectors, phagemids, transcription or expression cassettes which comprise at least one nucleic acid encoding a CDR, a $V_H$ domain, and/or a $V_L$ domain disclosed here.

[070] The disclosure further provides a host cell which comprises one or more constructs as above.

[071] Also provided are nucleic acids encoding any CDR (H1, H2, H3, L1, L2, or L3), $V_H$ or $V_L$ domain, as well as methods of making of the encoded products. The method comprises expressing the encoded product from the



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encoding nucleic acid. Expression may be achieved by culturing under appropriate conditions recombinant host cells containing the nucleic acid. Following production by expression a $V_H$ or $V_L$ domain, or specific binding member may be isolated and/or purified using any suitable technique, then used as appropriate.

[072] Antigen-binding fragments, $V_H$ and/or $V_L$ domains, and encoding nucleic acid molecules and vectors may be isolated and/or purified from their natural environment, in substantially pure or homogeneous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes of origin other than the sequence encoding a polypeptide with the required function.

[073] Systems for cloning and expression of a polypeptide in a variety of different host cells are well known in the art. For cells suitable for producing antibodies, see Gene Expression Systems, Academic Press, eds. Fernandez et al., 1999. Briefly, suitable host cells include bacteria, plant cells, mammalian cells, and yeast and baculovirus systems. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary cells, HeLa cells, baby hamster kidney cells, NS0 mouse myeloma cells, and many others. A common bacterial host is *E. coli*. Any protein expression system compatible with the invention may be used to produce the disclosed antibodies. Suitable expression systems include transgenic animals described in Gene Expression Systems, Academic Press, eds. Fernandez et al., 1999.

[074] Suitable vectors can be chosen or constructed, so that they contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Vectors may be plasmids or viral, e.g., phage, or phagemid, as appropriate. For further details see, for example, Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, 1989. Many known techniques and protocols for manipulation of nucleic acid, for example, in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into



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cells and gene expression, and analysis of proteins, are described in detail in Current Protocols in Molecular Biology, 2nd Edition, eds. Ausubel et al., John Wiley & Sons, 1992.

[075] A further aspect of the disclosure provides a host cell comprising a nucleic acid as disclosed here. A still further aspect provides a method comprising introducing such nucleic acid into a host cell. The introduction may employ any available technique. For eukaryotic cells, suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, e.g., vaccinia or, for insect cells, baculovirus. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation and transfection using bacteriophage. The introduction of the nucleic acid into the cells may be followed by causing or allowing expression from the nucleic acid, e.g., by culturing host cells under conditions for expression of the gene.

Methods of Use

[076] The disclosed anti-PD-1 antibodies are capable of modulating the PD-1-associated downregulation of the immune responses. In particular embodiments, the immune response is TcR/CD28-mediated. The disclosed antibodies can act as either agonists or antagonists of PD-1, depending on the method of their use. The antibodies can be used to prevent, diagnose, or treat medical disorders in mammals, especially, in humans. Antibodies of the invention can also be used for isolating PD-1 or PD-1-expressing cells. Furthermore, the antibodies can be used to treat a subject at risk of or susceptible to a disorder or having a disorder associated with aberrant PD-1 expression or function.

[077] Antibodies of the invention can be used in methods for induction of tolerance to a specific antigen (e.g., a therapeutic protein). In one embodiment, tolerance is induced against a specific antigen by co-administration of antigen and an anti-PD-1 antibody of the invention. For example, patients that received Factor VIII frequently generate antibodies to



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this protein; co-administration of an anti-PD-1 antibody of the invention in combination with recombinant Factor VIII is expected to result in the downregulation of immune responses to this clotting factor.

[078] Antibodies of the invention can be used in circumstances where a reduction in the level of immune response may be desirable, for example, in certain types of allergy or allergic reactions (e.g., by inhibition of IgE production), autoimmune diseases (e.g., rheumatoid arthritis, type I diabetes mellitus, multiple sclerosis, inflammatory bowel disease, Crohn's disease, and systemic lupus erythematosis), tissue, skin and organ transplant rejection, and graft-versus-host disease (GVHD).

[079] When diminished immune response is desirable, the anti-PD-1 antibodies of the invention may be used as agonists to PD-1 in order to enhance the PD-1-associated attenuation of the immune response. In these embodiments, co-presentation and physical proximity between positive (i.e., mediated by an antigen receptor, e.g., TcR or BcR) and negative (i.e., PD-1) signals are required. The preferred distance is less than or comparable to the size of a naturally occurring antigen-presenting cell, i.e., less than about 100 μm; more preferably, less than about 50 μm; and most preferably, less than about 20 μm.

[080] In some embodiments, the positive (activating) and the negative (inhibiting) signals are provided by a ligand or antibodies immobilized on solid support matrix, or a carrier. In various embodiments, the solid support matrix may be composed of polymer such as activated agarose, dextran, cellulose, polyvinylidene fluoride (PVDF). Alternatively, the solid support matrix may be based on silica or plastic polymers, e.g., as nylon, dacron, polystyrene, polyacrylates, polyvinyls, teflons, etc.

[081] The matrix can be implanted into the spleen of a patient. Alternatively, the matrix may be used for the ex vivo incubation of T cells obtained from a patient, which are then separated and implanted back into the patient. The matrix may also be made from a biodegradable material such polyglycolic acid, polyhydroxyalkanoate, collagen, or gelatin so that they can



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be injected into the patient's peritoneal cavity, and dissolve after some time following the injection. The carrier can be shaped to mimic a cell (e.g., bead or microsphere).

[082] In some embodiments, the positive signal is delivered by a T-cell-activating anti-CD3 antibody, which binds TcR. Activating anti-CD3 antibodies are known in the art (see, for example, U.S. Patent Nos. 6,405,696 and 5,316,763). The ratio between the activating TcR signal and negative PD-1 signal is determined experimentally using conventional procedures known in the art or as described in Examples 8, 9, and 10.

[083] Under certain circumstances, it may be desirable to elicit or enhance a patient's immune response in order to treat an immune disorder or cancer. The disorders being treated or prevented by the disclosed methods include but are not limited to infections with microbes (e.g. bacteria), viruses (e.g., systemic viral infections such as influenza, viral skin diseases such as herpes or shingles), or parasites; and cancer (e.g., melanoma and prostate cancers).

[084] Stimulation of T cell activation with anti-PD-1 antibodies enhances T-T cell responses. In such cases, antibodies act as antagonists of PD-1. Thus, in some embodiments, the antibodies can be used to inhibit or reduce the downregulatory activity associated with PD-1, i.e., the activity associated with downregulation of TcR/CD28-mediated immune response. In these embodiments, the antibodies are not coupled to a positive signal such as the TcR-mediated stimulation, e.g., the antibodies are in their soluble, support-unbound, form. As demonstrated in the Examples, a blockade of PD-1/PD-L interaction with antagonizing anti-PD-1 antibodies leads to enhanced T cell proliferative responses, consistent with a downregulatory role for the PD-1 pathway in T-T interactions. In various embodiments, the antibodies inhibit binding of PD-L to PD-1 with an $IC_{50}$ of less than 10 nM, and more preferably less then 5 nM, and most preferably less than 1 nM. Inhibition of PD-L binding can be measured as described in Example 6 or using techniques known in the art.



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[085] The antibodies or antibody compositions of the present invention are administered in therapeutically effective amounts. Generally, a therapeutically effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition of the subject. A therapeutically effective amount of antibody ranges from about 0.001 to about 30 mg/kg body weight, preferably from about 0.01 to about 25 mg/kg body weight, from about 0.1 to about 20 mg/kg body weight, or from about 1 to about 10 mg/kg. The dosage may be adjusted, as necessary, to suit observed effects of the treatment. The appropriate dose is chosen based on clinical indications by a treating physician.

[086] The antibodies may given as a bolus dose, to maximize the circulating levels of antibodies for the greatest length of time after the dose. Continuous infusion may also be used after the bolus dose.

[087] Immune cells (e.g., activated T cells, B cells, or monocytes) can also be isolated from a patient and incubated ex vivo with antibodies of the invention. In some embodiments, immune responses can be inhibited by removing immune cells from a subject, contacting the immune cells in vitro with an anti-PD-1 antibody of the invention concomitantly with activation of the immune cells (e.g., by antibodies to the TcR and/or BcR antigen receptor). In such embodiments, the anti-PD-1 antibody should be used in a multivalent form such that PD-1 molecules on the surface of an immune cell become "crosslinked" upon binding to such antibodies. For example, the anti-PD-1 antibodies can be bound to solid support, such as beads, or crosslinked via a secondary antibody. The immune cells may be then isolated using methods known in the art and reimplanted into the patient.

[088] In another aspect, the antibodies of the invention can be used as a targeting agent for delivery of another therapeutic or a cytotoxic agent (e.g., a toxin) to a cell expressing PD-1. The method includes administering an anti-PD-1 antibody coupled to a therapeutic or a cytotoxic agent or under conditions that allow binding of the antibody to PD-1.



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[089] The antibodies of the invention may also be used to detect the presence of PD-1 in biological samples. The amount of PD-1 detected may be correlated with the expression level of PD-1, which, in turn, is correlated with the activation status of immune cells (e.g., activated T cells, B cells, and monocytes) in the subject.

[090] Detection methods that employ antibodies are well known in the art and include, for example, ELISA, radioimmunoassay, immunoblot, Western blot, immunofluorescence, immunoprecipitation. The antibodies may be provided in a diagnostic kit that incorporates one or more of these techniques to detect PD-1. Such a kit may contain other components, packaging, instructions, or other material to aid the detection of the protein.

[091] Where the antibodies are intended for diagnostic purposes, it may be desirable to modify them, for example, with a ligand group (such as biotin) or a detectable marker group (such as a fluorescent group, a radioisotope or an enzyme). If desired, the antibodies of the invention may be labeled using conventional techniques. Suitable detectable labels include, for example, fluorophores, chromophores, radioactive atoms, electron-dense reagents, enzymes, and ligands having specific binding partners. Enzymes are typically detected by their activity. For example, horseradish peroxidase can be detected by its ability to convert tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a spectrophotometer. For detection, suitable binding partners include, but are not limited to, biotin and avidin or streptavidin, IgG and protein A, and the numerous receptor-ligand couples known in the art. Other permutations and possibilities will be readily apparent to those of ordinary skill in the art, and are considered as equivalents within the scope of the instant invention.

[092] Antibodies of the invention can be used in screening methods to identify inhibitors of the PD-1 pathway effective as therapeutics. In such a screening assay, a first binding mixture is formed by combining PD-1 and an antibody of the invention; and the amount of binding in the first binding mixture ($M_0$) is measured. A second binding mixture is also formed by



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combining PD-1, the antibody, and the compound or agent to be screened, and the amount of binding in the second binding mixture ($M_1$) is measured. A compound to be tested may be another anti-PD-1 antibody, as illustrated in the Examples. The amounts of binding in the first and second binding mixtures are then compared, for example, by calculating the $M_1/M_0$ ratio. The compound or agent is considered to be capable of modulating a PD-1-associated downregulation of immune responses if a decrease in binding in the second binding mixture as compared to the first binding mixture is observed. The formulation and optimization of binding mixtures is within the level of skill in the art, such binding mixtures may also contain buffers and salts necessary to enhance or to optimize binding, and additional control assays may be included in the screening assay of the invention. Compounds found to reduce the PD-1-antibody binding by at least about 10% (i.e., $M_1/M_0<0.9$), preferably greater than about 30% may thus be identified and then, if desired, secondarily screened for the capacity to ameliorate a disorder in other assays or animal models as described below. The strength of the binding between PD-1 and an antibody can be measured using, for example, an enzyme-linked immunoadsorption assay (ELISA), radio-immunoassay (RIA), surface plasmon resonance-based technology (e.g., Biacore), all of which are techniques well known in the art.

[093] The compound may then be tested in vitro as described in the Examples or in an animal model (see, generally, Immunologic Defects in Laboratory Animals, eds. Gershwin et al., Plenum Press, 1981), for example, such as the following: the SWR X NZB (SNF1) transgenic mouse model (Uner et al. (1998) J. Autoimmune. 11(3): 233-240), the KRN transgenic mouse (K/BxN) model (Ji et al. (1999) Immunol. Rev. 169: 139); NZB X NZW (B/W) mice, a model for SLE (Riemekasten et al. (2001) Arthritis Rheum., 44(10): 2435-2445); experimental autoimmune encephalitis (EAE) in mouse, a model for multiple sclerosis (Tuohy et al. (1988) J. Immunol. 141: 1126-1130, Sobel et al. (1984) J. Immunol. 132: 2393-2401, and Traugott, Cell Immunol. (1989)



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119: 114-129); the NOD mouse model of diabetes (Baxter et al. (1991) Autoimmunity, 9(1): 61-67), etc.).

[094] Preliminary doses as, for example, determined according to animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices. Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The data obtained from the cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. Therapeutically effective dosages achieved in one animal model can be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al. (1966) Cancer Chemother. Reports, 50(4): 219-244).

Pharmaceutical Compositions and Methods of Administration

[095] The disclosure provides compositions comprising anti-PD-1 antibodies. Such compositions may be suitable for pharmaceutical use and administration to patients. The compositions typically comprise one or more antibodies of the present invention and a pharmaceutically acceptable excipient. The phrase "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial agents and antifungal agents, isotonic agents, and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions. The pharmaceutical compositions may also be included in a container, pack, or dispenser together with instructions for administration.

[096] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Methods to accomplish the administration are known to those of ordinary skill in the art. The administration may, for example, be intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous or transdermal. It may also be



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possible to obtain compositions which may be topically or orally administered, or which may be capable of transmission across mucous membranes.

[097] Solutions or suspensions used for intradermal or subcutaneous application typically include one or more of the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol, or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. Such preparations may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[098] Pharmaceutical compositions suitable for injection include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for



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example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate, and gelatin.

[099] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For oral administration, the antibodies can be combined with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature; a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0100] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration may be accomplished, for example, through the use of lozenges, nasal sprays, inhalers, or suppositories. For example, in case of antibodies that comprise the Fc portion, compositions may be capable of transmission across mucous membranes in intestine, mouth, or lungs (e.g., via the FcRn receptor-mediated pathway as described in U.S. Patent No. 6,030,613). For transdermal administration, the active compounds may be formulated into ointments, salves, gels, or creams as generally known in the art. For administration by inhalation, the antibodies may be delivered in the



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form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0101] In certain embodiments, the presently disclosed antibodies are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions containing the presently disclosed antibodies can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0102] It may be advantageous to formulate oral or parenteral compositions in a dosage unit form for ease of administration and uniformity of dosage. The term "dosage unit form" as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0103] Toxicity and therapeutic efficacy of the composition of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the $LD_{50}$ (the dose lethal to 50% of the population) and the $ED_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio $LD_{50}/ED_{50}$. Compositions that exhibit large therapeutic indices are preferred.

[0104] For any composition used in the present invention, the therapeutically effective dose can be estimated initially from cell culture



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assays. Examples of suitable bioassays include DNA replication assays, cytokine release assays, transcription-based assays, PD-1/PD-L1 binding assays, creatine kinase assays, assays based on the differentiation of pre-adipocytes, assays based on glucose uptake in adipocytes, immunological assays other assays as, for example, described in the Examples. The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the $IC_{50}$ (i.e., the concentration of the antibody which achieves a half-maximal inhibition of symptoms). Circulating levels in plasma may be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay. The dosage lies preferably within a range of circulating concentrations with little or no toxicity. The dosage may vary depending upon the dosage form employed and the route of administration utilized.

[0105] The following Examples do not in any way limit the scope of the invention. One of ordinary skill in the art will recognize the numerous modifications and variations that may be performed without altering the spirit or scope of the present invention. Such modifications and variations are encompassed within the scope of the invention. The entire contents of all references, patents, and published patent applications cited throughout this application are herein incorporated by reference.

## EXAMPLES

### Example 1: Selection of PD-1 Binding ScFv's

[0106] An scFv phagemid library, which is an expanded version of the $1.38x10^{10}$ library described by Vaughan et al. (Nature Biotech. (1996) 14: 309-314) was used to select antibodies specific for human PD-1. Soluble PD-1 fusion protein (at 20 μg/ml in phosphate buffered saline (PBS)) or control fusion protein (at 50 μg/ml in PBS) was coated onto wells of a microtiter plate overnight at 4°C. Wells were washed in PBS and blocked for



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1 hour at 37°C in MPBS (3% milk powder in PBS). Purified phage ($10^{12}$ transducing units (tu)) was blocked for 1 hour in a final volume of 100 µl of 3% MPBS. Blocked phage was added to blocked control fusion protein wells and incubated for 1 hour. The blocked and deselected phage were then transferred to the blocked wells coated with the PD-1 fusion protein and were incubated for an additional hour. Wells were washed 5 times with PBST (PBS containing 0.1% v/v Tween 20), then 5 times with PBS. Bound phage particles were eluted and used to infect 10 ml exponentially growing *E. coli* TG1. Infected cells were grown in 2TY broth for 1 hour at 37°C, then spread onto 2TYAG plates and incubated overnight at 30°C. Colonies were scraped off the plates into 10 ml 2TY broth and 15% glycerol added for storage at –70°C.

[0107] Glycerol stock cultures from the first round of panning selection were superinfected with helper phage and rescued to give scFv antibody-expressing phage particles for the second round of panning. A total of two rounds of panning were carried out in this way for isolation of PD1-17, except in the second round of panning 20 µg/ml of control protein were used for deselection. Clones PD1-28, PD1-33, and PD1-35 were selected following three rounds of selection. Deselection in the second and third rounds was carried out using 10 µg/ml control fusion protein.

[0108] Antibodies to murine PD-1 were selected by soluble selection using biotinylated murine PD-1 fusion protein at a final concentration of 100 nM. An scFv phagemid library, as described above, was used. Purified scFv phage ($10^{12}$ tu) in 1 ml 3% MPBS were blocked for 30 minutes, then biotinylated antigen was added and incubated at room temperature for 1 hour. Phage/antigen was added to 250 µl of Dynal M280 Streptavidin magnetic beads that had been blocked for 1 hour at 37°C in 1 ml of 3% MPBS and incubated for a further 15 minutes at room temperature. Beads were captured using a magnetic rack and washed 4 times in 1 ml of 3% MPBS/ 0.1% (v/v) Tween 20 followed by 3 washes in PBS. After the last PBS wash, beads were resuspended in 100 µl PBS and used to infect 5 ml exponentially growing *E.*



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*coli* TG-1 cells. Infected cells were incubated for 1 hour at 37°C (30 minutes stationary, 30 minutes shaking at 250 rpm), then spread on 2TYAG plates and incubated overnight at 30°C. Output colonies were scraped off the plates and phage rescued as described above. A second round of soluble selection was carried out as described above.

Example 2: Specificity of Antibodies for PD-1 by a Phage ELISA

[0109] To determine the specificity of antibodies for PD-1, a phage ELISA was performed against PD-1 fusion protein and control proteins. Individual *E. coli* colonies from selection outputs were picked into 96 well plates containing 100 µl of 2TYAG medium per well. M13K07 helper phage was added to a multiplicity of infection (moi) of 10 to the exponentially growing culture and the plates incubated an additional 1 hour at 37°C. Plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 µl 2TYAK and incubated at 30°C overnight with shaking. The next day, plates were centrifuged at 2000 rpm for 10 minutes and phage-containing supernatant from each well was transferred to a fresh 96 well plate. Phage samples were blocked in a final concentration of 3% MPBS prior to ELISA.

[0110] Human or mouse PD-1 fusion protein and control fusion and non-fusion proteins were coated overnight at 4°C onto 96-well microtiter plates at 0.5-2.5 µg/ml in PBS. After coating, the solutions were removed from the wells, and the plates blocked for 1 hour in 3% MPBS. Plates were rinsed with PBS and then 50 µl of pre-blocked phage were added to each well. The plates were incubated for 1 hour and then washed 3 times with PBST followed by 3 washes with PBS. To each well, 50 µl of a 1:5000 dilution of anti-M13-HRP conjugate (Pharmacia, Peapack, NJ) was added, and the plates incubated for 40-60 minutes. Each plate was washed three times with PBST then 3 times with PBS. Fifty µl of TMB substrate was added to each well, and the samples were incubated until color development. The reaction was stopped by the addition of 25 µl of 0.5 M $H_2SO_4$. The signal



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generated was measured by reading the absorbance at 450 nm using a microtiter plate reader. Clones showing specific binding to PD-1 fusion protein but not to control fusion proteins were thus identified and confirmed.

[0111] Specificity data for the PD1-17 scFv is shown in Figure 1A. Reactivity of PD1-28, PD1-33, and PD1-35 scFv's with human PD-1 is shown in Figure 1B (an $IgG_1$ control did not bind PD-1).

Example 3: Identification of Antibody Clones

[0112] PD-1-binding scFv *E. coli* clones were streaked out onto 2TYAG plates and incubated overnight at 30°C. Colonies from these plates were sequenced using pCANTAB6 vector sequence oligos to amplify the $V_H$ and $V_L$ regions from the scFv clone. Unique PD-1 binding clones were assayed for neutralization of PD-L1 binding to PD-1 as described in Example 4. Sequence differences between scFv and IgG formats are due to changes introduced by PCR primers during the conversion from scFv to IgG.

Example 4: Biochemical Binding Inhibition Assay and Screen

[0113] ScFv production was induced by addition of 1 mM IPTG to exponentially growing cultures and incubation overnight at 30°C. Crude scFv-containing periplasmic extracts were obtained by subjecting the bacterial pellets from the overnight induction to osmotic shock. Pellets were resuspended in 20% (w/v) sucrose, 50mM Tris-HCl, pH 7.5, 1 mM EDTA and cooled on ice for 30 minutes. Cellular debris was removed by centrifugation, and the scFv was purified by chromatography and buffer-exchanged into PBS. Purified scFv's (PD1-17, PD1-28, PD1-33, and PD1-35) were tested for the ability to inhibit the binding of biotinylated human PD-L1 fusion protein to human PD-1 fusion protein immobilized on plastic in a 96 well microtiter plate assay. Binding of biotinylated PD-L1 fusion protein was detected with AMDEX-alkaline phosphatase, and the signal generated was measured by reading the absorbance at 405 nm using a microtiter plate reader. Data was expressed as a percentage of the total binding and a titration of scFv



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concentrations was tested to establish clone potency as calculated $IC_{50}$ values. Clone potency data for the scFv and IgG antibodies is shown in Table 5.

[0114] PD1-F2 scFv was produced and purified as described above. Cells expressing murine PD-1 were added at $10^5$ cells/well in a final volume of 100 µl to a poly-D-lysine-coated 96 well microtiter plate. Cells were centrifuged and washed twice in PBS, then blocked with 300 µl 1% BSA in PBS for 1 hour at room temperature. Blocked cells were washed three times in PBST, prior to addition of 25 µl/well of assay buffer (0.05% BSA, 0.05% Tween 20 in Dulbecco's PBS) or sample, followed by 25 µl of biotinylated murine PD-L1 fusion protein at 300 ng/ml. Binding of biotinylated PD-L1 fusion protein was detected with Amdex alkaline phosphatase and signals read as described above. Potencies of PD1-F2 scFv and IgG are shown in Table 6.

Table 6: Potency of Anti-PD-1 ScFv and IgG Antibodies

| Clone | ScFv $IC_{50}$ (nM) | IgG $IC_{50}$ (nM) |
|---|---|---|
| **PD1-17** | 726 | 2.5 |
| **PD1-28** | 560 | 1.4 |
| **PD1-33** | 74 | 1.8 |
| **PD1-35** | 85 | 2.3 |
| **PD1-F2** | 28 | 1.0 |

Example 5: Conversion of ScFv to IgG

[0115] Heavy and light chain V regions from scFv clones were amplified by PCR using clone-specific primers. PCR products were digested with appropriate restriction enzymes and subcloned into vectors containing human $IgG_1$ heavy chain constant domain (Takahashi et al. (1982) Cell 29, 671) or vectors containing human lambda or kappa light chain constant domains (Hieter et al. (1982) Nature 294, 536). Based on the germlines of the



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$V_H$ and $V_L$ segments, it was determined whether kappa or lambda light chain constant domains were used for conversion (Table 7).

Table 7: Germlines of $V_H$ and $V_L$ Regions of PD-1 Antibody Clones

| Clone | $V_H$ germline | $V_L$ germline |
|---|---|---|
| **PD1-17** | DP-70 | DPL-8 |
| **PD1-28** | DP-14 | DPL-23 |
| **PD1-33** | DP-7 | DPL-11 |
| **PD1-35** | DP-65 | DPL-2 |
| **PD1-F2** | DP-47 | L12 (κ) |

[0116] The insertion of V region domains into plasmids was verified by sequencing of plasmid DNA from individual *E. coli* colonies. Plasmids were prepared from *E. coli* cultures by standard techniques and heavy and light chain constructs cotransfected into eukaryotic cells using standard techniques. Secreted IgG was purified using Protein A Sepharose (Pharmacia) and buffer-exchanged into PBS.

[0117] The binding affinity of the anti-mouse PD1 antibody PD1-F2 was determined with a Surface Plasmon Resonance (SPR) system (BIAcore 3000) (Biacore, Piscataway, NJ) using murine PD-1 fusion immobilized on a CM5 sensor chip. The concentration of PD1-F2 in the flow cell ranged from 7.81 to 125 nM, while the concentration of the anti-mouse PD1 antibody J43 (eBioscience, San Diego, CA) ranged from 25 nM to 500 nM. The equilibrium constant $K_D$ for PD1-F2 is $6.7 \times 10^{-9}$ M ($K_A = 1.5 \times 10^8$ $M^{-1}$), whereas $K_D$ for J43 is $3.8 \times 10^{-7}$ M ($K_A = 2.6 \times 10^6$ $M^{-1}$).

[0118] The ability of anti-PD-1 IgG's to bind human or murine PD-1 was determined as follows. ELISA plates were incubated with 2.5 µg/ml human PD-1/IgG chimera overnight. Plates were washed with PBS/1 % BSA and incubated with serial dilutions of a test antibody for 2 hours at room temperature (RT). After washing, saturating concentrations of HRP-conjugated goat anti-human antibody or HRP-conjugated rabbit



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anti-murine antibody were added, and the samples were incubated for 1 hour at RT. Unbound goat and rabbit antibodies were washed using PBS/1 % BSA. The assay was developed using TBM. Results were expressed as OD 405 absorbency values and are presented in Figures 2A-2C. Murine anti-human PD-1 antibody J110 is commercially available (eBioscience, San Diego, CA) and was included for comparison.

Example 6: Selected PD-1 Antibodies Inhibit Binding of PD-L1 to PD-1

[0119] Inhibition assays were performed to assess the ability of the antibodies to block binding of PD-L1 to PD-1. ELISA was performed as described in Example 2 with modifications. After incubation with a primary, anti-PD-1 antibody for 2 hours at RT, a fixed concentration (1 µg/ml) of biotin-conjugated PD-L1-Ig was added, and the samples were further incubated for 1 hour at RT. After washing, saturating concentrations of avidin-HRP were added, and incubated for 1 hour at RT. Unbound avidin-HRP was washed using PBS/1% BSA. The assay was developed using TMB.

[0120] Results were compared to those obtained with J110 as shown in Figure 3. Anti-human PD-1 antibodies J110 and PD1-30 did not inhibit the binding of PD-L1 to PD-1. Anti-human antibodies PD1-17, PD1-28, PD1-33, and PD1-35 and anti-mouse antibody PD1-F2 block PD-1/PD-L1 interaction.

Example 7: PD-1 Antibodies Recognize Distinct Sites on PD-1

[0121] Inhibition assays were performed to map sites recognize by the various human anti-human PD-1 antibodies. ELISA was performed as described in Example 6 with minor modifications. After incubation with primary antibody for 2 hours at RT, a fixed concentration (0.25 µg/ml) of biotin-conjugated anti-PD-1 antibody J110 was added, and the samples were further incubated for 1 hour at RT. After washing, saturating concentrations of avidin-HRP were added, and incubated for 1 hour at RT. Unbound



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avidin-HRP was washed using PBS/1% BSA. The assay was developed using TMB.

[0122] As shown in Figure 4, binding of anti-human PD-1 antibodies (J110, J116, PD1-17, PD1-28, PD1-33, and PD1-35) defines at least two distinct sites on PD-1. Cross-blocking results show that J110 and J116, bind to identical or overlapping sites while PD1-17, 28, 33, and 35 bind to another distinct site. Binding of J116 or J110 to PD-1 blocks the binding of J110. In contrast, binding of PD1-17, PD1-28, PD1-33, and PD1-35 do not block binding of J110. This suggests that the tested anti-PD-1 antibodies bind to at least two distinct epitopes: one recognized by J110 and J116, and the other one recognized by PD1-17, PD1-28, PD1-33, and PD1-35.

Example 8: PD-1 Engagement Results in Decreased T Cell Responses

[0123] CD4+ T cells ($5 \times 10^4$ cells/well) were stimulated with tosyl-beads (Dynal, Great Neck, NY) coated with anti-hCD3 +/- PD-L1-Fc or anti-PD-1 (PD1-17 or J110). Concentration of fusion protein or antibody titer was as indicated in the X-axis of Figure 5. After 72 hours, proliferation was determined by $^3$H-thymidine incorporation. Incorporated radioactivity was determined using a LKB 1205 plate reader.

[0124] As shown in Figure 5, PD-1 engagement by anti-PD-1 antibody PD1-17 or PD-L1.Fc caused a decrease in T cell proliferation. Thus, PD1-17 can mimic PD-1 ligands and delivered an inhibitory signal. As discussed below (Example 9), this inhibitory signal results in decreased T cell proliferation and IL-2 production. Antibodies PD1- 28, PD1-33, and PD1-35 have the same effect as PD1-17. The effect is dose-dependent, as activation of cells in the presence of increasing concentrations of PD1-17 or PD-L1.Fc results in decreased T cell proliferation. The control anti-PD-1 antibodies, J110 (Figure 5) or J116 (data not shown), do not inhibit T cell responses and increasing the concentration of J110 has minimal effect on T cell proliferation. For comparison, values are represented as percentage of the anti-CD3 response. "100%" represents CPMs obtained when cells were activated with



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anti-CD3/murine IgG-coated microspheres. Altogether these results indicate that some but not all antibodies that recognize PD-1 can act as agonists of the PD-1 pathway.

[0125] Further experiments were performed to address whether PD-1 downregulation of T cell responses required coordinate TcR/PD-1 engagement on a single (CIS) or a separate (TRANS) cell surfaces. Two sets of microspheres were prepared: one set contained anti-CD3 and PD-L1.Fc (CIS), the other set contained anti-CD3 or PD-L1.Fc (TRANS). Inhibition through PD-1 was only observed under conditions where both PD-1 and TcR were engaged by ligands on the same surface (CIS). At all bead:cell ratios tested, no inhibition was observed in conditions where TCR and PD-1 signals were delivered on separate surfaces (TRANS).

[0126] To rule out steric hindrance in the TRANS experiments, similar assays were set up using anti-CD3 antibody and B7.2.Fc. In these assays, B7 costimulation of T cell responses was observed in both CIS and TRANS conditions. Altogether, these findings demonstrate that PD-1 proximity to TCR is required for the receptor modulatory function on T cell activation. Therefore, to modulate a T cell response, both activating and inhibitory signals must emanate from the same surface whether the surface is that of a cell or a bead.

Example 9: Blockage of PD-1 Engagement by Antibody Results in Enhanced Proliferation

[0127] For assessing effect of soluble anti-PD-1 antibody on proliferation, CD4+ T cells were pre-activated for 48 hours with anti-CD3/anti-CD28-coated beads, harvested, and restimulated with the indicated concentration of PHA plus 10 ng/ml IL-2 in the presence of PD1-17, J110, or control IgG. Each of the antibodies was added at various concentrations at initiation of the culture. Proliferation was measured at 72 hr.

[0128] The results demonstrate that PD1- 17 (Figure 6) and PD1-35 (data not shown) enhanced proliferation of primary T cells. The control



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antibody J110 did not enhance in vitro T cell responses. Selected anti-PD1 antibodies, as exemplified by PD1-17 and PD-35, inhibit the interaction of PD-1 with its natural ligands and thereby block delivery of a negative signal. The blockade of the negative signal also results in enhanced proliferation and IL-2 production.

Example 10: Treatment of Disorders

[0129] Modulation of immune response regulated by PD-1 is useful in instances where an immunosuppressive effect or augmentation of immune response is desired. This example describes the use of PD-1 antibodies as PD-1 agonists or antagonists to treat a subject at disease onset or having an established immune disorder or cancer, respectively.

[0130] Subjects at risk for or afflicted with cancer may be in need of immune response augmentation would benefit from treatment with a PD-1 antagonist, such as an anti-PD-1 antibody of the present invention in a soluble form. Most commonly, antibodies are administered in an outpatient setting by weekly administration at about 0.1-10 mg/kg dose by slow intravenous (IV) infusion. The appropriate therapeutically effective dose of an antagonist is selected by a treating clinician and would range approximately from 1 μg/kg to 20 mg/kg, from 1 μg/kg to 10 mg/kg, from 1 μg/kg to 1 mg/kg, from 10 μg/kg to 1 mg/kg, from 10 μg/kg to 100 μg/kg, from 100 μg to 1 mg/kg, and from 500 μg/kg to 5 mg/kg.

[0131] The antibodies are also used to prevent and/or to reduce severity and/or symptoms of diseases or conditions that involve an aberrant or undesirable immune response, such as in autoimmune disorders exemplified below.

[0132] Multiple sclerosis (MS) is a central nervous system disease that is characterized by inflammation and loss of myelin sheaths. In the experimental autoimmune encephalitis (EAE) mouse model for multiple sclerosis (Tuohy et al. (J. Immunol. (1988) 141: 1126-1130), Sobel et al. (J. Immunol. (1984) 132: 2393-2401), and Traugott (Cell Immunol. (1989) 119:



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114-129), treatment of mice with a PD-1 agonist prior (and continuously) to EAE induction is expected to prevent or delay the onset of MS.

[0133] Arthritis is a disease characterized by inflammation in the joints. In the collagen induced arthritis (CIA) mouse model for rheumatoid arthritis (Courtenay et al. (Nature (1980) 283: 666-628) and Williams et al. (Immunol. (1995) 84: 433-439)), treatment with a PD-1 agonist is expected to prevent or treat rheumatoid arthritis (RA) or other arthritic diseases.

[0134] Systemic Lupus Erythematosis (SLE) is an autoimmune disease characterized by the presence of autoantibodies. The antibodies and compositions of this invention can be used as PD-1 agonists to inhibit activities of autoreactive T cells and B cells, and prevent or treat SLE or related diseases in NZB X NZW mice (a mouse model for SLE) (Immunologic Defects in Laboratory Animals, Gershwin et al. eds., Plenum Press, 1981) or in humans.

[0135] It is anticipated that PD-1 antibodies of the invention would be administered as PD-1 agonists in ex vivo therapy with a frequency of one per month or less. Treatment duration could range between one month and several years.

[0136] To test the clinical efficacy of antibodies in humans, individuals with melanoma, prostate cancer, RA, SLE, MS, type I diabetes, are identified and randomized to a treatment group. Treatment groups include a placebo group and one to three groups treated with a PD-1 agonist (different doses). Individuals are followed prospectively for one to three years. It is anticipated that individuals receiving treatment would exhibit an improvement.

[0137] The specification is most thoroughly understood in light of the teachings of the references cited within the specification, all of which are hereby incorporated by reference in their entirety. The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan recognizes that many other embodiments are encompassed by the claimed invention and that it is intended that the specification and examples be



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considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.



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## CLAIMS

We claim:

1. An antibody comprising the amino acid sequence as set out in SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:31, SEQ ID NO:37, or SEQ ID NO:52.

2. Then antibody of claim 1, comprising an amino acid sequence substantially as set out in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:47, or SEQ ID NO: 49.

3. The antibody of claim 1, comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:47, and SEQ ID NO:49.

4. The antibody of claim 1, wherein the antibody specifically binds to an amino acid sequence that is at least 95% identical to any sequence of at least 100 of contiguous amino acids of at least one sequence selected from group consisting of SEQ ID NO:41 and SEQ ID NO:56.

5. The antibody of claim 1, wherein the antibody specifically binds to the extracellular domain of PD-1 with an affinity constant greater than $10^7$ $M^{-1}$.

6. The antibody of claim 4, where the antibody inhibits the binding of PD-L to PD-1 with an $IC_{50}$ of less than 10 nM.

7. The antibody of claim 1, wherein the antibody is human.

8. The antibody of claim 1, wherein the antibody is $IgG_1$ or $IgG_4$.

9. The antibody of claim 8, wherein the antibody is $IgG_{1\lambda}$ or $IgG_{1\kappa}$.



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10. The antibody of claim 1, wherein the antibody is PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2.

11. A pharmaceutical composition comprising the antibody of claim 1.

12. A method of treatment comprising administering an effective dose of the pharmaceutical composition of claim 11.

13. The method of claim 12, wherein the pharmaceutical composition is administered to a subject in need for treatment or prevention of a disorder selected from the group consisting of an autoimmune disorder, an immune response to a graft, an allergic reaction, and cancer.

14. The method of claim 12, wherein the subject is a human.

15. An antibody comprising human framework regions and means for specific binding to PD-1, wherein the antibody is capable of blocking binding between PD-1 and PD-L1.

16. The antibody of claim 15, wherein the means comprises a CDR derived from PD1-17, PD1-28, PD1-33, PD1-35, or PD1-F2.

17. An isolated nucleic acid encoding the antibody of claim 1.

18. An expression vector comprising the nucleic acid of claim 17.

19. A host cell comprising the vector of claim 18.

20. The host cell of claim 19, wherein the host cell is chosen from: an *E. Coli* bacterium, a Chinese hamster ovary cell, a HeLa cell, and a NS0 cell.

21. The nucleic acid of claim 17, wherein the nucleic acid encodes the amino acid sequence set out in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:47, or SEQ ID NO:49.



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22. The nucleic acid of claim 21, wherein the nucleic acid comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:46, and SEQ ID NO:48.

23. A method of making an antibody that specifically binds with PD-1, the method comprises:

(a) providing a starting repertoire of nucleic acids encoding a variable domain that either includes a CDR3 to be replaced or lacks a CDR3 encoding region;

(b) combining the repertoire with a donor nucleic acid encoding an amino acid sequence substantially as set out in SEQ ID NO:19, SEQ ID NO:25, SEQ ID NO:31, SEQ ID NO:37, or SEQ ID NO:52, such that the donor nucleic acid is inserted into the CDR3 region in the repertoire, so as to provide a product repertoire of nucleic acids encoding a variable domain;

(c) expressing the nucleic acids of the product repertoire;

(d) selecting an antigen-binding fragment specific for PD-1; and

(e) recovering the specific antigen-binding fragment or nucleic acid encoding the binding fragment.

24. An antibody produced by the method of claim 23.

25. A method of modulating adaptive immune response comprising contacting a lymphocyte with an anti-PD-1 antibody.

26. The method of claim 25, wherein the lymphocyte is a T cell, B cell, or monocyte.

27. The method of claim 25, wherein the antibody is as in claim 1.

28. The method of claim 25, wherein the antibody is as in claim 24.



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29. The method of claim 25, wherein the antibody is immobilized on a support matrix or crosslinked.

30. The method of claim 25, wherein the support matrix comprises one or more material chosen from agarose, dextran, cellulose, PVDF, silica, nylon, dacron, polystyrene, polyacrylates, polyvinyls, teflons, polyglycolic acid, polyhydroxyalkanoate, collagen, and gelatin.

31. The method of claim 25, wherein the anti-PD-1 antibody modulates immune cell response mediated by an antigen receptor.

32. The method of claim 31, wherein the antigen receptor signal is co-presented with the anti-PD-1 antibody.

33. The method of claim 31, wherein the antigen receptor signal and anti-PD-1 antibody are spaced by no more than 100 μm.

34. The method of claim 31, wherein the antigen receptor signal is delivered by an anti-CD3 antibody.



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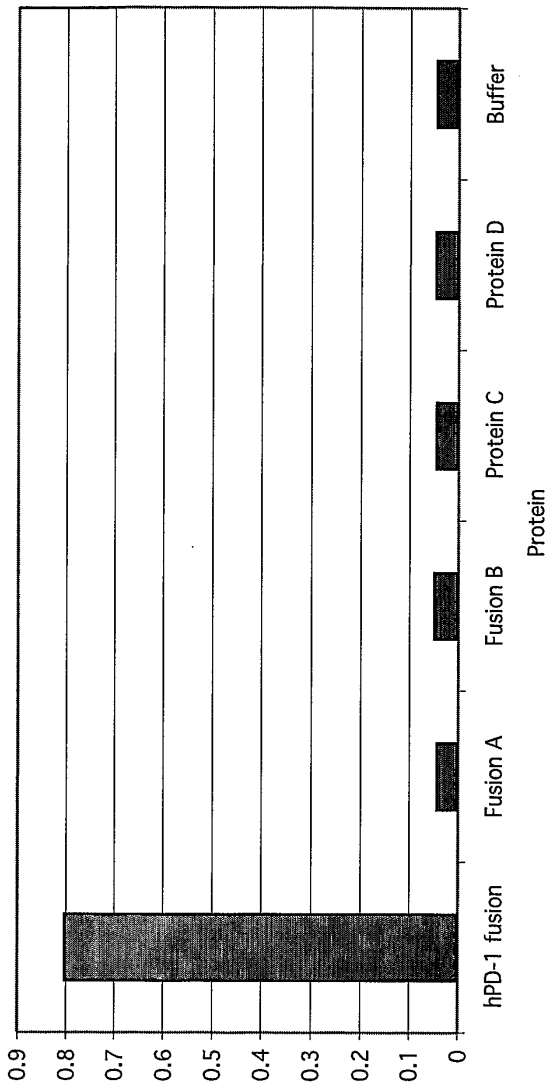



Fig. 1A

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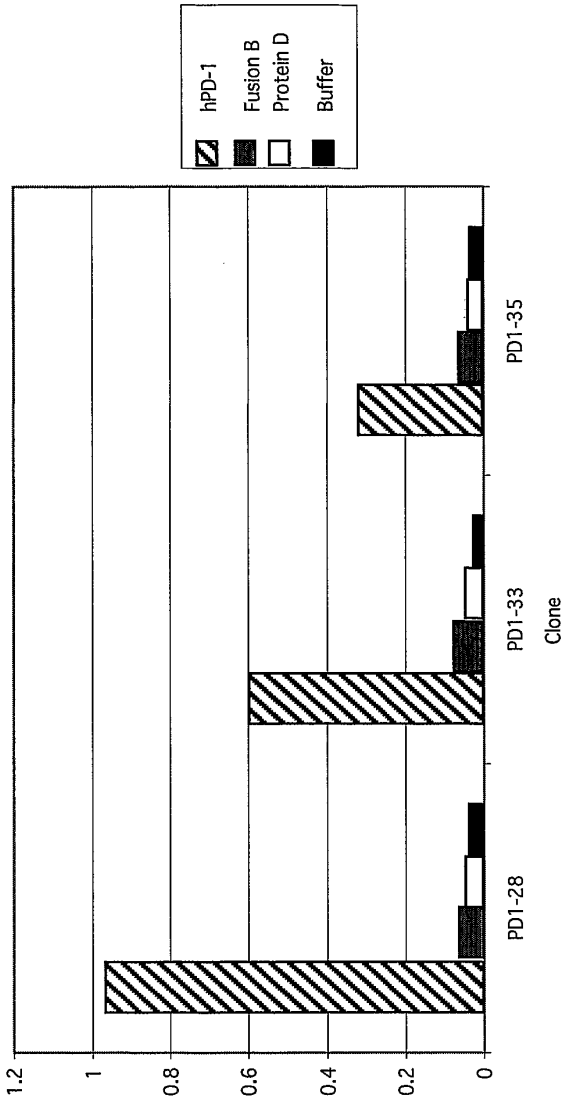



Fig. 1B

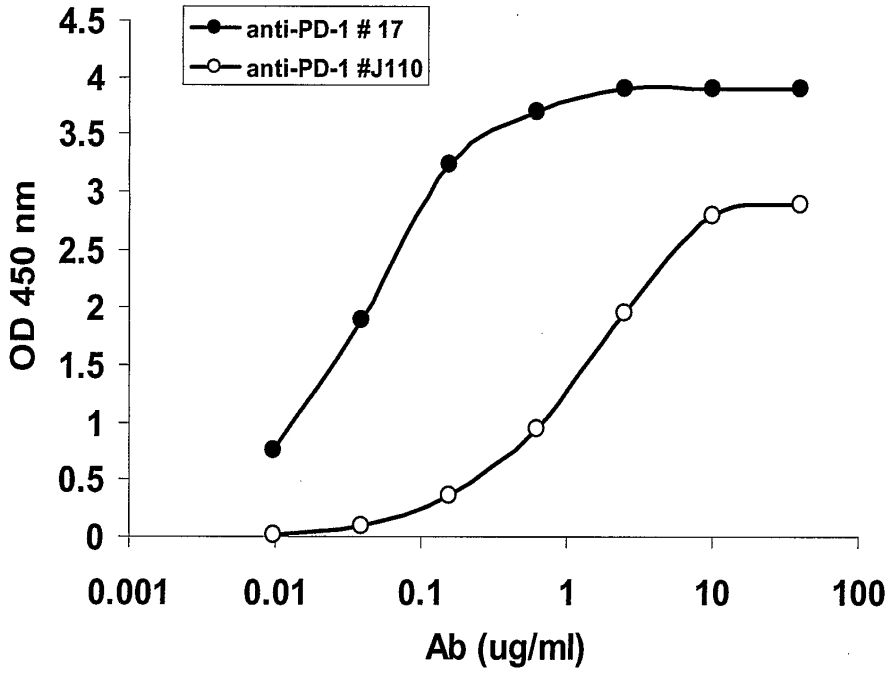

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3
2.5
2
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0.001
0.01
0.1
1
10
100
Ab (ug/ml)

Fig. 2A

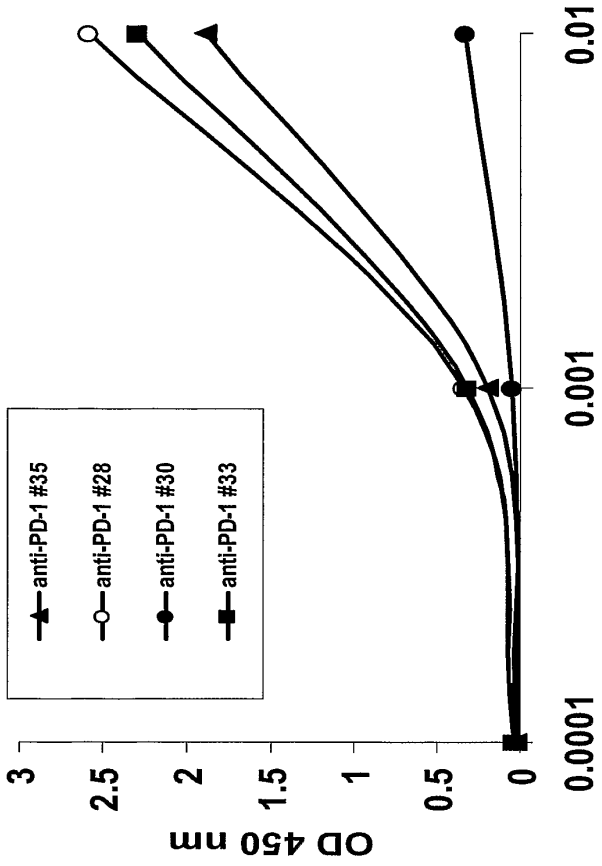



Fig. 2B

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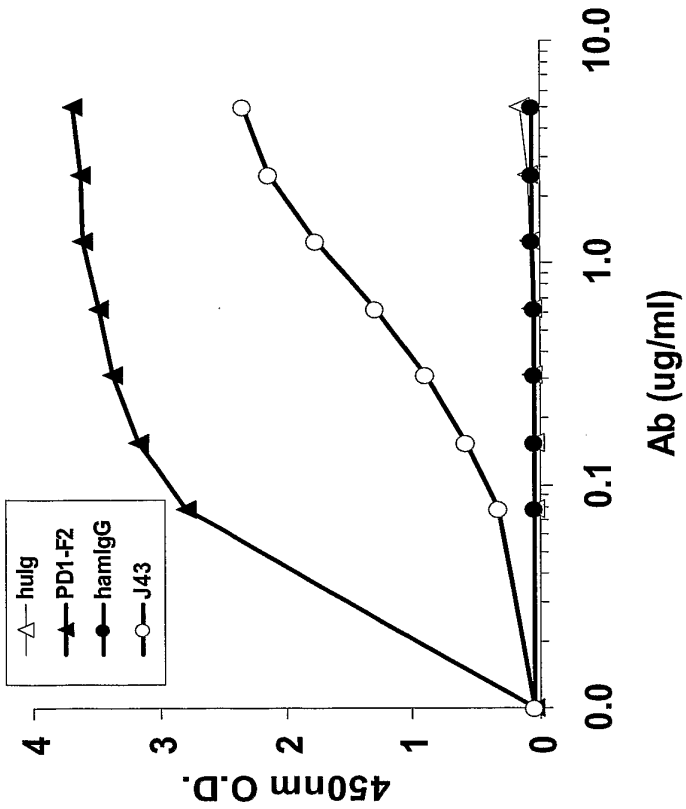



Fig. 2C

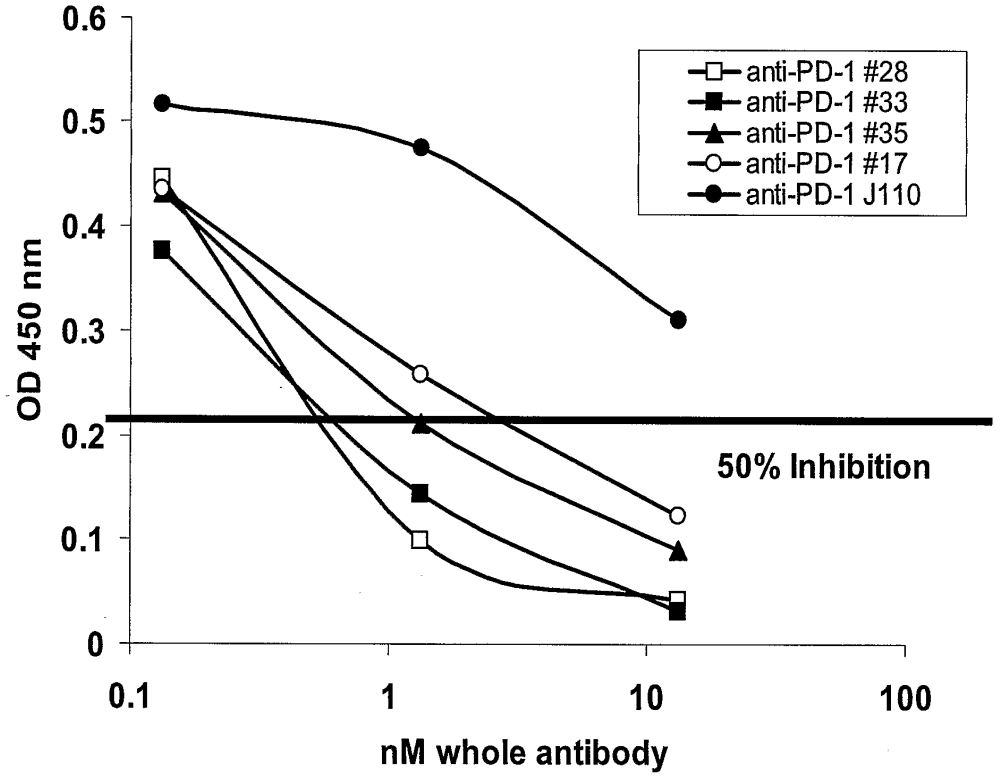

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0.2
0.1
0
OD 450 nm
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anti-PD-1 #33
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anti-PD-1 #17
anti-PD-1 J110
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1
10
100
nM whole antibody

Fig. 3

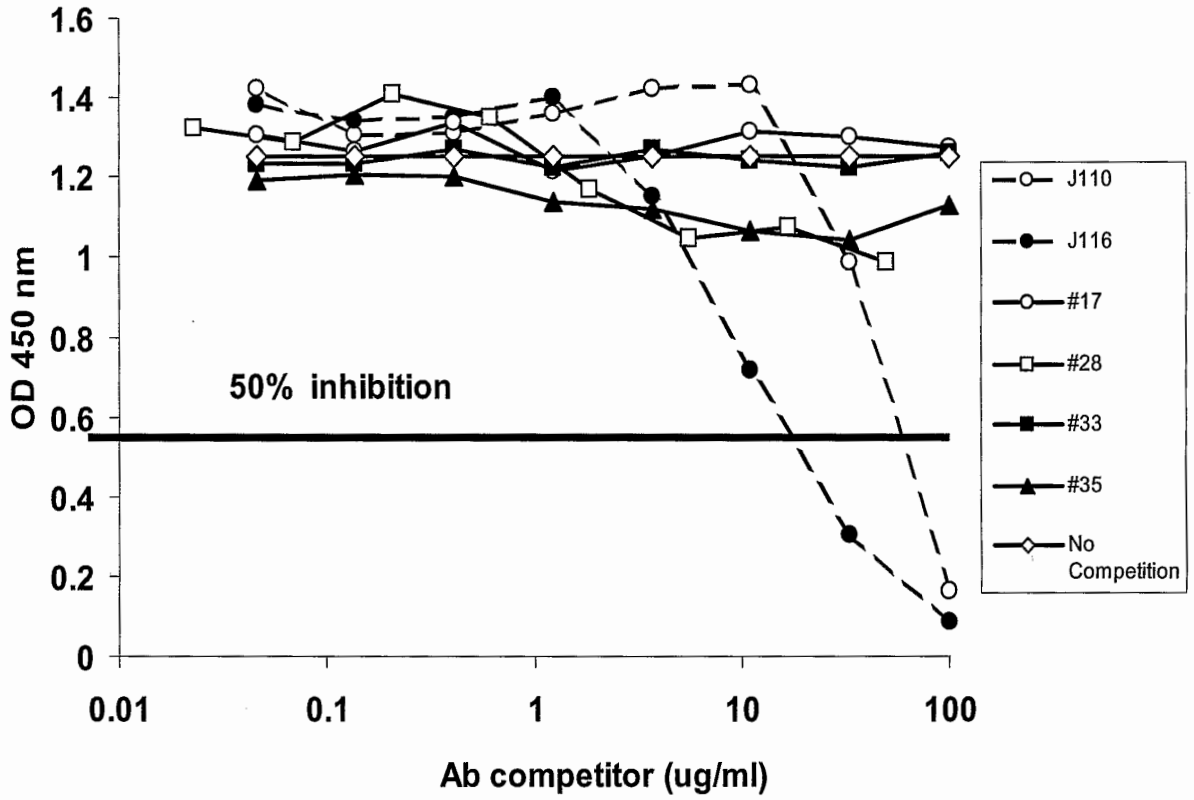

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1.4
1.2
1
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0.6
0.4
0.2
0
OD 450 nm
50% inhibition
0.01
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10
100
Ab competitor (ug/ml)
J110
J116
#17
#28
#33
#35
No Competition

Fig. 4

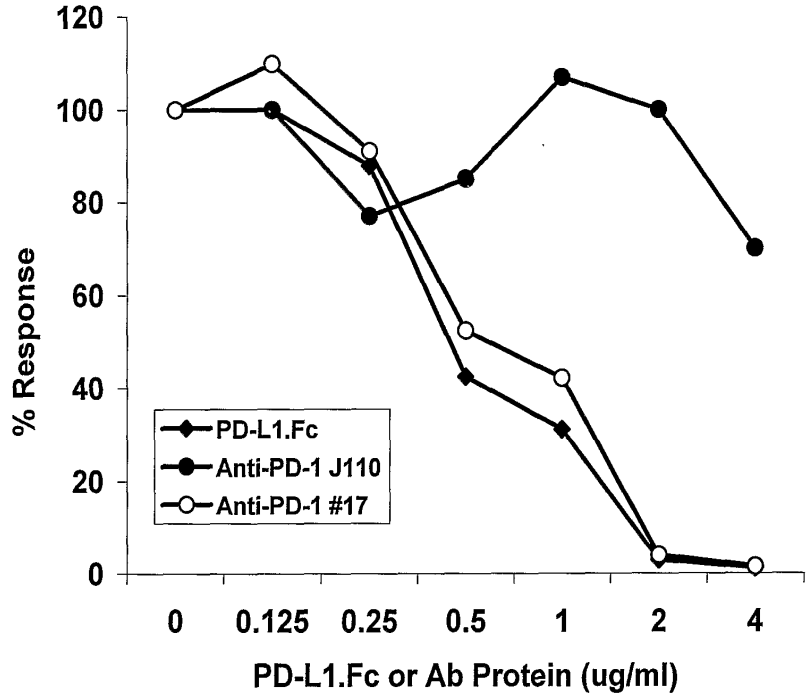

120
100
80
60
40
20
0
% Response
PD-L1.Fc
Anti-PD-1 J110
Anti-PD-1 #17
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0.25
0.5
1
2
4
PD-L1.Fc or Ab Protein (ug/ml)

Fig. 5

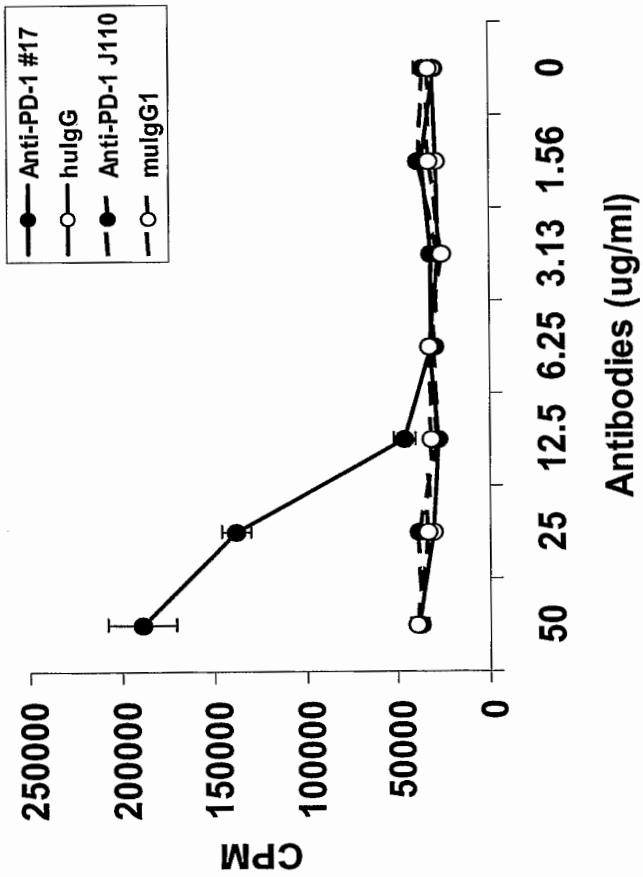



Fig. 6

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SEQUENCE LISTING

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35 40 45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
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Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Val Ser Gly
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35 40 45



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50 55 60

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65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
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35 40 45

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<213> Homo sapiens

<400> 24

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Dana-Farber v. BMS, IPR2023-00501
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<213> Homo sapiens

<400> 37

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Ile

<210> 38
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Dana-Farber v. BMS, IPR2023-00501
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<211> 288
<212> PRT
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Asn Pro Pro Thr Phe Phe Pro Ala Leu Leu Val Val Thr Glu Gly Asp
35 40 45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
50 55 60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65 70 75 80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
85 90 95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
100 105 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
130 135 140



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Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

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            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
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20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60



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Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
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35 40 45

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50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80



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Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240
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Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

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35 40 45

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50 55 60

Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
65 70 75 80

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
85 90 95

Asp Thr Ala Val Tyr Tyr Cys Ala Lys Glu Asn Trp Gly Ser Tyr Phe
100 105 110



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Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro
35 40 45

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Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
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<213> Homo sapiens

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Arg Ser Leu Thr Phe Tyr Pro Ala Trp Leu Thr Val Ser Glu Gly Ala
35 40 45

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50 55 60

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65 70 75 80

Ala Phe Cys Asn Gly Leu Ser Gln Pro Val Gln Asp Ala Arg Phe Gln
85 90 95



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Ile Ile Gln Leu Pro Asn Arg His Asp Phe His Met Asn Ile Leu Asp
100 105 110

Thr Arg Arg Asn Asp Ser Gly Ile Tyr Leu Cys Gly Ala Ile Ser Leu
115 120 125

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165 170 175

Leu Val Gly Ile Pro Val Leu Leu Leu Leu Ala Trp Ala Leu Ala Val
180 185 190

Phe Cys Ser Thr Ser Met Ser Glu Ala Arg Gly Ala Gly Ser Lys Asp
195 200 205

Asp Thr Leu Lys Glu Glu Pro Ser Ala Ala Pro Val Pro Ser Val Ala
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Tyr Glu Glu Leu Asp Phe Gln Gly Arg Glu Lys Thr Pro Glu Leu Pro
225 230 235 240

Thr Ala Cys Val His Thr Glu Tyr Ala Thr Ile Val Phe Thr Glu Gly
245 250 255



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Leu Gly Ala Ser Ala Met Gly Arg Arg Gly Ser Ala Asp Gly Leu Gln
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Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
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Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
        35                  40                  45

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
    50                  55                  60

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
                85                  90                  95

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105
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# INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PCT/IB 03/06304

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/28 A61K39/395 C12N15/13 C12N5/10 C12N15/63 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | AGATA Y ET AL: "Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes." INTERNATIONAL IMMUNOLOGY. ENGLAND MAY 1996, vol. 8, no. 5, May 1996 (1996-05), pages 765-772, XP000971773 ISSN: 0953-8178 page 770, left-hand column, line 9 -page 771, right-hand column, line 14 --- | 1-34 |
| X | WO 02/078731 A (WYETH) 10 October 2002 (2002-10-10) page 117; example 10 page 134; example 25 --- | 1-34 |

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[X] Further documents are listed in the continuation of box C.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 May 2004 | 18/05/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Le Flao, K |

Form PCT/ISA/210 (second sheet) (January 2004)



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1802 of 2058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 01/27272 A (MATSUO TOSHIHIKO ;HAMILTON BROOK SMITH & REYNOLD (US)) 19 April 2001 (2001-04-19) example SEQ | 2 |
| X | EP 0 945 464 A (CAMBRIDGE ANTIBODY TECH) 29 September 1999 (1999-09-29) example SEQ | 2 |
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| A | VAUGHAN T J ET AL: "HUMAN ANTIBODIES WITH SUB-NANOMOLAR AFFINITIES ISOLATED FROM A LARGE NON-IMMUNIZED PHAGE DISPLAY LIBRARY" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 14, 1 March 1996 (1996-03-01), pages 309-314, XP000196144 ISSN: 1087-0156 cited in the application the whole document | 1-34 |
| A | DAVIES J ET AL: "Affinity improvement of single antibody VH domains: residues in all three hypervariable regions affect antigen binding" IMMUNOTECHNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, NL, vol. 2, no. 3, 1 September 1996 (1996-09-01), pages 169-179, XP004070292 ISSN: 1380-2933 the whole document | 1-34 |

# INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/IB 03/06304

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-14 and 25-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1804 of 2058

## INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/IB 03/06304

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
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Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1805 of 2058

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Lisa Tyner/Danielle Gamache |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| 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($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **180** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8808474 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Danielle Gamache |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 10-NOV-2010 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 14:19:11 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $180 |
| RAM confirmation Number | 482 |
| Deposit Account | 024377 |
| Authorized User | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
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| 1 | | 0499IDS.pdf | 199209<br>5724fe9c8b2f7c1fb6f8c85263f5fda8d0d658b4 | yes | 7 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Transmittal Letter | 1 | 1 |
| Fee Worksheet (PTO-875) | 2 | 2 |
| Information Disclosure Statement (IDS) Filed (SB/08) | 3 | 7 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Foreign Reference | ref.pdf | 3280915<br>94a6da59b5ab5ecf0293e1361ebe42b224bbde4d | no | 96 |

**Warnings:**

**Information:**

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|---|---|---|---|---|---|
| 3 | Fee Worksheet (PTO-875) | fee-info.pdf | 30644<br>1ad3aa484f5357441a6aeb0f0770ec27e0ec28ba | no | 2 |

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**<u>New Applications Under 35 U.S.C. 111</u>**
**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.**

**<u>National Stage of an International Application under 35 U.S.C. 371</u>**
**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.**

**<u>New International Application Filed with the USPTO as a Receiving Office</u>**
**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/SB/21 (10-07)
Approved for use through 10/31/2007. OMB 0651-0031
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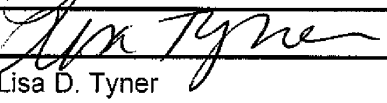
| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 10/31/2007 |
| First Named Inventor | Korman et al. |
| Art Unit | 1644 |
| Examiner Name | Ouspenski, Ilia I. |
| Attorney Docket Number | 077375.0499 |

## ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
- [✓] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [✓] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature |  | | |
| Printed name | Lisa D. Tyner | | |
| Date | 11/10/2010 | Reg. No. | 51,619 |

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# FEE TRANSMITTAL for FY 2007

| Complete if Known | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 10/31/2007 |
| First Named Inventor | Korman et al. |
| Examiner Name | Ouspenski, Ilia I. |
| Art Unit | 1644 |
| Attorney Docket No. | 077375.0499 |

☐ Applicant claims small entity status. See 37 CFR 1.27

| TOTAL AMOUNT OF PAYMENT | ($) 180 |
|---|---|

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

| Deposit Account Number | 02-4377 |
|---|---|
| Deposit Account Name | Baker Botts L.L.P. |

**The Director is authorized to:** *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

## FEE CALCULATION

### Extra Claim Fees

| | Extra Claims | | Fee | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | x | 52 | = | $0 |
| Independent Claims | | x | 220 | = | $0 |
| Multiple Dependent | | | | = | $0 |
| | | SUBTOTAL | | | $0 |

| Fee Description | Large Entity | Small Entity |
|---|---|---|
| Claims in excess of 20 | 52 | 26 |
| Independent claims in excess of 3 | 220 | 110 |
| Multiple dependent claim, if not paid | 390 | 195 |

## FEE CALCULATION (continued)

### ADDITIONAL FEES

| | | |
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| ☐ | Surcharge - late oath or filing fee | |
| ☐ | Non-English Specification | |
| ☐ | Extension for reply within first month | |
| ☐ | Extension for reply within second month | |
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| ☐ | Extension for reply within fourth month | |
| ☐ | Extension for reply within fifth month | |
| ☐ | Notice of Appeal | |
| ☐ | Filing a brief in support of an appeal | |
| ☐ | Petition to revive - unavoidable | |
| ☐ | Petition to revive - unintentional | |
| ☐ | Utility Issue Fee | |
| ☐ | Design Issue Fee | |
| ☐ | Publication Fee | |
| ☐ | Petitions to the Commissioner | |
| ☐ | Request for Continued Examination (RCE) | |
| ☑ | Information Disclosure Statement (IDS) | $180 |
| | Other fee - | |
| | SUBTOTAL | ($) 180 |

| SUBMITTED BY | | | | (Complete *(if applicable)*) | |
|---|---|---|---|---|---|
| *Name (Print/Type)* | Lisa D. Tyner | *Registration No. (Attorney/Agent)* | 51,619 | *Telephone* | 212-408-2500 |
| *Signature* | | | | *Date* | 11/10/2010 |

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : KORMAN *et al.* | Examiner | : OUSPENSKI, ILIA I |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| Filed | : 10/31/2007 | Group Art Unit | 1644 |
| For | : HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS | | |

**REQUEST FOR REFUND**

**VIA ELECTRONIC FILING ON NOVEMBER 10, 2010**
Commissioner for Patents
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Applicant hereby petitions for a refund in the amount of $180.00 due to the inadvertent payment of an Information Disclosure Statement fee on November 10, 2010

Applicant submitted an Information Disclosure Statement, filed under 37 C.F.R. §1.97(c), with a statement under, 37 C.F.R. §1.97(e) prior to either a final action or a notice of allowance. Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Information Disclosure Statement, and therefore does not believe that any fee was required by the submission of said Information Disclosure Statement on November 10, 2010. Accordingly, Applicant respectfully requests a refund of the inadvertently paid Information Disclosure Statement fee of $180.00.

Applicant does not believe any fee is due in connection with this submission. However, if any fee is due, or if any overpayment has been made, Applicant authorizes the Commissioner to charge such fee or credit any overpayment associated with this paper to Baker Botts L.L.P. Deposit Account No. 02-4377, Ref. No. 077375.0499.

Respectfully submitted,

BAKER BOTTS L.L.P.

November 10, 2010
Date

Lisa D. Tyner
Patent Office Reg. No. 51,619

30 Rockefeller Plaza
45th Floor
New York,, NY 10012-4498
Attorney for Applicant
212 408-2524

NY02:698151.1

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 8812226 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Danielle Gamache |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 10-NOV-2010 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 17:10:30 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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.) |
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| 1 | | Refund.pdf | 78959<br>50ad837480c5013cf573eddff1cfb9b1b7ca94cb | yes | 3 |

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| **Warnings:** | | | |
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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**
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**New International Application Filed with the USPTO as a Receiving Office**
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PTO/SB/21 (10-07)
Approved for use through 10/31/2007. OMB 0651-0031
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Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 10/31/2007 |
| First Named Inventor | Korman et al. |
| Art Unit | 1644 |
| Examiner Name | Ouspenski, Ilia I. |
| Attorney Docket Number | 077375.0499 |

## ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☑ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature | Lisa Tyner | | |
| Printed name | Lisa D. Tyner | | |
| Date | 11/10/2010 | Reg. No. | 51,619 |

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|---|---|---|---|
| Applicants | : | Korman *et al.* | Conf. No. | : | 1207 |
| Serial No. | : | 11/913,217 | Examiner | : | OUSPENSKI, ILIA I |
| Filed | : | January 29, 2009 | Group Art Unit: | | 1644 |
| For | : | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS | | | |

**AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION**

**Filed Electronically**

**Mail Stop: AMENDMENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a response to the non-final Office Action dated October 25, 2010 received from the United States Patent and Trademark Office in connection with the above-identified patent application. This response is timely filed within three months of the mail date of the Office Action. Applicants respectfully submit the following Remarks for entry into the file of the above-referenced application.

Applicants believe no additional fees are due. However, if any other fees are required, or if any overpayment has been made, the Commissioner is hereby authorized to charge any fees, or credit any overpayments made, to Deposit Account 02-4377, Ref. No. 077375.0499.

**Amendments to the Specification** begin on page 2 of this paper

**Amendments to the Claims** are reflected in the listing of claims that begins on page 3 of this paper.

**Remarks** begin on page 22 of this paper.



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## AMENDMENTS TO THE SPECIFICATION

Please replace paragraph **[0148]** of the page 5 of the published document of the instant application U.S. Patent Publication No. 2009/0217401 with the following:

**[0148]** FIG. 4B shows the nucleotide sequence (SEQ ID NO: 67) and amino acid sequence (SEQ ID NO: [[1]] 11) of the light chain variable region of the 5C4 human monoclonal antibody. The CDR1 (SEQ ID NO: 39), CDR2 (SEQ ID NO: 46) and CDR3 (SEQ ID NO: 53) regions are delineated and the V and J germline derivations are indicated.



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## AMENDMENTS TO THE CLAIMS

The listing of claims provided below will replace all prior versions, and listings, of claims in the application.

1. - 7. **(Canceled)**

8. **(Currently Amended)** An isolated human monoclonal antibody, or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion thereof cross-competes for binding to PD-1 with a reference antibody or reference antigen-binding portion thereof comprising~~, and wherein the reference antibody is selected from the group consisting of~~:

a) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 1 and a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 8;

b) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 2 and a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 9;

c) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 3 and a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 10;

d) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 4 and a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 11;

e) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 5 and [[the]] a



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human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 12;

f) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 6 and [[the]] a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 13; [[and]] or

g) ~~an antibody comprising~~ a human heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 7 and a human light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 14.

9. - 26. **(Canceled)**

27. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, comprising a heavy chain variable region that comprises CDR1, CDR2, and CDR3 domains; and a light chain variable region that comprises CDR1, CDR2, and CDR3 domains, wherein the heavy chain variable region and light chain variable region CDR1, CDR2, and CDR3 domains are ~~wherein the antibody is~~ selected from the group consisting of:

a) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 15;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 22;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 29;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 36;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 43; and



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a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 50;

b) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 16;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 23;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:30;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 37;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 44; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 51;

c) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 17;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 24;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 31;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 38;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 45; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 52;

d) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 18;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 25;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 32;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 39;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 46; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 53;

e) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 19;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 26;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 33;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 40;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 47; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 54;

f) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 20;



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a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 27;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 34;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 41;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 48; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 55; and

g) ~~an antibody comprising~~

a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 21;

a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 28;

a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 35;

a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 42;

a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 49; and

a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 56,

wherein the antibody or antigen-binding portion thereof specifically binds to PD-1.

28. - 34. **(Canceled)**

35. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, comprising a heavy chain variable region and a light chain variable region,



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wherein the heavy chain variable region and light chain variable region are ~~antibody is~~ selected from the group consisting of:

a) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 1; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 8;

b) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 2; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 9;

c) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 3; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 10;

d) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 4; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 11;

e) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 5; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 12; [[or]]

f) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 6; and a light chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 13; and

g) ~~an antibody comprising~~ a heavy chain variable region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 7; and a light chain variable



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region comprising ~~the amino acid~~ amino acids having the sequence [[of]] set forth in SEQ ID NO: 14,

wherein the antibody or antigen-binding portion thereof specifically binds to PD-1.

36. - 42. **(Canceled)**

43. **(Currently Amended)** A composition comprising the antibody, or antigen-binding portion thereof, of ~~claim 8~~ any one of claims 8, 27, 35, and 106-108, and a pharmaceutically acceptable carrier.

44. **(Currently Amended)** An immunoconjugate comprising the antibody, or antigen-binding portion thereof, of ~~claim 8~~ any one of claims 8, 27, 35, and 106-108, linked to a therapeutic agent.

45. - 49. **(Canceled)**

50. **(Currently Amended)** A bispecific molecule comprising the antibody, or antigen-binding portion thereof, of ~~claim 8~~ any one of claims 8, 27, 35, and 106-108, linked to a second functional moiety having a different binding specificity than said antibody, or antigen-binding portion thereof.

51. - 105. **(Canceled)**

106. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, ~~wherein the antibody is selected from the group consisting of~~ comprising:

a) a heavy chain variable region ~~comprising an amino acid~~ that comprises amino acids having a sequence ~~that is at least 90% identical to an amino acid sequence encoded by~~ derived from a human $V_H$ 3-33 ~~gene~~ germline sequence; and

b) a light chain variable region ~~comprising an amino acid~~ that comprises amino acids having a sequence ~~that is at least 90% identical to an amino acid sequence encoded by~~ derived from a human $V_K$ L6 ~~gene~~ germline sequence;

wherein the antibody or antigen-binding portion thereof specifically binds to PD-1.



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107. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, wherein the antibody is selected from the group consisting of:

a) a heavy chain variable region ~~comprising an amino acid~~ that comprises amino acids having a sequence ~~that is at least 90% identical to an amino acid sequence encoded by~~ derived from a human $V_H$ 4-39 ~~gene~~ germline sequence; and

b) a light chain variable region ~~comprising an amino acid~~ that comprises amino acids having a sequence ~~that is at least 90% identical to an amino acid sequence encoded by~~ derived from a human $V_K$ L15 ~~gene~~ germline sequence;

wherein the antibody or antigen-binding portion thereof specifically binds to PD-1.

108. **(Currently Amended)** An isolated monoclonal antibody, or antigen-binding portion thereof, comprising a heavy chain variable region that comprises CDR1, CDR2, and CDR3 ~~sequences~~ domains; and a light chain variable region that comprises CDR1, CDR2, and CDR3 ~~sequences~~ domains, wherein the heavy chain variable region and light chain variable region CDR3 domains are selected from the group consisting of:

~~a) the heavy chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 30, 31, 32, 33, 34 and 35, and conservative modifications thereof;~~

~~b) the light chain variable region CDR3 sequence comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 50, 51, 52, 53, 54, 55 and 56, and conservative modifications thereof; and c)~~

a) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 29; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 50 and conservative modifications thereof;

b) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 30; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 51 and conservative modifications thereof;

c) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 31; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 52 and conservative modifications thereof;



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d) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 32; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 53 and conservative modifications thereof;

e) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 33; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 54 and conservative modifications thereof;

f) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 34; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 55 and conservative modifications thereof; and

g) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 35; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 56 and conservative modifications thereof;

wherein the antibody or antigen-binding portion thereof specifically binds to PD-1.

109. **(Currently Amended)** The antibody or antigen-binding portion thereof of claim 108, wherein the heavy chain variable region and light chain variable region CDR2 domains are selected from the group consisting of: ~~sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 22, 23, 24, 25, 26, 27 and 28, and conservative modifications thereof; and the light chain variable region CDR2 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 43, 44, 45, 46, 47, 48 and 49, and conservative modifications thereof~~

a) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 22 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 43 and conservative modifications thereof;

b) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 23 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 44 and conservative modifications thereof;



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c) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 24 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 45 and conservative modifications thereof;

d) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 25 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 46 and conservative modifications thereof;

e) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 26 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 47 and conservative modifications thereof;

f) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 27 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 48 and conservative modifications thereof; and

g) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 28 and conservative modifications thereof; and a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 49 and conservative modifications thereof.

110. **(Currently Amended)** The antibody or antigen-binding portion thereof of claim 109, wherein the heavy chain variable region and light chain variable region CDR1 domains are selected from the group consisting of: ~~sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 15, 16, 17, 18, 19, 20 and 21, and conservative modifications thereof; and the light chain variable region CDR1 sequence comprises an amino acid sequence selected from the group consisting of amino acid sequences of SEQ ID NOs: 36, 37, 38, 39, 40, 41 and 42, and conservative modifications thereof~~



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a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 15 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 36 and conservative modifications thereof;

b) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 16 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 37 and conservative modifications thereof;

c) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 17 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 38 and conservative modifications thereof;

d) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 18 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 39 and conservative modifications thereof;

e) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 19 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 40 and conservative modifications thereof;

f) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 20 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 41 and conservative modifications thereof; and

g) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 21 and conservative modifications thereof; and a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 42 and conservative modifications thereof.

111. - 112. **(Cancelled)**



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113. **(Currently Amended)** The antibody or antigen-binding portion thereof of ~~claim 8~~ any one of claims 8, 27, and 35, wherein the antibody or antigen-binding portion thereof inhibits the suppression of CD4+ CD25- T cells by regulatory T cells.

114. **(Currently Amended)** The antibody or antigen-binding portion thereof of ~~claim 8~~ any one of claims 8, 27, and 35, wherein the antibody or antigen-binding portion thereof enhances the antigen specific-memory response to a tumor or a pathogen.

115. **(Currently Amended)** The antibody or antigen-binding portion thereof of ~~claim 8~~ any one of claims 8, 27, and 35, wherein the antibody or antigen-binding portion thereof confers a persistent immunity to tumor relapse.

116. **(Currently Amended)** The antibody or antigen-binding portion thereof of ~~claim 8~~ any one of claims 8, 27, and 35, wherein the antibody or antigen-binding portion thereof is an IgG4 isotype.

117. **(Currently Amended)** The antibody or antigen-binding portion thereof of claim 116, wherein the antibody or antigen-binding portion thereof has neither ADCC activity nor CDC activity.

118. **(New)** The antibody, or antigen-binding portion thereof of claim 27, which comprises:

(a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 17;

(b) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 24;

(c) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 31;

(d) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 38;



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(e) a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 45; and

(f) a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 52.

119. **(New)** The antibody, or antigen-binding portion thereof of claim 27, which comprises:

(a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 18;

(b) a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 25;

(c) a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 32;

(d) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 39;

(e) a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 46; and

(f) a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 53.

120. **(New)** The antibody, or antigen-binding portion thereof of claim 35, which comprises:

(a) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 3; and

(b) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 10.

121. **(New)** The antibody, or antigen-binding portion thereof of claim 35, which comprises:

(a) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4; and



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(b) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11.

122. **(New)** The antibody, or antigen-binding portion thereof of claim 8, wherein the reference antibody or reference antigen-binding portion thereof comprises:

(a) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 3; and

(b) a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 10.

123. **(New)** The antibody, or antigen-binding portion thereof of claim 8, wherein the reference antibody or reference antigen-binding portion thereof comprises:

(a) a human heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4; and

(b) a human light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11.

124. **(New)** The immunoconjugate of claim 44, wherein the therapeutic agent is a cytotoxin or a radioactive isotope.



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## REMARKS

Claims 8, 27, 35, 43-44, 50, 57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105-117 were pending. Claims 1-7, 9-26, 28-34, 36-42, 45-49, 51-56, 58-61, 63, 66, 73-78, 81-83, 85-87, 90-95, 98-100, and 102-104 have been previously cancelled, without prejudice. Claims 57, 62, 64-65, 67-72, 79-80, 84, 88-89, 96-97, 101, and 105 have been cancelled, without prejudice, as they are directed to a non-elected invention. In addition, claims 111-112 have been cancelled, without prejudice. Claims 8, 27, 35, 43-44, 50, 106-110, and 113-117 have been hereby amended. New claims 118-124 have been added. Accordingly, upon entry of this paper, claims 8, 27, 35, 43-44, 50, 106-110, and 113-124 will remain pending.

Support for the amendments to the claims and new claims can be found throughout the specification and claims as originally filed, for example, in the specification at ¶ [0036], [0061] to [0127], [0129], [0141] to [0159], FIG. 1A to FIG. 12, and claims 46 and 48 as originally filed. In addition, ¶ [0148] has been amended to correct a typographical error of the SEQ ID NO. of the amino acid sequence of the light chain variable region of human monoclonal antibody, 5C4. Support for this amendment can be found throughout the specification, for example, at ¶ [0121], [0248], [0343], [0545] of the instant specification. *No new matter is added.*

Applicants acknowledge the examination of all species of elected invention by the Examiner.

### I. *Allowable Subject Matter*

Applicants gratefully acknowledge the Examiner's indication that claims 8, 27, 35, 43-44, 50, and 113-117 are allowable. Amendments of primarily an editorial nature have been made to claims 8, 27, 35, 43-44, 50, and 113-117 to more clearly describe the claimed subject matter. Therefore, Applicants respectfully submit that claims 8, 27, 35, 43-44, 50, and 113-117, as amended, are in condition for allowance.

### II. *Rejection Under 35 U.S.C. §112, first paragraph*

Claims 108-112 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Examiner alleges that the specification does not provide enablement for an antibody wherein the sequences of the heavy chain and light chain variable regions are from different antibodies.

Applicants respectfully traverse the Examiner's rejection. However, in an effort to expedite prosecution, but in no way acquiescing to the rejection, claims 111-112 have been cancelled, rendering the rejection thereof moot. Claims 108-110 have also been amended to more clearly describe the claimed antibodies. As amended, claims 108-110 are directed to antibodies comprising heavy and light chain variable region CDR domains, wherein (1) the amino acid sequence of the heavy chain CDR3 is specified by its SEQ ID NO., and (2) heavy and light chain variable region CDR domains from different antibodies are not combined. Therefore, Applicants respectfully request reconsideration of the claims and withdrawal of the instant rejection.

## III. *Rejection Under 35 U.S.C. §112, first paragraph*

Claims 106-112 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the instant rejection. However, in an effort to expedite prosecution of the instant application, Applicants have cancelled claims 111 and 112, without prejudice; claims 106-107 have been amended, without prejudice, to remove the phrase "percent homology." Claim 108 has been amended, without prejudice, to remove the phrase "conservative modifications thereof" as it applies to the heavy chain CDR3.

With respect to claims 108-110, Applicants submit that the claims are fully enabled by the specification. Claims 108-110, as amended, specifically recite that the claimed antibodies contain all six CDR domains. Furthermore, on page 4 of the Office Action, the Examiner acknowledges that the specification is "enabling . . . for an antibody that specifically binds to human PD-1 ***wherein the sequence of at least the heavy chain CDR3 is defined***" (Emphasis added). In an effort to expedite prosecution of the instant application, Applicants have amended claim 108, without prejudice, to remove the phrase "conservative



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Page 1835 of 2058

modifications thereof" as it applies to the heavy chain CDR3. Therefore, claim 108 is directed to an antibody, or antigen binding portion thereof, wherein the heavy chain CDR3 is specifically defined by its amino acid sequence. Accordingly, based on the Examiner's statement in the Office Action regarding enablement of this subject matter, claim 108 is enabled.

Claims 109 and 110 are dependent upon claim 108. These claims further define the antibodies by providing particular CDR1 and CDR2 amino acid sequences. Because the subject matter of claim 108 is enabled and therefore one of ordinary skill in the art would be able to make and use the antibodies of claim 108 without undue experimentation, claims 109 and 110 are also enabled. Moreover, the instant specification clearly defines the term "conservative sequence modification" as amino acid modifications that ***do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.***" ¶ [0342], emphasis added. In addition, the instant specification explicitly discloses various techniques known in the art to introduce such conservative sequence modifications into an antibody, including, for example, site-directed mutagenesis and PCT-mediated mutagenesis. *See* ¶ [0342]. The instant specification further discloses that conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain, which is well defined in the art, and illustrated in the specification as well. *See* ¶ [0342]. Therefore, in order to determine whether a conservative sequence modification significantly affects or alters the binding features of the antibody, the retained function of the altered antibody with conservative amino acid substitutions can be tested using the functional assays described in the instant specification and/or well-known in the art, for example, using Bioacore analysis for examining binding affinity and binding kinetics, and using flow cytometry for examining binding specificity. *See* ¶ [0342] and Examples 3-4.

Therefore, based on all of the above, one of skill in the art could make and use the antibodies of claims 108-110 without undue experimentation.



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With respect to claims 106-107 and 111-112, the Examiner states that the specification does not provide enablement for an antibody wherein the sequence of any variable region is qualified by the "percent homology" language, as in claims 106-107, and 111-112. The Examiner acknowledges that "one of skill in the art is enabled to make monoclonal antibodies that specifically bind to PD-L1 [sic], and then determine the identity of the gene encoding the respective heavy and light chain variable regions," but states that given the unpredictability in the art, the quantity of experimentation is "unnecessarily, and improperly extensive and undue." *See* page 7 of the Office Action. Applicants respectfully submit that the Examiner intended to state that one of skill in the art is enabled to make monoclonal antibodies that specifically bind to PD-1, instead of PD-L1.

Applicants respectfully disagree with the Examiner's rejection and submit that the claims are enabled. However, in an effort to expedite prosecution, but in no way acquiescing to the rejection, claims 111-112 have been cancelled, and claims 106-107 have been amended to remove the phrase "percent homology," thereby rendering this ground of rejection moot. Claims 106-107, as amended, refer to antibodies comprising heavy and light chain amino acid sequences that are derived from specific germline sequences (*see* the specification at ¶ [0036]). Reconsideration of the claims and withdrawal of the instant rejection is, therefore, respectfully requested.

## IV. ***Rejection Under 35 U.S.C. §112, first paragraph***

Claims 106-107 are rejected under 35 U.S.C. §112 first paragraph, as allegedly failing to comply with the enablement requirement because, according to the Examiner, the specification does not provide a sufficient enabling description of an isolated monoclonal antibody comprising variable regions encoded by the specified genes, wherein the antibody specifically binds to PD-1. Applicants respectfully traverse this rejection.

As set forth above, in an effort to expedite the prosecution of the instant application, but in no way acquiescing to the rejection, the phrase "percent homology" has been removed from claims 106-107. In addition, claims 106-107 have been amended to more clearly recite

the heavy and light chain variable region "that comprises amino acids having a sequence derived from" a particular human germline sequence, for example, human $V_H$ 3-33 germline sequence, human $V_K$ L6 germline sequence, human $V_H$ 4-39 germline sequence, and human $V_K$ L15 germline sequence. In addition, the amino acid sequences encoded by these human germline sequences are explicitly disclosed in the instant specification, for example, SEQ ID NOs: 71-74, as well as FIG. 9 to FIG. 12. All the human monoclonal antibodies or antigen-binding portions claimed in claims 106-107 are capable of specially binding to PD-1.

In addition, Applicants respectfully submit that at the time the instant application was filed, one of skill in the art would have been able to generate multiple antibody sequences having specified binding characteristics from a particular germline sequence such as is recited in the claims. For example, Xu and Davis, (2000) *Immunity* Vol. 13, 37-45 (attached herewith as Appendix A) describes the generation of transgenic mice containing a single functional $V_H$ gene segment (human $V_H$5-51; *see* p. 38), and the production of high-affinity antibodies that bind to diverse antigens (including KLH, hen egg-white lysozyme, and chicken ovalbumin; *see* pp. 38-41).

Therefore, based on the knowledge available in the art at the time of filing, and the disclosure in the instant specification regarding the particular germline sequences recited in the claims, one of skill in the art would have been able to generate anti-PD-1 antibodies derived from the particular germline sequences recited in claims 106-107 without undue experimentation. Accordingly, Applicants respectfully request reconsideration of the claims and withdrawal of the instant rejection.

Request for Interview

Applicants submit that the instant application is in condition for allowance at least for the reasons set forth herein. If the instant application is not considered to be in condition for allowance by the Examiner, Applicants request an interview with the Examiner to discuss the present application and the prior art of record. Applicants' Attorney can be contacted by



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telephone at (212) 408-2585 to schedule a mutually convenient date and time and to provide assistance or additional information as required.

## CONCLUSION

In view of the foregoing, Applicant believes that the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues in an effort to expedite the allowance of this application.

Applicants believe no fees are due. However, if any fee is required in connection with this communication, or if any overpayment has been made, Applicant authorizes the Commissioner to charge any additional fees and/or credit any overpayments associated with this paper to Baker Botts L.L.P. Deposit Account No. 02-4377, Ref. No. 077375.0499. Further, if an additional fee is required for an extension of time under 37 C.F.R. § 1.136 not provided for above, Applicant requests such extension and authorizes the charging of the extension fee to Baker Botts L.L.P. Deposit Account No. 02-4377, Ref. No. 077375.0499.

Respectfully submitted,

BAKER BOTTS L.L.P.

January 25, 2011
Date

Lisa D. Tyner
Patent Office Reg. No. 51,619

30 Rockefeller Plaza
45th Floor
New York, NY 10012-4498
Attorney for Applicant(s)
212-408-2500



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1839 of 2058

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Lisa Tyner/Lillian Garcia |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| Claims in excess of 20 | 1615 | 22 | 52 | 1144 |
| Multiple dependent claims | 1616 | 1 | 390 | 390 |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1534** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 9301305 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Lillian Garcia |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 25-JAN-2011 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 15:02:23 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1534 |
| RAM confirmation Number | 1305 |
| Deposit Account | 024377 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 077375_0499_Response_to_OA.pdf | 774678<br>dcefd2ec8adeffc8102f35fa9a32b7c2d7cab31c | yes | 24 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Miscellaneous Incoming Letter | 1 | 2 |
| Amendment/Req. Reconsideration-After Non-Final Reject | 3 | 3 |
| Specification | 4 | 4 |
| Claims | 5 | 18 |
| Applicant Arguments/Remarks Made in an Amendment | 19 | 24 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (PTO-875) | fee-info.pdf | 31824<br>b09a01cad4bee68f15c96eacd69bc5fac1e00556 | no | 2 |

**Warnings:**

**Information:**

| Total Files Size (in bytes): | 806502 |
|---|---|

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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.**

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**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.**

# FEE TRANSMITTAL for FY 2007

| Complete if Known | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Examiner Name | OUSPENSKI, ILIA I. |
| Art Unit | 1644 |
| Attorney Docket No. | 077375.0499 |

☐ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) 1,534

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 02-4377

Deposit Account Name: Baker Botts L.L.P.

**The Director is authorized to:** *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

## FEE CALCULATION

### Extra Claim Fees

| | Extra Claims | | Fee | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | 22 | x | 52 | = | $1,144 |
| Independent Claims | | x | 220 | = | $0 |
| Multiple Dependent | | | 390 | = | $390 |
| | | | SUBTOTAL | | $1,534 |

| Fee Description | Large Entity | Small Entity |
|---|---|---|
| Claims in excess of 20 | 52 | 26 |
| Independent claims in excess of 3 | 220 | 110 |
| Multiple dependent claim, if not paid | 390 | 195 |

## FEE CALCULATION (continued)

### ADDITIONAL FEES

| | |
|---|---|
| ☐ Surcharge - late oath or filing fee | |
| ☐ Non-English Specification | |
| ☐ Extension for reply within first month | |
| ☐ Extension for reply within second month | |
| ☐ Extension for reply within third month | |
| ☐ Extension for reply within fourth month | |
| ☐ Extension for reply within fifth month | |
| ☐ Notice of Appeal | |
| ☐ Filing a brief in support of an appeal | |
| ☐ Petition to revive - unavoidable | |
| ☐ Petition to revive - unintentional | |
| ☐ Utility Issue Fee | |
| ☐ Design Issue Fee | |
| ☐ Publication Fee | |
| ☐ Petitions to the Commissioner | |
| ☐ Request for Continued Examination (RCE) | |
| ☐ Information Disclosure Statement (IDS) | |
| Other fee - | |
| SUBTOTAL | ($) 0 |

**SUBMITTED BY** (Complete *(if applicable)*)

| | | | | | |
|---|---|---|---|---|---|
| Name *(Print/Type)* | Lisa D. Tyner | Registration No. *(Attorney/Agent)* | 51,619 | Telephone | 212-408-2500 |
| Signature | | | | Date | |

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This collection of information is required by 37 CFR 1.17 and 1.27. 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.

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PTO/SB/21 (10-07)
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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

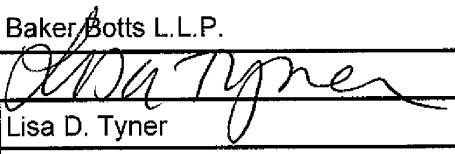
| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Art Unit | 1644 |
| Examiner Name | OUSPENSKI, ILIA I. |
| Attorney Docket Number | 077375.0499 |

## ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [x] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature |  | | |
| Printed name | Lisa D. Tyner | | |
| Date | 01/25/2011 | Reg. No. | 51,619 |

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# PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

| Application or Docket Number | Filing Date | ☐ To be Mailed |
|---|---|---|
| 11/913,217 | 01/29/2009 | |

## 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 | |
| ☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | |
| ☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | |
| TOTAL CLAIMS (37 CFR 1.16(i)) | minus 20 = | * | X $ = | | OR | X $ = | |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | minus 3 = | * | X $ = | | | X $ = | |
| ☐ APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 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 | | | TOTAL | |

## APPLICATION AS AMENDED – PART II

| AMENDMENT | 01/25/2011 | (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 ($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total (37 CFR 1.16(i)) | * 58 | Minus | ** 36 | = 22 | X $ = | | OR | X $52= | 1144 |
| | Independent (37 CFR 1.16(h)) | * 9 | Minus | ***9 | = 0 | X $ = | | OR | X $220= | 0 |
| | ☐ Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | ☒ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | 390 |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | 1534 |

| AMENDMENT | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | RATE ($) | ADDITIONAL FEE ($) | | RATE ($) | ADDITIONAL FEE ($) |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/EFREM WARREN/

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.**

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63367 7590 04/22/2011

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| EXAMINER |
|---|
| OUSPENSKI, ILIA I |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 04/22/2011

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

TITLE OF INVENTION: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 07/22/2011 |

**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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**





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Dana-Farber v. BMS, IPR2023-00501
Page 1847 of 2058

# PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (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)

63367 7590 04/22/2011

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| |
|---|
| (Depositor's name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

TITLE OF INVENTION: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 07/22/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| OUSPENSKI, ILIA I | 1644 | 530-388150 |

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 03-02 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 has been filed for recordation as set forth in 37 CFR 3.11. 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. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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 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, 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.

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Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1848 of 2058

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

63367 7590 04/22/2011

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| EXAMINER | |
|---|---|
| OUSPENSKI, ILIA I | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 04/22/2011

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 133 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 133 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.





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Dana-Farber v. BMS, IPR2023-00501
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## 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. | Applicant(s) | |
|---|---|---|---|
| | 11/913,217 | KORMAN ET AL. | |
| | Examiner | Art Unit | |
| | ILIA OUSPENSKI | 1644 | |

***-- 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 *01/25/2011*.

2. ☒ The allowed claim(s) is/are *8,27,35,43,44,50,106-110 and 113-124*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   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.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 11/10/2010; 10/07/2008.
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/ILIA OUSPENSKI/
Primary Examiner, Art Unit 1644



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1851 of 2058

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# BIB DATA SHEET

**CONFIRMATION NO. 1207**

| SERIAL NUMBER | FILING or 371(c) DATE<br>RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | 424 | 1644 | 077375.0499 |

**APPLICANTS**

Alan J. Korman, Piedmont, CA;
Mohan Srinivasan, San Jose, CA;
Changyu Wang, Fremont, CA;
Mark J. Selby, San Francisco, CA;
Bing Chen, Alameda, CA;
Josephine M. Cardarelli, San Carlos, CA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/JP2006/309606 05/02/2006
which claims benefit of 60/679,466 05/09/2005
and claims benefit of 60/738,434 11/21/2005
and claims benefit of 60/748,919 12/08/2005

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

05/15/2009

| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☑ No<br>Verified and Acknowledged /ILIA I OUSPENSKI/ Examiner's Signature | ☐ Met after Allowance<br>Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | CA | 58 | 31 | 7 |

**ADDRESS**

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498
UNITED STATES

**TITLE**

Human Monoclonal Antibodies To Programmed Death 1(PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination with Other Immunotherapeutics

| FILING FEE RECEIVED | FEES: Authority has been given in Paper | ☐ All Fees |
|---|---|---|
| 5266 | No._____ to charge/credit DEPOSIT ACCOUNT | ☐ 1.16 Fees (Filing) |
| | No._____ for following: | ☐ 1.17 Fees (Processing Ext. of time) |
| | | ☐ 1.18 Fees (Issue) |
| | | ☐ Other _____ |
| | | ☐ Credit |

## EAST Search History

### EAST Search History (Prior Art)

<This search history is empty>

### EAST Search History (Interference)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 383 | (pd-1 or cd279 or anti-pd-1 or anti-cd279) same antibod$ | US-PGPUB; USPAT; UPAD | OR | OFF | 2011/03/27 14:55 |
| L2 | 9 | L1 and (korman-a$ or srinivasan-m$ or wang-c$ or selby-m$ or chen-b$ or cardarelli-j$).in. | US-PGPUB; USPAT; UPAD | OR | OFF | 2011/03/27 14:57 |
| L3 | 59 | L1 and @pd>"20101019" | US-PGPUB; USPAT; UPAD | OR | OFF | 2011/03/27 14:57 |

**3/27/2011 2:58:12 PM**



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1853 of 2058

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | Examiner | Art Unit |
| | ILIA OUSPENSKI | 1644 |

| SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| | | | |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| Priority documents | 10/19/2010 | /I.O./ |
| Sequence search: in SCORE | 10/19/2010 | /I.O./ |
| WEST: attached | 10/19/2010 | /I.O./ |
| Dialog: same as WEST | 10/19/2010 | /I.O./ |
| Inventor search | 10/19/2010 | /I.O./ |
| Sequence, EAST and Inventor searches updated | 3/27/2011 | /I.O./ |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| See search notes | | 3/27/2011 | /I.O./ |

| Substitute for form 1449/PTO<br><br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br><br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | TBD |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

## U.S. PATENT DOCUMENTS

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 1. | 2003/0232323 | 12/18/2003 | FREEMAN, *et al.* |
| | 2. | 2004/0073957 | 04/15/2004 | TOMIZUKA, *et al.* |
| | 3. | 2007/0065427 | 03/22/2007 | FREEMAN, *et al.* |
| | 4. | 2007/0202100 | 08/30/2007 | WOOD, *et al.* |
| | 5. | 2008/0025979 | 01/31/2008 | HONJO, *et al.* |
| | 6. | 5,629,204 | 05/13/1997 | HONJO, *et al.* |
| | 7. | 5,698,520 | 12/16/1997 | HONJO, *et al.* |
| | 8. | 6,632,976 | 10/14/2003 | TOMIZUKA, *et al.* |
| | 9. | 6,808,710 | 10/26/2004 | WOOD, *et al.* |
| | 10. | 7,101,550 | 09/05/2006 | WOOD, *et al.* |
| | 11. | 7,105,328 | 09/12/2006 | WOOD, *et al.* |

## FOREIGN PATENT DOCUMENTS

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 12. | WO 01/14557 | 03/01/2001 | WOOD, *et al.* |
| | 13. | WO 02/079499 | 10/10/2002 | WOOD, *et al.* |
| | 14. | WO 03/042402 | 05/22/2003 | FREEMAN, *et al.* |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:637690.1

* Examiner: Initial citation 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.O./

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | TBD |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 15. | WO 2004/072286 | 08/26/2004 | HONJO, *et al.* |

| Exam Initial | No. | **OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, Etc.)** |
|---|---|---|
| | 16 | AGATA, *et al.*, 1996, "Expression of the PD-1 antigen on the surface of stimulation mouse T and B lymphocytes," *Int Immunol*, Vol. 8: p765-772 |
| | 17 | BENNETT, *et al.*, 2003, "Program Death-1 Engagement Upon TCR Activation Has Distinct Effects on Costimulation and Cytokine-Driven Proliferation: Attenuation of ICOS, IL-4, and IL-21, But Not CD28, IL-7, and IL-15 Responses," *J Immunol*, Vol. 170: p711-718 |
| | 18 | BLANK, *et al.*, 2005, "Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy," *Cancer Immunol. Immunother.*, Vol. 54: p307-314 |
| | 19 | BROWN, *et al.*, 2003, "Blockade of Programmed Death-1 Ligands on Dendritic Cells Enhances T Cell Activation and Cytokine Production," *J. Immunol.*, Vol. 170: p1257-1266 |
| | 20 | CARTER, *et al.*, 2002, "PD-1: PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2," *Eur J Immunol*, Vol. 32: p634-643 |
| | 21 | DONG, *et al.*, 2002, "Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion," *Nat Med.*, Vol. 8: p783-800 |
| | 22 | DONG, H. and CHEN, L., 2003, "B7-H1 pathway and its role in the evasion of tumor immunity," *J Mol Med*, Vol. 81: p281-287 |
| | 23 | FINGER, et al., 1997, "The human PD-1 gene: complete cDNA, genomic organization, and developmentally regulated expression in B cell progenitors," Gene, Vol. 197: p177-187 |
| | 24 | FREEMAN, *et al.*, 2000, "Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation," *J Exp Med*, Vol. 192: p1027-1034 |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:637690.1

* Examiner: Initial citation 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.O./

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | TBD |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

| | | |
|---|---|---|
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| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:637690.1

* Examiner: Initial citation 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.O./

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | TBD |
| | Inventor(s) | Korman, et al. |
| | Art Unit | 1656 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 077375.0499 |

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| Examiner Signature | /Ilia Ouspenski/ | Date Considered | 04/19/2011 |
|---|---|---|---|

NY02:637690.1

* Examiner: Initial citation 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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /I.O./

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | **Examiner** | **Art Unit** |
| | ILIA OUSPENSKI | 1644 |

| ORIGINAL | | INTERNATIONAL CLASSIFICATION | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CLASS | SUBCLASS | CLAIMED | | | | | NON-CLAIMED | | | | | |
| 530 | 388.15 | C | 0 | 7 | K | 16 / 28 (2006.01.01) | | | | | | |

| CROSS REFERENCE(S) | | | | | |
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| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | |
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☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 19 | | 37 | | 55 | | 73 | | 91 | 10 | 109 | | |
| | 2 | | 20 | | 38 | | 56 | | 74 | | 92 | 11 | 110 | | |
| | 3 | | 21 | | 39 | | 57 | | 75 | | 93 | | 111 | | |
| | 4 | | 22 | | 40 | | 58 | | 76 | | 94 | | 112 | | |
| | 5 | | 23 | | 41 | | 59 | | 77 | | 95 | 12 | 113 | | |
| | 6 | | 24 | | 42 | | 60 | | 78 | | 96 | 13 | 114 | | |
| | 7 | | 25 | 4 | 43 | | 61 | | 79 | | 97 | 14 | 115 | | |
| 1 | 8 | | 26 | 5 | 44 | | 62 | | 80 | | 98 | 15 | 116 | | |
| | 9 | 2 | 27 | | 45 | | 63 | | 81 | | 99 | 16 | 117 | | |
| | 10 | | 28 | | 46 | | 64 | | 82 | | 100 | 17 | 118 | | |
| | 11 | | 29 | | 47 | | 65 | | 83 | | 101 | 18 | 119 | | |
| | 12 | | 30 | | 48 | | 66 | | 84 | | 102 | 19 | 120 | | |
| | 13 | | 31 | | 49 | | 67 | | 85 | | 103 | 20 | 121 | | |
| | 14 | | 32 | 6 | 50 | | 68 | | 86 | | 104 | 21 | 122 | | |
| | 15 | | 33 | | 51 | | 69 | | 87 | | 105 | 22 | 123 | | |
| | 16 | | 34 | | 52 | | 70 | | 88 | 7 | 106 | 23 | 124 | | |

| NONE | | Total Claims Allowed: | |
|---|---|---|---|
| (Assistant Examiner) | (Date) | 23 | |
| /ILIA OUSPENSKI/<br>Primary Examiner.Art Unit 1644 | 03/30/2011 | O.G. Print Claim(s) | O.G. Print Figure |
| (Primary Examiner) | (Date) | 1 | NONE |



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Dana-Farber v. BMS, IPR2023-00501
Page 1859 of 2058

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | **Examiner** | **Art Unit** |
| | ILIA OUSPENSKI | 1644 |

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

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| | 17 | 3 | 35 | | 53 | | 71 | | 89 | 8 | 107 | | | | |
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|---|---|---|---|
| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>23 | |
| /ILIA OUSPENSKI/<br>Primary Examiner.Art Unit 1644<br><br>(Primary Examiner) | 03/30/2011<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>NONE |



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| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 10/31/2007 |
| | Inventor(s) | Korman, *et al.* |
| | Art Unit | 1644 |
| | Examiner Name | OUSPENSKI, ILIA I |
| | Attorney Docket Number | 077375.0499 |

## FOREIGN PATENT DOCUMENTS

| Exam Initial | No. | Document No. | Publication Date | Applicant(s) |
|---|---|---|---|---|
| /I.O./ | 1. | WO 2004/056875 | 07/08/2004 | WYETH CORP *et al.* |

| Examiner Signature | /Ilia Ouspenski/ | Date Considered | 03/27/2011 |
|---|---|---|---|

NY02:697997.1

* Examiner: Initial citation 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.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman et al. | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| Filed | : 1/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**INFORMATION DISCLOSURE STATEMENT**

**FILED BY EFS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed herewith are patents and/or publications for consideration by the Patent and Trademark Office in regard to the invention claimed in the above-identified application. In compliance with 37 C.F.R. §1.56, such documents are listed on the enclosed Form PTO-1449.

This Information Disclosure Statement is submitted according to the following selected paragraph(s):

☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(b) (1) within three months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. § 1.53(d); (2) within three months of the date of entry of the national stage as set forth in 37 C.F.R. § 1.491 in an international application; (3) before the mailing of a first Office action on the merits; or (4) before the mailing of a first Office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(c) prior to either a final action or a notice of allowance. Payment for the fee required by 37 C.F.R. §1.17(p) is hereby authorized to be charged to Deposit Account No. 02-4377.



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Dana-Farber v. BMS, IPR2023-00501
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☐ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(c), with a statement under, 37 C.F.R. §1.97(e) prior to either a final action or a notice of allowance. The undersigned hereby states that (check one):

- ☐ each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.
- ☐ no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the information disclosure statement.

☒ This Information Disclosure Statement is being filed under 37 C.F.R. §1.97(d), with a statement under 37 C.F.R. §1.97(e), after a final action or a notice of allowance but prior to payment of the issue fee. Payment for the fee required by 37 C.F.R. §1.17(p) is hereby authorized to be charged to Deposit Account No. 02-4377. The undersigned hereby petitions that this Information Disclosure Statement be considered prior to issuance of the patent. The undersigned hereby states that (check one):

- ☒ each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.
- ☐ no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of the information disclosure statement.



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Dana-Farber v. BMS, IPR2023-00501
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☐ The references listed on the accompanying PTO-1449 were either cited by the Examiner or previously submitted in parent application U.S. Serial No. _____, filed _____. Pursuant to 37 C.F.R. § 1.98(d), the references are not required if the earlier application is identified and relied upon for an effective filing date under 35 U.S.C. § 120 and therefore are not enclosed herewith.

**Co-Pending Application Disclosure**

☐ Applicants would like to bring to the attention of the Examiner the following co-pending patent applications, which are also listed on the accompanying PTO-1449:

| Serial No. | Filing Date |
|---|---|
| | |

**Disclosure of Office Actions and Responses in Co-Pending Applications**

☐ Applicants would like to bring to the attention of the Examiner the following Office Actions issued in co-pending patent applications and Responses to Office Actions filed in such applications, which are also listed on the accompanying PTO-1449:

| Serial No. | Date of Office Action or Response |
|---|---|
| | |

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that the listed documents are material or constitute "prior art." If the Examiner applies the documents as prior art against any claim in the application and applicants determine that the cited documents do not constitute "prior art" under United States law, applicants reserve the right to present to the Office the relevant facts and law regarding the appropriate status of the documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should the documents be applied against the claims of the present application.

Applicants believe no additional fee is due in connection with this submission. However, if any additional fee is due, or if any overpayment has been made, the Commissioner



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Page 1864 of 2058

is authorized to charge any such fee or credit any overpayment to our Deposit Account No. 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

May 24, 2011
Date

Yi Han
Limited Recognition No.: L0429

Lisa Tyner
Patent Office Reg. No. 51,619

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New York, NY 10012-4498
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212-408-2500



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Dana-Farber v. BMS, IPR2023-00501
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| Substitute for form 1449/PTO<br><br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br><br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 1/29/2009 |
| | Inventor(s) | Korman et al. |
| | Art Unit | 1644 |
| | Examiner Name | Ouspenski, Ilia I. |
| | Attorney Docket Number | 077375.0499 |

**FOREIGN PATENT DOCUMENTS**

| Exam. Initial. | No. | Document No. | Issue/Publication Date | Applicant(s) |
|---|---|---|---|---|
| | 1. | WO 2003/006636 | 1/2003 | GENETHOR GMBH et al. (English Abstract submitted) |

| Examiner Signature | | Date Considered | |
|---|---|---|---|

NY02:713478.1

* Examiner: Initial citation 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.

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# (WO/2003/006636) REDUCTION OF THE STIMULATORY CAPACITY OF ANTIGEN-PRESENTING CELLS

Biblio. Data | Description | Claims | National Phase | Notices | Documents

**Latest bibliographic data on file with the International Bureau**

**Pub. No.:** WO/2003/006636 **International Application No.:** PCT/EP2002/007740
**Publication Date:** 23.01.2003 **International Filing Date:** 11.07.2002

**IPC:** ***A61P 31/00*** (2006.01), ***A61P 33/00*** (2006.01), ***A61P 35/00*** (2006.01), ***A61P 37/00*** (2006.01), ***C12N 5/0784*** (2010.01), *A61K 48/00* (2006.01)

**Applicants:** **GENETHOR GMBH** [DE/DE]; Robert-Rössle-Str. 10 13125 Berlin (DE) *(All Except US)*.
**SHERIFF, Ahmed** [DE/DE]; (DE) *(US Only)*.

**Inventor:** **SHERIFF, Ahmed**; (DE).

**Agent:** **MEYERS, Hans-Wilhelm et al.**; Postfach 10 22 41 50462 Köln (DE) .

**Priority Data:** 101 33 926.7 12.07.2001 DE

**Title:**
(EN) REDUCTION OF THE STIMULATORY CAPACITY OF ANTIGEN-PRESENTING CELLS
(DE) REDUKTION DER STIMULATIONSFÄHIGKEIT VON ANTIGEN PRÄSENTIERENDEN ZELLEN

**Abstract:**
(EN) The invention relates to a method for reducing immune reactions. The inventive method is characterized by manipulating the stimulatory properties of antigen-presenting cells and optionally at the same time inducing the antigen-presenting cells to present defined antigens.

(DE) Die Erfindung beruht auf einer Reduktion von Immunreaktionen. Bei dem Verfahren werden die stimulatorischen Eigenschaften von Antigen präsentierenden Zellen manipuliert und die Antigen präsentierenden Zellen werden gegebenenfalls gleichzeitig zur Präsentation von definierten Antigenen veranlasst.

**Designated States:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
African Regional Intellectual Property Org. (ARIPO) (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Publication Language:** German (DE)

**Filing Language:** German (DE)



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1867 of 2058

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Yi Han/Danielle Gamache |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| 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($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **180** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 10156261 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Yi Han/Danielle Gamache |
| **Filer Authorized By:** | Yi Han |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 24-MAY-2011 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 13:25:53 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

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|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $180 |
| RAM confirmation Number | 11163 |
| Deposit Account | 024377 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 0499.PDF | 194198<br>57314deed3be002a65fc6dec2e7e074df95da022 | yes | 7 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Transmittal Letter | 1 | 1 |
| | Fee Worksheet (PTO-875) | 2 | 2 |
| | Information Disclosure Statement (IDS) Filed (SB/08) | 3 | 7 |

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| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Foreign Reference | 0499_Ref.pdf | 34358<br>f18dc9020db549355bbe10ba93536c79f8e3a158 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Fee Worksheet (PTO-875) | fee-info.pdf | 30915<br>ea96805f7897191d4503ce91a051913ad3464640 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 259471 | | |

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**New Applications Under 35 U.S.C. 111**
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**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**
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PTO/SB/21 (10-07)
Approved for use through 10/31/2007. OMB 0651-0031
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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Art Unit | 1644 |
| Examiner Name | Ouspenski, Ilia I. |
| Attorney Docket Number | 077375.0499 |

## ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature | | | |
| Printed name | Yi Han | | |
| Date | 05/24/2011 | Reg. No. | L0429 |

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

| | | | |
|---|---|---|---|
| Signature | | | |
| Typed or printed name | | Date | |

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 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, 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.*

# FEE TRANSMITTAL for FY 2007

☐ Applicant claims small entity status. See 37 CFR 1.27

| TOTAL AMOUNT OF PAYMENT | ($) 180 |
|---|---|

| Complete if Known | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Examiner Name | Ouspenski, Ilia I. |
| Art Unit | 1644 |
| Attorney Docket No. | 077375.0499 |

**METHOD OF PAYMENT** *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 02-4377

Deposit Account Name: Baker Botts L.L.P.

**The Director is authorized to:** *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

**FEE CALCULATION**

**Extra Claim Fees**

| | Extra Claims | | Fee | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | x | 52 | = | $0 |
| Independent Claims | | x | 220 | = | $0 |
| Multiple Dependent | | | | = | $0 |
| | | | SUBTOTAL | | $0 |

| Fee Description | Large Entity | Small Entity |
|---|---|---|
| Claims in excess of 20 | 52 | 26 |
| Independent claims in excess of 3 | 220 | 110 |
| Multiple dependent claim, if not paid | 390 | 195 |

**FEE CALCULATION** (continued)

**ADDITIONAL FEES**

| | | |
|---|---|---|
| ☐ | Surcharge - late oath or filing fee | |
| ☐ | Non-English Specification | |
| ☐ | Extension for reply within first month | |
| ☐ | Extension for reply within second month | |
| ☐ | Extension for reply within third month | |
| ☐ | Extension for reply within fourth month | |
| ☐ | Extension for reply within fifth month | |
| ☐ | Notice of Appeal | |
| ☐ | Filing a brief in support of an appeal | |
| ☐ | Petition to revive - unavoidable | |
| ☐ | Petition to revive - unintentional | |
| ☐ | Utility Issue Fee | |
| ☐ | Design Issue Fee | |
| ☐ | Publication Fee | |
| ☐ | Petitions to the Commissioner | |
| ☐ | Request for Continued Examination (RCE) | |
| ☑ | Information Disclosure Statement (IDS) | $180 |

Other fee -

SUBTOTAL ($) 180

**SUBMITTED BY** (Complete *(if applicable)*)

| Name (Print/Type) | Yi Han | Registration No. (Attorney/Agent) | L0429 | Telephone | 212-408-2500 |
|---|---|---|---|---|---|
| Signature | | | | Date | 05/24/2011 |

**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 1.17 and 1.27. 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.**

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United States Patent and Trademark Office
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www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

63367 7590 06/06/2011

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| EXAMINER | |
|---|---|
| OUSPENSKI, ILIA I | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/06/2011 | 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):

DLNYDOCKET@BAKERBOTTS.COM

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 11/913,217 | 29 January, 2009 | KORMAN ET AL. | 077375.0499 |

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30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

| EXAMINER | |
|---|---|
| ILIA OUSPENSKI | |
| ART UNIT | PAPER |
| 1644 | 20110527 |

DATE MAILED:

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner for Patents**

Applicant's IDS filed on 05/24/2011 is acknowledged and has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on 571-272-0735. 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 http://pair-direct.uspto.gov. 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.

/ILIA OUSPENSKI/
Primary Examiner, Art Unit 1644

PTO-90C (Rev.04-03)

| Substitute for form 1449/PTO<br>**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**<br>**(Use as many sheets as necessary)** | | |
|---|---|---|
| | Application Number | 11/913,217 |
| | Filing Date | 1/29/2009 |
| | Inventor(s) | Korman et al. |
| | Art Unit | 1644 |
| | Examiner Name | Ouspenski, Ilia I. |
| | Attorney Docket Number | 077375.0499 |

**FOREIGN PATENT DOCUMENTS**

| Exam. Initial. | No. | Document No. | Issue/Publication Date | Applicant(s) |
|---|---|---|---|---|
| /I.O./ | 1. | WO 2003/006636 | 1/2003 | GENETHOR GMBH et al. (English Abstract submitted) |

(only the Abstract has been considered by the Examiner, since only the Abstract has been provided by Applicant - /I.O./)

| Examiner Signature | /Ilia Ouspenski/ | Date Considered | 05/27/2011 |
|---|---|---|---|

NY02:713478.1

* Examiner: Initial citation 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.

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | **Examiner** | **Art Unit** |
| | ILIA OUSPENSKI | 1644 |

| ORIGINAL | | INTERNATIONAL CLASSIFICATION | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CLASS | SUBCLASS | CLAIMED | | | | | NON-CLAIMED | | | | |
| 530 | 388.15 | C | 0 | 7 | K | 16 / 28 (2006.01.01) | | | | | |

| CROSS REFERENCE(S) | | | | | |
|---|---|---|---|---|---|
| CLASS | SUBCLASS (ONE SUBCLASS PER BLOCK) | | | | |
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original | Final | Original |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 19 | | 37 | | 55 | | 73 | | 91 | 10 | 109 | | |
| | 2 | | 20 | | 38 | | 56 | | 74 | | 92 | 11 | 110 | | |
| | 3 | | 21 | | 39 | | 57 | | 75 | | 93 | | 111 | | |
| | 4 | | 22 | | 40 | | 58 | | 76 | | 94 | | 112 | | |
| | 5 | | 23 | | 41 | | 59 | | 77 | | 95 | 12 | 113 | | |
| | 6 | | 24 | | 42 | | 60 | | 78 | | 96 | 13 | 114 | | |
| | 7 | | 25 | 7 | 43 | | 61 | | 79 | | 97 | 14 | 115 | | |
| 1 | 8 | | 26 | 8 | 44 | | 62 | | 80 | | 98 | 15 | 116 | | |
| | 9 | 2 | 27 | | 45 | | 63 | | 81 | | 99 | 16 | 117 | | |
| | 10 | | 28 | | 46 | | 64 | | 82 | | 100 | 17 | 118 | | |
| | 11 | | 29 | | 47 | | 65 | | 83 | | 101 | 18 | 119 | | |
| | 12 | | 30 | | 48 | | 66 | | 84 | | 102 | 19 | 120 | | |
| | 13 | | 31 | | 49 | | 67 | | 85 | | 103 | 20 | 121 | | |
| | 14 | | 32 | 9 | 50 | | 68 | | 86 | | 104 | 21 | 122 | | |
| | 15 | | 33 | | 51 | | 69 | | 87 | | 105 | 22 | 123 | | |
| | 16 | | 34 | | 52 | | 70 | | 88 | 4 | 106 | 23 | 124 | | |

| NONE<br><br>(Assistant Examiner) (Date) | **Total Claims Allowed:**<br>23 | |
|---|---|---|
| /ILIA OUSPENSKI/<br>Primary Examiner.Art Unit 1644 03/30/2011<br>(Primary Examiner) (Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>NONE |



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1878 of 2058

| Issue Classification | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 11913217 | KORMAN ET AL. |
| | **Examiner** | **Art Unit** |
| | ILIA OUSPENSKI | 1644 |

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 17 | 3 | 35 | | 53 | | 71 | | 89 | 5 | 107 | | | | |
| | 18 | | 36 | | 54 | | 72 | | 90 | 6 | 108 | | | | |

| | | | |
|---|---|---|---|
| NONE<br><br>(Assistant Examiner) | (Date) | **Total Claims Allowed:**<br>23 | |
| /ILIA OUSPENSKI/<br>Primary Examiner.Art Unit 1644<br><br>(Primary Examiner) | 03/30/2011<br><br>(Date) | O.G. Print Claim(s)<br>1 | O.G. Print Figure<br>NONE |



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1879 of 2058

## PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**
**or Fax (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)

63367 7590 04/22/2011
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30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

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 facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 | 1207 |

TITLE OF INVENTION: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 07/22/2011 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| OUSPENSKI, ILIA I | 1644 | 530-388150 |

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 03-02 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 Baker Botts L.L.P.
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 has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

| (A) NAME OF ASSIGNEE | (B) RESIDENCE: (CITY and STATE OR COUNTRY) |
|---|---|
| Medarex, Inc. | Princeton, NJ |
| Ono Pharmaceutical Co., Ltd. | Osaka, Japan |

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 024377 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Lisa Tyner Date July 21, 2011

Typed or printed name Lisa D. Tyner Registration No. 51,619

This collection of information 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 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, 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.

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Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1880 of 2058

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Lisa Tyner/Danielle Gamache |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| 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 | 1501 | 1 | 1510 | 1510 |
| Publ. Fee- early, voluntary, or normal | 1504 | 1 | 300 | 300 |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Extension-of-Time:** | | | | |
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **1810** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 10567580 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/Danielle Gamache |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 21-JUL-2011 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 12:48:02 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $1810 |
| RAM confirmation Number | 10241 |
| Deposit Account | 024377 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)<br>Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) | |

| | |
|---|---|
| Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees) | |
| Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees) | |
| Charge any Additional Fees required under 37 C.F.R. Section 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 | Issue Fee Payment (PTO-85B) | 0499.PDF | 65406<br>54d2c122bd039858ae3fd45d0aeec33e682a90ba | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 32269<br>edbcbbc8f3f40983e8b00b28059a436abb9602ef | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 97675 | | |

**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. |
|---|---|---|---|---|
| 11/913,217 | 08/30/2011 | 8008449 | 077375.0499 | 1207 |

63367 7590 08/10/2011

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30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

# 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 413 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.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Alan J. Korman, Piedmont, CA;
Mohan Srinivasan, San Jose, CA;
Changyu Wang, Fremont, CA;
Mark J. Selby, San Francisco, CA;
Bing Chen, Alameda, CA;
Josephine M. Cardarelli, San Carlos, CA;



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1885 of 2058

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| Patentees: | Alan J. Korman *et al.* | |
| U.S. Serial No.: | 11/913,217 | Patent No.: 8,008,449 |
| Filed: | January 29, 2009 | Issued: August 30, 2011 |
| Examiner: | OUSPENSKI, Ilia I. | Group Art Unit: 1644 |
| Confirmation No.: | 1207 | |
| For: | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS | |

***TRANSMITTED VIA EFS-WEB***
Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

**REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT FOR USPTO MISTAKE (37 C.F.R. §1.322)**

The patentees through their undersigned attorney hereby respectfully request that a Certificate of Correction be issued in connection with the above-identified patent to correct printing errors in accordance with the attached Certificate of Correction Form 1050.

Pursuant to 37 C.F.R. §1.322, patentees request that the Certificate of Correction enclosed herewith be issued for mistakes by the Patent and Trademark Office. Support for the requested corrections can be found in the Request for Corrected Filing Receipt filed July 8, 2009 and the Amendment filed January 25, 2011.

Please send the Certificate to the address registered with Customer No. 63367. The assignments on the application from which the subject patent issued were recorded on October 31, 2007, and can be found on Reel 020043, Frame 0830 (8 pages) to Assignee, Medarex, Inc., and on June 8, 2009, and can be found on Reel 022792, Frame 0026 (3 pages), and on June 9,

2009, and can be found on Reel 022800, Frame 0283 (6 pages) to Assignee, Ono Pharmaceutical Co., Ltd.

As the errors listed above are ascribable to the USPTO, no fee is believed to be due. However, if any fee is required in connection with this paper, the Commissioner is hereby authorized to charge any such fee under 37 C.F.R. §1.17, or credit any overpayment, to Deposit Account 02-4377, Ref. No. 077375.0499.

Respectfully submitted,

BAKER BOTTS L.L.P.

November 8, 2011
Date

Lisa D. Tyner
Patent Office Reg. No. 51,619

30 Rockefeller Plaza
45th Floor
New York, NY 10012-4498
Attorney for Applicant(s)
212-408-2500



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1887 of 2058

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO.: 8,008,449
DATED: August 30, 2011
INVENTOR(S): Alan J. Korman et al.

It is certified that there is an error in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (75), Inventors:

Change "**Changyu Wang**, Fremont, CA" to -- **Changyu Wang**, Union City, CA --.

Change "**Bingliana Chen**" to -- **Bingliang Chen** --.

In the Claims:

Claim 1:

Column 125, line 60, change "SEO" to -- SEQ --.

Claim 2:

Column 125, line 65, change "CDR3domains" to -- CDR3 domains --.

Claim 23:

Column 132, line 34, change "claim 5" to -- claim 8 --.

MAILING ADDRESS OF SENDER:
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
45th Floor
New York, NY 10012-4498

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 11360022 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/chanelle rogers |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 08-NOV-2011 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 14:35:19 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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 | Request for Certificate of Correction | CertofCorr.pdf | 69258<br>10ea145f874536bb4d7ebcb626ba4998b22c6a5c | no | 3 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| Total Files Size (in bytes): | 69258 |
|---|---|

**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

# CERTIFICATE OF CORRECTION



PATENT NO. : 8,008,449 B2
APPLICATION NO. : 11/913217
DATED : August 30, 2011
INVENTOR(S) : Alan J. Korman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

Item (75), Inventors:

Change "**Changyu Wang**, Fremont, CA" to -- **Changyu Wang**, Union City, CA --.

Change "**Bingliana Chen**" to -- **Bingliang Chen** --.

Claim 1:

Column 125, line 60, change "SEO" to -- SEQ --.

Claim 2:

Column 125, line 65, change "CDR3domains" to -- CDR3 domains --.

Claim 23:

Column 132, line 34, change "claim 5" to -- claim 8 --.

Signed and Sealed this
Twentieth Day of December, 2011

David J. Kappos

David J. Kappos
*Director of the United States Patent and Trademark Office*

Atty. Docket No. 077375.0499
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman et al. | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**PETITION TO CORRECT INVENTORSHIP PURSUANT TO 37 C.F.R. § 1.324 (a)**

P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is a petition pursuant to 37 C.F.R. §1.324(a) to correct inventorship of the above-identified patent. As originally filed, the above-identified patent names as inventors:

1. Alan J. Korman
2. Mohan Srinivasan
3. Changyu Wang
4. Mark J. Selby
5. Bing Chen
6. Josephine M. Cardarelli

The present petition seeks to add as inventor:

7. Haichun Huang



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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This petition is supported by the accompanying:

(a) Declaration of Haichun Huang in which the declarant avers that the error in inventorship in the above-identified application occurred through error and without deceptive intention on her part (Exhibit 1);

(b) Statement from each of the current named inventors agreeing to the change of inventorship to add Haichun Huang as inventor (Exhibit 2);

(c) Declaration and Power of Attorney executed by all of the inventors (Alan J. Korman, Mohan Srinivasan, Changyu Wang, Mark J. Selby, Bing Chen, Josephine M. Cardarelli, and Haichun Huang) (Exhibit 3);

(d) Consent of Assignee Medarex Inc. (Exhibit 4); and

(e) Consent of Assignee Ono Pharmaceutical Ltd. (Exhibit 5).

An assignment from Alan J. Korman, Mohan Srinivasan, Changyu Wang, Mark J. Selby, Bing Chen, and Josephine M. Cardarelli to Medarex, Inc. was recorded at Reel 020043, Frame 0830. An assignment of an undivided 50% of Medarex, Inc.'s interest to Ono Pharmaceutical Co., Ltd. was recorded at Reel 022800, Frame 0283.

The required petition fee of $130.00 as specified in 37 C.F.R. §1.20(b) is enclosed.

In consideration of the foregoing it is respectfully requested that the Patent and Trademark Office amend the inventorship of this application by adding Bartley Griffith as co-inventor.

Respectfully submitted,

Dated: 8/21/12

Lisa D. Tyner
Reg. No. 51,619
Attorney for Applicants
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112-4498
(212) 408-2500



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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# EXHIBIT 1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**DECLARATION OF HAICHUN HUANG UNDER 37 CFR § 1.324(b)(1)**

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

Sir:

I, Haichun Huang, declare that through an error that occurred without deceptive intention on my part, I was inadvertently omitted as an inventor in the above-identified patent.

I expressly declare that I am a joint inventor of the above-identified patent.

Subscribed and executed at Milpitas, CA USA
(Place)

on 4/12/12
(Date)

Haichun Huang

# EXHIBIT 2

077375.0499
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**DECLARATION OF MARK J. SELBY UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Mark J. Selby, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

8/7/12
Dated

Mark J. Selby

NY02:739566.1

077375.0499
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : | Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : | 1207 |
| U.S. Patent No. | 8,008,449 | | | |
| Filed | : 01/29/2009 | Group Art Unit | : | 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | | |

**DECLARATION OF MOHAN SRINIVASAN UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Mohan Srinivasan, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

April 23rd 2012
Dated

Mohan Srinivasan

NY02:739562.1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | | |
|---|---|---|---|---|---|
| Applicant(s) | : | Korman *et al.* | Examiner | : | Ouspenski, Ilia I. |
| Serial No. | : | 11/913,217 | Confirmation No. | : | 1207 |
| U.S. Patent No. | | 8,008,449 | | | |
| Filed | : | 01/29/2009 | Group Art Unit | : | 1644 |
| For | : | Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | | |

**DECLARATION OF BING CHEN UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Bing Chen, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

4/24/2012
Dated

Bing Chen

NY02:739567.1

077375.0499
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : | Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : | 1207 |
| U.S. Patent No. | 8,008,449 | | | |
| Filed | : 01/29/2009 | Group Art Unit | : | 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | | |

**DECLARATION OF CHANGYU WANG UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Changyu Wang, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

4/12/12
Dated

Changyu Wang

NY02:739564.1

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**DECLARATION OF JOSEPHINE M. CARDARELLI UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Josephine M. Cardarelli, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

April 23, 2012
Dated

Josephine M. Cardarelli
Josephine M. Cardarelli



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Dana-Farber v. BMS, IPR2023-00501
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077375.0499
PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | | |
|---|---|---|---|---|
| Applicant(s) | : | Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : | 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | | 8,008,449 | | |
| Filed | : | 01/29/2009 | Group Art Unit | : 1644 |
| For | : | Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**DECLARATION OF ALAN J. KORMAN UNDER 37 CFR § 1.324(b)(2)**

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

Sir:

I, Alan J. Korman, declare that I agree to the change of inventorship in the above-identified patent to add Haichun Huang as co-inventor.

Apr. 19, 2012
Dated

Alan J. Korman

NY02:739561.1

# EXHIBIT 3

# COMBINED DECLARATION AND POWER OF ATTORNEY

## (Original, Design, National Stage of PCT, Divisional, Continuation or C-I-P Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS**

This declaration is of the following type:

- ☐ Original
- ☐ Design
- ☒ National Stage of PCT/JP2006/309606 filed May 2, 2006
- ☐ Divisional
- ☐ Continuation
- ☐ Continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b), or (c))*

(a) ☐ is attached hereto.
(b) ☒ was filed as United States Patent Application Serial No. 11/913,217 on 10/31/2007 and was amended on 10/31/2007, 3/3/2008, 9/9/2010 and 11/25/2011 *(if applicable)*.
(c) ☐ was described and claimed in PCT International Application No. _____ filed on _____ and was amended on _____ *(if applicable)*.

### Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

☐ In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

### Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

*(complete (d) or (e))*

(d) ☒ no such applications have been filed.
(e) ☐ such applications have been filed as follows:

| PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION | | | |
|---|---|---|---|
| COUNTRY APPLICATION NO. | DATE OF FILING (month, day, year) | DATE OF ISSUE (month, day, year) | PRIORITY CLAIMED UNDER 35 USC 119 |
| | | | |
| | | | |
| ALL FOREIGN APPLICATION[S], IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION | | | |
| | | | |

**Claim for Benefit of Prior U.S. Provisional Application(s)**

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

| Provisional Application Number | Filing Date |
|---|---|
| 60/679,466 | 05/09/2005 |
| 60/738,434 | 11/21/2005 |
| 60/748,919 | 12/08/2005 |
| | |
| | |

**Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120**

*(complete this part only if this is a divisional, continuation or C-I-P application)*

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

| Application Serial No. | Filing Date | Status |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

**Power of Attorney**

As a named inventor, I hereby appoint the practitioners at Customer Number **63367** of the firm of BAKER BOTTS L.L.P., with offices at 30 Rockefeller Plaza, New York, New York 10112, as attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

| SEND CORRESPONDENCE TO: | DIRECT TELEPHONE CALLS TO: |
|---|---|
| BAKER BOTTS L.L.P.<br>30 ROCKEFELLER PLAZA, NEW YORK, N.Y. 10112<br>CUSTOMER NUMBER: **63367** | BAKER BOTTS L.L.P.<br>(212) 408-2500 |



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1906 of 2058

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.

| | | | | |
|---|---|---|---|---|
| FULL NAME OF FIRST INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Korman | Alan | J. | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | Piedmont | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/9/12 | | | | |
| FULL NAME OF SECOND INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Srinivasan | Mohan | | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | San Jose | California | India | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 08/07/12 | | | | |
| FULL NAME OF THIRD INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Wang | Changyu | | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | Fremont | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/9/12 | | | | |
| FULL NAME OF FOURTH INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Selby | Mark | J. | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | San Francisco | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/7/12 | | | | |
| FULL NAME OF FIFTH INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Chen | Bing | | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | Alameda | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/7/2012 | | | | |

| | | | | |
|---|---|---|---|---|
| FULL NAME OF SIXTH INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Cardarelli | Josephine | M. | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | San Carlos | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/9/12 | Josephine M Cardarelli | | | |
| FULL NAME OF SIXTH INVENTOR | LAST NAME | FIRST NAME | MIDDLE NAME | |
| | Huang | Haichun | | |
| RESIDENCE & CITIZENSHIP | CITY | STATE or FOREIGN COUNTRY | COUNTRY OF CITIZENSHIP | |
| | San Carlos | California | United States | |
| POST OFFICE ADDRESS | POST OFFICE ADDRESS | CITY | STATE or COUNTRY | ZIP CODE |
| | 521 Cottonwood Drive | Milpitas | California | 95035 |
| DATE | SIGNATURE OF INVENTOR | | | |
| 8/7/12 | | | | |

Check proper box(es) for any added page(s) forming a part of this declaration

☒ Signature for subsequent joint inventors. Number of pages added 1.

☐ Signature by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor.
Number of pages added _____.

☐ Signature for inventor who refuses to sign, or cannot be reached, by person authorized under 37 CFR 1.47.
Number of pages added _____.

# EXHIBIT 4

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**CONSENT OF ASSIGNEE FOR CHANGE IN INVENTORSHIP PURSUANT TO 37 C.F.R. § 1.324(b)(3)**

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

Sir:

Pursuant to 37 C.F.R. § 1.324(b)(3), I, Paul Golian, as Assistant General Counsel on behalf of Medarex, Inc., hereby consent to the addition of Haichun Huang as inventor to the above-identified patent. Medarex, Inc. is the owner of the above-identified patent by virtue of an assignment recorded at the U.S. Patent & Trademark office on October 31, 2007 at Reel/Frame 020043/0830.

I hereby state under 37 CFR 3.73(b)(2)(i) that I am authorized to act on behalf of the assignee, Medarex, Inc, as indicated in the attached certification.

April 9, 2012
Dated

Paul Golian
Assistant General Counsel
On Behalf of Medarex, Inc.

# EXHIBIT 5

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | | |
|---|---|---|---|
| Applicant(s) | : Korman *et al.* | Examiner | : Ouspenski, Ilia I. |
| Serial No. | : 11/913,217 | Confirmation No. | : 1207 |
| U.S. Patent No. | 8,008,449 | | |
| Filed | : 01/29/2009 | Group Art Unit | : 1644 |
| For | : Human Monoclonal Antibodies To Programmed Death 1 (PD-1) And Methods For Treating Cancer Using Anti-PD-1 Antibodies Alone Or In Combination With Other Immunotherapeutics | | |

**CONSENT OF ASSIGNEE FOR CHANGE IN INVENTORSHIP PURSUANT TO 37 C.F.R. § 1.324(b)(3)**

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

Sir:

Pursuant to 37 C.F.R. § 1.324(b)(3), I, Kazuhito Kawabata, as Member of the Board of Directors, Executive Officer, and Executive Director, Discovery and Research, on behalf of Ono Pharmaceutical Co., Ltd., hereby consents to the addition of Haichun Huang as inventor to the above-identified patent. Ono Pharmaceutical Co., Ltd. is the co-owner of the above-identified patent by virtue of an assignment recorded at the U.S. Patent & Trademark office on June 9, 2009 at Reel/Frame 022800/0283.

11 April, 2012
Dated

Kazuhito Kawabata, Ph.D.
Member of the Board of Directors
Executive Officer
Executive Director, Discovery and Research
On Behalf of Ono Pharmaceutical Co., Ltd.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1912 of 2058

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 11913217 |
| **Filing Date:** | 29-Jan-2009 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Filer:** | Lisa Tyner/chanelle rogers |
| **Attorney Docket Number:** | 077375.0499 |

Filed as Large Entity

## U.S. National Stage under 35 USC 371 Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| Petition fee- 37 CFR 1.17(h) (Group III) | 1464 | 1 | 130 | 130 |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | **Total in USD ($)** | | **130** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 13544890 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Lisa Tyner/chanelle rogers |
| **Filer Authorized By:** | Lisa Tyner |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 21-AUG-2012 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 13:57:26 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## Payment information:

| | |
|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $130 |
| RAM confirmation Number | 280 |
| Deposit Account | 024377 |
| Authorized User | |
| The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:<br>Charge any Additional Fees required under 37 C.F.R. Section 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 | | 0499Petition.pdf | 537794<br>1aea109c82aae01be4cea1aa2a95bfe2c810d79d | yes | 23 |

| Multipart Description/PDF files in .zip description | | |
|---|---|---|
| **Document Description** | **Start** | **End** |
| Transmittal Letter | 1 | 1 |
| Fee Worksheet (SB06) | 2 | 2 |
| Petition for review by the Office of Petitions. | 3 | 23 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30596<br>21fbadab775361fa7a8e747a23005dd48ef9221a | no | 2 |

**Warnings:**

**Information:**

| Total Files Size (in bytes): | 568390 |
|---|---|

**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/SB/21 (10-07)
Approved for use through 10/31/2007. 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.

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

Total Number of Pages in This Submission

| | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Art Unit | 1644 |
| Examiner Name | Ouspenski, Ilia I. |
| Attorney Docket Number | 077375.0499 |

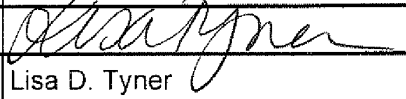
## ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Petition To Correct Inventorship Pursuant To 37 C.F.R. 1.324(a)

Remarks

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Baker Botts L.L.P. | | |
| Signature |  | | |
| Printed name | Lisa D. Tyner | | |
| Date | 08/21/2012 | Reg. No. | 51,619 |

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

| | | | |
|---|---|---|---|
| Signature | | | |
| Typed or printed name | | Date | |

This collection of information is required by 37 CFR 1.5. 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 and1.14. This collection is estimated to 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, 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.*

# FEE TRANSMITTAL

| Complete if Known | |
|---|---|
| Application Number | 11/913,217 |
| Filing Date | 01/29/2009 |
| First Named Inventor | Korman et al. |
| Examiner Name | Ouspenski, Ilia I. |
| Art Unit | 1644 |
| Attorney Docket No. | 077375.0499 |

☐ Applicant claims small entity status. See 37 CFR 1.27

| TOTAL AMOUNT OF PAYMENT | ($) 130 |
|---|---|

## METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 02-4377

Deposit Account Name: Baker Botts L.L.P.

**The Director is authorized to:** *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

## FEE CALCULATION

### Extra Claim Fees

| | Extra Claims | | Fee | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | x | 60 | = | $0 |
| Independent Claims | | x | 250 | = | $0 |
| Multiple Dependent | | | | = | $0 |

SUBTOTAL $0

| Fee Description | Large Entity | Small Entity |
|---|---|---|
| Claims in excess of 20 | 60 | 30 |
| Independent claims in excess of 3 | 250 | 125 |
| Multiple dependent claim, if not paid | 450 | 225 |

## FEE CALCULATION (continued)

### ADDITIONAL FEES

| | |
|---|---|
| ☐ Surcharge - late oath or filing fee | |
| ☐ Non-English Specification | |
| ☐ Extension for reply within first month | |
| ☐ Extension for reply within second month | |
| ☐ Extension for reply within third month | |
| ☐ Extension for reply within fourth month | |
| ☐ Extension for reply within fifth month | |
| ☐ Notice of Appeal | |
| ☐ Filing a brief in support of an appeal | |
| ☐ Petition to revive - unavoidable | |
| ☐ Petition to revive - unintentional | |
| ☐ Utility Issue Fee | |
| ☐ Design Issue Fee | |
| ☐ Publication Fee | |
| ☐ Petitions to the Commissioner | |
| ☐ Request for Continued Examination (RCE) | |
| ☐ Information Disclosure Statement (IDS) | |
| Other fee - Petition To Correct Inventorship Pursuant To 37 CFR 1.324(a) | $130 |

SUBTOTAL ($) 130

| SUBMITTED BY | | | | (Complete *(if applicable)*) | |
|---|---|---|---|---|---|
| *Name (Print/Type)* | Lisa D. Tyner | *Registration No. (Attorney/Agent)* | 51,619 | *Telephone* | 212-408-2500 |
| *Signature* | | | | *Date* | 08/21/2012 |

**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 1.17 and 1.27. 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.**

## POWER OF ATTORNEY FROM MULTIPLE ASSIGNEES

(1) MEDAREX, L.L.C., a corporation of United States, having a principal place of business at Route 206 and Province Line Road, Princeton, NJ 08540 and (2) ONO PHARMACEUTICAL CO., LTD., a company of JAPAN, having a principal place of business at 1-5, Doshomachi 2-Chrome, Chuo-Ku, Osaka-Shi, Osaka, 541-8526 JAPAN, are, collectively, assignees of the entire right, title and interest for the United States of America (as defined in 35 U.S.C. § 100), by reason of Assignments executed to Assignee (1) MEDAREX, L.L.C., and to Assignee (2) ONO PHARMACEUTICAL CO., LTD., on June 20, 2007, June 21, 2007, June 25, 2007, June 26, 2007, December 27, 2007, April 12, 2012, and December 31, 2012, of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies** that is disclosed and claimed in a patent application of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, and Selby, Mark J., (said application having a filing date of May 9, 2005, at the U.S. Patent and Trademark Office, and having Application Number **60/679,466,** (Atty. Dkt. No. 3338.0180000/ELE/C-K/BMB)), of an invention known as **Combined Use of CTLA-4 Antibody and PD-1 Antibody For Treatment of Hyperproliferative Disease** that is disclosed and claimed in patent applications of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, and Cardarelli, Josephine M. (an application having a filing date of December 8, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/748,919** (Atty. Dkt. No. 3338.01800021/ELE/C-K/BMB), and another application having a filing date of November 21, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/738,434** (Atty. Dkt. No. 3338.0180001/ELE/C-K/BMB), of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination With Other Immunotherapeutics** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on August 30, 2011, at the U.S. Patent and Trademark Office, and having Patent Number **8,008,449** (Atty. Dkt. No. 3338.0180003/ELE/C-K/BMB)), and of an invention known as **Monoclonal Antibodies to Programmed Death 1 (PD-1)** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on July 15, 2014, at the U.S. Patent and Trademark Office, and having Patent Number **8,779,105** (Atty. Dkt. No. 3338.0180004/ELE/C-K/BMB)).

For the purpose of PAIR, the **Customer Number is 115018**.

The Assignees hereby appoint the practitioners associated with **CUSTOMER NUMBER 115018** as our attorneys or agents to prosecute the application identified above, and any continuation, divisional, continuation-in-part, or reissue application thereof, and to transact all business in the U.S. Patent and Trademark Office connected therewith. The Assignees hereby grant said practitioners associated with **CUSTOMER NUMBER 115018** the power to insert on this Power of Attorney any further identification that may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1919 of 2058

Send correspondence to:

CUSTOMER NUMBER 115018

Direct phone calls to 202-371-2600.

FOR: MEDAREX, L.L.C.
SIGNATURE:
BY: Paul D. Golian
TITLE: Vice President & Assistant General Cnsl.
DATE: Jul 23, 2014

FOR: ONO PHARMACEUTICAL CO., LTD
SIGNATURE:
BY: Kazuhito Kawabata
TITLE: Member of the Board of Directors Executive Officer
Executive Director, Discovery and Research
DATE: July 28, 2014



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
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PTO/SB/96 (07-09)
Approved for use through 07/31/2012. 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.

## STATEMENT UNDER 37 CFR 3.73(b)

Atty. Docket No. 3338.0180003/ELE/C-K/BMB

Applicant/Patent Owner: KORMAN et al.

Application No./Patent No.: 8,008,449 Filed/Issue Date: August 30, 2011

Titled: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

Ono Pharmaceutical Co., LTD. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;

2. ☒ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is 50 %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

**OR**

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

KORMAN, Alan J. SRINIVASAN, Mohan, WANG, Changyu

1. From: SELBY, Mark, J., CHEN, Bing, CARDARELLI, Josephine M. To: Medarex, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 020043, Frame 0830, or for which a copy thereof is attached.

2. From: Medarex Inc. To: Ono Pharmaceutical Co., LTD.

The document was recorded in the United States Patent and Trademark Office at
Reel 022792, Frame 0026, or for which a copy thereof is attached.

3. From: Medarex, Inc. To: Ono Pharmaceutical Co., LTD.

The document was recorded in the United States Patent and Trademark Office at
Reel 022800, Frame 0283, or for which a copy thereof is attached.

☒ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature October 2, 2014
Date

Ji-Eun Kim, Reg. No. 68,504 Attorney for Applicants
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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*



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1921 of 2058

# Supplemental Sheet to Chain of Title, Item B of the Statement Under 37 CFR 3.73(b) (PTO/SB/96)

Applicant/Owner: KORMAN et al.

Application No./Patent No.: 8,008,449

Application Date/Issue Date: August 30, 2011

Title: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

Name of Assignee: Ono Pharmaceutical Co., LTD. Type of Assignee: Corporation

**Supplemental Sheet to Part B: Continuation of the chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:**

4. From: HUANG, Haichun To: Medarex, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 028820, Frame 0044, or for which a copy thereof is attached.

5. From: Medarex, Inc. To: Medarex, L.L.C.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 032347, Frame 0262, or for which a copy thereof is attached.

6. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

7. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

8. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

9. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

10. From: _____ To: _____
    The document was recorded in the United States Patent and Trademark Office at
    Reel _____, Frame _____, or for which a copy thereof is attached.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. 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.

# STATEMENT UNDER 37 CFR 3.73(b)

Atty. Docket No. 3338.0180003/ELE/C-K/BMB

Applicant/Patent Owner: KORMAN et al.

Application No./Patent No.: 8,008,449 Filed/Issue Date: August 30, 2011

Titled: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

Medarex, L.L.C. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;

2. ☒ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is 50 %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

KORMAN, Alan J. SRINIVASAN, Mohan, WANG, Changyu

1. From: SELBY, Mark, J., CHEN, Bing, CARDARELLI, Josephine M. To: Medarex, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 020043, Frame 0830, or for which a copy thereof is attached.

2. From: Medarex, Inc. To: Ono Pharmaceutical Co., LTD.

The document was recorded in the United States Patent and Trademark Office at
Reel 022792, Frame 0026, or for which a copy thereof is attached.

3. From: Medarex, Inc. To: Ono Pharmaceutical Co., LTD.

The document was recorded in the United States Patent and Trademark Office at
Reel 022800, Frame 0283, or for which a copy thereof is attached.

☒ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — October 2, 2014 (Date)

Ji-Eun Kim, Reg. No. 68,504 (Printed or Typed Name) — Attorney for Applicants (Title)

This collection of information is required by 37 CFR 3.73(b). 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.*

# Supplemental Sheet to Chain of Title, Item B of the Statement Under 37 CFR 3.73(b) (PTO/SB/96)

Applicant/Owner: KORMAN et al.

Application No./Patent No.: 8,008,449

Application Date/Issue Date: August 30, 2011

Title: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

Name of Assignee: Medarex, L.L.C. Type of Assignee: Corporation

**Supplemental Sheet to Part B: Continuation of the chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:**

4. From: HUANG, Haichun To: Medarex, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 028820, Frame 0044, or for which a copy thereof is attached.

5. From: Medarex, Inc. To: Medarex, L.L.C.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 032347, Frame 0262, or for which a copy thereof is attached.

6. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at
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7. From: _____ To: _____
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    Reel _____, Frame _____, or for which a copy thereof is attached.

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 20313883 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Ji Eun Kim/Dana Bennett Jackson |
| **Filer Authorized By:** | Ji Eun Kim |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 02-OCT-2014 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 16:15:45 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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 | | 33380180003.pdf | 959966<br>a883b32d59ddebc2c5055bcea08cbac0a4429598 | yes | 7 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Miscellaneous Incoming Letter | 1 | 1 |
| | Power of Attorney | 2 | 3 |
| | Assignee showing of ownership per 37 CFR 3.73. | 4 | 5 |
| | Assignee showing of ownership per 37 CFR 3.73. | 6 | 7 |
| **Warnings:** | | | |
| **Information:** | | | |
| | **Total Files Size (in bytes):** | 959966 | |

**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.**

JI-EUN KIM
DIRECTOR
(202) 772-8619
CKIM@SKGF.COM

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

October 2, 2014

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

*Confirmation No. 1207*
*Art Unit 1644*

Re: U.S. Patent No. 8,008,449; Issue Date: August 30, 2011
(from U.S. Appl. No. 11/913,217; Int'l Filing Date: May 2, 2006)
For: **HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS**
Inventor: KORMAN *et al.*
Our Ref: 3338.0180003/ELE/C-K/BMB

Commissioner:

Transmitted herewith for appropriate action are the following documents:

1. Power Of Attorney From Multiple Assignees;

2. Statement Under 37 C.F.R. § 3.73(b) for Medarex, L.L.C.; and

3. Statement Under 37 C.F.R. § 3.73(b) for Ono Pharmaceutical Co., LTD.

The above-listed documents are filed electronically through EFS-Web.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Ji-Eun Kim
Attorney for Applicants
Registration No. 68,504

C-K/BMB/bls
Enclosures

1876628_1.DOCX



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1927 of 2058

Doc Code: N572

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Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 |

**CONFIRMATION NO. 1207**

*OC000000071158534*

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

Cc: STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE NW
WASHINGTON, DC 20005

Date Mailed: **10/03/2014**

## DENIAL OF REQUEST FOR POWER OF ATTORNEY

The request for Power of Attorney filed **10/02/2014** is acknowledged. However, the request cannot be granted at this time for the reason stated below.

☐ The Power of Attorney you provided did not comply with the new Power of Attorney rules that became effective on June 25, 2004. See 37 CFR 1.32.

☐ The revocation is not signed by the applicant, the assignee of the entire interest, or one particular principal attorney having the authority to revoke.

☑ The Power of Attorney is from an assignee and the Certificate required by 37 CFR 3.73(c) has not been received.

☐ The person signing for the assignee has omitted their empowerment to sign on behalf of the assignee.

☐ The inventor(s) is without authority to appoint attorneys since the assignee has intervened as provided by 37 CFR 3.71.

☐ The signature(s) of _____, co-inventor(s) in this application, has been omitted. The Power of Attorney will be entered upon receipt of confirmation signed by said co-inventor(s).

☐ The person(s) appointed in the Power of Attorney is not registered to practice before the U.S. Patent and Trademark Office.

☐ Only one Customer Number can be designated for the Power of Attorney in an application. The Customer Number that was captured is the first Customer Number provided on the Power of Attorney document.

☐ A request under 37 CFR 1.48 to add an inventor was granted in this application, however, no power of attorney consistent with the power of attorney granted by the originally named inventive entity has been

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received. Thus, the addition of the inventor has resulted in the loss of power of attorney in the application. See 37 CFR 1.32(e).

- ☐ The power of attorney has not been accepted because the party who is giving power of attorney has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A patent owner who was not the applicant must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).
- ☐ The power of attorney from the inventors has not been accepted because it is a copy from a prior national application for which benefit is claimed and the continuing application names an inventor who was not named as an inventor in the prior application.
- ☐ The power of attorney from the inventors has not been accepted because the power of attorney must be signed by the applicant for patent. See 37 CFR 1.32(b)(4).
- ☐ Any request to correct or update the name of the applicant must include an application data sheet (ADS) in compliance with 37 CFR 1.76 specifying the correct or updated name of the applicant in the applicant information section. Any request to change the applicant after an original applicant has been specified under 37 CFR 1.46(b) must include a new ADS in compliance with 37 CFR 1.76 specifying the applicant in the applicant information section and comply with 37 CFR 3.71 and 3.73. See 37 CFR 1.46(c).

Any inquiries regarding this notice should be directed to the Application Assistance Unit at 571-272-4200.

MB

Application Assistance Unit
571-272-4200

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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 |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 |

**CONFIRMATION NO. 1207**

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

**MISCELLANEOUS NOTICE**

*OC000000071158534*

Date Mailed: 10/06/2014

A communication which cannot be delivered in electronic form has been mailed to the applicant.

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COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
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ALEXANDRIA, VA 22313-1450
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*In re* Patent No. KORMAN ET AL.
Issue Date: August 30 2011
Appl No.: 11/913,217
Filed: January 29, 2009

**DECISION GRANTING PETITION**
*37 CFR 1.324*

This is a decision on the petition filed August 21 2012 to correct inventorship under 37 CFR 1.324.

The petition is granted.

The patented file is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

Daniel Kolker
Supervisory Patent Examiner
Art Unit 1644
Technology Center 1600

BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

## POWER OF ATTORNEY FROM MULTIPLE ASSIGNEES

(1) MEDAREX, L.L.C., a corporation of United States, having a principal place of business at Route 206 and Province Line Road, Princeton, NJ 08540 and (2) ONO PHARMACEUTICAL CO., LTD., a company of JAPAN, having a principal place of business at 1-5, Doshomachi 2-Chrome, Chuo-Ku, Osaka-Shi, Osaka, 541-8526 JAPAN, are, collectively, assignees of the entire right, title and interest for the United States of America (as defined in 35 U.S.C. § 100), by reason of Assignments executed to Assignee (1) MEDAREX, L.L.C., and to Assignee (2) ONO PHARMACEUTICAL CO., LTD., on June 20, 2007, June 21, 2007, June 25, 2007, June 26, 2007, December 27, 2007, April 12, 2012, and December 31, 2012, of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies** that is disclosed and claimed in a patent application of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, and Selby, Mark J., (said application having a filing date of May 9, 2005, at the U.S. Patent and Trademark Office, and having Application Number **60/679,466,** (Atty. Dkt. No. 3338.0180000/ELE/C-K/BMB)), of an invention known as **Combined Use of CTLA-4 Antibody and PD-1 Antibody For Treatment of Hyperproliferative Disease** that is disclosed and claimed in patent applications of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, and Cardarelli, Josephine M. (an application having a filing date of December 8, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/748,919** (Atty. Dkt. No. 3338.01800021/ELE/C-K/BMB), and another application having a filing date of November 21, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/738,434** (Atty. Dkt. No. 3338.0180001/ELE/C-K/BMB), of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination With Other Immunotherapeutics** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on August 30, 2011, at the U.S. Patent and Trademark Office, and having Patent Number **8,008,449** (Atty. Dkt. No. 3338.0180003/ELE/C-K/BMB)), and of an invention known as **Monoclonal Antibodies to Programmed Death 1 (PD-1)** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Sellby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on July 15, 2014, at the U.S. Patent and Trademark Office, and having Patent Number **8,779,105** (Atty. Dkt. No. 3338.0180004/ELE/C-K/BMB)).

For the purpose of PAIR, the **Customer Number is 115018**.

The Assignees hereby appoint the practitioners associated with **CUSTOMER NUMBER 115018** as our attorneys or agents to prosecute the application identified above, and any continuation, divisional, continuation-in-part, or reissue application thereof, and to transact all business in the U.S. Patent and Trademark Office connected therewith. The Assignees hereby grant said practitioners associated with **CUSTOMER NUMBER 115018** the power to insert on this Power of Attorney any further identification that may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office.



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1932 of 2058

Send correspondence to:

CUSTOMER NUMBER 115018

Direct phone calls to 202-371-2600.

FOR: MEDAREX, L.L.C.
SIGNATURE:
BY: Paul D. Golian
TITLE: Vice President & Assistant General Cnsl.
DATE: July 23, 2014

FOR: ONO PHARMACEUTICAL CO., LTD
SIGNATURE:
BY: Kazuhito Kawabata
TITLE: Member of the Board of Directors Executive Officer
Executive Director, Discovery and Research
DATE: July 28, 2014

PTO/SB/96 (07-09)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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## STATEMENT UNDER 37 CFR 3.73(b)

Atty. Dkt No. 3338.0180003/ELE/C-K/E-H

Applicant/Patent Owner: KORMAN et al.

Application No./Patent No.: 8,008,449 Filed/Issue Date: August 30, 2011

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(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

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[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Ji-Eun Kim, #68,504/ October 21, 2014
Signature Date

Ji-Eun Kim, Reg. No. 68,504 Attorney for Applicants
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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.**



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Ono Pharmaceutical Co., LTD. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

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(The extent (by percentage) of its ownership interest is 50 %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

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OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:
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The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Ji-Eun Kim, #68,504/ October 21, 2014
Signature Date

Ji-Eun Kim, Reg. No. 68,504 Attorney for Applicants
Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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.*

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 20479520 |
| **Application Number:** | 11913217 |
| **International Application Number:** | |
| **Confirmation Number:** | 1207 |
| **Title of Invention:** | HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS |
| **First Named Inventor/Applicant Name:** | Alan J. Korman |
| **Customer Number:** | 63367 |
| **Filer:** | Ji Eun Kim/Mark Koper |
| **Filer Authorized By:** | Ji Eun Kim |
| **Attorney Docket Number:** | 077375.0499 |
| **Receipt Date:** | 21-OCT-2014 |
| **Filing Date:** | 29-JAN-2009 |
| **Time Stamp:** | 19:05:50 |
| **Application Type:** | U.S. National Stage under 35 USC 371 |

## 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 | Miscellaneous Incoming Letter | 3338-018-3-CL-.pdf | 154501<br>b49e3c19313f113459b8014f0567ebdb4908c371 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| 2 | Power of Attorney | 3338-018-3-POA.pdf | 378049<br>d6274343aea46fc0f1ada9a06ee3603188a81c83 | no | 2 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Assignee showing of ownership per 37 CFR 3.73. | 3338-018-3-medarex373.pdf | 128245<br>9851d7f8ff5207df8c41bf740b081b03e5880a38 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Assignee showing of ownership per 37 CFR 3.73. | 3338-018-3-Ono373.pdf | 128214<br>4960f60ad537483b986b200b872f45f14a1bcaa9 | no | 1 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 789009 | | |

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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.**

JI-EUN KIM
DIRECTOR
(202) 772-8619
CKIM@SKGF.COM

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

October 21, 2014

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

***Confirmation No. 1207***
***Art Unit 1644***

Re: U.S. Patent No. 8,008,449; Issue Date: August 30, 2011
(from U.S. Appl. No. 11/913,217; Int'l Filing Date: May 2, 2006)
For: **HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS**
Inventor: KORMAN *et al*.
Our Ref: 3338.0180003/ELE/C-K/E-H

Commissioner:

Transmitted herewith for appropriate action are the following documents:

1. Power Of Attorney From Multiple Assignees;

2. Statement Under 37 C.F.R. § 3.73(b) for Medarex, L.L.C.; and

3. Statement Under 37 C.F.R. § 3.73(b) for Ono Pharmaceutical Co., LTD.

The above-listed documents are filed electronically through EFS-Web. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Pursuant to Erin Heenan's telephone conversation with N. Tang (Ref. No. 1-314-216294) on October 21, 2014, the additional references to assignments to Medarex, L.L.C previously included on the Supplemental Sheet are not included in the Statement Under 37 C.F.R. § 3.73(b) for Ono Pharmaceutical Co., LTD. Additionally, the references to assignments to Ono Pharmaceutical Co., LTD. are not included on the Statement Under 37 C.F.R. § 3.73(b) for Medarex, L.L.C.



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Page 1938 of 2058

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Ji-Eun Kim
Attorney for Applicants
Registration No. 68,504

C-K/E-H/mik
Enclosures

1918835_1.DOCX



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1939 of 2058

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 077375.0499 |

**CONFIRMATION NO. 1207**

63367
BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44th Floor
NEW YORK, NY 10112-4498

**POWER OF ATTORNEY NOTICE**

*OC000000071527341*

Date Mailed: 10/24/2014

## NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/21/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/deelliott/

Office of Data Management, 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
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| APPLICATION NUMBER | FILING OR 371(C) DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO./TITLE |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 3338.018003./ELE/C-K/E |

**CONFIRMATION NO. 1207**

115018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

**POA ACCEPTANCE LETTER**

*OC000000071527452*

Date Mailed: 10/24/2014

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/21/2014.

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.

/deelliott/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

**UNITED STATES PATENT AND TRADEMARK OFFICE**
**Certificate**

Patent No. 8,008,449 B2 Patented: August 30, 2011

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without any deceptive intent, improperly sets forth the inventorship.

Accordingly, it is hereby certified that the correct inventorship of this patent is: Alan J. Korman, Piedmont, CA (US); Mohan Srinivasan, San Jose, CA (US); Changyu Wang, Fremont, CA (US); Mark J. Selby, San Franscisco, CA (US); Bingliana Chen, Alameda, CA (US); and Josephine M. Cardarelli, San Carlos, CA (US); Haichun Huang, San Carlos, CA (US).

Signed and Sealed this Eleventh Day of November 2014.

EDAN ORGAD
*Supervisory Patent Examiner*
Art Unit 2414
Technology Center 2400

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 8,008,449 B2

Issued: August 30, 2011

Applicants: E.R. Squibb & Sons, L.L.C. and Ono Pharmaceutical Co., Ltd.

For: **HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS**

01/13/2016 GARTAS 02000002 190036 11913217
Sale Ref: 02000002 DAN: 190036 11913217
01 FC:1457 1120.00 DA

Atty. Docket: 3338.0180003/ELE/C-K

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PATENT EXTENSION
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Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

**FEE TRANSMITTAL LETTER**
**FOR AN APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Commissioner:

Transmitted herewith is an Application for Extension of Patent Term Under 35 U.S.C. § 156 for U.S. Patent No. 8,008,449, accompanied by two additional copies. The undersigned attorney for Applicants hereby states that these copies are certified to be duplicates of the original. Each copy contains the following attachments:

| | |
|---|---|
| Exhibit 1 | U.S. Patent No. 8,008,449 B2 |
| Exhibit 2 | Chain of title for U.S. Patent No. 8,008,449 B2 |
| Exhibit 3 | Bristol-Myers Squibb Company's authorization letter |
| Exhibit 4 | Notice of Acceptance of Power of Attorney, Executed Power of Attorney, and Statement Under 37 C.F.R. § 3.73(b) |
| Exhibit 5 | OPDIVO™ Approved Label |
| Exhibit 6 | FDA Approval Letter for OPDIVO™ |
| Exhibit 7 | Certificate of Correction for U.S. Patent No. 8,008,449 B2 (December 20, 2011) |

| | |
|---|---|
| Exhibit 8 | Certificate of Correction for U.S. Patent No. 8,008,449 B2 (November 11, 2014) |
| Exhibit 9 | Maintenance Fee Payment Record |
| Exhibit 10 | FDA letter acknowledging IND No. 100052 |
| Exhibit 11 | FDA letter acknowledging BLA 125554 |
| Exhibit 12 | Significant Activities During the Applicable Regulatory Review Period |

Please find a Credit Card payment Form for the $1,120.00 fee estimated to be due in connection with this Application. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Sterne, Kessler, Goldstein & Fox P.L.L.C. Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Ji-Eun Kim
Reg. No. 68,504

for Eldora L. Ellison
Attorney for Applicants
Registration No. 39,967

Date: Feb. 13, 2015

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

1965722_1.docx

PTO-2038 (12-2013)
Approved for use through 11/30/2014. OMB 0651-0043
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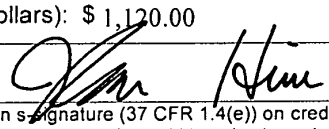
**Credit Card Type:** ☐ Visa ☐ MasterCard ☒ American Express ☐ Discover

Credit Card Account #: 3785 727438 01005

Credit Card Expiration Date (mm/yyyy): 08/2017

Name as it Appears on Credit Card: SKGF PLLC

Payment Amount (US Dollars): $ 1,120.00

Cardholder Signature:  Date (mm/dd/yyyy): 02/13/2015

The USPTO does not accept an s-signature (37 CFR 1.4(e)) on credit card payment forms.
**Refund Policy:** The USPTO may refund a fee paid by mistake or in excess of that required. A change of purpose after the payment of a fee will not entitle a party to a refund of such fee. The USPTO will not refund amounts of $25.00 or less unless a refund is specifically requested and will not notify the payor of such amounts (37 CFR 1.26). Refund of a fee paid by credit card will be issued as a credit to the credit card account to which the fee was charged.
**Maximum Daily Limit:** There is a $49,999.99 daily limit per credit card account. There is no daily limit for debit cards.

## Credit Card Billing Address

Street Address 1: Sterne, Kessler, Goldstein & Fox P.L.L.C.

Street Address 2: 1100 New York Avenue, N.W.

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Country: U.S.A.

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## Request and Payment Information

Description of Request and Payment Information:

$1,120.00 - Application for Extension of Patent Term Under 35 U.S.C. § 156

| ☒ Patent Fee | ☐ Patent Maintenance Fee | ☐ Trademark Fee | ☐ Other Fee |
|---|---|---|---|
| Application No. 11/913,217 | Application No. | Application No. | IDON Customer No. |
| Patent No. 8,008,449 B2 | Patent No. | Registration No. | |
| Attorney Docket No. 3338.0180003/ELE/C-K | | Identify or Describe Mark | |

***If the cardholder includes a credit card number on any form or document other than the Credit Card Payment Form or submits this form electronically via EFS-Web, the United States Patent and Trademark Office will not be liable in the event that the credit card number becomes public knowledge.***

1965644

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re United States Patent of:

E. R. Squibb & Sons, L.L.C. and Ono Pharmaceutical Co., Ltd.

Patent No.: 8,008,449 B2

Issued: August 30, 2011

For: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

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

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156**

Madam or Sir:

Applicants E. R. Squibb & Sons, L.L.C. ("E. R. Squibb") and Ono Pharmaceutical Co., Ltd. ("Ono") hereby submit this application for extension of U.S. Patent No. 8,008,449 B2 ("the '449 patent") (Exhibit 1) under 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791.

E. R. Squibb represents that it is the record owner of a 50% interest in the '449 patent by virtue of (1) an assignment from inventors Alan J. Korman, Mohan Srinivasan, Changyu Wang, Mark J. Selby, Bingliang Chen, and Josephine M. Cardarelli to Medarex, Inc., recorded on October 31, 2007 at Reel 020043, Frame 0830 (the spelling of inventor Bingliang Chen's name in this recordation was corrected by a corrective assignment, recorded on December 19, 2014 at

Reel 034683, Frame 0398), (2) an assignment from inventor Haichun Huang to Medarex, Inc., recorded on August 21, 2012 at Reel 028820, Frame 0044, (3) a merger that transferred ownership from Medarex, Inc. to Medarex, L.L.C., recorded on March 4, 2014 at Reel 032347, Frame 0262, and (3) a merger that transferred ownership from Medarex, L.L.C. to E. R. Squibb, recorded on November 7, 2014 at Reel 034126, Frame 0342. *Exhibit 2* provides the chain of title.

Ono is also the record owner of a 50% interest in the '449 patent by virtue of an assignment from Medarex, Inc. to Ono, recorded on June 8, 2009 at Reel 022792, Frame 0026 (the application number of this recordation was corrected by a corrective assignment, recorded on June 9, 2009 at Reel 022800, Frame 0283) (see Exhibit 2).

The approved product that is relevant to this application is OPDIVO™ (nivolumab) injection, for intravenous infusion, referred to herein as "OPDIVO" or "Approved Product."

The Marketing Applicant for OPDIVO is Bristol-Myers Squibb Company ("BMS"). E. R. Squibb is a wholly-owned subsidiary of BMS. E.R. Squibb and Ono are authorized to rely on the activities of BMS, its predecessors and affiliates, for purposes of this patent term extension application (see *Exhibit 3*).

The undersigned Attorneys for Applicants are authorized to act on behalf of the Applicants. Copies of the executed Power of Attorney, Statements Under 37 C.F.R § 3.73(b), and Notice of Acceptance of Power of Attorney are attached (see *Exhibit 4*).

The following information is submitted in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term (§§1.710 to 1.791) and follows the numerical format set forth in 37 C.F.R. §1.740.



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Dana-Farber v. BMS, IPR2023-00501
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**(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:**

The Approved Product is OPDIVO (nivolumab), an injection for intravenous infusion of the active ingredient nivolumab, available in two dosage forms, namely, 40 mg/4 ml (10 mg/mL) and 100 mg/10 mL (10 mg/mL). OPDIVO has been approved for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (approved labeling attached as *Exhibit 5*). Nivolumab is an isolated, human, monoclonal antibody that blocks programmed death receptor 1 (PD-1). It is comprised of 1,308 amino acids. Table 1 shows the amino acid sequence for nivolumab.

**Table 1**

| Antibody Segment | Amino Acid Sequence* |
|---|---|
| Heavy Chain Variable Region<br><br>(SEQ ID NO:4 of the '449 patent; see Fig. 4A of the '449 patent) | QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQ APGKGLEWVAVIWYDGSKRYYADSVKGRFTISRDNSKNTL FLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSS |
| Heavy Chain Constant Region | ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTC NVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG K |
| Light Chain Variable Region<br><br>(SEQ ID NO:11 of the '449 patent; see Fig. 4B of the '449 patent) | EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPG QAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQSSNWPRTFGQGTKVEIK |
| Light Chain Constant Region | RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC |



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Dana-Farber v. BMS, IPR2023-00501
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* The one-letter amino acid code used in the tables in this paper follows the nomenclature developed by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochmistry and Molecular Biology (IUB) in the IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN). See "Nomenclature and Symbolism for Amino Acids and Peptides," http://www.chem.qmul.ac.uk/iupac/AminoAcid/AA1n2.html#AA1 (1983) (last visited February 4, 2015).

Nivolumab's heavy chain and light chain variable regions (see Table 1) include framework regions (FRs) and complementarity determining regions (CDRs) (see Table 2).

**Table 2**

| Antibody Segment | Amino Acid Sequence |
|---|---|
| **Heavy Chain Variable Region** | |
| FR1 | QVQLVESGGGVVQPGRSLRLDCKASGITFS |
| CDR1 (SEQ ID NO:18 of the '449 patent; see Fig. 4A of the '449 patent) | NSGMH |
| FR2 | WVRQAPGKGLEWVA |
| CDR2 (SEQ ID NO:25 of the '449 patent; see Fig. 4A of the '449 patent) | VIWYDGSKRYYADSVKG |
| FR3 | RFTISRDNSKNTLFLQMNSLRAEDTAVYYCA T |
| CDR3 (SEQ ID NO:32 of the '449 patent; see Fig. 4A of the '449 patent) | NDDY |
| FR4 | WGQGTLVTVSS |
| **Light Chain Variable Region** | |
| FR1 | EIVLTQSPATLSLSPGERATLSC |
| CDR1 (SEQ ID NO:39 of the '449 patent; see Fig. 4B of the '449 patent) | RASQSVSSYLA |
| FR2 | WYQQKPGQAPRLLIY |
| CDR2 (SEQ ID NO:46 of the '449 patent; see Fig. 4B of the '449 patent) | DASNRAT |
| FR3 | GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC |
| CDR3 (SEQ ID NO:53 of the '449 patent; see Fig. 4B of the '449 patent) | QQSSNWPRT |
| FR4 | FGQGTKVEIK |

Nivolumab's heavy chain variable region comprises a sequence derived from a human $V_H$ 3-33 germline sequence. Its light chain variable region comprises a sequence derived from a human $V_K$ L6 germline sequence. It is an $IgG_4$ isotype antibody.



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Dana-Farber v. BMS, IPR2023-00501
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Nivolumab specifically binds to PD-1, inhibits the suppression of CD4+ CD25- T cells by regulatory T cells, enhances the antigen specific memory response to a tumor, confers a persistent immunity to tumor relapse, and has neither ADCC activity nor CDC activity.

OPDIVO is supplied as a sterile solution containing mannitol, pentenic acid, polysorbate 80, sodium chloride, sodium citrate dehydrate, and Water for Injection that may also contain hydrochloric acid and/or sodium hydroxide to adjust the pH. Before administration, it is diluted with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

**(2) A complete identification of the federal statute including the applicable provision of law under which the regulatory review occurred:**

The Approved Product is a drug product that was approved under section 351 of the Public Health Service Act (PHSA) (42 U.S.C. §262).

**(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:**

The FDA approved OPDIVO (nivolumab) for commercial marketing or use on December 22, 2014. A copy of the approval letter is attached as *Exhibit 6*.

**(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug And Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved: (37 C.F.R. § 1.740(a)(4))**

The active ingredient in OPDIVO is nivolumab. Nivolumab has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the PHSA, or the Virus-Serum-Toxin Act (either alone or in combination with other active ingredients).



Dana-Farber EX1017
Dana-Farber v. BMS, IPR2023-00501
Page 1950 of 2058

**(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to section 1.720(f) and an identification of the date of the last day on which the application could be submitted:**

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day period that began on December 22, 2014 and that will expire on February 19, 2015.

**(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:**

**UNITED STATES PATENT NO.:** 8,008,449 B2

**INVENTORS:** ALAN J. KORMAN
MOHAN SRINIVASAN
CHANGYU WANG
MARK J. SELBY
BINGLIANG CHEN
JOSEPHINE CARDARELLI
HAICHUN HUANG[1]

**DATE OF ISSUE:** AUGUST 30, 2011

**EXPIRATION DATE:** JUNE 19, 2027

The present expiration date of the '449 patent is June 19, 2027 (*i.e.,* 20 years after its earliest non-provisional filing date + 413 days of PTA). The patent application that issued as the '449 patent was filed under 35 U.S.C. §371 as a U.S. National Phase Application of PCT Application No. PCT/JP2006/309606, filed on May 2, 2006.

**(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:**

A copy of the '449 patent is attached as *Exhibit 1*.

**(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:**

---

[1] A certificate of correction that issued on November 11, 2014 added Haichun Huang as an inventor (see Exhibit 8).



Dana-Farber EX1017
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No terminal disclaimer has been filed in the '449 patent. Two certificates of correction have issued. The first issued on December 20, 2011 to correct the spelling of an inventor's name, update the residence of an inventor, and correct several typographical errors (*Exhibit 7*). The second certificate of correction issued on November 11, 2014 to add the inventor Haichun Huang (*Exhibit 8*). The '449 patent has not been reexamined.

The first maintenance fee for the '449 patent (due August 31, 2015) has been paid (*Exhibit 9*).

**(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product or a method of using or manufacturing the approved product:**

The '449 patent claims the Approved Product. At least claims 1-4, 6-7, 10-16, 18, 20 and 22 read on the Approved Product. See Section (1), pages 3-5, above. A showing that demonstrates the manner in which at least one claim reads on the Approved Product is set forth below.

**Table 3**

| Claim | The Approved Product |
|---|---|
| 3. An isolated monoclonal antibody, or antigen-binding portion thereof, | Nivolumab (the active ingredient in OPDIVO) is an isolated monoclonal antibody. |
| comprising a heavy chain variable region and a light chain variable region, | Nivolumab comprises a heavy chain variable region and light chain variable region as set forth for the "Heavy Chain Variable Region" and "Light Chain Variable Region," respectively, in Table 1 (pages 3-4) of this Application. |
| wherein the heavy chain variable region and light chain variable region are selected from the group consisting of:<br><br>a) a heavy chain variable region comprising amino acids having the | |

| Claim | The Approved Product |
|---|---|
| sequence set forth in SEQ ID NO: 1; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 8;<br><br>b) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 2; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 9;<br><br>c) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 3; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 10; | |
| d) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 4; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 11; | Nivolumab comprises a heavy chain variable region amino acid sequence, as shown by the bold underlined sequence in the "Heavy Chain Variable Region" in Table 1 (pages 3-4) of this Application, that is identical to the sequence in SEQ ID NO: 4 of the '449 patent.<br><br>Nivolumab comprises a light chain variable region amino acid sequence, as shown by the bold underlined sequence in the "Light Chain Variable Region" in Table 1 (pages 3-4) of this Application, that is identical to the sequence in SEQ ID NO:11 of the '449 patent. |
| e) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 5; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 12;<br><br>f) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 6; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 13; and<br><br>g) a heavy chain variable region comprising amino acids having the sequence set forth in | |

| Claim | The Approved Product |
|---|---|
| SEQ ID NO: 7; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 14, | |
| wherein the antibody or antigen-binding portion thereof specifically binds to PD-1. | Nivolumab specifically binds to PD-1. |

Claim 20 depends from claim 3 and specifies that the antibody's heavy chain variable region comprise amino acids having the sequence of SEQ ID NO:4 and that its light chain variable region comprise amino acids having the sequence of SEQ ID NO:11. As shown above in Table 3, the Approved Product meets these limitations (also see Table 1, pages 3-4, above).

Claim 1 is independent and recites an isolated human monoclonal antibody that "cross-competes for binding to PD-1 with a reference antibody" wherein the reference antibody comprises a heavy chain variable region comprising a sequence selected from a Markush group that includes SEQ ID NO:4 and a light chain variable region comprising a sequence selected from a Markush group that includes SEQ ID NO:11. Claim 22 depends from claim 1 and specifies that the heavy and light chain variable regions comprise SEQ ID NOs:4 and 11, respectively. OPDIVO (nivolumab) is an isolated human monoclonal antibody that comprises a heavy chain variable region comprising SEQ ID NO:4 and a light chain variable region comprising SEQ ID NO:11 (Table 1, pages 3-4, above) and thus cross-competes for binding with itself.

Claim 2 is independent and recites an isolated monoclonal antibody comprising heavy chain variable region CDR1, CDR2, and CDR3 comprising sequences selected from Markush groups that include SEQ ID NOs:18, 25, and 32, and comprising light chain variable region CDR1, CDR2, and CDR3 comprising sequences selected from Markush groups that include SEQ

ID NOs:39, 46, and 53. Claim 18 depends from claim 2 and specifies that the antibody CDRs comprise SEQ ID NOs:18, 25, 32, 39, 46, and 53 (Table 2, page 4, above). The Approved Product comprises these sequences in the CDRs (Table 2, page 4, above) and thus meets all the elements of claims 2 and 18.

Claim 4 is independent and recites an isolated monoclonal antibody comprising a heavy chain variable region sequence derived from a human $V_H$ 3-33 germline sequence. It also requires the antibody to comprise a light chain variable region sequence derived from a human $V_K$ L6 germline sequence. Claim 4 also requires that the antibody specifically bind to PD-1. The Approved Product meets all the elements of claim 4 (see pages 4 and 5, above).

Claim 6 is independent and recites an isolated monoclonal antibody comprising a heavy chain variable region CDR3 comprising SEQ ID NO:32 and a light chain variable region CDR3 comprising SEQ ID NO:53. The Approved Product meets all the elements of claim 6 (see Table 2, page 4, above). Claim 10 depends from claim 6 and further requires that the antibody comprise a heavy chain variable region CDR2 comprising SEQ ID NO:25 and a light chain variable region CDR2 comprising SEQ ID NO:46. The Approved Product meets these elements (see Table 2, page 4, above). Claim 11 depends from claim 10 and further requires that the antibody comprise a heavy chain variable region CDR1 comprising SEQ ID NO:18 and a light chain variable region CDR1 comprising SEQ ID NO:39. The Approved Product also meets these elements (see Table 2, page 4, above).

Claim 7 is dependent and recites a composition comprising the antibody of any of claims 1-6 and a pharmaceutically acceptable carrier. The Approved Product therefore meets the elements of claim 7 (see page 5, above).



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Claims 12 and 13 are dependent and further require the antibody of any of claims 1-3 to inhibit the suppression of CD4+ CD25- T cells by regulatory T cells or to enhance the antigen-specific memory response to a tumor or a pathogen, respectively. The Approved Product has these activities (see page 5, above), and thus meets all elements of claim 12 and 13.

Claims 14 and 15 are dependent and further require the antibody of any of claims 1-3 to confer a persistent immunity to tumor relapse or be an $IgG_4$ isotype. The Approved Product meets these elements (see page 5, above). Claim 16 depends from claim 15 and further requires the antibody to have neither ADCC nor CDC activity. The Approved Product has neither of these activities (see page 5, above), and thus meets every element of claim 16.

Therefore, the '449 patent's claims 1-4, 6-7, 10-16, 18, 20 and 22 read on the Approved Product.



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**(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:**

**for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug application (IND) and the IND number; the date on which a new drug application (NDA) or a product license application (PLA) was initially submitted and the NDA or PLA number; and the date on which the NDA was approved or the products license issued:**

(A) OPDIVO's IND (No. 100052) was submitted on June 28, 2006. The FDA received it on June 29, 2006. *Exhibit 10* provides a copy of FDA's acknowledgement letter. IND No. 100052 became effective 30 days after FDA's receipt date, namely, on **July 29, 2006**. (B) OPDIVO's biologics license application ("BLA"), BLA 125554, was submitted on July 30, 2014, and the FDA acknowledged it on **July 30, 2014** (*see Exhibit 11*).

(C) The FDA approved BLA 125554 on **December 22, 2014**, as shown in *Exhibit 6*.



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**(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:**

The FDA administratively split IND No. 100052 into IND No. 115195 for the melanoma indication in 2012. Both INDs support OPDIVO's BLA. Marketing Applicant BMS collaborated with Ono during the regulatory review period to develop OPDIVO (see Exhibit 3).

A brief description of significant activities undertaken by the Marketing Applicant, its predecessors and affiliates, in IND No. 100052, IND No. 115195, and BLA 125554 during the applicable regulatory review period with respect to the Approved Product and the significant dates applicable to such activities is provided at *Exhibit 12*.



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**(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:**

(i) Applicants are of the opinion that the '449 patent is eligible for extension under 35 U.S.C. §156(a) because it satisfies all of the requirements for such extension as follows.

Section 156(a): The '449 patent claims the active ingredient of the Approved Product.

Section 156(a)(i): The term of the '449 patent has not expired before submission of this application.

Section 156(a)(ii): The term of the '449 patent has never been extended under 35 U.S.C. §156(e)(1).

Section 156(a)(iii): This application for extension is being submitted by the owners of record of the '449 patent, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d) and the rules of the PTO.

Section 156(a)(4): The Approved Product has been subject to a regulatory review period before its commercial marketing or use.

Section 156(a)(5)(a): The permission for the commercial marketing or use of the Approved Product is the first permitted commercial marketing or use of the product under the provision of section 351 of the PHSA (42 U.S.C. §262) under which such regulatory review period occurred.

Section 156(c)(4): No other patent term has been extended for the same regulatory review period for OPDIVO (nivolumab).



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(ii) Statement as to length of extension claimed.

The term of the '449 patent should be extended for **552** days, or to **December 22, 2028**, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period ("RRP") equals the length of time between the effective date of IND No. 100052 of **July 29, 2006**, and the submission of the BLA 125554 on **July 30, 2014** (*i.e.*, the "testing" phase), a period of **2,924** days, plus the length of time between the submission of the BLA 125554 on **July 30, 2014** to BLA approval on **December 22, 2014** (*i.e.*, the "approval" phase), a period of **146** days. These two periods added together equal **3,070** days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 3,070 day regulatory review period the following:

(a) **1,859** days, which is the number of days in the testing and approval periods on or before the issuance of the '449 patent on August 30, 2011; and

(b) **532** days, which is one-half the number of days remaining (1,065) in the testing period (2,924) after the subtraction of 1,859 days on or before issuance (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

The number of days as determined above (3,070 – 1859 – 532 = **679** days), when added to the expiration date of the original term of the '449 patent (June 19, 2027), would result in the expiration date of **April 28, 2029**. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156. One of these potential limitations does further limit the term of the patent and the other does not.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. Since the current expiry date of the '449 patent is June 19, 2027, no patent term extension could



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extend the term of the patent beyond June 19, 2032. Consequently, this provision does *not* operate to limit the possible extension available to the '449 patent.

Second, under 35 U.S.C. §156(c)(3), the calculated extension period cannot lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, or December 22, 2028. In this case, 35 U.S.C. §156(c)(3) *does* operate to limit the possible extension available to the '449 patent. Since the expiration date of December 22, 2028 is earlier than April 28, 2029, the expiration of the '449 patent cannot extend past December 22, 2028.

Thus, the '449 patent is eligible for a patent term extension of **552** days from June 19, 2027 to **December 22, 2028** (counting from midnight to midnight).

**(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (see 37 C.F.R. §1.765).**

Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information that is material to the determination of entitlement to the extension sought.

**(14) The prescribed fee for receiving and acting upon the application for extension (see 37 C.F.R. §1.20(j)):**

Please charge our Deposit Account No. 19-00036 in the amount of $1,120.00 to cover the fee for an application for extension of patent term. The Commissioner is authorized to charge any fee deficiency or any additional fees required by this application, and to credit any overpayment, to our Deposit Account No. 19-00036.

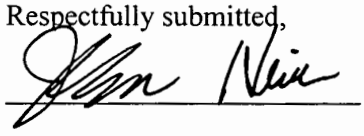
**(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:**

Eldora L. Ellison, Reg. No. 39,967
Ji-Eun Kim, Reg. No. 68,504
Attorneys for Applicants
Sterne Kessler Goldstein & Fox PLLC
1100 New York Ave. NW
Washington, DC 20005
Telephone No.: (202) 371-2600
Facsimile No.: (202) 371-2540

This Application for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits 1-12, is being submitted as one original and two copies. 37 C.F.R. §1.740(b).

Dated: Feb. 13, 2015

Respectfully submitted,



Ji-Eun Kim
Reg. No 68,504

for Eldora L. Ellison, Reg. No. 39,967
Attorney for Applicants

Encl.: Exhibits 1-12

1965368_1.DOCX



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Exhibit 2
Atty Docket No. 3338.0180003/ELE/C-K

United States Patent and Trademark Office



Assignments on the Web > **Patent Query**

# Patent Assignment Abstract of Title

***NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.***

**Total Assignments: 7**

**Patent #:** 8008449 **Issue Dt:** 08/30/2011 **Application #:** 11913217 **Filing Dt:** 01/29/2009

**Publication #:** 20090217401 **Pub Dt:** 27-AUG-09

**Inventors:** Alan J. Korman, Mohan Srinivasan, Changyu Wang, Mark J. Selby, Josephine M. Cardarelli et al

**Title:** HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1(PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

**Assignment: 1**

**Reel/Frame:** 020043/0830 **Recorded:** 10/31/2007 **Pages:** 8

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignors:** KORMAN, ALAN J. **Exec Dt:** 06/20/2007

SRINIVASAN, MOHAN **Exec Dt:** 06/21/2007

WANG, CHANGYU **Exec Dt:** 06/21/2007

SELBY, MARK J. **Exec Dt:** 06/26/2007

CHEN, BING **Exec Dt:** 06/25/2007

CARDARELLI, JOSEPHINE M. **Exec Dt:** 06/25/2007

**Assignee:** MEDAREX, INC.
707 STATE ROAD
PRINCETON, NEW JERSEY 08540

**Correspondent:** BAKER BOTTS L.L.P.
30 ROCKEFELLER PLAZA
44TH FLOOR
NEW YORK, NY 10112-4498

**Assignment: 2**

**Reel/Frame:** 022792/0026 **Recorded:** 06/08/2009 **Pages:** 3

**Conveyance:** ASSIGNMENT OF UNDIVIDED 50% OF ASSIGNOR'S INTEREST

**Assignor:** MEDAREX, INC. **Exec Dt:** 12/27/2007

**Assignee:** ONO PHARMACEUTICAL CO., LTD.
1-5, DOSHOMACHI 2-CHOME
CHUO-KU, OSAKA-SHI
OSAKA, JAPAN 541-8526

**Correspondent:** BAKER BOTTS LLP
30 ROCKEFELLER CENTER
NEW YORK, NY 10112

**Assignment: 3**

**Reel/Frame:** 022800/0283 **Recorded:** 06/09/2009 **Pages:** 6

**Conveyance:** CORRECTIVE ASSIGNMENT TO CORRECT THE SERIAL NUMBER 11/917727 PREVIOUSLY RECORDED ON REEL 022792 FRAME 0026. ASSIGNOR(S) HEREBY CONFIRMS THE ASSIGNMENT OF AN UNDIVIDED 50% OF ASSIGNOR'S INTEREST.

**Assignor:** MEDAREX, INC. **Exec Dt:** 12/27/2007

**Assignee:** ONO PHARMACEUTICAL CO., LTD.
1-5 DOSHOMACHI 2-CHOME
CHUO-KU, OSAKA-SHI

OSAKA, JAPAN 541-8526

**Correspondent:** BAKER BOTTS LLP
30 ROCKEFELLER CENTER
NEW YORK, NY 10112

**Assignment: 4**

**Reel/Frame:** 028820/0044 **Recorded:** 08/21/2012 **Pages:** 5

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignor:** HUANG, HAICHUN **Exec Dt:** 04/12/2012

**Assignee:** MEDAREX, INC.
ROUTE 206 & PROVINCE LINE RD.
PRINCETON, NEW JERSEY 08543

**Correspondent:** BAKER BOTTS L.L.P
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

**Assignment: 5**

**Reel/Frame:** 032347/0262 **Recorded:** 03/04/2014 **Pages:** 3

**Conveyance:** MERGER (SEE DOCUMENT FOR DETAILS).

**Assignor:** MEDAREX, INC. **Exec Dt:** 12/31/2012

**Assignee:** MEDAREX, L.L.C.
ROUTE 206 AND PROVINCE LINE ROAD
PRINCETON, NEW JERSEY 08540

**Correspondent:** BRISTOL-MYERS SQUIBB COMPANY
ROUTE 206 AND PROVINCE LINE ROAD
PRINCETON, NJ 08540

**Assignment: 6**

**Reel/Frame:** 034126/0342 **Recorded:** 11/07/2014 **Pages:** 5

**Conveyance:** MERGER (SEE DOCUMENT FOR DETAILS).

**Assignor:** MEDAREX, L.L.C. **Exec Dt:** 09/30/2014

**Assignee:** E. R. SQUIBB & SONS, L.L.C.
ROUTE 206 AND PROVINCE LINE ROAD
PRINCETON, NEW JERSEY 08540

**Correspondent:** BRISTOL-MYERS SQUIBB COMPANY
ROUTE 206 AND PROVINCE LINE ROAD
PRINCETON, NJ 08540

**Assignment: 7**

**Reel/Frame:** 034683/0398 **Recorded:** 12/19/2014 **Pages:** 6

**Conveyance:** CORRECTIVE ASSIGNMENT TO CORRECT THE SPELLING OF INVENTOR PREVIOUSLY RECORDED AT REEL: 020043 FRAME: 0830. ASSIGNOR(S) HEREBY CONFIRMS THE ASSIGNMENT.

**Assignor:** CHEN, BINGLIANG **Exec Dt:** 12/02/2014

**Assignee:** MEDAREX, INC.
707 STATE ROAD
PRINCETON, NEW JERSEY 08540

**Correspondent:** STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

Search Results as of: 02/06/2015 10:30 AM
If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.5
Web interface last modified: July 25, 2014 v.2.5

Exhibit 3
Atty Docket No. 3338.0180003/ELE/C-K

February 13, 2015

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450, Alexandria,
VA 22313-1450

Re: **Patent Term Extension Application for U.S. Patent No. 8,008,449 B2**
SKGF Ref: 3338.0180003

Dear Ms. Till:

On behalf of Bristol-Myers Squibb Company ("BMS"), Marketing Applicant for Biologic License Application No. 125554 for OPDIVO™ (nivolumab), its predecessors and affiliates, I hereby authorize the patent owners of record, E. R. Squibb & Sons, L.L.C. and Ono Pharmaceutical Co., Ltd., in connection with their application for extension of U.S. Patent No. 8,008,449 B2, to rely upon the activities of BMS, its predecessors (*e.g.*, Medarex, Inc., which BMS acquired on September 1, 2009) and affiliates, undertaken in connection with seeking the U.S. Food and Drug Administration's approval to market OPDIVO™ (nivolumab). E. R. Squibb is a wholly-owned subsidiary of BMS. BMS also collaborated with Ono during the regulatory review period in connection with seeking the FDA's approval to market OPDIVO™ (nivolumab).

Very truly yours,

Paul D. Golian
Vice President & Assistant General Counsel
Bristol-Myers Squibb Company

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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 |
|---|---|---|---|
| 11/913,217 | 01/29/2009 | Alan J. Korman | 3338.018003./ELE/C-K/E |

**CONFIRMATION NO. 1207**

115018
Sterne, Kessler, Goldstein & Fox P.L.L.C.
1100 New York Avenue NW
Washington, DC 20005

**POA ACCEPTANCE LETTER**

*OC000000071527452*

Date Mailed: 10/24/2014

## NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/21/2014.

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.

/deelliott/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Best Available Copy



# POWER OF ATTORNEY FROM MULTIPLE ASSIGNEES

(1) MEDAREX, L.L.C., a corporation of United States, having a principal place of business at Route 206 and Province Line Road, Princeton, NJ 08540 and (2) ONO PHARMACEUTICAL CO., LTD., a company of JAPAN, having a principal place of business at 1-5, Doshomachi 2-Chrome, Chuo-Ku, Osaka-Shi, Osaka, 541-8526 JAPAN, are, collectively, assignees of the entire right, title and interest for the United States of America (as defined in 35 U.S.C. § 100), by reason of Assignments executed to Assignee (1) MEDAREX, L.L.C., and to Assignee (2) ONO PHARMACEUTICAL CO., LTD., on June 20, 2007, June 21, 2007, June 25, 2007, June 26, 2007, December 27, 2007, April 12, 2012, and December 31, 2012, of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies** that is disclosed and claimed in a patent application of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, and Selby, Mark J., (said application having a filing date of May 9, 2005, at the U.S. Patent and Trademark Office, and having Application Number **60/679,466**, (Atty. Dkt. No. 3338.0180000/ELE/C-K/BMB)), of an invention known as **Combined Use of CTLA-4 Antibody and PD-1 Antibody For Treatment of Hyperproliferative Disease** that is disclosed and claimed in patent applications of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Selby, Mark J., Chen, Bing, and Cardarelli, Josephine M. (an application having a filing date of December 8, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/748,919** (Atty. Dkt. No. 3338.01800021/ELE/C-K/BMB), and another application having a filing date of November 21, 2005, at the U.S. Patent and Trademark Office and having Application Number **60/738,434** (Atty. Dkt. No. 3338.0180001/ELE/C-K/BMB), of an invention known as **Human Monoclonal Antibodies to Programmed Death 1 (PD-1) and Methods for Treating Cancer Using Anti-PD-1 Antibodies Alone or in Combination With Other Immunotherapeutics** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Selby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on August 30, 2011, at the U.S. Patent and Trademark Office, and having Patent Number **8,008,449** (Atty. Dkt. No. 3338.0180003/ELE/C-K/BMB)), and of an invention known as **Monoclonal Antibodies to Programmed Death 1 (PD-1)** that is disclosed and claimed in a patent of the same title by the inventors Korman, Alan J., Srinivasan, Mohan, Wang, Changyu, Selby, Mark J., Chen, Bing, Cardarelli, Josephine M., and Huang, Haichun (said patent issued on July 15, 2014, at the U.S. Patent and Trademark Office, and having Patent Number **8,779,105** (Atty. Dkt. No. 3338.0180004/ELE/C-K/BMB)).

For the purpose of PAIR, the **Customer Number is 115018**.

The Assignees hereby appoint the practitioners associated with **CUSTOMER NUMBER 115018** as our attorneys or agents to prosecute the application identified above, and any continuation, divisional, continuation-in-part, or reissue application thereof, and to transact all business in the U.S. Patent and Trademark Office connected therewith. The Assignees hereby grant said practitioners associated with **CUSTOMER NUMBER 115018** the power to insert on this Power of Attorney any further identification that may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office.

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Send correspondence to:

CUSTOMER NUMBER 115018

Direct phone calls to 202-371-2600.

FOR: MEDAREX, L.L.C.
SIGNATURE:
BY: Paul D. Golian
TITLE: Vice President & Assistant General Cnsl.
DATE: July 23, 2014

FOR: ONO PHARMACEUTICAL CO., LTD
SIGNATURE:
BY: Kazuhito Kawabata
TITLE: Member of the Board of Directors Executive Officer
Executive Director, Discovery and Research
DATE: July 28, 2014



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Exhibit 4

Atty Docket No. 3338.0180003/ELE/C-K

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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## STATEMENT UNDER 37 CFR 3.73(b)

Atty. Dkt No. 3338.0180003/ELE/C-K/E-H

Applicant/Patent Owner: KORMAN et al.

Application No./Patent No.: 8,008,449 Filed/Issue Date: August 30, 2011

Titled: HUMAN MONOCLONAL ANTIBODIES TO PROGRAMMED DEATH 1 (PD-1) AND METHODS FOR TREATING CANCER USING ANTI-PD-1 ANTIBODIES ALONE OR IN COMBINATION WITH OTHER IMMUNOTHERAPEUTICS

Medarex, L.L.C. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

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1. ☐ the assignee of the entire right, title, and interest in;

2. ☒ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is 50 %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:
KORMAN, Alan J., SRINIVASAN, Mohan, WANG, Changyu,

1. From: SELBY, Mark, J., CHEN, Bing, CARDARELLI, Josephine M. To: Medarex, Inc.

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Reel 020043, Frame 0830, or for which a copy thereof is attached.

2. From: HUANG, Haichun To: Medarex, Inc.

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3. From: Medarex, Inc. To: Medarex, L.L.C.

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The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Ji-Eun Kim, #68,504/ October 21, 2014
Signature Date

Ji-Eun Kim, Reg. No. 68,504 Attorney for Applicants
Printed or Typed Name Title

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Exhibit 4

Atty Docket No. 3338.0180003/ELE/C-K/E-H

PTO/SB/96 (07-09)

Approved for use through 07/31/2012. OMB 0651-0031

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Ono Pharmaceutical Co., LTD. , a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

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2. ☒ an assignee of less than the entire right, title, and interest in
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the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

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The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Ji-Eun Kim, #68,504/ October 21, 2014

Signature Date

Ji-Eun Kim, Reg. No. 68,504 Attorney for Applicants

Printed or Typed Name Title

This collection of information is required by 37 CFR 3.73(b). 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.**

1918955 *If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use OPDIVO safely and effectively. See full prescribing information for OPDIVO.**

**OPDIVO (nivolumab) injection, for intravenous use**
**Initial U.S. Approval: 2014**

### ----------INDICATIONS AND USAGE----------

OPDIVO is a human programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1, 14)

### ----------DOSAGE AND ADMINISTRATION----------

Administer 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)

### ----------DOSAGE FORMS AND STRENGTHS----------

Injection: 40 mg/4 mL and 100 mg/10 mL solution in a single-use vial (3)

### ----------CONTRAINDICATIONS----------

None. (4)

### ----------WARNINGS AND PRECAUTIONS----------

Immune-mediated adverse reactions: Administer corticosteroids based on the severity of the reaction. (5.1, 5.2, 5.3, 5.4, 5.6)

- Immune-mediated pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (5.1)
- Immune-mediated colitis: Withhold for moderate or severe and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (5.3)
- Immune-mediated nephritis and renal dysfunction: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening serum creatinine elevation. (5.4)
- Immune-mediated hypothyroidism and hyperthyroidism: Monitor for changes in thyroid function. Initiate thyroid hormone replacement as needed. (5.5)
- Embryofetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.7, 8.1, 8.3)

### ----------ADVERSE REACTIONS----------

Most common adverse reaction (≥20%) was rash. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

### ----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Discontinue breastfeeding. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 12/2014**

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

OPDIVO® (nivolumab) is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor *[see Clinical Studies (14)]*.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

### 2.2 Dose Modifications

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Withhold OPDIVO for any of the following:

- Grade 2 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 2 or 3 colitis *[see Warnings and Precautions (5.2)]*
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN *[see Warnings and Precautions (5.3)]*
- Creatinine greater than 1.5 and up to 6 times ULN or greater than 1.5 times baseline *[see Warnings and Precautions (5.4)]*
- Any other severe or Grade 3 treatment-related adverse reactions *[see Warnings and Precautions (5.6)]*

Resume OPDIVO in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue OPDIVO for any of the following:

- Any life-threatening or Grade 4 adverse reaction
- Grade 3 or 4 pneumonitis *[see Warnings and Precautions (5.1)]*
- Grade 4 colitis *[see Warnings and Precautions (5.2)]*
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN *[see Warnings and Precautions (5.3)]*
- Creatinine greater than 6 times ULN *[see Warnings and Precautions (5.4)]*
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks

- Persistent Grade 2 or 3 treatment-related adverse reactions that do not recover to Grade 0-1 within 12 weeks after last dose of OPDIVO

## 2.3 Preparation and Administration

Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

### Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

### Storage of Infusion

The product does not contain a preservative.

After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

### Administration

Administer the infusion over 60 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

## 4 CONTRAINDICATIONS

None.

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Immune-Mediated Pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, occurred with OPDIVO treatment. Across the clinical trial experience in 574 patients with solid tumors, fatal immune-mediated pneumonitis occurred in 0.9% (5/574) of patients receiving OPDIVO. No cases of fatal pneumonitis occurred in Trial 1; all five fatal cases occurred in a dose-finding study with OPDIVO doses of 1 mg/kg (two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient).

In Trial 1, pneumonitis, including interstitial lung disease, occurred in 3.4% (9/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: one with Grade 3 and five with Grade 2 pneumonitis. The median time to onset for the six cases was 2.2 months (range: 25 days-3.5 months). In two patients, pneumonitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 pneumonitis led to interruption or permanent discontinuation of OPDIVO in the remaining four patients. All six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day); immune-mediated pneumonitis improved to Grade 0 or 1 with corticosteroids in all six patients. There were two patients with Grade 2 pneumonitis that completely resolved (defined as improved to Grade 0 with completion of corticosteroids) and OPDIVO was restarted without recurrence of pneumonitis.

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold OPDIVO until resolution for moderate (Grade 2) pneumonitis *[see Dosage and Administration (2.2)]*.

## 5.2 Immune-Mediated Colitis

In Trial 1, diarrhea or colitis occurred in 21% (57/268) of patients receiving OPDIVO and 18% (18/102) of patients receiving chemotherapy. Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, occurred in 2.2% (6/268) of patients receiving OPDIVO: five patients with Grade 3 and one patient with Grade 2 colitis. The median time to onset of immune-mediated colitis from initiation of OPDIVO was 2.5 months (range: 1-6 months). In three patients, colitis was diagnosed after discontinuation of OPDIVO for other reasons, and Grade 2 or 3 colitis led to interruption or permanent discontinuation of OPDIVO in the remaining three patients. Five of these six patients received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 1.4 months (range: 3 days-2.4 months) preceding corticosteroid taper. The sixth patient continued on low-dose corticosteroids started for another immune-mediated adverse reaction. Immune-mediated colitis improved to Grade 0 with corticosteroids in five patients, including one patient with Grade 3 colitis retreated after complete resolution (defined as improved to Grade 0 with completion of corticosteroids) without additional events of colitis. Grade 2 colitis was ongoing in one patient.

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold OPDIVO for Grade 2 or 3 immune-mediated colitis. Permanently discontinue OPDIVO for Grade 4 colitis or for recurrent colitis upon restarting OPDIVO *[see Dosage and Administration (2.2)]*.

### 5.3 Immune-Mediated Hepatitis

In Trial 1, there was an increased incidence of liver test abnormalities in the OPDIVO-treated group as compared to the chemotherapy-treated group, with increases in AST (28% vs. 12%), alkaline phosphatase (22% vs. 13%), ALT (16% vs. 5%), and total bilirubin (9% vs. 0). Immune-mediated hepatitis, defined as requirement for corticosteroids and no clear alternate etiology, occurred in 1.1% (3/268) of patients receiving OPDIVO: two patients with Grade 3 and one patient with Grade 2 hepatitis. The time to onset was 97, 113, and 86 days after initiation of OPDIVO. In one patient, hepatitis was diagnosed after discontinuation of OPDIVO for other reasons. In two patients, OPDIVO was withheld. All three patients received high-dose corticosteroids (at least 40 mg prednisone equivalents). Liver tests improved to Grade 1 within 4-15 days of initiation of corticosteroids. Immune-mediated hepatitis resolved and did not recur with continuation of corticosteroids in two patients; the third patient died of disease progression with persistent hepatitis. The two patients with Grade 3 hepatitis that resolved restarted OPDIVO and, in one patient, Grade 3 immune-mediated hepatitis recurred resulting in permanent discontinuation of OPDIVO.

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

### 5.4 Immune-Mediated Nephritis and Renal Dysfunction

In Trial 1, there was an increased incidence of elevated creatinine in the OPDIVO-treated group as compared to the chemotherapy-treated group (13% vs. 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction (defined as ≥ Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology) occurred in 0.7% (2/268) of patients at 3.5 and 6 months after OPDIVO initiation, respectively. OPDIVO was permanently discontinued in both patients; both received high-dose corticosteroids (at least 40 mg prednisone equivalents). Immune-mediated nephritis resolved and did not recur with continuation of corticosteroids in one patient. Renal dysfunction was ongoing in one patient.

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue OPDIVO. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold OPDIVO and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue OPDIVO *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

### 5.5 Immune-Mediated Hypothyroidism and Hyperthyroidism

In Trial 1, where patients were evaluated at baseline and during the trial for thyroid function, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving OPDIVO and none of the 102 patients receiving chemotherapy. The median time to onset was 2.5 months (range: 24 days-11.7 months). Seventeen of the 21 patients with hypothyroidism received levothyroxine. Fifteen of 17 patients received subsequent OPDIVO dosing while continuing to receive levothyroxine.

Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients receiving OPDIVO and 1% (1/102) of patients receiving chemotherapy. The median time to onset in OPDIVO-treated patients was 1.6 months (range: 0-3.3 months). Four of five patients with Grade 1 hyperthyroidism and two of three patients with Grade 2 hyperthyroidism had documented resolution of hyperthyroidism; all three patients received medical management for Grade 2 hyperthyroidism.

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.

### 5.6 Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy.

The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of OPDIVO-treated patients in Trial 1: pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis.

Across clinical trials of OPDIVO administered at doses of 3 mg/kg and 10 mg/kg the following additional clinically significant, immune-mediated adverse reactions were identified: hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.

For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate

corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event *[see Dosage and Administration (2.2)]*.

### 5.7 Embryofetal Toxicity

Based on its mechanism of action and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO and for at least 5 months after the last dose of OPDIVO *[see Use in Specific Populations (8.1, 8.3)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.4)]*
- Immune-Mediated Hypothyroidism and Hyperthyroidism *[see Warnings and Precautions (5.5)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.6)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described in the WARNINGS and PRECAUTIONS section and below reflect exposure to OPDIVO in Trial 1, a randomized, open-label trial in which 370 patients with unresectable or metastatic melanoma received OPDIVO 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine 1000 mg/m$^2$ every 3 weeks or the combination of carboplatin AUC 6 every 3 weeks plus paclitaxel 175 mg/m$^2$ every 3 weeks *[see Clinical Studies (14)]*. The median duration of exposure was 5.3 months (range: 1 day-13.8+ months) with a median of eight doses (range: 1 to 31) in OPDIVO-treated patients and was 2 months (range: 1 day-9.6+ months) in chemotherapy treated patients. In this ongoing trial, 24% of patients received OPDIVO for greater than 6 months and 3% of patients received OPDIVO for greater than 1 year.

Clinically significant adverse reactions were also evaluated in 574 patients with solid tumors enrolled in two clinical trials receiving OPDIVO at doses of 0.1 to 10 mg/kg every 2 weeks,

supplemented by immune-mediated adverse reaction reports across ongoing clinical trials *[see Warnings and Precautions (5.1, 5.6)]*.

In Trial 1, patients had documented disease progression following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, prior ipilimumab-related Grade 4 adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event, patients with a condition requiring chronic systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications, a positive test for hepatitis B or C, and a history of HIV.

The study population characteristics in the OPDIVO group and the chemotherapy group were similar: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. There were more patients in the OPDIVO group with elevated LDH at baseline (51% vs. 38%).

OPDIVO was discontinued for adverse reactions in 9% of patients. Twenty-six percent of patients receiving OPDIVO had a drug delay for an adverse reaction. Serious adverse reactions occurred in 41% of patients receiving OPDIVO. Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in 2% to less than 5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

Table 1 summarizes the adverse reactions that occurred in at least 10% of OPDIVO-treated patients. The most common adverse reaction (reported in at least 20% of patients) was rash.

**Table 1: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)**

| Adverse Reaction | OPDIVO (n=268) | | Chemotherapy (n=102) | |
|---|---|---|---|---|
| | All Grades | Grades 3-4 | All Grades | Grades 3-4 |
| | Percentage (%) of Patients | | | |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Rash[a] | 21 | 0.4 | 7 | 0 |
| Pruritus | 19 | 0 | 3.9 | 0 |
| **Respiratory, Thoracic, and Mediastinal Disorders** | | | | |
| Cough | 17 | 0 | 6 | 0 |



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**Table 1: Selected Adverse Reactions Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)**

| Adverse Reaction | OPDIVO (n=268) | | Chemotherapy (n=102) | |
|---|---|---|---|---|
| | All Grades | Grades 3-4 | All Grades | Grades 3-4 |
| | Percentage (%) of Patients | | | |
| **Infections and Infestations** | | | | |
| Upper respiratory tract infection[b] | 11 | 0 | 2.0 | 0 |
| **General Disorders and Administration Site Conditions** | | | | |
| Peripheral edema | 10 | 0 | 5 | 0 |

[a] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, and dermatitis acneiform.

[b] Upper respiratory tract infection is a composite term which includes rhinitis, pharyngitis, and nasopharyngitis.

Other clinically important adverse reactions in less than 10% of patients treated with OPDIVO were:

*Cardiac Disorders:* ventricular arrhythmia

*Eye Disorders:* iridocyclitis

*General Disorders and Administration Site Conditions:* infusion-related reactions

*Investigations:* increased amylase, increased lipase

*Nervous System Disorders:* dizziness, peripheral and sensory neuropathy

*Skin and Subcutaneous Tissue Disorders:* exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis.

**Table 2: Selected Laboratory Abnormalities Increased from Baseline Occurring in ≥10% of OPDIVO-Treated Patients and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (Trial 1)**

| | Percentage of Patients with Worsening Laboratory Test from Baseline[a] | | | |
|---|---|---|---|---|
| | OPDIVO | | Chemotherapy | |
| Test | All Grades | Grades 3-4 | All Grades | Grades 3-4 |
| Increased AST | 28 | 2.4 | 12 | 1.0 |
| Increased alkaline phosphatase | 22 | 2.4 | 13 | 1.1 |
| Hyponatremia | 25 | 5 | 18 | 1.1 |
| Increased ALT | 16 | 1.6 | 5 | 0 |
| Hyperkalemia | 15 | 2.0 | 6 | 0 |

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDIVO group (range 252 to 256 patients) and chemotherapy group (range 94 to 96 patients).

### 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Of 281 patients who were treated with OPDIVO 3 mg/kg every 2 weeks and evaluable for the presence of anti-product antibodies, 24 patients (8.5%) tested positive for treatment-emergent anti-product antibodies by an electrochemiluminescent (ECL) assay. Neutralizing antibodies were detected in two patients (0.7%). There was no evidence of altered pharmacokinetic profile or toxicity profile with anti-product binding antibody development based on the population pharmacokinetic and exposure-response analyses.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to OPDIVO with the incidences of antibodies to other products may be misleading.

## 7 DRUG INTERACTIONS

No formal pharmacokinetic drug-drug interaction studies have been conducted with OPDIVO.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]* and data from animal studies, OPDIVO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of nivolumab to