Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	62/680,522
Filing Date	June 4, 2018
First Named Inventor	Yang LI
Title	WNT SURROGATE MOLECULES AND USES THEREOF
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	SRZN-006/02US 328202-2023

SIGNATURE of Applicant or Patent Practitioner

Signature	/Carol D. Laherty/	Date (Optional)	August 7, 2018
Name	Carol D. Laherty	Registration Number	51,909
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

182850694 v1

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
62/680,522	June 4, 2018

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[x] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 58249

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

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OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Surrozen, Inc.

[ ] Inventor or Joint Inventor (title not required below)

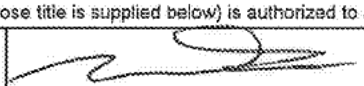
[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[x] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	August 7, 2018
Name	Wen-Chen Yeh		
Title	Chief Scientific Officer		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[x] Total of 1 forms are submitted.

178287171 v1

Electronic Acknowledgement Receipt

EFS ID:	33397076
Application Number:	62680522
International Application Number:	
Confirmation Number:	4895
Title of Invention:	WNT SURROGATE MOLECULES AND USES THEREOF
First Named Inventor/Applicant Name:	Yang LI
Customer Number:	58249
Filer:	Carol Denise Laherty/Lynnette Harvey Jones
Filer Authorized By:	Carol Denise Laherty
Attorney Docket Number:	SRZN-006/02US 328202-2023
Receipt Date:	07-AUG-2018
Filing Date:	04-JUN-2018
Time Stamp:	15:32:44
Application Type:	Provisional

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	SRZN-006-02US_Transmittal-POA.pdf	1251368 149b794eea348caf181e6234d36d9ea48a58ac19	no	2

Warnings:

Information:	
Total Files Size (in bytes):	1251368

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
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www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
62/680,522	06/04/2018		540	SRZN-006/02US 328202-2023		

CONFIRMATION NO. 4895

FILING RECEIPT

58249
COOLEY LLP
ATTN: IP Docketing Department
1299 Pennsylvania Avenue, NW
Suite 700
Washington, DC 20004

Date Mailed: 06/08/2018

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. 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**

Inventor(s)

Yang LI, Mountain View, CA;
Tom Zhiye YUAN, Union City, CA;
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Wen-Chen YEH, Belmont, CA;
Claudia Yvonne JANDA, Palo Alto, CA;
Tristan William FOWLER, San Francisco, CA;
Helene BARIBAULT, Redwood City, CA;
Kuo-Pao LAI, Campbell, CA;

Applicant(s)

Surrozen, Inc., South San Francisco, CA

Power of Attorney:
Carol Laherty--51909

Permission to Access Application via Priority Document Exchange: No

Permission to Access Search Results: No

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 06/07/2018
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/680,522**
Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

WNT SURROGATE MOLECULES AND USES THEREOF

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866) 217-9197 (toll free).
Reviewer: Saleem, Syed (ASRC)
Timestamp: [year=2018; month=6; day=6; hr=13; min=21; sec=50; ms=917;]
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Validated By CRFValidator v 1.0.5

Application No: 62680522 Version No: 1.0

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Output Set:

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Finished: 2018-06-04 20:47:06.408
Elapsed: 0 hr(s) 0 min(s) 5 sec(s) 972 ms
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Total Errors: 0
No. of SeqIDs Defined: 157
Actual SeqID Count: 157

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Total Warnings: 157
Total Errors: 0
No. of SeqIDs Defined: 157
Actual SeqID Count: 157

Error code	Error Description

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Li, Yang
Yuan, Tom Zhiye
Sato, Aaron Ken
Yeh, Wen-Chen

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35 40 45

Trp Ile Gly Ser Ile Tyr His Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Phe Tyr Tyr Asp Ile Leu Thr Gly Tyr Ser Tyr Phe Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys

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Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
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145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
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Lys Ser Cys
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Asn Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Ser Ile Tyr Phe Thr Gly Gly Thr Tyr Tyr Asn Pro Ser
    50                  55                  60
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Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Val Met Leu Ile Thr Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
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Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
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Ser Tyr Phe Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
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Trp Ile Gly Ser Ile Tyr Tyr Thr Gly Asn Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Val Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Asn Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ile Gly Ile Ala Val Ala Ala Pro Val Asp His Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
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Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
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Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
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Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Ala Thr Tyr Gly Gly Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
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Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
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Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
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Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
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Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
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Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
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Cys Ala Arg Val Arg Asp Tyr Tyr Asp Ser Ser Gly Tyr Tyr Tyr Asp
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Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
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Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
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Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
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Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
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Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
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Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
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Tyr Trp Thr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp His Thr Gly Ser Thr Asn Tyr Glu Pro Ser Leu Arg
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Asn Leu Lys Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Gly Gln Gly Gly Tyr Asp Trp Gly His Tyr His Gly Leu Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
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    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
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Lys Ser Cys
225


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            20                  25                  30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Gly Asn Tyr Ala Gln Lys Phe
    50                  55                  60

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65                  70                  75                  80
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Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
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Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
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Cys
225
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ala Lys Asn Thr Val His
65                  70                  75                  80

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


Ala Met Thr Trp Val Arg Gln Ser Pro Gly Lys Arg Leu Glu Trp Val
        35                  40                  45
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
Mr.	Yang		LI	

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

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State/Province	CA
Postal Code	94040
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Tom	Zhiye	YUAN	

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

City	State/Province	Country of Residence
Union City	CA	US

Mailing Address of Inventor:

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City	Union City
State/Province	CA
Postal Code	94587
Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Aaron	Ken	SATO	

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

City	Burlingame	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

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Address 2			
City	Burlingame	State/Province	CA
Postal Code	94010	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wen-Chen		YEH	

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

City	Belmont	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2920 Belmont Woods Way		
Address 2			
City	Belmont	State/Province	CA
Postal Code	94002	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Claudia	Yvonne	JANDA	

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

City	Palo Alto	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	485 B Hawthorne Ave.		
Address 2			
City	Palo Alto	State/Province	CA
Postal Code	94301	Country	US

Inventor 6 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Tristan	William	FOWLER	

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

City	San Francisco	State/Province	CA	Country of Residence	US

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Mailing Address of Inventor:

Address 1	145 Gardenside Drive #3		
Address 2			
City	San Francisco	**State/Province**	CA
Postal Code	94131	**Country**	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Helene		BARIBAULT	

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

City	Redwood City	**State/Province**	CA	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	816 Bain Place		
Address 2			
City	Redwood City	**State/Province**	CA
Postal Code	94062	**Country**	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kuo-Pao		LAI	

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

City	Campbell	**State/Province**	CA	**Country of Residence**	US

Mailing Address of Inventor:

Address 1	2200 Curtner Ave. Apt 5		
Address 2			
City	Campbell	**State/Province**	CA
Postal Code	95008	**Country**	US

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

Correspondence Information:

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

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

Customer Number	58249

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	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Email Address	zIPPatentDocketingMailbox@Cooley.com	Add Email	Remove Email

Application Information:

Title of the Invention	WNT SURROGATE MOLECULES AND USES THEREOF		
Attorney Docket Number	SRZN-006/02US 328202-2023	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	59	Suggested Figure for Publication (if any)	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	58249		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Domestic Benefit/National Stage Information:

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

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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

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

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Authorization or Opt-Out of Authorization to Permit Access:

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

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☒ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☒ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor

● Person to whom the inventor is obligated to assign. | Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Surrozen, Inc.

Mailing Address Information For Applicant:

Address 1	171 Oyster Point Blvd.		
Address 2	Suite 400		
City	South San Francisco	**State/Province**	CA
Country	US	Postal Code	94080
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Carol D. Laherty/			Date (YYYY-MM-DD)	2018-06-04
First Name	Carol D.	Last Name	Laherty	Registration Number	51,909

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	SRZN-006/02US 328202-2023
	Application Number	
Title of Invention	WNT SURROGATE MOLECULES AND USES THEREOF	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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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 the Freedom of Information Act requires disclosure of these records.

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 CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

WNT SURROGATE MOLECULES AND USES THEREOF

BACKGROUND

Technical Field

The present invention relates generally to Wnt signaling pathway agonist molecules, compositions, and methods of using the same. Such molecules are useful, for example, in modulating Wnt signaling pathways.

Statement Regarding Sequence Listing

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is SRZN_006_02US_ST25.txt. The text file is 362 KB, was created on June 1, 2018, and is being submitted electronically via EFS-Web.

Description of the Related Art

Wnt ("Wingless-related integration site" or "Wingless and Int-1" or "Wingless-Int") ligands and their signals play key roles in the control of development, homeostasis and regeneration of many essential organs and tissues, including bone, liver, skin, stomach, intestine, kidney, central nervous system, mammary gland, taste bud, ovary, cochlea and many other tissues (reviewed, e.g., by Clevers, Loh, and Nusse, 2014; 346:1248012). Modulation of Wnt signaling pathways has potential for treatment of degenerative diseases and tissue injuries.

One of the challenges for modulating Wnt signaling as a therapeutic is the existence of multiple Wnt ligands and Wnt receptors, Frizzled 1-10 (Fzd1-10), with many tissues expressing multiple and overlapping Fzds. Canonical Wnt signals also involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors, which are broadly expressed in various tissues, in addition to Fzds. Accordingly, there is clearly a need in the art for binding moieties that specifically

bind to one or more Fzd, LRP5, or LRP6 to modulate Wnt signaling pathways. The present invention addresses this need.

BRIEF SUMMARY

In various embodiments, the present invention provides WNT surrogate molecules and related uses thereof.

In one embodiments, the disclosure provides a soluble, bivalent, bispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises: (i) one or more regions that specifically binds to one or more Frizzled (Fzd) receptor (a Fzd binding region); and (ii) one or more regions that specifically binds to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) (a LRP5/6 binding region).

In particular embodiments, the Wnt surrogate molecule comprises two or more Fzd binding regions and two or more LRP5/6 binding regions. In particular embodiments, one or more Fzd binding regions comprise one or more antigen-binding fragments of an antibody. In particular embodiments, one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and Nanobodies®.

In particular embodiments, any of the Fzd antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Tables 1A or 1B; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Tables 1A or 1B, or a variant of said Fzd binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, any of the Fzd binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:1-65 or 129-132, or an antigen-binding fragment thereof.

In particular embodiments, any of the Fzd binding regions bind to one or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzle 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10). In particular embodiments, any of

the Fzd binding region binds to two or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10). In particular embodiments, any of the Fzd binding region binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii) Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8.

In particular embodiments, any of the surrogate molecules comprise one or more LRP5/6 binding regions comprise one or more antigen-binding fragments of an antibody. In particular embodiments, the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and Nanobodies®. In particular embodiments, any of the one or more LRP5/6 binding regions or antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2, or a variant of said LRP5/6 binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences. In particular embodiments, any of the one or more LRP5/6 binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:66-88 or 133, or an antigen-binding fragment thereof.

In particular embodiments of any of the Wnt surrogate molecules, the Fzd binding region comprising a Fab, and the LRP5/6 binding region comprising a Nanobody®. In particular embodiments, the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In particular embodiments, the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain. In particular embodiments, the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the light chain. In certain embodiments, the LRP5/6 binding region is fused to the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig. In certain embodiments, the LRP5/6 binding region is fused to the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain

of the full Ig. In certain embodiments, the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig. In certain embodiments, the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable light chain region of the full IgG. In particular embodiments, any of the LRP5/6 binding region is fused to the heavy chain or the light chain via one or more linker moiety.

In certain embodiments of any of the Wnt surrogate molecules, the Fzd binding region comprises a Nanobody®, and the LRP5/6 binding region comprises a Fab. In particular embodiments, the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In certain embodiments, the Fzd binding region is fused to the N-terminus or the C-terminus of the heavy chain. In certain embodiments, the Fzd binding region is fused to the N-terminus or the C-terminus of the light chain. In some embodiment, the Fzd binding region is fused to the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig. In some embodiments, the Fzd binding region is fused to the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig.In some embodiments, the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig. In some embodiments, the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fab is fused to the N-terminus of the variable light chain region of the full IgG. In certain embodiments, any of the the Fzd binding region is fused to the heavy chain or the light chain via one or more linker moiety.

In another embodiment, any of the Fzd binding region comprises a Fab, and the LRP5/6 binding region comprises a Fab. In particular embodiments, the Fab of the Fzd binding region or the Fab of the LRP5/6 binding region is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain. In particular embodiments, only one of the Fab of the Fzd binding region or the Fab of the LRPp5/6 binding region is

present within the full immunoglobulin (Ig). In particular embodiments, the Fab of the Fzd binding region is present within the full Ig. In particular embodiments, the Fab of the LRP5/6 binding region is fused to the N-terminus of the Ig. In particular embodiments, the Fab of the LRP5/6 binding region is fused to the C-terminus of the Ig. In a further embodiment, the Fab of the LRP5/6 binding region is present within the full Ig. In particular embodiments, the Fab of the Fzd binding region is fused to the N-terminus of the Ig. In particular embodiments, the Fab of the Fzd binding region is fused to the C-terminus of the Ig.

In another embodiment, any of the Fzd binding regions comprises a Nanobody®, and the LRP5/6 binding region comprises a Nanobody®. In particular embodiments, the Fzd binding region is fused to the Lrp5/6 binding region, and wherein the Fzd binding region or the LRP5/6 binding region is fused to an Fc region. In particular embodiments, the Fzd binding region is fused to the N-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the C-terminus of an Fc region. In particular embodiments, the Fzd binding region is fused to the C-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the N-terminus of an Fc region.

In a further embodiment, any of the antibodies or one or more antigen-binding fragment thereof, is humanized. In a further embodiment, any of the Wnt surrogate molecules binds to one or more Fzd receptor with a K_D of 50 μM or lower. In further embodiments, any of the Wnt surrogate molecules binds to LRP5 and/or LRP6 with a K_D of 50 μM or lower.

In a further embodiment, any of the Wnt surrogate molecule modulates a Wnt signaling pathway in a cell, optionally a mammalian cell. In particular embodiments, the Wnt surrogate molecule increases signaling via the Wnt signaling pathway in the cell. In particular embodiments, the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway.

In a related embodiment, the present disclosure provides an isolated polynucleotide encoding a polypeptide sequence comprising one or more of the Fzd binding regions and/or one or more of the LRP5/6 binding regions of a Wnt surrogate molecule. In particular embodiments, the present disclosure provides an expression vector comprising the isolated

polynucleotide. In further particular embodiments, the present disclosure provides an isolated host cell comprising the expression vector.

In a related embodiment, the present disclosure provides a pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of any of the Wnt surrogate molecules disclosed herein.

In related embodiments, the present disclosure provides a method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell any of the Wnt surrogate molecules, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

In particular embodiments, the present disclosure provides a method for treating a subject having a disease or disorder associated with reduced Wnt signaling, comprising administering to the subject an effective amount of the pharmaceutical composition, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway. In particular embodiments, the disease or disorder is selected from the group consisting of: bone fractures, osteoporosis, osteoporotic fractures, spinal fusion, osseointegration of orthopedic devices, tendon-bone integration, tooth growth and regeneration, dental implantation, periodontal diseases, maxillofacial reconstruction, osteonecrosis of the jaw, alopecia, hearing loss, vestibular hypofunction, macular degeneration, vitreoretinopathy, diseases of retinal degeneration, Fuchs' dystrophy, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, spinal cord injuries, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), metabolic syndrome, diabetes, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, coronary artery disease, acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), acute liver failure, acute alcoholic liver injuries, chronic liver diseases with hepatitis C virus (HCV), HCV subjects post-antiviral drug therapies, chronic liver diseases with hepatitis B virus (HBV), fibrosis, HBV subjects post-antiviral drug therapies, chronic alcoholic liver diseases, non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis (NASH), cirrhosis, and chronic liver insufficiencies of all causes. In certain embodiments, the disease or disorder is a bone disease or disorder. In

particular embodiments, the disease or disorder is a bone disease or disorder, and the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6. In certain embodiments, the disease or disorder is a bone disease or disorder, and the Wnt surrogate molecule binds Fzd1, Fzd2, FZD7, Fzd5 and Fzd8, and also binds LRP5 and/or LRP6.

In another related embodiment, the present disclosure provides a method for increasing bone mineral density, increasing bone volume, increasing bone cortical thickness, increasing bone mineral apposition rate, increasing bone stiffness, increasing bone biomechanical strength, increasing resistance to bone fracture, or decreasing bone loss associated with osteoporosis, in a subject in need thereof, comprising providing to the subject an effective amount of a pharmaceutical composition comprising a Wnt surrogate molecule, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway. In certain embodiments, the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6. In certain embodiments, the Wnt surrogate molecule binds Fzd1, Fzd2, FZD7, Fzd5 and Fzd8, and also binds LRP5 and/or LRP6.

In a further related embodiment, the present disclosure provides a method for increasing liver to body weight ratio, promoting liver regeneration, increasing liver cell proliferation or mitosis, decreasing liver fibrosis, optionally following a chronic liver injury, increasing hepatocyte function, or decreasing coagulation time in liver, in a subject in need thereof, comprising providing to the subject an effective amount of a pharmaceutical composition comprising a Wnt surrogate molecule, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A-D. Schematic diagrams of illustrative formats of Wnt surrogate molecules.

FIGS. 2A-2D. Characterization of a Wnt surrogate molecule, R2M3-26.

FIGS. 3A-3D. Characterization of a Wnt surrogate molecule, R2M3-32.

FIGS. 4A-4B. Graphs showing that R2M3-26 and R2M3-32 activities can be inhibited by soluble Fzd ECD and by R2M3 IgG alone without the Lrp binding arm.

FIG. 5. Characterization of illustrative R2M3-Lrp6 binder fusions in 293, Huh7, A375, and BNL.CL2 Wnt dependent reporter assays.

FIG. 6. Characterization of illustrative 18R5-Lrp6 binder fusions in 293, A375, and BNL.CL2 Wnt dependent reporter assays.

FIG. 7. Characterization of illustrative18R5-Lrp5 binder fusions in 293 Wnt dependent reporter assays.

FIG. 8A-8B. Characterization of illustrative Fzd binders-Lrp6 binder 26 fusions in 293 Wnt dependent reporter assays.

FIG. 9. SAR analysis of illustrative Wnt surrogate molecules in the IgG-Nab fusion format.

FIG. 10. Characterization of R2M3-26 in the Fab format.

FIG. 11. Characterization of R2M3-32 in the Fab format.

FIG. 12. Characterization of R2M3-26 in the Hetero-Ig format.

FIG. 13. Characterization of 26-17SB9 in the Nab-Nab format.

FIG. 14. In vivo PK/PD characterization of R2M3-26.

FIG. 15. Sequences of polypeptide chains of illustrative Wnt surrogates.

FIGS. 16A-16E. Images and graphs showing that systemic expression of 18R5-DKK1c for 14 days results in increased bone mineral density. *P value <0.05; ** P value <0.0001. For each time point, the bars from left to right are as follows: vehicle (diamond), romosozumab (square), AAV CAG-GFP (triangle), AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His (inverted triangle), and AAV 18R5-DKK1c-FLagHis (circle).

FIGS. 17A-17D. Images and graphs showing that systemic expression of 18R5-DKK1c for 14 days or 28 days results in increased bone volume. For each time point, the bars from left to right are as follows: vehicle,

romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FLagHis. *P value <0.05; ** P value <0.0001, **** P value <0.0001.

FIGS.18A-18B. Graphs showing the dynamic parameters of bone formation based on fluorochrome labelling. For each time point, the bars from left to right are as follows: vehicle, romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FLagHis.

FIGS. 19A-19D. Graphs and images showing that systemic expression of 18R5-DKK1c results in increased osteoblast and reduced osteoclast on bone surface. For each time point, the bars from left to right are as follows: vehicle, romosozumab, AAV CAG-GFP, AAV ScFv (anti-GFP)-DKK1cF234K-Flag-His, and AAV 18R5-DKK1c-FLagHis. ** P value <0.05.

FIGS. 20A-20C. Diagram of assay for bone stiffness and fracture and graphs showing ultimate load to failure and stiffness in mice treated as indicated.

FIGS. 21A-21D. Graphs and images showing that systemic treatment with R2M3-26 results in rapid and sustained increase in bone after one week. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom. **** indicates P value <0.0001.

FIGS. 22A-22E. Images and graphs showing that R2M3-26 treatment rapidly reverses the bone loss associated with ovariectomy-induced osteoporosis. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom.

FIGS. 23A-23C. Figures and graphs showing that a single injection of R2M3-26 rapidly increases bone volume.

FIGS. 24A-24D. Graphs showing that high doses of R2M3-26 and 1R-C07-26 significantly and rapidly increase bone formation in naïve mice. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom.

FIGS. 25A-25E. Graphs showing that R2M3-26 and 1R-C07-3 increase bone mineral density in naïve mice. For each timepoint, the bars from left to right correspond to the treatments indicated from top to bottom.

FIGS. 26A-26C. Liver (A), small intestine (B) and colon (C) to body weight ratio after treatment with AAV-delivered Wnt surrogates. (**) $p<0.01$. For each graph, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 27A-27B. Body weight (A) and liver to body weight (B) ratio after treatment with recombinantly produced Wnt surrogate proteins. (*) $p<0.05$. For each timepoint, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 28A-28D. Induction of proliferation markers in response to R2M3-26 and Rspo2 recombinant proteins. Liver Ki67 (A) and cyclinD1 (B) mRNA expression. Average count of PCNA (C) or phospho-histone H3 (D) positive nuclei per 10x field after immunohistochemistry staining with PCNA and phospho-histone H3 antibodies respectively. (*) $p<0.05$, (**) $p<0.01$, (***) $p<0.001$, (****) $p<0.0001$. For each timepoint, the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 29A-29H. Efficacy of AAV-delivered Wnt surrogate and R-Spondin in a thioacetamide-induced chronic liver disease model. Design for study 1 (A) and study 2 (B). Liver to body weight ratio (C-D), liver weight (E-F), liver collagen A1 mRNA expression (G) and percentage red area in liver histological sections stained with Sirius red (H) in response to AAV-delivered wnt surrogate and R-spondin in study 1 (C, E, G and H) and study 2 (D, F, H). (*) $p<0.05$, (**) $p<0.01$, (***) $p<0.001$, (****) $p<0.0001$. For each graph, the treatments shown from left to right correspond to those in the legend from top to bottom (not including baseline).

FIGS. 30A-30M. Efficacy of recombinantly produced Wnt surrogate and R-Spondin in a thioacetamide-induced chronic liver disease model. Study design (A). D-2, D0, D3, D7, D10, D14 represents days relative to the start of treatment with recombinant proteins. Liver to body weight ratio (B,

C), liver axin2 mRNA (D, E), cyclinD1 mRNA (F, G) and Ki67 mRNA (H, I) expression, average count of PCNA (J, K) or phospho-histone H3 (L, M) positive nuclei per 10x field after immunohistochemistry staining with PCNA and phospho-histone H3 antibodies respectively, in a study using Rspo2 mono treatment (B, D, F, H, J, L) or R2M3-26/Rspo2 combination treatment (C, E, G, I, K, M). Pro-thrombin time ratio relative to the average pro-thrombin time in plasma collected from control naïve mice without TAA exposure (N). (*) $p<0.05$, (**) $p<0.01$, (****) $p<0.0001$. No TAA treatment is indicated by the dashed line. For each bar graph timepoint, the treatments shown from left to right correspond to those in the legend shown above from top to bottom.

FIGS. 31A-31C. Efficacy of recombinantly produced Wnt surrogate and R-Spondin in a CCl_4-induced chronic liver disease model. Study design (A). Liver to body weight ratio (B) and pro-thrombin time (C) in response to CCl_4 treatment, R2M3-26 and Rspo2. (*) $p<0.05$, (**) $p<0.01$, (***) $p<0.001$, (****) $p<0.0001$. For each graph, the treatments shown from left to right correspond to those in the legend from top to bottom (not including baseline).

FIGS. 32A-32D. Induction of proliferation markers in response to recombinantly produced Wnt surrogate in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24 and 48 hours after treatment with acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (*) $p<0.05$, (***) $p<0.001$, (****) $p<0.0001$.

FIGS. 33A-33D. Induction of proliferation markers in response to R-Spondin in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24 and 48 hours after treatment with acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (**) $p<0.01$, (***) $p<0.001$, (****) $p<0.0001$.

FIGS. 34A-34D. Induction of proliferation markers in response to Wnt surrogate and R-Spondin in an acetaminophen-induced acute liver injury model. Study design (A). Serum level of alanine transferase at 24, 36, 48 and 60 hours after treatment with acetaminophen (B). Relative cyclinD1 (C) and Ki67 (D) mRNA expression. (*) $p<0.05$, (****) $p<0.0001$. For each timepoint,

the treatments shown from left to right correspond to those in the legend from top to bottom.

FIGS. 35A-35D. Efficacy of recombinantly produced Wnt surrogate and R-Spondin on the survival of mice after acetaminophen-induced liver injury. Study design (A). Survival curve of mice treated with the control anti-eGFP control protein or R2M3-26 (B), Rspo2 (C) or a combination of R2M3-26 and Rspo2 (D) recombinant proteins.

DETAILED DESCRIPTION

The present disclosure relates to Wnt surrogate molecules that bind to one or more Fzd receptor and one or more LRP5 or LRP6 receptor and modulate a downstream Wnt signaling pathway. In particular embodiments, the Wnt surrogate molecules activate a Wnt signaling pathway or increase signaling via a Wnt signaling pathway. In particular embodiments, the Wnt surrogate molecules disclosed herein comprise: (i) one or more antibodies or antigen-binding fragments thereof that specifically bind to one or more Fzd receptor, including antibodies or antigen-binding fragments thereof having particular Fzd receptor specificity and/or functional properties; and (ii) one or more antibodies or antigen-binding fragments thereof that specifically bind to LRP5 and/or LRP6. Certain embodiments encompass specific structural formats or arrangements of the Fzd binding region(s) and LRP5/6 binding region(s) of Wnt surrogate molecules advantageous in increasing downstream Wnt pathway signaling and related biological effects.

Embodiments of the invention pertain to the use of Wnt surrogate molecules for the diagnosis, assessment and treatment of diseases and disorders associated with Wnt signaling pathways. In certain embodiments, the subject Wnt surrogate molecules are used to modulate a Wnt signaling pathway in a cell or tissue. In certain embodiments, the subject Wnt surrogate molecules are used in the treatment or prevention of diseases and disorders associated with aberrant or deregulated (e.g., reduced) Wnt signaling, or for

which modulating, e.g., increasing, Wnt signaling would provide a therapeutic benefit.

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, *Current Protocols in Molecular Biology* or *Current Protocols in Immunology*, John Wiley & Sons, New York, N.Y.(2009); Ausubel *et al.*, *Short Protocols in Molecular Biology*, 3rd ed., Wiley & Sons, 1995; Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); Maniatis *et al. Molecular Cloning: A Laboratory Manual* (1982); *DNA Cloning: A Practical Approach*, vol. I & II (D. Glover, ed.); *Oligonucleotide Synthesis* (N. Gait, ed., 1984); *Nucleic Acid Hybridization* (B. Hames & S. Higgins, eds., 1985); *Transcription and Translation* (B. Hames & S. Higgins, eds., 1984); *Animal Cell Culture* (R. Freshney, ed., 1986); Perbal, *A Practical Guide to Molecular Cloning* (1984) and other like references.

As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the content clearly dictates otherwise.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Each embodiment in this specification is to be applied *mutatis mutandis* to every other embodiment unless expressly stated otherwise.

Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly

accomplished in the art or as described herein. These and related techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of, molecular biology, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques may be used for recombinant technology, molecular biological, microbiological, chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of subjects.

Embodiments of the present invention relate to antibodies and antigen-binding fragments thereof that bind to one or more Fzd receptor. Sequences of illustrative antibodies, or antigen-binding fragments, or complementarity determining regions (CDRs) thereof, are set forth in SEQ ID NOs:1-65 or 129-132, Tables 1A and 1B, and Table 3. Anti-Fzd antibodies and antigen-binding fragments there that may be used or present in the Wnt surrogate molecules disclosed herein include, but are not limited to, those described in the U.S. provisional application no. 62/607,877, titled Anti-Frizzled Antibodies and Methods of Use, Attorney docket no. SRZN-004/00US, filed on December 19, 2017.

Embodiments of the present invention relate to antibodies and antigen-binding fragments thereof that bind to LRP5 and/or LRP6. Sequences of illustrative antibodies, or antigen-binding fragments, or complementarity determining regions (CDRs) thereof, are set forth in SEQ ID NOs:66-88 or 133, Tables 2A and 2B, and Table 3. Anti-LRP5/6 antibodies and antigen-binding fragments there that may be used or present in the Wnt surrogate molecules disclosed herein include, but are not limited to, those described in the U.S. provisional application no. 62/607,879, titled Anti-LRP5/6 Antibodies and

Methods of Use, Attorney docket no. SRZN-005/00US, filed on December 19, 2017.

As is well known in the art, an antibody is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one epitope recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as dAb, Fab, Fab', $F(ab')_2$, Fv), single chain (scFv), Nanobodies®, synthetic variants thereof, naturally occurring variants, fusion proteins comprising an antibody or an antigen-binding fragment thereof, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment (epitope recognition site) of the required specificity. "Diabodies", multivalent or multispecific fragments constructed by gene fusion (WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993) are also a particular form of antibody contemplated herein. Minibodies comprising a scFv joined to a CH3 domain are also included herein (S. Hu et al., Cancer Res., 56, 3055-3061, 1996). See *e.g.*, Ward, E. S. *et al.*, Nature 341, 544-546 (1989); Bird et al., Science, 242, 423-426, 1988; Huston et al., PNAS USA, 85, 5879-5883, 1988); PCT/US92/09965; WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993; Y. Reiter et al., Nature Biotech, 14, 1239-1245, 1996; S. Hu et al., Cancer Res., 56, 3055-3061, 1996.

The term "antigen-binding fragment" as used herein refers to a polypeptide fragment that contains at least one CDR of an immunoglobulin heavy and/or light chain, or of a Nanobody®, that binds to the antigen of interest, in particular to one or more Fzd receptor or LRP5 or LRP6 receptor. In this regard, an antigen-binding fragment of the herein described antibodies may comprise 1, 2, 3, 4, 5, or all 6 CDRs of a VH and VL sequence set forth herein from antibodies that bind one or more Fzd receptor or LRP5 and/or LRP6. In particular embodiments, an antigen-binding fragment may comprise all three

VH CDRs or all three VL CDRs. Similarly, an antigen binding fragment thereof may comprise all three CDRs of a Nanobody®. An antigen-binding fragment of a Fzd-specific antibody is capable of binding to a Fzd receptor. An antigen-binding fragment of a LRP5/6-specific antibody is capable of binding to a LRP5 and/or LRP6 receptor. As used herein, the term encompasses not only isolated fragments but also polypeptides comprising an antigen-binding fragment of an antibody disclosed herein, such as, for example, fusion proteins comprising an antigen-binding fragment of an antibody disclosed herein, such as, e.g., a fusion protein comprising a Nanobody® that binds one or more Fzd receptors and a Nanobody® that binds LRP5 and/or LRP6.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. In certain embodiments, a binding agent (e.g., a Wnt surrogate molecule or binding region thereof) is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In certain embodiments, a Wnt surrogate molecule or binding region thereof (e.g., an antibody or antigen-binding fragment thereof) is said to specifically bind an antigen when the equilibrium dissociation constant is $\leq 10^{-7}$ or $\leq 10^{-8}$ M. In some embodiments, the equilibrium dissociation constant may be $\leq 10^{-9}$ M or $\leq 10^{-10}$ M.

In certain embodiments, antibodies and antigen-binding fragments thereof as described herein include a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain framework region (FR) set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*,

a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

The structures and locations of immunoglobulin CDRs and variable domains may be determined by reference to Kabat, E. A. et al., Sequences of Proteins of Immunological Interest. 4th Edition. US Department of Health and Human Services. 1987, and updates thereof, now available on the Internet (immuno.bme.nwu.edu).

A “monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an epitope. Monoclonal antibodies are highly specific, being directed against a single epitope. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal

antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$, Fv), single chain (scFv), Nanobodies®, variants thereof, fusion proteins comprising an antigen-binding fragment of a monoclonal antibody, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding fragment (epitope recognition site) of the required specificity and the ability to bind to an epitope, including Wnt surrogate molecules disclosed herein. It is not intended to be limited as regards the source of the antibody or the manner in which it is made (*e.g.*, by hybridoma, phage selection, recombinant expression, transgenic animals, etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the F(ab) fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the $F(ab')_2$ fragment which comprises both antigen-binding sites. An Fv fragment for use according to certain embodiments of the present invention can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions of an IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent $V_H::V_L$ heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar *et al.* (1972) *Proc. Nat. Acad. Sci. USA 69*:2659-2662; Hochman *et al.* (1976) *Biochem 15*:2706-2710; and Ehrlich *et al.* (1980) *Biochem 19*:4091-4096.

In certain embodiments, single chain Fv or scFV antibodies are contemplated. For example, Kappa bodies (Ill *et al.*, *Prot. Eng*. 10: 949-57 (1997); minibodies (Martin *et al.*, *EMBO J* 13: 5305-9 (1994); diabodies (Holliger *et al.*, *PNAS* 90: 6444-8 (1993); or Janusins (Traunecker *et al.*, *EMBO J* 10: 3655-59 (1991) and Traunecker *et al., Int. J. Cancer Suppl*. 7: 51-52

(1992), may be prepared using standard molecular biology techniques following the teachings of the present application with regard to selecting antibodies having the desired specificity. In still other embodiments, bispecific or chimeric antibodies may be made that encompass the ligands of the present disclosure. For example, a chimeric antibody may comprise CDRs and framework regions from different antibodies, while bispecific antibodies may be generated that bind specifically to one or more Fzd receptor through one binding domain and to a second molecule through a second binding domain. These antibodies may be produced through recombinant molecular biological techniques or may be physically conjugated together.

A single chain Fv (scFv) polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston *et al.* (1988) *Proc. Nat. Acad. Sci. USA 85*(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an scFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston *et al.*; and U.S. Pat. No. 4,946,778, to Ladner *et al.*

In certain embodiments, an antibody as described herein is in the form of a diabody. Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (*e.g.* by a peptide linker) but unable to associate with each other to form an antigen binding site: antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide within the multimer (WO94/13804).

A dAb fragment of an antibody consists of a VH domain (Ward, E. S. *et al.*, Nature 341, 544-546 (1989)).

Where bispecific antibodies are to be used, these may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. *Current Opinion Biotechnol*. 4, 446-449 (1993)), *e.g.* prepared chemically or from hybrid hybridomas, or may be any of the bispecific antibody fragments mentioned above. Diabodies and scFv can be constructed without an Fc region, using only variable domains, potentially reducing the effects of anti-idiotypic reaction.

Bispecific diabodies, as opposed to bispecific whole antibodies, may also be particularly useful because they can be readily constructed and expressed in *E. coli*. Diabodies (and many other polypeptides such as antibody fragments) of appropriate binding specificities can be readily selected using phage display (WO94/13804) from libraries. If one arm of the diabody is to be kept constant, for instance, with a specificity directed against antigen X, then a library can be made where the other arm is varied and an antibody of appropriate specificity selected. Bispecific whole antibodies may be made by knobs-into-holes engineering (J. B. B. Ridgeway et al., *Protein Eng*., 9, 616-621, 1996).

In certain embodiments, the antibodies described herein may be provided in the form of a UniBody®. A UniBody® is an IgG4 antibody with the hinge region removed (see GenMab Utrecht, The Netherlands; see also, *e.g.*, US20090226421). This proprietary antibody technology creates a stable, smaller antibody format with an anticipated longer therapeutic window than current small antibody formats. IgG4 antibodies are considered inert and thus do not interact with the immune system. Fully human IgG4 antibodies may be modified by eliminating the hinge region of the antibody to obtain half-molecule fragments having distinct stability properties relative to the corresponding intact IgG4 (GenMab, Utrecht). Halving the IgG4 molecule leaves only one area on the UniBody® that can bind to cognate antigens (*e.g.*, disease targets) and the UniBody® therefore binds univalently to only one site on target cells.

In certain embodiments, the antibodies of the present disclosure may take the form of a Nanobody®. Nanobody® technology was originally

developed following the discovery and identification that *camelidae* (e.g., camels and llamas) possess fully functional antibodies that consist of heavy chains only and therefore lack light chains. These heavy-chain only antibodies contain a single variable domain(V_{HH}) and two constant domains (C_H2, C_H3). The cloned and isolated single variable domains have full antigen binding capacity and are very stable. These single variable domains, with their unique structural and functional properties, form the basis of "Nanobodies®". Nanobodies® are encoded by single genes and are efficiently produced in almost all prokaryotic and eukaryotic hosts *e.g. E. coli* (see *e.g.* U.S. Pat. No. 6,765,087), molds (for example *Aspergillus* or *Trichoderma*) and yeast (for example *Saccharomyces, Kluyvermyces, Hansenula* or *Pichia* (see *e.g.* U.S. Pat. No. 6,838,254). The production process is scalable and multi-kilogram quantities of Nanobodies® have been produced. Nanobodies® may be formulated as a ready-to-use solution having a long shelf life. The Nanoclone® method (see, e.g., WO 06/079372) is a proprietary method for generating Nanobodies® against a desired target, based on automated high-throughput selection of B-cells. Nanobodies® are single-domain antigen-binding fragments of camelid-specific heavy-chain only antibodies. Nanobodies®, also referred to as VHH antibodies, typically have a small size of around 15 kDa.

In certain embodiments, the antibodies or antigen-binding fragments thereof as disclosed herein are humanized. This refers to a chimeric molecule, generally prepared using recombinant techniques, having an antigen-binding site derived from an immunoglobulin from a non-human species and the remaining immunoglobulin structure of the molecule based upon the structure and/or sequence of a human immunoglobulin. The antigen-binding site may comprise either complete variable domains fused onto constant domains or only the CDRs grafted onto appropriate framework regions in the variable domains. Epitope binding sites may be wild type or modified by one or more amino acid substitutions. This eliminates the constant region as an immunogen in human individuals, but the possibility of an immune response to the foreign variable region remains (LoBuglio, A. F. *et al.*, (1989) *Proc Natl Acad Sci USA*

86:4220-4224; Queen *et al.*, *PNAS* (1988) 86:10029-10033; Riechmann *et al.*, *Nature* (1988) 332:323-327). Illustrative methods for humanization of the anti-Fzd antibodies disclosed herein include the methods described in U.S. patent no. 7,462,697.

Another approach focuses not only on providing human-derived constant regions, but modifying the variable regions as well so as to reshape them as closely as possible to human form. It is known that the variable regions of both heavy and light chains contain three complementarity-determining regions (CDRs) which vary in response to the epitopes in question and determine binding capability, flanked by four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When nonhuman antibodies are prepared with respect to a particular epitope, the variable regions can be "reshaped" or "humanized" by grafting CDRs derived from nonhuman antibody on the FRs present in the human antibody to be modified. Application of this approach to various antibodies has been reported by Sato, K., *et al.*, (1993) *Cancer Res* 53:851-856. Riechmann, L., *et al.*, (1988) *Nature* 332:323-327; Verhoeyen, M., *et al.*, (1988) *Science* 239:1534-1536; Kettleborough, C. A., *et al.*, (1991) *Protein Engineering* 4:773-3783; Maeda, H., *et al.*, (1991) *Human Antibodies Hybridoma* 2:124-134; Gorman, S. D., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:4181-4185; Tempest, P. R., *et al.*, (1991) *Bio/Technology* 9:266-271; Co, M. S., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:2869-2873; Carter, P., *et al.*, (1992) *Proc Natl Acad Sci USA* 89:4285-4289; and Co, M. S. *et al.*, (1992) *J Immunol* 148:1149-1154. In some embodiments, humanized antibodies preserve all CDR sequences (for example, a humanized mouse antibody which contains all six CDRs from the mouse antibodies). In other embodiments, humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

In certain embodiments, the antibodies of the present disclosure may be chimeric antibodies. In this regard, a chimeric antibody is comprised of

an antigen-binding fragment of an antibody operably linked or otherwise fused to a heterologous Fc portion of a different antibody. In certain embodiments, the heterologous Fc domain is of human origin. In other embodiments, the heterologous Fc domain may be from a different Ig class from the parent antibody, including IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG (including subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. In further embodiments, the heterologous Fc domain may be comprised of CH2 and CH3 domains from one or more of the different Ig classes. As noted above with regard to humanized antibodies, the antigen-binding fragment of a chimeric antibody may comprise only one or more of the CDRs of the antibodies described herein (*e.g.*, 1, 2, 3, 4, 5, or 6 CDRs of the antibodies described herein), or may comprise an entire variable domain (VL, VH or both).

Wnt Surrogates

The disclosure provides, in certain aspects, Wnt surrogate molecules that bind both one or more Fzd receptors and one or both of LRP5 and/or LRP6. Wnt surrogate molecules may also be referred to as "Wnt surrogates" or "Wnt mimetics." In particular embodiments, the Wnt surrogate molecules bind one or more human Fzd receptors and one or both of a human LRP5 and/or a human LRP6.

In certain embodiments, a Wnt surrogate molecule is capable of modulating or modulates Wnt signaling events in a cell contacted with the Wnt surrogate molecule. In certain embodiments, the Wnt surrogate molecule increases Wnt signaling, e.g., via the canonical Wnt/β-catenin pathway. In certain embodiments, the Wnt surrogate molecule specifically modulates the biological activity of a human Wnt signaling pathway.

Wnt surrogate molecules of the present invention are biologically active in binding to one or more Fzd receptor and to one or more of LRP5 and LRP6, and in activation of Wnt signaling, i.e., the Wnt surrogate molecule is a Wnt agonist. The term "Wnt agonist activity" refers to the ability of an agonist to mimic the effect or activity of a Wnt protein binding to a frizzled protein and/or LRP5 or LRP6. The ability of the Wnt surrogate molecules and other Wnt

agonists disclosed herein to mimic the activity of Wnt can be confirmed by a number of assays. Wnt agonists typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the Wnt agonists disclosed herein activate, enhance or increase the canonical Wnt/β-catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of a Wnt agonist, e.g., a Wnt surrogate molecule disclosed herein. In particular embodiments, the increase in the level of Wnt/β-catenin signaling is at least 10%, at least 20%, at least 50%, at least two-fold, at least five-fold, at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold as compared to the level of Wnt/β-catenin signaling in the absence of the Wnt agonist, e.g., in the same cell type. Methods of measuring Wnt/β-catenin signaling are known in the art and include those described herein.

In particular embodiments, Wnt surrogate molecules disclosed herein are bispecific, i.e., they specifically bind to two or more different epitopes, e.g., one or more Fzd receptor, and LRP5 and/or LRP6.

In particular embodiments, Wnt surrogate molecules disclosed herein are multivalent, e.g., they comprise two or more regions that each specifically bind to the same epitope, e.g., two or more regions that bind to an epitope within one or more Fzd receptor and/or two or more regions that bind to an epitope within LRP5 and/or LRP6. In particular embodiments, they comprise two or more regions that bind to an epitope within one or more Fzd receptor and two or more regions that bind to an epitope within LRP5 and/or LRP6. In certain embodiments, Wnt surrogate molecules comprise a ratio of the number of regions that bind one or more Fzd receptor to the number of regions that bind LRP5 and/or LRP6 of or about: 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 2:3, 2:5, 2:7, 7:2, 5:2, 3:2, 3:4, 3:5, 3:7, 3:8, 8:3, 7:3, 5:3, 4:3, 4:5, 4:7, 4:9, 9:4, 7:4, 5:4, 6:7, 7:6, 1:2, 1:3, 1:4, 1:5, or 1:6. In certain embodiments, Wnt surrogate molecules are bispecific and multivalent.

Wnt surrogate molecules disclosed herein may have any of a variety of different structural formats or configurations. Wnt surrogate molecules may comprise polypeptides and/or non-polypeptide binding moieties, e.g., small molecules. In particular embodiments, Wnt surrogate molecules comprise both a polypeptide region and a non-polypeptide binding moiety. In certain embodiments, Wnt surrogate molecules may comprise a single polypeptide, or they may comprise two or more, three or more, or four or more polypeptides. In certain embodiments, one or more polypeptides of a Wnt surrogate molecule are antibodies or antigen-binding fragments thereof. In certain embodiments, Wnt surrogates comprise two antibodies or antigen binding fragments thereof, one that binds one or more Fzd and one that binds LRP5 and/or LRP6. In certain embodiments, the Wnt surrogates comprises one, two, three, or four polypeptides, e.g., linked or bound to each other or fused to each other.

When the Wnt surrogate molecules comprise a single polypeptide, they may be a fusion protein comprising one or more Fzd binding domain and one or more LRP5/6 binding domain. The binding domains may be directly fused or they may be connected via a linker, e.g., a polypeptide linker, including but not limited to any of those disclosed herein.

When the Wnt surrogate molecules comprise two or more polypeptides, the polypeptides may be linked via covalent bonds, such as, e.g., disulfide bonds, and/or noncovalent interactions. For example, heavy chains of human immunoglobulin IgG interact at the level of their CH3 domains directly, whereas, at the level of their CH2 domains, they interact via the carbohydrate attached to the asparagine (Asn) N84.4 in the DE turn. In particular embodiments, the Wnt surrogate molecules comprise one or more regions derived from an antibody or antigen-binding fragment thereof, e.g., antibody heavy chains or antibody light chains or fragments thereof. In certain embodiments, a Wnt surrogate polypeptide comprises two antibody heavy chain regions (e.g., hinge regions) bound together via one or more disulfide bond. In certain embodiments, a Wnt surrogate polypeptide comprises an

antibody light chain region (e.g., a C_L region) and an antibody heavy chain region (e.g., a C_H1 region) bound together via one or more disulfide bond.

Wnt surrogate polypeptides may be engineered to facilitate binding between two polypeptides. For example, Knob-into-holes amino acid modifications may be introduced into two different polypeptides to facilitate their binding. Knobs-into-holes amino acid (AA) changes is a rational design strategy developed in antibody engineering, used for heterodimerization of the heavy chains, in the production of bispecific IgG antibodies. AA changes are engineered in order to create a knob on the CH3 of the heavy chains from a first antibody and a hole on the CH3 of the heavy chains of a second antibody. The knob may be represented by a tyrosine (Y) that belongs to the 'very large' IMGT volume class of AA, whereas the hole may be represented by a threonine (T) that belongs to the 'small' IMGT volume class. Other means of introducing modifications into polypeptides to facilitate their binding are known and available in the art. For example, specific amino acids may be introduced and used for cross-linking, such as Cysteine to form an intermolecular disulfide bond.

Wnt surrogate molecules may have a variety of different structural formats, including but not limited to those shown in FIG. 1.

In one embodiment, a Wnt surrogate molecule comprises an scFv or antigen-binding fragment thereof fused to a Nanobody® or antigen-binding fragment thereof. In certain embodiments, the scFv specifically binds one or more Fzd receptor, and the Nanobody® specifically binds LRP5 and/or LRP6. In certain embodiments, the scFv specifically binds LRP5 and/or LRP6, and the Nanobody® specifically binds one or more Fzd receptor. In particular embodiments, the scFv or antigen-binding fragment thereof is fused directly to the Nanobody® or antigen-binding fragment thereof, whereas in other embodiments, the two binding regions are fused via a linker moiety. In particular embodiments, the Nanobody® is fused to the N-terminus of the scFV, while in other embodiments, the Nanobody® is fused to the C-terminus of the scFv. In particular embodiments, the scFv is described herein or comprises any

of the CDR sets described herein. In particular embodiments, the Nanobody® is described herein or comprises any of the CDR sets disclosed herein.

In various embodiments, including but not limited to those depicted in FIG. 1A, a Wnt surrogate molecule comprises one or more Fab or antigen-binding fragment thereof and one or more Nanobody® or antigen-binding fragment thereof (or alternatively, one or more scFv or antigen-binding fragment thereof). In certain embodiments, the Fab specifically binds one or more Fzd receptor, and the Nanobody® (or scFv) specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds LRP5 and/or LRP6, and the Nanobody® (or scFv) specifically binds one or more Fzd receptor. In certain embodiments, the Nanobody® (or scFv) is fused to the N-terminus of the Fab, while in some embodiments, the Nanobody (or scFv) is fused to the C-terminus of the Fab. In particular embodiments, the Fab is present in a full IgG format, and the Nanobody® (or scFv) is fused to the N-terminus and/or C-terminus of the IgG light chain. In particular embodiments, the Fab is present in a full IgG format, and the Nanobody® (or scFv) is fused to the N-terminus and/or C-terminus of the IgG heavy chain. In particular embodiments, two or more Nanobodies® (or scFvs) are fused to the IgG at any combination of these locations.

Fabs may be converted into a full IgG format that includes both the Fab and Fc fragments, for example, using genetic engineering to generate a fusion polypeptide comprising the Fab fused to an Fc region, i.e., the Fab is present in a full IgG format. The Fc region for the full IgG format may be derived from any of a variety of different Fcs, including but not limited to, a wild-type or modified IgG1, IgG2, IgG3, IgG4 or other isotype, e.g., wild-type or modified human IgG1, human IgG2, human IgG3, human IgG4, human IgG4Pro (comprising a mutation in core hinge region that prevents the formation of IgG4 half molecules), human IgA, human IgE, human IgM, or the modified IgG1 referred to as IgG1 LALAPG. The $L_{235}A$, $P_{329}G$ (LALA-PG) variant has been shown to eliminate complement binding and fixation as well as Fc-γ dependent antibody-dependent cell-mediated cytotoxity

(ADCC) in both murine IgG2a and human IgG1. These LALA-PG substitutions allow a more accurate translation of results generated with an "effectorless" antibody framework scaffold between mice and primates. In particular embodiments of any of the IgG disclosed herein, the IgG comprises one or more of the following amino acid substitutions: N297G, N297A, N297E, L234A, L235A, or P236G.

Non-limiting examples of bivalent and bispecific Wnt surrogate molecules that are bivalent towards both the one or more Fzd receptor and the LRP5 and/or LRP6 are provided as the top four structures depicted in FIG. 1A, where the Nanobody® or scFv is depicted in white, and the Fab or IgG is depicted in black. As shown, the Nanobodies® (or scFvs) may be fused to the N-termini of both light chains, to the N-termini of both heavy chains, to the C-termini of both light chains, or to the C-termini of both heavy chains. It is further contemplated, e.g., that Nanobodies® (or scFvs) could be fused to both the N-termini and C-termini of the heavy and/or light chains, to the N-termini of the light chains and the heavy chains, to the C-termini of the heavy and light chains, to the N-termini of the heavy chains and C-termini of the light chains, or to the C-termini of the heavy chains and the N-termini of the light chains. In other related embodiments, two or more Nanobodies® (or scFvs) may be fused together, optionally via a linker moiety, and fused to the Fab or IgG at one or more of these locations. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas the Fab is present as a half antibody, and one or more Nanobody® (or scFv) is fused to one or more of the N-terminus of the Fc, the N-terminus of the Fab, the C-terminus of the Fc, or the C-terminus of the Fab. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1A. In certain embodiments, the Fab or antigen-binding fragment (or IgG) thereof is fused directly to the Nanobody® (or scFv) or antigen-binding fragment thereof, whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments, the Fab is described herein or comprises any of the CDR sets described herein. In

particular embodiments, the Nanobody® or scFv is described herein or comprises any of the CDR sets disclosed herein.

In various embodiments, including but not limited to those depicted in FIG. 1B, a Wnt surrogate molecule comprises one or more Fab or antigen-binding fragment thereof that binds one or more Fzd receptor and one or more Fab or antigen-binding fragment thereof that binds LRP5 and/or LRP6. In certain embodiments, it comprises two Fab or antigen-binding fragments thereof that bind one or more Fzd receptor and/or two Fab or antigen-binding fragments thereof that bind LRP5 and/or LRP6. In particular embodiments, one or more of the Fab is present in a full IgG format, and in certain embodiments, both Fab are present in a full IgG format. In certain embodiments, the Fab in full IgG format specifically binds one or more Fzd receptor, and the other Fab specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds one or more Fzd receptor, and the Fab in full IgG format specifically binds LRP5 and/or LRP6. In certain embodiments, the Fab specifically binds LRP5 and/or LRP6, and the Fab in full IgG format specifically binds one or more Fzd receptor. In certain embodiments, the Fab is fused to the N-terminus of the IgG, e.g., to the heavy chain or light chain N-terminus, optionally via a linker. In certain embodiments, the Fab is fused to the N-terminus of the heavy chain of the IgG and not fused to the light chain. In particular embodiments, the two heavy chains can be fused together directly or via a linker. An example of such a bispecific and bivalent with respect to both receptors is shown at the top of FIG. 1B. In other related embodiments, two or more Nanobodies® may be fused together, optionally via a linker moiety, and fused to the Fab or IgG at one or more of these locations. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas one of the Fab is present as a half antibody, and the other Fab is fused to one or more of the N-terminus of the Fc, the N-terminus of the Fab, or the C-terminus of the Fc. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1B. In certain embodiments, the Fab or antigen-binding fragment thereof is fused directly to the other Fab or IgG or

antigen-binding fragment thereof, whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments, the one or both of the two Fabs are described herein or comprise any of the CDR sets described herein.

In certain embodiments, Wnt surrogate molecules have a format as described in PCT Application Publication No. WO2017/136820, e.g., a Fabs-in-tandem IgG (FIT-IG) format. Shiyong Gong, Fang Ren, Danqing Wu, Xuan Wu & Chengbin Wu (2017). FIT-IG also include the formats disclosed in "Fabs-in-tandem immunoglobulin is a novel and versatile bispecific design for engaging multiple therapeutic targets" mAbs, 9:7, 1118-1128, DOI: 10.1080/19420862.2017.1345401. In certain embodiments, FIT-IGs combine the functions of two antibodies into one molecule by re-arranging the DNA sequences of two parental monoclonal antibodies into two or three constructs and co-expressing them in mammalian cells. Examples of FIT-IG formats and constructs are provided in FIGS. 1A and 1B and FIGS. 2A and 2B of PCT Application Publication No. WO2017/136820. In certain embodiments, FIT-IGs require no Fc mutation; no scFv elements; and no linker or peptide connector. The Fab-domains in each arm work "in tandem" forming a tetravalent bi-specific antibody with four active and independent antigen binding sites that retain the biological function of their parental antibodies In particular embodiments, Wnt surrogates comprises a Fab and an IgG. In certain embodiments, the Fab binder LC is fused to the HC of the IgG, e.g., by a linker of various length in between. In various embodiment, the Fab binder HC can be fused or unfused to the LC of the IgG. A variation of this format has been called Fabs-in-tandem IgG (or FIT-Ig).

In particular embodiments, Wnt surrogate molecules comprise two or more Nanobodies® (or scFvs), including at least one that binds one or more Fzd receptor and at least one that binds LRP5 and/or LRP6. In certain embodiments, one of the binding regions is a Nanobody® and the other is an scFv. Wnt memetic molecules comprising two or more Nanobodies® (or scFvs) may be formatted in a variety of configurations, including but not limited to

those depicted in FIG. 1C. In certain bispecific, bivalent formats, two or more Nanobodies® (or scFvs) are fused in tandem or fused to two different ends of an Fc, optionally via one or more linkers. Where linkers are present, the linker and its length may be the same or different between the Nanobody® (or scFv) and the other Nanobody® (or scFv), or between the Nanobody® and Fc. For example, in certain embodiments, the Nanobody® is fused to the N-terminus and/or C-terminus of the IgG heavy chain. In particular embodiments, two or more Nanobodies® are fused to the IgG at any combination of these locations. Non-limiting examples of bivalent and bispecific Wnt surrogate molecules of this format are depicted as the top seven structures depicted in FIG. 1C, where the first Nanobody® is depicted in white, the Fc or IgG is depicted in black, and the second Nanobody® is depicted as light gray. In various embodiments, both Nanobodies® may be fused to the N-termini of the Fc, to the C-termini of the Fc, or one or more Nanobody® may be fused to either or both of an N-terminus or C-terminus of the Fc. In a related embodiment, the Wnt surrogate molecule has a Hetero-IgG format, whereas one Nanobody® is present as a half antibody, and the other is fused to the N-terminus of the Fc or the C-terminus of the Fc. A bispecific but monovalent to each receptor version of this format is depicted at the bottom of FIG. 1C. In certain embodiments, the Nanobody® is fused directly to the other Nanobody®, whereas in other embodiments, the binding regions are fused via a linker moiety. In particular embodiments, the Nanobodies® are described herein or comprises any of the CDR sets described herein. In various embodiments, any of these formats may comprise one or more scFvs in place of one or more Nanobodies®.

In certain embodiments, a Wnt surrogate molecule is formatted as a diabody. As shown in Fig. 1D, the binders against Fzd and LRP can also be linked together in a diabody (or DART) configuration. The diabody can also be in a single chain configuration. If the diabody is fused to an Fc, this will create a bivalent bispecific format. Without fusion to Fc, this would be a monovalent bispecific format. In certain embodiments, a diabody is a noncovalent dimer scFv fragment that consists of the heavy-chain variable (VH) and light-chain

variable (VL) regions connected by a small peptide linker. Another form of diabody is a single-chain (Fv)2 in which two scFv fragments are covalently linked to each other.

As discussed, Wnt surrogate molecules, in various embodiments, comprise one or more antibodies or antigen-binding fragments thereof disclosed herein. Thus, in particular embodiments, a Wnt surrogate comprises two polypeptides, wherein each polypeptide comprises an Nab or scFv that binds LRP5/6 and an Nab or scFv that binds one or more Wnts, optionally wherein one of the binding domains is an scFv and the other is an Nab. In certain embodiments, a Wnt surrogate comprises three polypeptides, wherein the first polypeptide comprises an antibody heavy chain and the second polypeptide comprises an antibody light chain, wherein the antibody heavy chain and light chain bind LRP5/6 or one or more Fzds, and wherein the third polypeptide comprises a nanobody fused to a heavy chain Fc region, wherein the nanobody binds to either LRP5/6 or one or more Fzds. In other embodiments, Wnt polypeptides comprise four polypeptides, including two heavy chain polypeptides and two light chain polypeptides, wherein the two heavy chains and two light chains bind LRP5/6 or one or more Fzds, and further comprise one or more Nab or scFv fused to one or more of the heavy chains and/or light chains, wherein the Nab or scFv binds to LRP5/6 or one or more Fzds. In another illustrative embodiment, a Wnt surrogate comprises at least four polypeptides, including two heavy chain polypeptides and two light chain polypeptides that bind either LRP5/6 or one or more Fzds, wherein the Wnt surrogate further comprises a Fab that binds either LRP5/6 or one or more Fzds. For example, the Fab may comprise two polypeptides, each fused to one of the two heavy chain polypeptides, and two polypeptides, each fused to one of the two light chain polypeptides, or it may comprise two polypeptides each fused to one of the two heavy chain polypeptides and two additional polypeptides, each bound to one of the two polypeptides fused to the heavy chain polypeptides, thus making a second Fab. Other configurations may be used to produce the Wnt surrogates disclosed herein.

In particular embodiments, a Wnt surrogate molecule comprises a Fzd binding region, e.g., an anti-Fzd antibody, or antigen-binding fragment thereof, fused or bound to a polypeptide that specifically binds to one or more Fzd receptor. In particular embodiments, the polypeptide that specifically binds to one or more Fzd receptor is an antibody or antigen-binding fragment thereof. If certain embodiments, it is an antibody or antigen-binding fragment thereof disclosed herein or in the U.S. provisional patent application no. 62/607,877, titled, "Anti-Frizzled antibodies and Methods of Use," Attorney docket number SRZN-004/00US, filed on December 19, 2017, which is incorporated herein by reference in its entirety. In particular embodiments, the Fzd binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1A. In particular embodiments, the Fzd binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1A, wherein the CDRs collectively comprise one, two, three, four, five, six, seven, or eight amino acid modifications, e.g., substitutions, deletions, or additions. In certain embodiments, the Fzd binding domain is a Nanobody® or was derived from a Nanobody®, so Table 1A only includes the three heavy chain CDRs. In particular embodiments, the Fzd binding domain comprises the three CDR HC sequences provided in Table 1A or variants wherein the CDRs collectively comprise one, two, three, four, five, six, seven or eight amino acid modifications. In particular embodiments, the Fzd binding domain comprises the heavy chain fragment and/or light chain fragment of any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 1B or SEQ ID NOs:1-65 or 129-132 (or an antigen-binding fragment or variant of either). In certain embodiments, the Fzd binding domain is an Fab or was derived from an Fab, so the heavy chain of Table 1B includes VH and CH1 sequence, but not CH2 or CH3 sequences. In certain embodiments, the Fzd binding domain is a Nanobody® or was derived from a Nanobody®, so Table

1B includes the VHH domain. In certain embodiments, the Fzd binding region is a polypeptide, e.g., an antibody or antigen-binding fragment thereof, that competes with any of these antibodies for binding to one or more Fzd receptor.

Table 1A: Anti-Fzd Antibody Clone IDs and CDR sequences

Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
001S-A01	Fzd1	YTFTSYGIS	GWISAYNGNTNYA	CARASAWTPYGAFDIW	SGSSSNIGSHTVS	SNYQRPS	CAAWDGSLFGHWVF
001S-B01	Fzd1	GSISSGGYSWS	GSIYHSGSTYYN	CARFYYDILTGYSYFDYW	RSSRSLLDTDDGNTYLD	TLSHRAS	CMQSIQLPWTF
001S-E01	Fzd1	GSISNYYWS	GEIDRSGDTNYN	CARVRARRFLVSDRSAFDIW	SGNTLGSHYVS	QDSKRPS	CQVWDSSTVVF
001S-F01	Fzd1	GSISGNNYYZG	GSIYFTGGTYYN	CARVMLITDAFDIW	RSSQSLLHSNGYNYLD	LGSNRAS	CMQGTHWPYTF
001S-G01	Fzd1	GSISSSSYYWG	GYIYYSGSTYYN	CARATYGGDAFDIW	TRSSSNIGAGYDVH	GNSIRPS	CGTWDSSLSAWVF
001S-H01	Fzd1	GSISSGGYYWS	GYIYYSGSTYYN	CARHAGFYGLADYFDYW	RSSQSLLHSNGYNYLD	LGSKRAS	CMQALQIPPTF
001S-A02	Fzd1	GSISSGGYYWS	GYIYYSGSTYYN	CARGKGYSYGYGKDWFDPW	QASQDIGKYLN	DASNLET	CQQNDYLPLTF
001S-E02	Fzd1	GSISGNNYYWG	GSIYFTGGTYYN	CARVMLITDAFDIW	RSSQSLLHSNGYNYLD	LGSNRAS	CMQGTHWPYTF
001S-G02	Fzd1	GAISGTSYFWG	GSIYYTGNTYYN	CARIGIAVAAPVDHW	RASQSVGTYLT	DASNRAT	CMQATQFPLTF
001S-H02	Fzd1	GSISSSSYYWG	GYIYYSGSTYYN	CARATYGGDAFDIW	TRSSSNIGAGYDVH	GNSIRPS	CGTWDSSLSAWVF
001S-A03	Fzd1	GSISSGGYYWS	GYIYYSGSTYYN	CARVRDYYDSSGYYYDYFDYW	RASRSISSYFN	AASSLQS	CQQADTFPPTF
001S-B03	Fzd1	ASFSGHYWT	GEIDHTGSTNYE	CARGGQGGYDWGHYHGLDVW	SGDKVGHKYAS	EDSQRPS	CQAWDSSTDVVF
001S-H08	Fzd5	RAFTDNVMA	ATISGGGGSTFDD	CAAASSLTSTPYDLW			
001S-A09	Fzd5	RSFRTNALG	AAISWTGGSTYYA	CNTVTYTGGSYKNYW			
001S-B09	Fzd5	SIDSINAMA	AALTSGGITYHA	CNVITIVRGMGPRAYW			
001S-C09	Fzd5	SIFSINAMG	ATIQSGGRTNYA	CNVITIVRGMGPRAYW			
001S-C07	Fzd8	YTFTSYGIS	GWISAYNGNTNYA	CARDGTPFYSGSYYGSW	QGDSLRTYYAS	GKNNRPS	CNSRDNSGKHKVF
001S-D07	Fzd8	GTFSSYAIS	GRIIPILGIANYA	CARVPTSPYDILTGPFDYW	RSSQSLLHSNGFNYVD	FGSYRAS	CMQNLQTPWTF
001S-E07	Fzd8	ASVSSNSAAWN	GRTYYRSKWYNDYA	CARWKNYFDPW	RASQGIRSDLA	AASTLES	CLQDYSYPRTF
001S-H07	Fzd8	FTFSSYAMS	STISGGGGSTYYA	CAKDLVPWGSSAFNIW	RASQSVSSYLA	GASSRAT	CQQYGSSPPTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
004S-E05	Fzd5	FTFSTYEMN	SGVSWNGSRTHYV	CARGQSEKWWSGLYGMDVW	RASQGISSALA	AASALQS	CQQTYSTPRTF
004S-E03	Fzd5	GTFSTYAIS	GWINSGNGNTKYS	CWTGLLWFGESTDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-G06	Fzd5	GTFTYRYLH	GGIIPIFGTGNYA	CASSMVRVPYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
001S-D09	Fzd8	GPFNLFAMG	AGISRTGGNTGYA	CASKTTINSGWSREYHYW			
001S-E09	Fzd8	GPFNLFAMG	AGISRTGGNTGYA	CASKTTINSGWSREYHYW			
001S-F09	Fzd8	GFFSSFTMG	AAISRNGVYTRFA	CNALAPGVRGSW			
001S-G09	Fzd8	SLFRLNGMG	ATISTRGTTHYA	CTDEESW			
001S-H09	Fzd8	GPFNLLAMG	AGISRTGGNTGYA	CASKTTINSGWSREYHYW			
001S-A10	Fzd8	SVVNFVVMG	AAITSGGSTNYA	CNRVGSREYSYW			
001S-B10	Fzd8	RTSDLYTMG	AAIGYKVKWNGERTYYL	CNAVTYNGYTIW			
001S-G12	Fzd1	SIFSSNTIY	ALITTSGNTNYA	CNAGAPAWTYRMGTYYPQFGSW			
002S-A01	Fzd1	STFSTYAMG	AAISGSGENTYYA	CVKFGMNLGYSGYDYW			
002S-B01	Fzd1	STFSNYAMG	AAISWGGGSTFYS	CAAGPIARWYRGDMDYW			
002S-C01	Fzd1	RMFSNYAMG	AAISSGGSGTYYS	CAAGPIARWYRGDMDYW			
002S-D01	Fzd1	RTDGGYVMG	ATVTWRTGTTYYA	CAAGPIARWYRGDMDYW			
002S-E01	Fzd1	RTFSSAAMG	AAISWSGSTAYYA	CATLTPYGTVASY			
002S-F01	Fzd1	RTFSSYAMG	AAVNWSGGSTYYA	CAAVFLSRNYEIQEYYRYQ			
002S-G01	Fzd1	RTFSSYAMG	AAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-H01	Fzd1	RSFSTYPMG	TVISGSGGSTYYS	CAAGPIARWYRGDMDYW			
002S-A02	Fzd1	RRFTTYGMG	AAVTWRSGSTYYA	CYLEGPLDVYW			

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
002S-B02	Fzd1	RTFNRHVMG	AAISWSGDSTYYA	CAKLGGSSWLREYDYW			
002S-C02	Fzd1	RTFRAYAMG	SAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-D02	Fzd1	RTFSEYAMG	AAISWSGGSTHYA	CNADSLRGIDYW			
002S-E02	Fzd1	FTFREYAMT	SGISRDGGRTSYS	CAPRVLVTAPSGGMDYW			
002S-F02	Fzd1	GDFTNYAMA	AAVNWRGDGTYYS	CAAVFLSRNYEIQEYYRYQ			
002S-G02	Fzd1	RTFGTWAMG	AAISYNGFSTYYS	CAAGPIARWYRGDMDYW			
002S-H02	Fzd1	RTFSSYAMG	AAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-D03	Fzd1	RTFGSYAMG	AAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-E03	Fzd1	SIFSIYAMG	AVVATGGATNYA	CNMRGNWYREGRPAEFLSW			
002S-F03	Fzd1	RTSSSYAMG	AAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-G03	Fzd1	RTFGSYAMG	AAISWSGGSTYYA	CAAGPIARWYRGDMDYW			
002S-H03	Fzd1	QTFTAYAMG	AAISWSGSATHYA	CNAWVLVAGSRGTSADYW			
002S-A04	Fzd1	RTFSSYAMG	AAISWSGRSTYYA	CAAGPIARWYRGDMDYW			
002S-B04	Fzd1	RTFSSYAMG	AAISWSGGSTYYA	CAAGPNYSWFMPSSSRLIW			
002S-C04	Fzd1	RRFTTYGMG	AAVTWRAGSTYYA	CSADKLDYLDDQPFKTWDYW			
002S-D04	Fzd1	GTSSTYAMG	AAINRSGGSTYYA	CAAVFLSRNYEIQEYYRYQ			
002S-E04	Fzd1	GTFSTYAMG	AAISWSGDSTYYL	CAAGPIARWYRGDMDYW			
004S-H04	Fzd5	GTFSSYAIS	GWISTYNGATNYA	CARGGAGRFGEGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
001S-A04	Fzd5	YTFTSYGIS	GWISAYNGNTNYA	CASSKEKATYYYGMDVW	GLSSGSVSTNYYPS	YTNTRSS	CLLYLGRGIWVF
001S-D03	Fzd5	GTFSSYAIS	GRIIPILGIANYA	CARLDPGYYYGMDVW	TGTSSDVGGYNSVS	DVTKRPS	CFSYAGSRF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
001S-F03	Fzd5	GTFSSYAIS	GGIIPIFGTANYA	CARVIFSTVTTTNDIW	TRSSGSIASNYVQ	ENDKRPS	CQSYDYDHRWVF
004S-E04	Fzd5	YTFSGYYLH	GTVTPILGTANYA	CARVDGSGYYGIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-A06	Fzd5	GSFSNYAIS	GRIIPILGSANYA	CARTYLKAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F04	Fzd5	YTFTNNFMH	GRINPNSGGTNYA	CARDRFDNWFDPW	RASQGISSALA	AASTLQS	CQQSYNTPWTF
001S-C03	Fzd5	GTFSSYAIS	GRIIPILGIANYA	CAREGRSRVYGGNSFDYW	RSSQSLLRRNGHNYVD	MGSNRAP	CMHGLHPPFTF
003S-A01	Fzd1	YIFTDYYMH	GGIIPIFGTANYA	CARMSSDYYDSSGYYRRGMDVW	RASQGISNNLN	GASTLQS	CQQADSFPPTF
003S-E01	Fzd1	YIFTDYYMH	GGIIPIFGTANYA	CARAWKGLWFGEGTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-F01	Fzd1	GTFSSYAIS	GWINAGNGNTTYA	CARLAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-A02	Fzd1	YTFTGYYMH	GWINAGNGNTTYA	CAKDRGNYGDYLDYW	RASQGISNYLA	EVSSVQG	CQQSYSTPLAF
003S-C02	Fzd1	FTFSNSDMN	ALISYDGSHTYYA	CTRGSRIGWFDPW	RASQSIGRWLA	AASRLQS	CQQGFNFPLTF
003S-E02	Fzd1	GTFSSYTIS	GGIIPISGKTDYA	CARARGGDSPLSL	RASQGISNNLN	TASSLQS	CLQDYSYPYTF
003S-F02	Fzd1	GTFRSYAIN	GGIIPIFGTANYA	CARGGWRPDYYGSGSYYSFDYW	RASQSVSSDLA	GASTRAT	CQQYETWPVLTF
003S-G02	Fzd1	FTFGTYWVT	SGITGSGGRTFYA	CARMKDWFGAFDIW	RASESVSSSSFA	GASTRAT	CQQYNNWPPNYTF
003S-C03	Fzd1	FTFSRYAMS	SYISGDSGYTNYA	CARGLVIATNWFDPW	QANQDISNYLN	AASSLQS	CQQTYNPPRTF
003S-D03	Fzd1	YTFTSYYMH	GWINTYNGNTNYP	CAESLTSTADW	RASQGISNNLN	AASSLQR	CQQSYSTPFTF
003S-E03	Fzd1	YIFTDYYMH	GWVNPTTGNTGYA	CARNVEGATSFPEFDYW	RASQGISNNLN	SASNLQS	CQQSYSPPPYTF
003S-H03	Fzd1	GTFSSYAIS	GGIIPIFGTANYA	CAKDIGSSWYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-A04	Fzd1	FTFGTYWVT	SGITGSGGRTFYA	CARMKDWFGAFDIW	RTSERSSISSFA	GASTRAT	CQQYNNWPRNYTF
003S-C04	Fzd1	FAVSSSYMS	ASIWFDGSNQDYA	CAPNESGNVDYW	RASQGISNNLN	KASSLEN	CQQSYSTPHTF
003S-D04	Fzd1	FTFSSYAMH	SAISGSGGSTYYA	CARDHGSSWYQNTDAFDIW	QASQDIGNYLN	DVSNLER	CQHLNSYPPGDTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
003S-G04	Fzd1	FRFISHPIH	GRVIPILGVTNYA	CASSSDYGDYLKEPNYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-D05	Fzd2	FTFSNYAMT	SAIGTGGGTYYA	CATAYRRPGGLDVW	RSSQSLLHSDGKTYLY	LGSNRAS	CMQNTHWPLTR
003S-E05	Fzd2	FTFSSYTMS	GRIKSKANGGTTDYA	CARGSSSWYDW	KSSQSLLHSDGKTYLY	LGSNRAS	CMQNTHWPLTR
003S-A06	Fzd2	FTFADYGMH	SYISSGSYTIYYS	CARGTFDWLLSPSYDYW	RASQGISNNLN	AASRLES	CQQSYSTPLTF
003S-C06	Fzd2	FTFSNYGMH	SAISNSGGSTYYA	CTSSFLTGSQPSGYW	RASQDISSYLA	AASSLQS	CQQSYRTPLTF
003S-G06	Fzd2	FTFSDYGMH	SSTSGSGGNSKYS	CARHNPGYMGYYYGMDVW	RASQSVSSNLA	DASNRAT	CQHRTSWPLTF
003S-H06	Fzd2	GTFSSYTIS	GLVDPEDGETIYA	CTILPAAAAGTYYYYGMDVW	RASQRVGNNLA	DASIRAT	CQQYKDWPTF
003S-B07	Fzd2	FTFSDHYMS	SSITRTPSGGTTEYA	CARDGGYW	RASQSVGSYLA	GSSNRAA	CQQYGTSLLTF
003S-D07	Fzd2	YTFTNNFMH	GIINPSGGSTSYA	CARATSLGRRYCSSTSCYPRDAFDIW	QASQGISNNLN	LGSDRAS	CQQSYSTPFTF
003S-E07	Fzd2	YTFTNNFMH	GWINPNSGGTKYA	CARSVGEVGATMLGIGVWYWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPFTF
003S-A08	Fzd2	FTFSNYAMT	SAIGTGGGTYYA	CATAYRRPGGLDVW	RSSQSLLHSDGKTYLY	LGFNRAS	CMQNTHWPLTR
003S-C08	Fzd2	LTVSTNFMS	AGIGWDSTNIGYA	CARDLVAARPSNWDYW	RASQGIRNDLG	GASTLQR	CQQSYSTPRVTF
003S-E08	Fzd2	FTFRNSAMH	STISGSGGSTYYS	CARGGGYSSSW	RSSRSLLHSDGKTYLY	LGSNRAS	CMQSSHWPKTF
003S-G09	Fzd4	FTFDHNPMN	SAIGAGGGTYYA	CASPTVTRR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-C10	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-D10	Fzd4	FNFGIYSMT	SYISGDSGYTNYA	CARVGPGGWFDPW	RASQGISSYLA	AASNLLG	CQQTYSTPWTF
003S-E10	Fzd4	FTFSSYAMH	AGISASGGSTYYA	CARPSTTGTKAFDIW	RASQSIGSNLD	AASTLET	CQQSYSVPDTF
003S-A11	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	RASQSISZYZN	ZASSLQS	CQQSYSTPLTF
003S-G11	Fzd4	GTFSSYAIS	GRIIPIFGTVNYA	CARGARLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-H11	Fzd4	YTFTGYYMH	GGIIPIFGTPHYA	CASTDPSSGLDYW	RASQSIGSNLD	DASSLES	CQQSFIMPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
003S-C12	Fzd4	GTFSSYAIS	GWINPNSGGTNYA	CARGGSSDVR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-F12	Fzd4	FTFSSYAMH	SVISTSGDTVLYT	CARGGSSDVR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-B01	Fzd4	GTFSSYAIS	GIINPSGGSTSYA	CAKDGVVR	RAIQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-C01	Fzd4	FTFSNHYTS	STISSSGGRTFYA	CARASRIDGGWPIIDHL	RASQDIRDELA	AASTLQS	CQQADSFPLTF
004S-D01	Fzd4	FTFTNYAMS	SAISGSGGSTYYA	CARATGFGTVVFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-E01	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	ZACLRIISYLN	FASSLQS	CQQSYSTPLTF
004S-F01	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARDGVE	RASQGISNWLA	DASSLQS	CQQSHITPYTF
004S-H01	Fzd4	FTFSNYAMH	ALMSPDGTIIYYA	CAKGIVGDYGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-B02	Fzd4	FTFSSYGMH	SSINNSSRTVFYA	CAKDHLAVADAHGR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-E02	Fzd4	FTFSSYAMH	AVISYDGSNEYYA	CAGGEVYEL	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F02	Fzd4	FTFSTYAMH	AVISSDGNNKYYT	CAAPDVVVTADGYYW	RASQGISSALA	AASTLQS	CQQANTVPFTF
004S-G02	Fzd4	FTFANYAMN	ALISYDGGTKYYA	CAKTLVTSHALHIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-H02	Fzd4	FTFANYAMH	ALISYDGGNKYYA	CAKTLVTSHALHIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
001S-E03	Fzd5	GSFSGYYWH	GEINHSGSTNYN	CARGRRLVRFTVTSAFDIW	TGSSSNIGAGFGVH	SDRNRPS	CQSYDSSLRASVF
001S-B05	Fzd5	GTFSSYAIS	GGIIPILGIANYA	CARIPKPRGYSYGDNGSW	RSSQSLLHSNGNTYLD	LGSDRTS	CMQSLQTPYTF
004S-A07	Fzd6	GNFKNYGIT	GRIIPALGTANYA	CARQYCSGGSCYPDAFDIR	RASQDIRSALA	QASSLIS	CQQSYSMPQTF
004S-B07	Fzd6	FTFSSYSMN	GVISKDGDNKYYA	CASSRDGYNRLAFDIW	QASQDIRNYLN	AASSLQS	CQQSSRFWTF
004S-A08	Fzd6	GTFSSYAIS	GRIIPILGIANYA	CARDGGDYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-B08	Fzd6	YTFTNNFMH	GRINPNSGGTNYA	CASQNYYGSGSYPGFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-D08	Fzd6	YTFTYRYLH	GGIIPIFGTANYA	CATHDSSGYYSFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
004S-E08	Fzd6	FSVSSNYMN	SAIGTGGGTYYA	CTTRTYDSSGYYETQNYYMDVW	RSSRSLLHSNGNTYLQ	LGSNRAS	CVQTTQSPLTF
004S-G08	Fzd6	FTFSDYYMS	AAISYDESNKFYA	CARSAVAGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-A09	Fzd6	FTFRDYAMN	SGISWNSGSIGYA	CARRSGYSGSVYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-B09	Fzd6	FTFSSFGMH	AGINWNGGSVVYA	CARGPSHQHTFDIW	RASQGISSALA	AASSLQS	CQQSYSHTAFTF
004S-C09	Fzd6	YTFTNNFMH	GGFDPEDGETIYA	CARVGRGYSFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-E09	Fzd6	DTFSNYVIS	GRISAYNGYKSYA	CARSSGYVGWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F09	Fzd6	FTFSNYYTS	SYISGAGGSTEYA	CARLPRRSGKGSAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-H09	Fzd6	GTFSSYTIS	GWMNPNSGNTGYA	CARVGATSAGGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-C10	Fzd6	YIFTDYYMH	GLVDPEDGETIYA	CAHSDFFSGLSFGDW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-D10	Fzd6	FTFSNSDMN	SSISTSGGSTYYA	CARGSYW	RASQNINNYLA	RASTLQS	CQQYSSYPYTI
004S-E10	Fzd6	TTLNKYAIS	GRITPVVGVTNYA	CALSSSWYGGFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F10	Fzd6	GFTFSDHY	ALVGYDGSQQFYG	CNTGIPMLYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-G10	Fzd6	FTFSDYYMS	SAISGSGFTYYA	CARVSRGFAFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-A11	Fzd6	GTFSSYAIS	GRIIPILGIANYA	CARESVNNYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-C11	Fzd6	FTFSSYAMH	ALTSYDGSKKFYA	CAKTGRGYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-E11	Fzd6	FTFSSYNMN	GRIKSKANGGTTDYA	CAKAGQQLDW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-H11	Fzd6	FTFTSSAMQ	GGIIPIFGTANYA	CATVQTNYYDSSGRFSYRAHYFDYW	RASQSISRWLA	AASSLQS	CQQYVSYPLTF
004S-A12	Fzd6	YTFTNNFMH	GRINPNSGGTNYA	CARGQGYSSGWYRGDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-D12	Fzd6	FAFDDYAMH	GFIRSKAYGGTTEYA	CAKDRGYSSGWYLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-H01	Fzd7	FNFSSYTMR	SVIYGGGNTNYA	CARGGSGGNLSYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
005S-A02	Fzd7	GTFSSYAIS	GMIIPFLGITNYA	CTRPYDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-C02	Fzd8	YTFASYGMH	GWINAGNGNTTYA	CARLSVWKWEQVTNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-E02	Fzd8	GTFTSYAIS	GWINAGNGNTKYS	CTTGLFPYYRYNWNNDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-A03	Fzd8	GTFSSYAIS	GWMNPNSGNTGYA	CAKWHIGATGNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-H03	Fzd8	YTFTNNFMH	GGIFPIYGISTYA	CARDRPTSSWYAFDYW	RASQGISNNLN	DASTLQT	CQQSFSAPITF
005S-F04	Fzd8	FSFSSTAMS	SYISSSGSITHYA	CARYGDYGDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-H04	Fzd8	YTFTNNFMH	GWINAGNGNTTYA	CARVATGNAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-B05	Fzd8	FTFSSYWMH	AGISGSGKTTFYA	CARGGLLFDYW	QASQDISNYLN	KASSLES	CQQSYSTPRTF
005S-F05	Fzd8	FTFTSSAVQ	GWMNPNSGNTGYA	CARRTAVAGTIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-G05	Fzd8	GTFSSYAIS	GWISPYNGNTNYA	CARGGWTNYGGNLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-H05	Fzd8	YTFTSYYMH	GRINPNSGGTNYA	CARVPDFWSGYLDYW	RASQGISRTLZ	AASSLQS	CQQTYSMPITF
005S-D06	Fzd8	YTFTYRYLH	GGIIPIFGTANYA	CARDSYPYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-F06	Fzd8	GTFSSYAIS	GRVIPILGVTNYA	CAREYLGSFDIW	RASQSVGSNLA	GASSRAT	CQQYGSSPPFTF
005S-A07	Fzd9	FTFTGSAVQ	GGILPIYGTTKYA	CARGARLYGFDYW	RASQSVSRNLA	GASTRAT	CQQRSNWPITF
005S-B07	Fzd9	FTFTSSAVQ	GWMNPNSGNTGYA	CARGRGQQWLTGYYGMDVW	RASQGISSALA	GASTLQS	CLQDYNYPFTF
005S-C07	Fzd9	FTFSSYSMN	SYIENDGSITTYA	CARAPYYYGSGSLFRLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D07	Fzd9	GTFNSYAIA	GGIIPIFGTANYA	CARAGSGYYNFDYW	RASQSINRWLA	AASSLQS	CQQTYNIPITF
005S-F07	Fzd9	FSFSSYGMH	AYINSRGSLMYYA	CAKTKLPIW	RASQSINRNYLG	AASSRVT	CQQYDSWPPTF
005S-G07	Fzd9	GSFSGYAIN	GGIIPIFGTANYA	CATGYYYDYYFDYW	RASQGISNNLN	AASSLQS	CQHYYNLPLTF
005S-H07	Fzd9	GTFTNNFMH	GLVDPEDGETIYA	CARTYRIVGATPRYYYYGMDVW	RASQTINNQLA	KASNLET	CQQANSFPVTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
005S-B08	Fzd9	YIFTDYYMH	GWINPNSGGTIYA	CARGPRDSGYYPGGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D08	Fzd9	FAFSSHWMH	SAIDGSGGSTYYA	CARDRQLGWAHWYFDLW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-G08	Fzd9	YTFTGYYMH	GWINAGNGNTTYA	CARDRDYW	QTSQDINNNLN	KASSLES	CQQSYSSPPTF
005S-C09	Fzd9	FTFSSYGMH	SAIGTGGGTYYA	CALLVGAARGISYYYYYGMDVW	QASQDISNYLN	AASTLQS	CLQHKSFPTF
005S-D09	Fzd9	YTFTSYAMH	GWINAGNGNTTYA	CARDRPYSSGWYYPAFDIW	RASQSVSSNQLA	GASTRAT	CQQRYNWPPSITF
005S-E09	Fzd9	FNLRRYNMN	SRISNSGSLVYYA	CARDADSSGYYRYDAFDIW	RASQSVSSNLA	DASNRAT	CQQRNNWLYTF
005S-A10	Fzd9	YTFTDYYMH	GIINPSGGSTSYA	CARHVYGSGTYNNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D10	Fzd9	YTFTSYYMH	GWMSPNSANTGYA	CARGGPIHYYYYYYMDVW	RASQGISNNLN	AASTLQS	CQQTNLFPYTF
005S-H10	Fzd9	GAFSTSSIS	GRIIPVLGTANYA	CAKGGWRSSFDPW	RASQSVSSNLA	GASTRAT	CQQYNSWPLTF
005S-B11	Fzd9	YTFTSYDIN	GGFDPEDGETIYA	CAKAGDWGLYGMDVW	RASQSISRWLA	AASSLQS	CQQTNTFPFTF
005S-C11	Fzd9	FTFTGSAVQ	GGILPIYGTTKYA	CARGARLYGFDYW	RASQSVSRKLA	GASTRAT	CQQRSNWPITF
005S-D11	Fzd9	YTFTNNFMH	GWINPNSGDTKFA	CAREANYDILTGYIRPDAFDIW	RASQSLRSKLA	GASTRAT	CQQYANSPWTF
005S-E11	Fzd9	GTFSSYAIS	GWINAGNGNTKYS	CTTTEYSSSPDYYYGMDVW	QASQDISNYLN	GASTLQS	CQQLSRYPSLF
005S-G11	Fzd9	GTFTRNSIS	GGIIPIFGTANYA	CARSSDLRIFDYW	RASQSVSSNLA	GASNRPT	CQQYGSSPYTF
005S-H11	Fzd10	YTFASYDIH	GWINAGNGNTTYA	CARDGIWDIFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-E12	Fzd10	YIFTDYYMH	GVIFPVYPTPDYA	CARGGSTGYYGMDVW	RASQSVGRWMA	AASSLQS	CQQANTFPFTF
005S-F12	Fzd10	GTFSSYAIS	GRIVPIVDVVKYA	CARDTCSSTSCSPDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
006S-A01	Fzd10	FTFSSYSMN	SAIGTGGGTYYA	CAREGWFGESPFGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
006S-F01	Fzd10	YTFTRYAVH	GWISTFNDNTNYA	CASPTGMTTNFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
006S-H01	Fzd10	YIFTDYYMH	GGIIPIFGTANYA	CAKGSYYYDSSGYYWDAFDIW	RASQGISNNLN	AASNLET	CQQTSSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
006S-A02	Fzd10	YIFTDYYMH	GGIIPLFGTTDYA	CARDITGADGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
006S-D02	Fzd10	GTFSSYAIS	GRIIPTVGTANYA	CARDVCSGGSCSPDVW	RASQGISNNLN	DASSLES	CQQTYNTPRTF
006S-E02	Fzd10	FTFTSSATQ	GGIIPIFGTANYA	CARDGSSGWYSPNAFDIW	RASQGISNNLN	AASSLQS	CLQHNGYPITF
006S-H02	Fzd10	FTFRMYGMH	SRISPDGRTTTYA	CARSPRWYDAFDIW	RSSQSLLHSNGYNYLD	RVSSRFS	CMQGTHWPPTF
006S-A03	Fzd10	YIFTDYYMH	GWINAGNGNTTYA	CARDPIMFGDQPGWFDPW	RASESVSSNLA	GASSRAT	CQQYNKSPSF
006S-B03	Fzd10	GTFSSYAIS	GWINAGNGNTKYA	CAREGYDFWSGPYAFDIW	RASQTISRYLN	EVSSLQG	CQQSYSTPWTF
006S-C03	Fzd10	GTFSSNVIS	GGIIPIFGTANYA	CARGGYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-B01	Fzd1	YIFTDYYMH	GGIIPIFGTANYA	CARMSSDYYDSSGYYRRGMDVW	RASQGISNNLN	GASTLQS	CQQADSFPPTF
014S-D01	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	RASQSISSHZN	AASSLQS	CQQSYSTPLTF
014S-E01	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	RASQSIZZYZN	AASSLQS	CQQSYSTPLTF
014S-G01	Fzd4	GTFSSYAIS	GWMNPNNGNTTYA	CARHYYGSGNYRDW	RASQSISSYLN	AASSLQS	CQQSYSTPFTF
014S-A02	Fzd4	FTFSSNAMH	SGISGSGGSTYYA	CAKPGIAAAGTNNWFDPW	RASQGISSALA	GASTVES	CQQSYSTPRTF
014S-B02	Fzd4	FTFSSYAMH	SGISGSGSSTYYA	CARPSTTSFGMDVW	RASQSVSSNLA	GASTRAT	CQQYDTPLRTF
014S-C02	Fzd5	YTFTSYYMH	GRINPNSGGTNYA	CARVPDFWSGYLDYW	RASQGISSALA	AASSLQS	CQQTYSMPITF
014S-D02	Fzd5	GTFSTYAIS	GIINPSGGSTSYA	CARAKGSGWYVGSAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-E02	Fzd5	FTFSDSYMS	GFIRSKAYGGTTEYA	CARATQELLLPYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-F02	Fzd5	YTFTSYYMH	GRINPNSGGTNYA	CARVPDFWSGYLDYW	RASQGVSTZLS	AASSLQS	CQQTYSMPITF
014S-G02	Fzd6	YTFTSYYMN	GIISPSGGSTSYA	CARWGDYGDLYYFDYW	RASQGISSALA	ATSTLQS	CQQVNSYPPTF
014S-H02	Fzd6	YIFTDYYMH	GRINPNSGGTNYA	CARARSSGWTDAFDIW	RASQSVSSWLA	AASTLQT	CQQSYSTPTF
014S-A03	Fzd6	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
014S-B03	Fzd6	FTFSSYNMN	GRIKSKANGGTTDYA	CARAGDSPDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-E03	Fzd8	GTFSSYAIS	GWISPYNGYTKYA	CARAMWSYGQQNAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-G03	Fzd8	FTFTSSAVQ	GWMNPNSGNTGYA	CARRTAVAGTIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-H03	Fzd8	YTFTSSAIH	GRINPNSGGTNYA	CARVKWELAIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-B04	Fzd8	YIFTDYYMH	GWMNPNSGNTGYA	CARGGSRYDFWSGHWYFDLW	RASQGISNYLA	AASSLQS	CQQSYSTPFTF
014S-E04	Fzd8	YTFTGYYMH	GRINPNSGGTNYA	CARDVPKLVTRGVAYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-F04	Fzd8	YSFTTYGMN	GWINAGNGNTTYA	CARAAAGSYGGGYW	RASQGISNNLN	EASSVAS	CQQSYTSTPLNSF
014S-G04	Fzd8	FTFSSYGMS	SAISGSGGSTYYA	CARDLTPFTQQQLVLGLL	RASQSVSGYLA	GASTRAA	CQQYNYWPPAF
014S-H04	Fzd8	FTFTSSAVQ	GRIVPAIGFTQYA	CARSGYNRRGYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-A05	Fzd8	GTFSSYAIS	GGIIPIFGTANYA	CARVTLGASVDAFDIW	RASQGISNNLN	DASSLES	CLQHNSLPFTF
014S-B05	Fzd8	GTFSSYAIS	GWVSPNTGNTVYA	CTTDRRYSTYFDLW	RASQSVSSNLA	GVSNRAT	CQQYNIWPRTF
014S-C05	Fzd8	YTFASYGMH	GWINAGNGNTTYA	CARLSVWKWEQVTNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-D05	Fzd8	GTFTSYAIS	GWINAGNGNTKYS	CTTGLFPYYRYNWNNDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-F05	Fzd9	FTFTGSAVQ	GGILPIYGTTKYA	CARGARLYGCDYW	RASQZVSRZZA	GASTRAT	CQQRSNWPITF
014S-G05	Fzd9	FTFSSSWMH	SAIGTGGGTYYA	CARKVKGYCSGGSCYGYW	RVSQGISSALA	AASSLQS	CQQTFSVPWTF
014S-H05	Fzd9	FTFSNYAMT	STISGSGVSTFYA	CARHGRIAADIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-A06	Fzd9	FTFZZSZVQ	GGILPIYGTTKYA	CARGARLYGFDYW	RASQSVSRNLA	GASTRAT	CQQRSNWPITF
014S-B06	Fzd9	FTFSSYSMN	SYIENDGSITTYA	CARAPYYYGSGSLFRLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-C06	Fzd10	FTFTGSAVQ	GGILPIYGTTKYA	CARGARLYGFDYW	RASQSVSRNLA	GASTRAT	CQQRSNWPITF
014S-D06	Fzd10	FTFSRYAMH	SGIGVGGGTYYA	CARDAYNWFDPR	RASQSISRYLN	AASSLQS	CQQRYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
014S-F06	Fzd10	YIFTDYYMH	GVIFPVYPTPDYA	CARGGSTGYYGMDVW	RASQSVGRWMA	AASSLQS	CQQANTFPFTF
014S-G06	Fzd10	FTFSSYAMH	SAIGAGGGTYYA	CARDAYNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-H06	Fzd10	FTFSSYDMN	SAIGTGGGTYYA	CARDAYNWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-A07	Fzd10	FTFSNAQMS	SAIGTGGGTYYA	CAREGSYYDWYFDLW	RASQNIGSRLA	GASNRAS	CQQYNHWPPLFTF
017S-E08	Fzd8	IIFSPNDMG	ALISSGGSTSYA	CHFGVASVGLNYW			
017S-H08	Fzd8	RTFSSFVMG	AAVSASGGYTWYA	CNLAQRGETYW			
017S-A09	Fzd8	LAFNGYTMG	AAISWSDNTYYA	CAAGFPTVFVVDGEYDYW			
017S-B09	Fzd8	FTLDYYAIS	ADITSGGSTNYA	CNAVTYNGYTIW			
017S-C09	Fzd8	LTFSDYTVG	ASSTGGGVFENYA	CNAVTYNGYTIW			
018S-D06	Fzd4	RIFSSYAQA	PRIPSDSTTFYA	CEVHNFGATYW			
018S-E06	Fzd4	RTFSNYVMG	AVISRSGGNTYYT	CNAVSTDWTTDYW			
018S-F06	Fzd4	RTFSTYGMG	AAISWSDNTYYA	CNSFPLRLHDW			
018S-G06	Fzd5	LAIDDYYMV	SYISTSDGSTYYA	CNAVTYNGYSIW			
018S-H06	Fzd5	LAFNGYTMG	AQISWTGGSTDYA	CNADYGTWYGIGW			
018S-A07	Fzd5	LAFNGYTMG	AAISWMSNTYYA	CNMGLGYSEYRPLGYW			
018S-B07	Fzd5	SAFSNYAMG	AAITWSGARTYYA	CNAVWKFGTTHW			
018S-C07	Fzd7	LTIDDYYVV	SYISAGDGFTYYA	CNAVTYNGYTIW			
017S-F09	Fzd4	GSFSGYYWS	GEINHSGSTNYN	CARDLRFYSSSWRRVGMDVW	RSSRSLLHTSGYNYLD	LGSNRAS	CMQGTRWPTF
017S-G09	Fzd4	YTITTYAIH	GWINADTGDTAYS	CARGWTTISSLGVW	RSSRSLLHTNGYNYLD	LGSNRAS	CMQALQTPLTF
017S-H09	Fzd5	NIFRIYAIA	AALTGQRTTNYA	CNTVTYNAGCYKKYW			

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
017S-A10	Fzd5	LAFNGYTMG	ASITWNGRYTYYA	CNARLDAVYGHSRYDSW			
017S-B10	Fzd5	NFFSNYPLG	GAISRTGSGTFYA	CAAGVTGSWRYW			
017S-C10	Fzd8	RSFSNYRVA	AVSWSVGMTYYA	CNAVTYNGYTIW			
017S-D10	Fzd8	GTFGSYAVG	GLISRNAGNTLYA	CNAVNGRLNYW			
017S-E10	Fzd8	RTFSSYSLA	AAVSASGANTYYA	CAAPQSPNMYIRTDQLWWYKYW			
018S-D07	Fzd1	RSFSTYPMG	TVISGSGGSTYYA	CAAGPTLPFRYW			
018S-E07	Fzd1	RAFSNYAMG	AAINWSGDSAYYA	CNARLSFAGGMGYW			
018S-F07	Fzd1	IKSMFDMNFMG	AFITRGGTTRYG	CNAVSTDWTRDYW			
018S-G07	Fzd1	LTIDDYYMV	SYIGTSDGTTYYA	CNAVTYNGYTIW			
018S-H07	Fzd4	RVFSSYAQA	AGIASDSTTFYA	CKVHNFGATYW			
018S-A08	Fzd4	RIFSSYAQA	ASIPSDGTTFYA	CKVHNFEATYW			
018S-B08	Fzd4	LTFSTYGMG	AAINWSGRSTVYA	CNSFPLRLHDW			
018S-C08	Fzd4	RTLSSYVVG	ALISLSGASTYYA	CNAVSTDWTTDYW			
018S-D08	Fzd5	IKSMFDMNFMG	AFITRGGTTRYG	CNAVSTDWTRDYW			
018S-E08	Fzd5	RTDGMQAMG	GAITWSLGSAFYA	CNVLAQNDGDYRTYG			
018S-F08	Fzd5	RTFSSFVMG	AAVSASGGYTWYA	CNAVWKFGTTHW			
018S-G08	Fzd5	RTFSSFVMG	AAVSASGGYTWYA	CNAVCKFGTTHW			
018S-H08	Fzd5	RTFSSFVMG	AAVTASGGYAWYA	CNAVWKFGTTHW			
018S-A09	Fzd8	ITFSFNSVG	AVFIAGYGAYYA	CNGVTYNGYTIW			
018S-B09	Fzd8	HDFSSTYGVG	ATISWGGTNIA	CAAQKPYYNGHFYADDKHYDHW			

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
018S-C09	Fzd8	ITFGFDSVG	AVFNAGYRAYYA	CNAVTYNGYTIW			
018S-D09	Fzd8	RTFSWYSMG	AAVSWSGVSTYYP	CNAVTYNGYTIW			
018S-E09	Fzd8	ITFSFNSVG	AVFIAGYGAYYA	CIGVTYNGYTIG			
018S-F09	Fzd8	RTDGMQAMG	GAITWSLGIAFYA	CNVLAQNDGDYRTYW			
018S-G09	Fzd8	HDFSSTYGVG	AAISWRGTNIA	CAAQKPYYNGHFYADDKHYDHW			
021S-A01	Fzd8	DSVSSNSAAWN	GRAYYKSRWYYDYA	CVRDLRPSGDLNFDYW	RASQSIGSSLH	YASQSVS	CHQSGRVPVTF
021S-C01	Fzd1	GSISSGGYSWS	GSIYHSGSTYYN	CARFYYDILNGYSYFDYW	RSSRSLLDTDDGNTYLD	TLSHRAS	CMQSIQLPWTF
021S-D01	Fzd1	FTFSSYGMH	AVISYDGSNKYYA	CAKGSVFGLKAGGYADYW	RSSQSLVHSDGNTYLS	KISNRFS	CMQATQFPHTF
021S-E02	Fzd8	YTFTSYGIS	GWISAYNGNTNYA	CARDGTPFYSGSYYGSW	QGDSLRTYYAS	GKNNRPS	CNSRDNSGKHKVF
021S-G02	Fzd8	DSVSSNSGAWN	GRTYYRSKYYNGYA	PRLDYW	RSSQSLLDSDDGNTYLD	MLSSRAP	CMQRLEFPYTF
021S-A03	Fzd8	DSVSSNSAAWN	GRTYYRSKWYNDYA	CARSQATGERFDYW	RSSQNIFQSLN	SASSLQS	CQQSYNSPITF
022S-H06	Fzd4	FTFSSYAMS	SVISTSGGTVLYT	CADGSGTSHR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
022S-A11	Fzd10	YIFTDYYMH	GGIFPIFGTANYA	CAKGSYYYDNSGYYWDAFDIW	RASQGISNNIN	AASNLET	CQQTYSIPFTF
OMP-18R5		GFTFSHYTLS	VISGDGSYTYYADSVKG	NFIKYVFAN	SGDKLGKKYAS or SGDNIGSFYVH	EKDNRPSG or DKSNRPSG	SSFAGNSLE or QSYANTLSL
027S-H02	Fzd5	FTFSSYAMS	SAISGSGGSTYYA	CAKGLWGPLLNW	RASQSVSSNYLS	GASSRAP	CQQRTNWPPRVTF
027S-B03	Fzd8	DSVSSNSATWN	GRTYYRSKWYSDYA	CTRGNWNVGLANW	SGTSSNIGAGYDVH	GNNNRPS	CSAWDDNLNGVVF
027S-E01	Fzd5	RSFSIYNTA	AAISWSGGSTYYA	CNVITIVRGMGPRAYW			
004S-D05	Fzd5	LTFSIYAMH	SAISGDGALTYYA	CARGVYPYSSKHKPSYYYYGMDVW	QASQDISNYLN	AASSLQS	CQQSYSTPLFTF
004S-D04	Fzd5	YDFTTYGIH	GGVIPAFGATDYS	CARGYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-B05	Fzd5	GTFSSYAIS	GWINAGNGNTTYA	CASGLGYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
004S-G03	Fzd5	YTFTNNFMH	GGIIPIFGTPHYA	CARTLTTPPYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F03	Fzd5	FTFSNSDMN	SAIGTGGDTYYA	CTRDLYGGYRDYW	KSSQSLLHSDGYTYLY	LGSNRAS	CMQGLQTPWTF
004S-C04	Fzd5	YIFTGYYMH	GRINPNSGGTNYA	CARGGEYSSGWTYYYYYGMDVW	RATQTISTYLN	AASRLQS	CQQYYSYPWTS
004S-B06	Fzd5	YTFTYRYLH	GMINPIGGSINYA	CARDVMDVW	RASQGISNNLN	AASALQS	CQHLNNFPLTF
004S-F06	Fzd5	FSVGSNYMT	SSISSGNSYIYYA	CARGPKTMWEDRPDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-A04	Fzd5	FTFSTYSMI	GFIRSKDYGGTTEYA	CARLTGGAVAGTHRDYW	RASQGISNNLN	GASSLQS	CQQSHSSPRTF
004S-A05	Fzd5	FTFSSYVMS	SAIGTGGGTYYA	CARGSSGYYVAW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F05	Fzd5	FTFSNHYMS	AGVSIDANKKYYA	CARDQNDSWYRSDYW	RSSQSLLHSDGYTYLY	LGSHRAS	CMQGLQTPHTF
003S-C01	Fzd1	GTFSSYAIS	GRINPNSGGTNYA	CARGSGYDFFDYGMDVW	RASQSISNNLN	AASSLQS	CQQSYNTPFTF
003S-H01	Fzd1	DTFSNYVLS	GLVDPEDGETIYA	CAKASTPMVQGAPDYW	RASQSIGSNLD	AASTLQS	CQQNYATPRTF
003S-H02	Fzd1	GTFNRYAIT	GGIIPIFGTANYA	CATTQGVYSSSWYGGGRAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-H04	Fzd1	YTFTYRYLH	GRINPNSGGTNYA	CWGGSYYGDYW	RASQGISNNLN	AASSLQS	CQQANSFPITF
003S-A05	Fzd2	FTFSSYAMH	SSISWNSGRVDYA	CARGSGIAASGSYW	TSSQSLLHSDGKTYLY	LGSNRAS	CMQGTHWPYTF
003S-B05	Fzd2	FTFSNAWMS	STIAGSGGRTYYS	CAKDSIGRRGRGAPQPYYYYGMDVW	KSSQSLLHSDGKTYLY	LGSNRAS	CMQSLQSPLTF
003S-F05	Fzd2	FSFSTYTMS	SRINGDGSSTRYA	CARAIVGATGLNRFKAFDIW	KSSQSLLHSDGKTYLY	LGSNRAS	CMQNTHWPLTR
003S-G05	Fzd2	STFTNAWMS	SAIGTGGGTYYA	CARDRVTLRGGYSYGTDAFDIW	RSSRSLLHSNGNTYLR	LASRRAS	CIQNTHWPLTR
003S-H05	Fzd2	FTLSTYNMN	SRINYDGSATTYA	CARDRDIVVVPAQRGEGGFDPW	KSSQSLLHSDGKTYLY	MGSYRAS	CMQGTHWPLTF
003S-A07	Fzd2	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSQSLLHSDGKTYLY	LGSNRAS	CMQNTHWPLTL
003S-C07	Fzd2	FSFRSYSMS	SAIGTGGGTYYA	CTTTTVTTSW	RTSQSVSSNLA	DASNRAS	CQQYGSSPYNF
003S-F07	Fzd2	FSFSSYGMS	SHISSGGATIDYA	CARDGGYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
003S-G07	Fzd2	FTFSSYWMH	SYISGDSGYTNYA	CARDNGYCSGGSCYATYYGMDVR	RASQAISSYLA	KASTLDT	CQQADTFPFTF
003S-B08	Fzd2	FTFSSZZMH	AVISYDGSNRZYA	CARSYYDSSGYPRKDAFDIW	KSSQSLLHSDGKTYLY	LGSNRAS	CMQTLKAPLTF
003S-F08	Fzd2	ZSVSSNYMS	SRINSDGSTISYA	CARARLLGGYYTPDRMDVW	RSSQYLSSAYLA	GASSRAT	CQQYGSSPTF
003S-H08	Fzd2	FTFNRHALS	ALISSNGDHKYYT	CARDLMVGRNKLDYW	QASQGISNNLN	AASSLQS	CQQSYSTPAFTF
003S-A09	Fzd2	FTFSSSNMN	SGISGSGSSTYYA	CARGRVWSSRDYW	RSSQSLLHSDGYTYLY	LGSNRAS	CMQGTHWPLTF
003S-B09	Fzd2	FNIRRZNMZ	SAIGTGGGTYYA	CARGDSGSYRDYW	RSSESLLHSDGKTYLY	LGSNRAS	CTQTVQFPITF
003S-C09	Fzd2	FTFSSSAMH	SGISGSGTTTYYR	CARRLIAVAGAEFDPW	RASQGISNNLN	SASNLQS	CQQSYSTPWTF
003S-F09	Fzd4	FTFSNSDMN	GRIKSKAYGGTTEYA	CARQYYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-H09	Fzd4	FTFSSFGMH	SVISSGGSPYYA	CATASGDFDYW	RASQSIGSNLN	RASTLES	CQQTYTTPRF
003S-A10	Fzd4	FTFDDYAMH	AIVSYDGTYKYYS	CARQTRGGTTDGW	RASQGISNNLN	YASSLQS	CQQSHSPPGTF
003S-B10	Fzd4	FTFSSHSTH	SAISASGDSTFYA	CARPIVGATAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-G10	Fzd4	FTZSSYSMN	SYSSGNSGYTNYA	CARGVVGSGAFDIW	RASQSIVSYLN	DASNLQS	CQQGYSAPWTF
003S-B11	Fzd4	FTFSDYYMS	SAIDGAGRTYYT	CARAIPGDYDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-C11	Fzd4	FTFTSYAMH	GGIIPIFGIANYA	CARTGRGYYGMDVW	RASQSIGSNLD	AASTLQS	CQQSYSTPRTF
003S-D11	Fzd4	FTFSSYSMS	SYISGDSGYTNYA	CARAGVATIAFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-F11	Fzd4	FTFDDYGMH	SAISGSGGSTYYA	CTTPNYYDSR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
003S-E12	Fzd4	GTFSSYAIS	GWINAGNGNTTYA	CARHYYGSGSYPDW	ZPZQTZZSHLN	PASSLQS	CQQSYSTPLTF
004S-A01	Fzd4	FTFSTYGMH	SYISSSSSAIYYA	CARGGLDGPIDYR	RASQGISNNLN	AASTLQS	CQQGNNFPFTF
004S-G01	Fzd4	FTVSSHSMG	SLVSFDGSKEHYA	CARLGSTPDYW	RASQGISNNLN	AASSLQS	CQQYYTYPYTF
004S-C02	Fzd4	FTFSSYGMH	AVISYDGSNKYYA	CASDPVTAATR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
004S-D02	Fzd4	FSFSSYGMS	SGISGSGRSTYYA	CAKDGYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-A03	Fzd4	FTFSSYAMH	SGINWNGGSTGYA	CARPAGSAQNWFDPW	RASQGISNNLN	DASNLET	CHQSYSIPRTF
004S-B03	Fzd4	FSFSRYGMS	SGVGGSGGSTZYA	CARDGSW	RASQDVDTWLA	DASTLET	CQQGYNIPWTF
004S-C03	Fzd4	YTFTSYAIS	GIINPSGGSTSYA	CARQIGWELMPDIW	QASQDISSYLN	AASTLQS	CQQAISFPLTF
004S-C05	Fzd5	ZZZTDYYZQ	GGMNZNRGNTGYA	CANGSYAQHLW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-G05	Fzd5	FTFSSYWMH	STISPSGLYIYQA	CAKDKVPYSYGPNFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-E06	Fzd5	FFFSGYWMS	ANIKQDGSEKYYV	CARVFPLHDYW	QASQDISNYLN	KASSLES	CQQANSFPYTF
004S-C06	Fzd5	FPFSTFSMN	AGISWNSGTIDYA	CARSGPAAMVYYYYGMDVW	RSSQNVSSYLA	GASTRAT	CQHRANWPQTF
004S-E07	Fzd6	FTLSSHHMN	SAIGTGGGTYYA	CAAPDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F07	Fzd6	FSFSKKYMT	SSIDGNGDHVFYA	CARPYYYDSSGYDPMGDYW	QASQDITNYLN	KASTLES	CQQSYSAPYTF
004S-C08	Fzd6	FTVSSNYMN	SAIGTGGGTYYA	CAQGTYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-F08	Fzd6	FTFDDYYMN	SAVSGNGGGTFYA	CARGGNYGSGDYW	RASQSISZWLA	EASTLQS	CQQTYTPPFTF
004S-G09	Fzd6	GTLNNHTLS	GRIIPIFGTANYA	CARDRRGYGMDVW	RASQAISNSLA	DASNLET	CQQAYSFPWTF
004S-B10	Fzd6	FTFSDYYMS	SGINWNSAKIGYV	CARIGAGGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-H10	Fzd6	FIFSDYYMS	AVITSGGTFKYYA	CARNGIAAAEDYW	RASQSISTYLS	GASSLES	CQQSYSPPFTF
004S-B11	Fzd6	FTFSSSWMH	SGISWNSGSIGYA	CARYSSGGSLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-D11	Fzd6	YZFZZZYMH	GRINPNSGGTNYA	CARARSSGWTDAFDIW	RASQSVSSWLA	AASTLQT	CQQSYSTPTF
004S-F11	Fzd6	FTFSSYAMS	SSISGGGRHTYYA	CARPYSSSRQGDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
004S-G11	Fzd6	YIFTDYYMH	GWINPNSGGTNYA	CARDRPGFDPW	RASQSVSSYLA	GASSRAT	CQQYAISYTF
004S-B12	Fzd6	FTFSSYWIH	SYISGDSGYTNYA	CAKGIRWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
004S-C12	Fzd6	YIFTDYYMH	GWMNPNSGNTGYA	CASSHYAPGMDVW	RASQGISSYLA	RTSTLES	CQQSYSTPWTF
004S-F12	Fzd7	FTVGNNYMS	SSITTTSTLYA	CARGKEGRYSNYEAAW	RASQSISSYLN	AASTLQT	CQQSYSIPFTF
005S-B01	Fzd7	FTFRSYGMH	SLISGSGDNTNYA	CARREPLYSSRRGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-C01	Fzd7	FTFSSYSMS	SAISGSGGSTYYA	CTRTIVGATPHYW	RASQGISNNLN	KASSLQS	CQQSYSLPYTF
005S-F01	Fzd7	FTVSSNYMS	SAISGSGATTTYA	CAKGAGYGSGSWQAAW	RASQSVSSSYLS	GASSRAT	CQQRYKSYTF
005S-B02	Fzd8	YSFTNYAMH	GRIIPIFGTAZYA	CARGTFLEWLLTNYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D02	Fzd8	GTFSSYVIS	GWIGPHNGNTNYA	CATGWPRYYYGMDVW	RASQSVSSNLA	NTSNRAT	CQHYNNWPFTF
005S-G02	Fzd8	YTFTSYYMH	GGIIPIFGTAZYA	CARLPYYDFWSGYYGGRTGFDYW	RASQSVSTNLA	DASNRAT	CQQRSNWPPQITF
005S-H02	Fzd8	YTFTYRYLH	GWINAGNGNTTYA	CARASLYYDYVWGSYRHYYFDYW	QASQDISHYLN	AASSLQS	CQQSYSTPLTF
005S-B03	Fzd8	GTFSSYAIS	GIINPSGGRTTYA	CATSFGGGWIVVDTSLWYW	RASQSINSNLA	GASSRAT	CQQYGSSPYTF
005S-C03	Fzd8	GSFSGYAIS	GGIIPIFGTANYA	CRVDAFDIW	RASQSVSSSYLS	DTSNRAT	CQQYGSSPITF
005S-E03	Fzd8	FTFTSSAVQ	GGIIPIFGTANYA	CARSSGWQNRFAFDIW	RTSQSISSYLN	AASTSQS	CQQSFSSWTF
005S-F03	Fzd8	YTFTYRYLH	GWINAGNGNTKYS	CATDLPVRKGFTYYDILTGSYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-B04	Fzd8	YTFTNNFMH	GGIIPIFGTANHA	CARGLRYFDWPQGIYYYYGMDVW	QASHDINIALN	AASSLQS	CQQSYSSPLTF
005S-C04	Fzd8	YTFTSYYMH	GRINPNSGGTNYA	CARGGLLFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D04	Fzd8	FTFSTYSMS	STIGTGGGTYYA	CARVGWLRFLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-G04	Fzd8	GTFSSYAIS	GWMSPSSGNAGYA	CARNNFLRAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-A05	Fzd8	FAFSSYAMS	SRIDTDGSTTVYA	CARAPSYSSGWYVRW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-C05	Fzd8	YTFTYYAMH	GIINPSGGSTSYA	CARELLPMTTVTSPFIW	RASQGISNNLN	RASSLQS	CQQANSYPLTF
005S-E05	Fzd8	GTFSSYAIS	GGIIPIFGTANYA	CAIRAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
005S-C06	Fzd8	ZTFSZYDMH	SSISSSSHYKYYA	CARVRSKAVAGTLPKRLFDIW	RASQSVSSSYLS	AASRRAT	CQQYSNWPFTF
005S-E06	Fzd8	YTFTSYYMH	GWMNPNSGNTGYA	CARGNPTSGHIVVVPAATFSDYW	QASQDISNRLN	SASRLQI	CQQSYRTPRTF
005S-G06	Fzd8	GTFSZZTIS	GWMNPDSGKTGYA	CARWAFPIPNAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-H06	Fzd8	YTFTNNFMH	GGIFPIYGISTYA	CARDRPSSSWYAFDYW	RASQGISNNLN	DASTLQT	CQQSFSAPITF
005S-A08	Fzd9	GTFSZYAIS	GGIIPIFGTANYA	CARGGLLRFGDGWGMGMDVW	RASQSISSKSLA	GASTRAT	CQQYGIAPTF
005S-C08	Fzd9	YTFTDYHMH	GWINAGNGNTTYA	CARASSWYLHYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-E08	Fzd9	FIFSZYAMS	SSISAAGAYKYYA	CARRGYSSGWRDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-F08	Fzd9	YTFTSYYMH	GWINAGNGNTTYA	CAKDVNYW	QASQGISNYLN	AASSLQS	CQQTYSTPTTF
005S-H08	Fzd9	GTFSSYAIS	GRIIPILGTPNYA	CARDRLAFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-A09	Fzd9	FAFSSHWMH	SAISVSGGTTFYA	CARWGKRLRGSPYYFDYW	RASQSIGSNLD	RASTLQS	CQQSYSTPSF
005S-F09	Fzd9	FTFSIYGMH	SGISWNSGNIGYA	CARGPLPTKIGGHYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-B10	Fzd9	FTFSTXWMS	AVMYSGGTTYYA	CARLSYYYDSSGPKGDAFDIW	RASQGISNNLN	AASSLQS	CQQGNNFPLTF
005S-C10	Fzd9	FSLSSYGMH	SSISSSSSYIYYA	CARSGMVKWLRSFDYW	RASQDIGSFLA	AASSLQS	CQKYNRAPFTF
005S-E10	Fzd9	FTFTSSAMQ	GVINPGSGGTSYN	CARGYGDYVWGENYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-F10	Fzd9	YTLSNYGIS	GWISAYNGDTKYA	CARFDYFGGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-G10	Fzd9	YTFTRYAVH	GGIIPFFNTVNYA	CAADRSPYYYDSSGYYPDAFDIW	RASQGISNNLN	QASSLDS	CQQSYNVPYTF
005S-A11	Fzd9	FTFSSYDMN	SGISWNSGYIGYA	CAKGSLLLGYYGMDVW	RASQSISNNLN	DASTLKR	CQQSYNTPRTF
005S-B12	Fzd10	FTZSSYDMH	SSISGLGGSTYZA	CAREAGTTGGWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
005S-D12	Fzd10	FTFSDHYMD	STIGPAGDTYYP	CARASTSGDYSLW	RASQSVSTSYLA	GASTRAT	CQQYGASPWTF
006S-B01	Fzd10	YTFTNYCTR	GLVCPSDGSTSYA	CARRTSASDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
006S-C01	Fzd10	FTFTZSAVQ	GGFDPEDGETIYA	CTTDPLELPWYW	RASQGISSALA	SASNLQS	CQQAISFPLTF
006S-E01	Fzd10	YTFTGYYMH	GIINPSSGRTDYA	CARDLTYYYDSSGHSPLGAFDIW	RASQSVTSSLA	GASTRAT	CQQYNDWPPTF
006S-G01	Fzd10	FTFSDFGMN	AGISGGGGSTDYA	CARDSDFWYYYGMDVW	KSSQSVLYSSNNKNYLA	STNTRSS	CQHRNFF
006S-B02	Fzd10	VSFSGYAMH	AYINSGSSEMNYA	CAREEWELFGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
006S-G02	Fzd10	YTVTSYAMH	GGIIPIFGTAKYA	CAKGGQWLYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-A01	Fzd1	YTFTSYYMH	GWVSPSSGNTAYA	CARDEGAGYYYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-C01	Fzd2	FTFSNYAMT	SAIGTGGGTYYA	CATAYRRPGGLDVW	RSSQSLLHSDGKTYLY	LGSNRAS	CMQNTHWPLTR
014S-F01	Fzd4	FTFSSYAMH	SVISTSGDTVLYT	CARGGSSDVR	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-H01	Fzd4	FTFSNYGMH	SYISSSSSTIYYA	CARAALGYCTGGVCPPVDYW	RASQGISNNLN	AASRLQS	CQQSYSPPLTF
014S-C03	Fzd7	YTFTNNFMH	GIIZPGGGRTIYA	CAKGDYGALDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-D03	Fzd7	FNFSSYTMR	SVIYGGGNTNYA	CARGGSGGNLSYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-F03	Fzd8	YTFTNNFMH	GGIIPLFGTANYA	CARLVVRGGYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-A04	Fzd8	GTFSSYAIS	GWISSFNGNTKYA	CARADDYYDSSGYYYGFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-C04	Fzd8	FTFSSYTMN	SRINGDGSNTNYA	CARGWAGFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-D04	Fzd8	HTFSGYHIH	GWINAGNGNTTYA	CARDLSPMVRGVISGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-E05	Fzd8	YTFTNNFMH	GIISPGGGRTIYA	CAKGDYGALDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
014S-E06	Fzd10	FTFGNYDMN	SSLSWNSGTIVYA	CARDSSSGWYASYYGMDVW	RASQSISRYLN	AASSLQS	CLQHHSYPFTF
027S-C02	Fzd5	YTLTTWYMX	GWMNPNSGNTAYA	CARGALGMDVW	QASQDISNYLN	AASSLHT	CQESYSSPYTF
027S-E03	Fzd8	YTFTGHYMH	GWMNPNSGNTGYA	CARGTGGFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPYTF
027S-F03	Fzd8	YTFTGHYIH	GWMNPISGNTGYA	CARSTPFDPW	RASHDIGTFLA	AASTLQS	CQQSYRTPYTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
027S-G03	Fzd8	YTFTHSYIH	GWINAKSGGTFYA	CARGDYDFWSGYHEYYYYGMDVW	QATQNIKKYLN	KASTLES	CQQSYSTPLTF
027S-H03	Fzd8	YTFTSYYMH	GWINPNSGGTNYA	CARAPLDGSGSYYVDW	RSSQSLLHSNGYNYLD	LGSNRAS	CMQALQTPQTF
027S-A04	Fzd8	YTFTNHFMH	GWISPNRGGTNYA	CARDCSGGSCYSHFDYW	RASQSISRSLA	AASNLQS	CQQAYSFPQTF
027S-B04	Fzd8	FTVGSWYMS	SAIGTGGGTYYA	CAKDITPYGDYSILSHW	RASQAISNYLN	AASSLQS	CQQTFSPPLTF
027S-C04	Fzd8	YTFTSHWMH	GGIIPIFGTTNYA	CARDSSSWYSYYYYYMDVW	RASQGINNYLA	QASNLES	CQQTYSSPLTF
027S-D04	Fzd8	YTFTTYFMH	GWIYPNSGGTKYA	CTTDLRYDSSGPAAFDIW	QASQDIDNYLN	AASSLQS	CQQSYSTPVTF
027S-E04	Fzd8	FTFSDHYMS	SGISGSGGTTYYA	CATYGDFGYFDLW	RASQGIRNDLG	AASTLQS	CQQAYSFPWTF
027S-C05	Fzd8	GSFSTSVFG	GRIIPLFGTTNYA	CVKDRAWGFDYW	RASQGIRNDLA	AASSLQR	CQQSYSKPTF
027S-D05	Fzd8	YTFTSYYMH	GWINPKSGGTNYA	CARGGFVFDYW	QASQDISNYLN	ASSTLQT	CQQSYSAPYTF
027S-E05	Fzd8	GTFSSYAIS	GMINPSGGSTTYA	CARQAGLHCSSTSCYLGNWFDPW	RASQGITKSLA	AASNLQL	CQQYNTFPITF
027S-F05	Fzd8	GTFNRYGIS	GGIIPRLGATDYA	CAKGNWAFDIW	RASQSISTYLA	GASTRAT	CQQYGSSPTF
027S-G05	Fzd8	GTFSSYAIS	GWISPYNGNTKYA	CARGVWTTPMGGGGNWFDPW	RASQSISSYLN	YASSLQN	CQQSYSTPFTF
027S-H05	Fzd8	GTFGNYGIN	GWINPNSGGTNYA	CARETTDYYYGMDVW	RASQSIGTYLN	DASNLET	CQQANSFPLTF
027S-A06	Fzd8	GTFSSYAIN	GVIDPSTGGTNYA	CARVLPGDSSGWYRGYYYYYGMDVW	RASQGISNNLN	KASSLES	CQQANSFPITF
027S-C06	Fzd8	GTFTSYPIS	GWINTYNGNTIYA	CARDLDSGFDLW	RASQGVGDYLA	DASNLQS	CQQHNAYPLTF
027S-D06	Fzd8	GTFSSYAIS	GWISAYNGHTNYA	CARGGYSYGTVFDYW	RASQDISSWLA	KASTLES	CQQSYGAPLTF
027S-E06	Fzd8	YTFTKDYMH	GGIIPIFGTANYA	CARGLPPAAGGGGYFQHW	RASQNVNDWLA	SASNLQS	CQQSYSTPFTF
027S-F06	Fzd8	FTFSSYAMH	AVTWYDGSNKYYA	CAKDLVPYCSGGSCPPSGW	RASQSISSYLN	GASNLQS	CQQSYSTPLTF
027S-G06	Fzd5	YTFTDYYMH	GWMSPNSGNAGFA	CARGKSGSFDYW	RASQSVNNTYVA	GTSTRAT	CQQYDTSPPTF
027S-H06	Fzd5	YTFTGHYIH	GIINPSGGSTSYA	CARGFCSGGSCLWYGMDVW	RASQSISSYLN	AASSLQS	CQQSYTTPFTF

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Clone ID	Initial Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
027S-A07	Fzd5	GTFGSYAIT	GGIIPIFGTANYA	CAKDNGWYFDLW	RASQSISTNVN	AASSLQS	CQQSYSTPYTF

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Table 1B: Anti-Fzd Antibody Clone IDs, Heavy Chain (HC) and Light Chain (LC) Seq ID Nos, and Binding Characteristics.

Clone ID	HC SID NO	LC SID NO	Confirmed Binding
001S-B01	1	38	Fzd1,2,7,9
001S-E02	2	39	Fzd1,2,7
001S-G02	3	40	Fzd1,2,7
001S-H02	4	41	Fzd1,2,7
001S-A03	5	42	Fzd1,2,7,9
001S-B03	6	43	Fzd1,2,7
004S-G06	7	44	Fzd5
002S-B01	8		Fzd1
002S-C02	9		Fzd1
002S-E02	10		Fzd1
002S-G02	11		Fzd1
002S-F03	12		Fzd1
002S-A04	13		Fzd1
002S-B04	14		Fzd1
002S-D04	15		Fzd1
004S-H04	16	45	Fzd5
001S-A04	17	46	Fzd1,2,5,7,8
003S-E07	18	47	Fzd2
003S-D10	19	48	Fzd4
004S-B08	20	49	Fzd6
004S-D08	21	50	Fzd6
004S-C09	22	51	Fzd6
004S-F10	23	52	Fzd6
004S-A11	24	53	Fzd6
004S-A12	25	54	Fzd6
005S-B07	26	55	Fzd9
005S-D08	27	56	Fzd9
005S-E09	28	57	Fzd9
005S-H10	29	58	Fzd9
005S-B11	30	59	Fzd9
005S-D11	31	60	Fzd9
014S-G02	32	61	Fzd6
014S-B04	33	62	Fzd8
014S-B06	34	63	Fzd9
014S-G06	35	64	Fzd10
014S-A07	36	65	Fzd10
017S-B09	37		Fzd8
004S-D01	129	130	Fzd4
004S-E09	131	132	Fzd6

In certain embodiment, the Fzd binding domain may be selected from any binding domain that binds a Fzd with an affinity of, e.g., a K_D of at least about 1 x 10^{-4} M, at least about 1 x 10^{-5} M, at least about 1 x 10^{-6} M, at least about 1 x 10^{-7} M, at least about 1 x 10^{-8} M, at least about 1 x 10^{-9} M, or at least about 1 x 10^{-10} M. In certain embodiment, the Fzd binding domain may be

selected from any binding domain that binds one or more Fzd receptor at high affinity, e.g., a K_D of less than about 1 x 10^{-7} M, less than about 1 x 10^{-8} M, less than about 1 x 10^{-9} M, or less than about 1 x 10^{-10} M. In certain embodiment, the Fzd binding domain may be selected from any binding domain that binds Fzd at high affinity, e.g. a K_D of less than or equal to about 1 x 10^{-4} M, less than or equal to about 1 x 10^{-5} M, less than or equal to about 1 x 10^{-6} M, less than or equal to about 1 x 10^{-7} M, less than or equal to about 1 x 10^{-8} M, less than or equal to about 1 x 10^{-9} M, or at least about 1 x 10^{-10} M in the context of a Wnt surrogate molecule.

Suitable Fzd binding domains include, without limitation, de novo designed Fzd binding proteins, antibody derived binding proteins, e.g. scFv, Fab, etc. and other portions of antibodies that specifically bind to one or more Fzd proteins; nanobody derived binding domains; knottin-based engineered scaffolds; norrin and engineered binding fragments derived therefrom, naturally occurring Fzd binding domains, and the like. A Fzd binding domain may be affinity selected to enhance binding to a desired Fzd protein or plurality of Fzd proteins, e.g. to provide tissue selectivity.

In some embodiments, the Fzd binding domain binds to one, two, three, four, five or more different frizzled proteins, e.g. one or more of human frizzled proteins Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, Fzd10. In some embodiments, the Fzd binding domain binds to Fzd1, Fzd2, and Fzd 7. In some embodiments, the Fzd binding domain binds to Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8. In other embodiments the Fzd binding domain is selective for one or more frizzled protein of interest, e.g. having a specificity for the one or more desired frizzled protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other frizzled proteins.

In certain embodiments, the Fzd binding domain comprises the six CDR regions of the pan specific frizzled antibody OMP-18R5 (vantictumab). In certain embodiments, the Fzd binding domain is an scFv comprising the six CDR regions of the pan-specific frizzled antibody OMP-18R5 (vantictumab). See, for example, U.S. Patent no. 8507442, herein specifically incorporated by

reference. For example, the CDR sequences of OMP-18R5 include a heavy chain CDR1 comprising GFTFSHYTLS, a heavy chain CDR2 comprising VISGDGSYTYYADSVKG, and a heavy chain CDR3 comprising NFIKYVFAN, and (ii) a light chain CDR1 comprising SGDKLGKKYAS or SGDNIGSFYVH, a light chain CDR2 comprising EKDNRPSG or DKSNRPSG, and a light chain CDR3 comprising SSFAGNSLE or QSYANTLSL. In particular embodiments, the Fzd binding domain is an antibody or derivative thereof, including without limitation scFv, minibodies, nanobodies and various antibody mimetics comprising any of these CDR sequences. In certain embodiments, these CDR sequences comprise one or more amino acid modifications.

In other embodiments, the Fzd binding domain comprises a variable region sequence, or the CDRs thereof, from any of a number of frizzled specific antibodies, which are known in the art and are commercially available, or can be generated de novo. Any of the frizzled polypeptides can be used as an immunogen or in screening assays to develop an antibody. Non-limiting examples of frizzled binding domains include antibodies available from Biolegend, e.g. Clone CH3A4A7 specific for human frizzled 4 (CD344); Clone W3C4E11 specific for human Fzd9 (CD349); antibodies available from Abcam, e.g. ab64636 specific for Fzd7; ab83042 specific for human Fzd4; ab77379 specific for human Fzd7; ab75235 specific for human Fzd8; ab102956 specific for human Fzd9; and the like. Other examples of suitable antibodies are described in, inter alia, US Patent application 20140105917; US Patent application 20130230521; US Patent application 20080267955; US Patent application 20080038272; US Patent application 20030044409; etc., each herein specifically incorporated by reference.

The Fzd binding region of a Wnt surrogate molecule may be an engineered protein that is selected for structural homology to the frizzled binding region of a wnt protein. Such proteins can be identified by screening a structure database for homologies. The initial protein thus identified, for example the microbial Bh1478 protein. The native protein is then engineered to provide amino acid substitutions that increase affinity, and may further be

selected by affinity maturation for increased affinity and selectivity in binding to the desired frizzled protein. Non-limiting examples of frizzled binding moieties include the Fz27 and Fz27-B12 proteins.

In particular embodiments, a Wnt surrogate molecule comprises an LRP5/6 binding domain, e.g., an anti-LRP5/6 antibody, or antigen-binding fragment thereof, fused to a polypeptide that specifically binds to one or more Fzd receptors. In particular embodiments, the polypeptide that specifically binds to LRP5/6 is an antibody or antigen-binding fragment thereof. If certain embodiments, it is an antibody or antigen-binding fragment thereof disclosed in the U.S. provisional patent application no. 62/607,879, titled, "Anti-LR5/6 Antibodies and Methods of Use," Attorney docket number SRZN-005/00US, filed on December 19, 2017, which is incorporated herein by reference in its entirety. In particular embodiments, the LRP5/6 binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to LRP5 and/or LRP6 provided in Table 2A. In particular embodiments, the LRP5/6 binding domain comprises the three heavy chain CDRs and/or the three light chain CDRs disclosed for any of the illustrative antibodies or fragments thereof that bind to one or more Fzd receptor provided in Table 2A, wherein the CDRs collectively comprise one, two, three, four, five, six, seven, or eight amino acid modifications, e.g., substitutions, deletions, or additions. In certain embodiments, the LRP5/6 binding domain is a Nanobody® or was derived from a Nanobody®, so Table 2A only includes the three heavy chain CDRs. In certain embodiments, the LRP5/6 biding domain comprises the three heavy chain CDRs shown in Table 2A or variants wherein the CDRs collectively comprise one, two, three, four, five, six, seven or eight amino acid modifications. In particular embodiments, the LRP5/6 binding domain comprises the heavy chain fragment and/or light chain fragment of any of the illustrative antibodies or fragments thereof that bind to LRP5 and/or LRP6 provided in Table 2B or SEQ ID NOs:66-88 or 133 (or an antigen-binding fragment or variant of either). In certain embodiments, the LRP5/6 binding

domain is an Fab or was derived from an Fab, so Table 2B includes VH and CH1 sequence, but not CH2 or CH3 sequences. In certain embodiments, the LRP5/6 binding domain is a Nanobody® or was derived from a Nanobody®, so Table 2B includes the VHH domain. In certain embodiments, the LRP5/6 binding region is a polypeptide, e.g., an antibody or antigen-binding fragment thereof, that competes with one of these antibodies for binding to LRP5 and/or LRP6.

Table 2A: Anti-LRP5/6 Antibody Clone IDs and CDR sequences.

Clone ID	Confirmed Binding	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
001S-C08	LRP6e1e2	YTISNYYIH	GMINPSGGSTTYA	CAIVRGKKWYFDLW	RASQYISNYLN	AASSLQS	CQQSYITPLTF
001S-C10	LRP6e1e2	RTFGTYPNG	AAISWGGRTAYA	CYARTVIGGFGAFRAHW			
001S-D10	LRP6e1e2	RTFSRYAMA	AAIRWSGGGTYYA	CAASMEAMNSLRVNKERYYQSW			
001S-E10	LRP6e1e2	LTFSNAAMA	AAISRSGANTAYS	CTLVNEIKTWW			
001S-F10	LRP6e1e2	RTFSSYAMA	AAIKWSGTNTYYA	CAASMEAMNSLRVNKERYYQSW			
001S-G10	LRP6e1e2	RTFSRYVMG	AAITWRGGSTYYA	CATGPNSIY			
001S-A11	LRP6e1e2	RTFGNYDMG	AGIRWSGSTLYA	CYARTVIGGFGAFRAHW			
001S-B11	LRP6e1e2	RRFTTYGMG	AAVTWRSGSTYYA	CAAGSTVVAEFNYW			
001S-C11	LRP6e1e2	SISSFNTMG	AVITTGGDTSYS	CNKVNAITKL			
001S-E11	LRP6e1e2	RTLSRYSMG	AAISRSGDRIYYS	CTLVNEIKTWW			
001S-F11	LRP6e1e2	RTFSSYAMS	AVIGRSGGIKYYA	CATRRPFNSYNTEQSYDSW			
001S-G11	LRP6e1e2	SIFRLGTMY	ASIGKSGSTNYA	CKQHPNGYR			
001S-H11	LRP6e1e2	RTLSSFAMG	ATISRSGGNTYYA	CNLREWNNSGAGYW			
001S-A12	LRP6e1e2	IAFRYYDMG	AAITWNGRSSDYA	CAAVFTGRFYGRPPREKYDYW			
001S-B12	LRP6e1e2	RLLSYYALA	AAISRNGDKSHYS	CTLVNEIKTWW			
001S-C12	LRP6e1e2	RTFSNYAVG	AAISRFGGSTYYV	CAADRIENYLGRYYDPSEYEYW			
001S-D12	LRP6e1e2	RTFSRYAMG	GAISRSGNNTYYA	CTLVNEIKTWW			
001S-F12	LRP6e1e2	RTFRSYTMG	AAISGSGGSTTYA	CNADIKTTTYSPLRNYW			
008S-B01	LRP5	TIFSINTMG	ATMTSGGNTNYA	CYRRQWASSWGARNYEYW			
008S-C01	LRP5	NINSIETLG	ANMRGGGYMKYA	CHGRDYGSNAPQYW			
008S-D01	LRP5	NINSIETLG	ANMRGGGYMKYA	CYVKLRDDDYVYR			
008S-E01	LRP5	NINSIETLG	ANMRGGGYMKYA	CNAVTYNGYTIR			
008S-G01	LRP5	NINSIETLG	ANMRGGGYMKYA	CYARTQRMGVVNSYW			
008S-A02	LRP5	NINSIETLG	ANMRGGGYMKYA	CNAVTFGGNTIR			
008S-C02	LRP5	NINSIETLG	ANMRGGGYMKYA	CNAVTYDGY			
008S-D02	LRP5	NINSIETLG	ANMRGGGYMKYA	CAAQFRNDYGLRYQSTNNYW			
008S-E02	LRP5	NINSIETLG	ANMRGGGYMKYA	CNANYRGNRYW			
009S-C01	LRP6e3e4	GSFSGYYWT	GEINHSGATNYN	CVRYAWPEFDHW	RASQRVSNYLN	AASSLQG	CQQSYSVPYTF
009S-B02	LRP6e3e4	GSLSGYYWS	GEINHSGSTNYN	CVRYAWPEFDHW	RASQSISNYLN	AASSLQS	CQQSYSLPLTF
009S-C02	LRP6e3e4	GSFSDYYWS	GEINHSGSTNYN	CVRYAWPEFDHW	RASQSISNYLN	AASSLQS	CQQSYSMPLTF
009S-D02	LRP6e3e4	GTFSSYAIS	GGIIPIFGTANYA	CVYGRDFDYW	SGSSSNVGNNYVS	DNDKRPS	CESWDSSLSSEVF
010S-A02	LRP6e1e2	HTFSSYAMG	AAISQSGYVRYYA	CKIYGLNGQPLGSW			
010S-B02	LRP6e1e2	RTFNSGTMG	AAITWRGGITYYA	CNADGYSWDGRSGRRLELW			
010S-D02	LRP6e1e2	RTFSSYAVG	AAISYSGGSTKYA	CAASVYISRRDSDYGYW			
010S-E02	LRP6e1e2	LSSGRPFSSYVMG	AAISWSGGSTKYA	CKLQVRPIGYSSAYSRNYW			
010S-F02	LRP6e1e2	RSFNSYVIG	AAIRWSGDNTYYA	CAASMEAMNSLRVNKERYYQSW			
009S-E02	LRP6e1e2	RRFTTYGMG	AAVTWRSGSTYYA	CAAGSTVVAEFNYW			
009S-F02	LRP6e1e2	RTFSYYAMG	AAISRSGGIYYA	CNTVRPLWAW			
009S-G02	LRP6e1e2	SIFSIYAMG	AVITSGGKTVYA	CYADSRSSWYDEYLEHW			
009S-H02	LRP6e1e2	SIVRSLPMA	ATINDAQRYYA	CNTSPYMHDVW			

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009S-A03	LRP6e1e2	RTFSVYGVG	AAVSASGGYTWYA	CKAAPRWGGATAYW			
010S-G02	LRP6e1e2	SIVRSLPMA	ATINDAQRYYA	CNTSPYMHDVW			
010S-A03	LRP6e1e2	RTFRRYAMG	ATISASGGNTAYA	CNAPAWLYDDDYW			
009S-B03	LRP6e1e2	RTFSNYAVG	AAISRFGGSTYYV	CAADRIENYLGRYYDPSEYEYW			
010S-B03	LRP6e1e2	RTFSNYAVG	AAISRFGGSTYYA	CHAKQLRNGQMYTYW			
010S-D03	LRP6e1e2	ISSVYGMG	AAIQWSADNTFYA	CAARTSGGLFHYRRSDHWDTW			
009S-C03	LRP6e1e2	LPFSRYAMA	AGMSGEGRNTKYR	CSSRGYW			
009S-D03	LRP6e1e2	SIFSDGAMG	AVISGGRTGYA	CNTYPFPIYKKGYPFW			
009S-E03	LRP6e1e2	RRFTTYGMG	AAVTWRSGSTYYA	CAAGSTVVAEFNYW			
009S-F03	LRP6e1e2	RTFSSYAMS	AVIGRSGGIKYYA	CATRRPFNSYNTEQSYDSW			
010S-E03	LRP6e1e2	RSVSIYPMG	AAINWSGDSTKYA	CNAVVVGLSRRIDNIW			
010S-F03	LRP6e1e2	RTFSRYVMG	AAITWRGGSTYYA	CATGPNSIY			
009S-G03	LRP6e1e2	RSVSSYNMG	AAISRRGGIIEYG	CHAVENILGRFVDYW			
009S-H03	LRP6e1e2	SIFSINTMG	AVITSGGKTVYA	CYADSRSSWYDEYLEHW			
009S-A04	LRP6e1e2	RTLSAYDMG	GGIRWSGGTTLYP	CYARTVIGGFGAFRAHW			
009S-B04	LRP6e3e4	SIFMINTMA	ATIRPVVSETTYA	CNAKRPWGTRDEYW			
010S-G03	LRP6e3e4	RSFNSYTTT	AAIRGSSGSTFYA	CNAASTVTAWPYYGPDYW			
009S-C04	LRP6e3e4	FRFSISTMG	AYITGGGRTMDG	CNAFVRSDFDRYYDYW			
009S-D04	LRP6e3e4	TIVSIYRIN	AGITSSGRTIYA	CNAASTVTAWPYYGPDYW			
010S-H03	LRP6e3e4	RIFSIYDMG	SGIRWSGGTSYA	CSSRGYW			
009S-E04	LRP6e3e4	RIFAIYDIA	AMIRPVVTEIDYA	CNAKRPWGSRDEYW			
010S-A04	LRP6e3e4	SLFSFNAVG	ASISSGGRTNYA	CSKGGVYGGTYVPDSW			
009S-F04	LRP6e3e4	RSLSSFAMG	ARISRGDGYTDEA	CAAVQAVIGGTLTTAYDYW			
010S-B04	LRP6e3e4	RVLSYYAMA	AGITRGGATTYYS	CAAGPNWSTRNREYDYW			
009S-G04	LRP6e3e4	GTFSRYHMG	SAITWSGGRTYYA	CALTWAPTPTNRRSDYAYW			
009S-H04	LRP6e3e4	RIFAIYDMA	ATIRPVVSETTYA	CNAKRPWGTRDEYW			
010S-C04	LRP6e3e4	SLFSFNAMG	ASISSGSRTNYA	CSKGGVYGGTYVPDSW			
010S-D04	LRP6e3e4	RIFAIYDIA	ATIRPVVTQIDYA	CNAKRPWGSRDEYW			
010S-E04	LRP6e3e4	RTFGSDVMG	ALTGWGDGSTTYYE	CAAARRSGTYDIGQYLRESAYVFW			
010S-F04	LRP6e3e4	RTFSRYAMG	AAITRSGSNTYYA	CAADPRGVTLPRATAYEYW			
009S-A05	LRP6e3e4	RTFSDYSMG	AGISWIADNRYYA	CTAGRSRYLYGSSLNGPYDYW			
010S-G04	LRP6e3e4	VIFALYDIA	ATIRPVVTETDYA	CNAKRPWGSRDEYW			
010S-H04	LRP6e3e4	RSFSDFFMG	ATISWSGSSANYE	CAAAYSYSQYGSSYSYW			
010S-A05	LRP6e3e4	LSFSSYAMG	AAISRSGVSTYYA	CAAKFGVLATTESRHDYW			
010S-C05	LRP6e3e4	RTFNIDDMG	ASIRWSGQSPYYA	CNAETYSGNTIW			
010S-D05	LRP6e3e4	RTFSDYSMA	AGISWIADNRYYA	CAGDRSRYLYGDSLRGPYGYW			
010S-E05	LRP6e3e4	SVFTTFAKG	ASITASSDRTFYA	CAAYSTFNTDVASMKPDYW			
010S-F05	LRP6e3e4	RIFSIYDIA	ATIRPVVTETDYA	CNAKRPWGSRDEYW			
013S-G04	LRP6e3e4	RIFAIYDIA	ATIRPVVSETTYA	CNAKRPWGTRDEYW			
013S-H04	LRP6e3e4	RTFSMYDMG	ASIRWSSGNTWYA	CYANIYYTRRAPEEYW			
013S-A05	LRP6e3e4	RTFNTYAMG	ASVSWRYDRTYYT	CAADTNWRAGPRVGIDEYAYW			
013S-B05	LRP6e3e4	FAFSTTAMS	STINPGGLSKSYA	CTKGGIQ			
013S-C05	LRP6e3e4	NIFPIDDMS	ATVTSGGRINYA	CNVDRTLYGKYKEYW			

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013S-D05	LRP6e3e4	RIFSIYDMG	SGIRWSGGTSYA	CGSRGYW			
013S-E05	LRP6e3e4	YTFTYRYLH	GGIIPIFGTADYA	CARDWELYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
013S-F05	LRP6e3e4	GTFSSYAIS	GIINPSGGSTSYA	CARAGYYDSSGYYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
013S-G05	LRP6e3e4	YTFTYRYLH	GGVIPIFGTADYA	CASDIVVDDAFDTW	RASQDISNYLN	AASTLQS	CQQGNSFPYTF
010S-G06	LRP6e3e4	FSFETYGMS	SGISGSGGRTHYA	CARDLDYW	QASQDISNYLN	AASSLQS	CQQSYRIHWTF
009S-B05	LRP6e3e4	FTFDAYAMH	STLSGDANNAYYA	CARGGSGWSNYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-C05	LRP6e3e4	YTFTYRYLH	GRIIPVLKITNYA	CAVVDDAFDIW			
009S-D05	LRP6e3e4	FTLRNHWLS	SAISGSGGSTYYA	CATRTGYSYGFNFWAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-E05	LRP6e3e4	YTFTNNFMH	GHVDPGDGETIYA	CARDWGIAAAGDYYYYGMDVW	RASQGINSYLA	DAKGLHP	CQQSYSAPLSF
009S-F05	LRP6e3e4	FTFDDYGMS	SAIGTGGGTYYA	CARLGSYGSPYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-G05	LRP6e3e4	FTFSDYYMS	SGVSWNGSRTHYA	CAKDSGLV	QASQDISNYLN	AASTLQR	CQQSYSAPLTF
009S-C06	LRP6e3e4	YTFASYDIH	GWMNPNSGNTGYA	CARATGSGWYTDLGYW	RASRNINRYLN	AASSLLS	CQQSYNVPFTF
009S-D06	LRP6e3e4	FTFSSHSTH	STISDTNSGTYYA	CAKAQATGWSGYYTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-E06	LRP6e3e4	FTFTDYGLH	AVISYGGSNKYYA	CASGYSYGLYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-F06	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATEAALDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-G06	LRP6e3e4	YIFTDYYMH	GWINPNSGGTNYA	CARDFLGSTGDYW	RASQNIGLYLN	DASSLQR	CQQSYSTPYTF
009S-H06	LRP6e3e4	FTFSSSAMH	SAIGTGGSTYYA	CAKGGDYFYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATAYGSSSLNIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-B07	LRP6e3e4	YTFTGYYMH	GWINPNSGGTNYA	CVKDGGSFPLAYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-D07	LRP6e3e4	FPFRYYGMS	ARIGWNGGSIVYA	CARDYSDRSGIDYW	RSSQSLLHSNGYNYLD	LGSNRAS	CMQATQFPLTF
009S-F07	LRP6e3e4	GTFSSYAIS	GIINPSGGSTSYA	CARAAGNFWSGYYTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-G07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARGSYGMDVW	RASQGISNYLA	DASNLET	CLQDFSFPWTF
009S-H07	LRP6e3e4	YTFTGYYMH	GWMNPNSGNTGYA	CASSVVPAGPAGVYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A08	LRP6e3e4	GTFSSHAIN	GWISANNGNTDYA	CARDQDYGDYGWYYYGMDVW	RASQGISNYLA	GSSTLQS	CQQTYSIPPTF
011S-C01	LRP6e3e4	LTFTSHGMS	SYVSDSGSSVYYA	CARHPGSFGGYSYAWYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-C08	LRP6e3e4	FSFNTFGIH	AVISYDGSNKYYA	CAKSIAAAGTGYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-D08	LRP6e3e4	YTFTSYDIN	GGIIPIFGTANYA	CARGPYYFDYW	RASQGISNNLN	DASSLES	CLQHNSYPFTF
011S-F01	LRP6e3e4	FSFSDYYMS	SGISESGGRTYYA	CASAADFDYW	RASQDISNYLN	AASSLQS	CLQDYSYPRTF
009S-E08	LRP6e3e4	YGFTGYYIH	GWMNPNSGNTGYA	CARGYGDYDLW	QASQDISNYLN	DASSLES	CQQSYRYPTF
009S-F08	LRP6e3e4	DTFANYGFS	GXVNAGNGNTTYA	CAKGWLDFDYW	QASQDISNYLN	DASSLES	CQQSYSTSITF
009S-G08	LRP6e3e4	FTFSDFAMT	SYISGDSGYTNYA	CARLGSYPGPYYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-H08	LRP6e3e4	YTFTDYFMN	GIINPSGDSTRFA	CARDDGLGGMDVW	QASQDISNYLA	AASSLQS	CQQSYSTPLTF
009S-A09	LRP6e3e4	YTFTYRYLH	GRIIPILGSTNYA	CTTDLWDYW	QASQGITNYLN	AASSLQS	CLQDYTDPFTF
011S-F02	LRP6e3e4	FTFSTYGMH	SSISVSSGTTHYA	CARGGSGSYYYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-G02	LRP6e3e4	YTFTSYAMN	GGIIPIFGTANYA	CARDASGGSTGWYYFDSW	RASQGISSYLA	AASSLQS	CQQAYSFPWTF
011S-A03	LRP6e3e4	FTFSSYWMH	STISGSGGRTYYA	CATSPYGVFTLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-C03	LRP6e3e4	YTFSYRYLH	GGIIPIFGTANYA	CASTVTTDAFDIW	QASQDISNYLN	DASSLES	CQQSYSFPPFTF
011S-D03	LRP6e3e4	FSFDDYGMS	SVISSGGTIYYA	CARHLSSGYLSYYGMDVW	RASQSISSYLA	AASTLQS	CQQSYSTPLTF
011S-F03	LRP6e3e4	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSQSVLYTTTNRNHIA	WASSRKS	CQQYYSTPYTF
011S-C04	LRP6e1e2	GTFNSNAIS	GWMNPNSGNTGYA	CARDYYGSGSYNYGMDVW	GASQSVPRNSLA	GASQRAT	CQQYHNWPPEYTF
011S-D04	LRP6e1e2	YTFTSYDIN	GIINPSGGSTSYA	CAREAYYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-H04	LRP6e1e2	YIFTDYYMH	GRIIPILGRANYA	CARGGYSTLDYW	QASQDISNYLN	AASTLQS	CQQSFSTPRTF
008S-F02	LRP5	YTFTNYCMH	GIINPSDGSTSHA	CAKDMVHLIVALAIDYW	RSSQSLLHSDGYTYLY	TLSYRAS	CMQALEALFTF

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010S-C06	LRP6e1e2	FTFNSYSMD	SSISPRGGSTYYA	CAPYYYDKSAKPLRSYFDHW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-E06	LRP6e3e4	LTVSSNYMS	SGISWNSGSIGYA	CARGSDCSGGSCYYSFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-F06	LRP6e3e4	FTFSSSWMH	SAIGTGGGTYYA	CAREVAVKDYYYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-H06	LRP6e3e4	YTFTSYDIN	GRIIPILGRTNYA	CAREERGATGRAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-A07	LRP6e3e4	FTFSSYAMH	ASISSTSGSKYYA	CAKTYYDFWSGYYTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-B07	LRP6e3e4	FTFSDYYMS	SMISYNGGRAFYA	CARGNPYYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-C07	LRP6e3e4	FTFSKTDMH	STITTDSRGTYYA	CAKGGDYYYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-D07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CANGLEDAYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-D05	LRP6e3e4	FTLRNHWLS	SAISGSGGSTYYA	CATRTGYSYGFNFWAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-E05	LRP6e3e4	YTFTNNFMH	GHVDPGDGETIYA	CARDWGIAAAGDYYYYGMDVW	RASQGINSYLA	DAKGLHP	CQQSYSAPLSF
010S-E07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CAKDDFSLYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-F05	LRP6e3e4	FTFDDYGMS	SAIGTGGGTYYA	CARLGSYGSPYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-F07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARLDYGETEGNGDW	RASQSVYSNLA	DTSNRAT	CQQYNNWPPITF
010S-G07	LRP6e3e4	FTFSSYAMH	STISGSGGSTYYA	CARAGYGRYYYGMDVW	RVSQGISSYLN	AASSLQS	CQQTYTIPFTF
009S-G05	LRP6e3e4	FTFSDYYMS	SGVSWNGSRTHYA	CAKDSGLV	QASQDISNYLN	AASTLQR	CQQSYSAPLTF
010S-H07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARDDSMGAFDIW	QASQDISNYLN	GTSNLQS	CQQSYSTPYTF
010S-A08	LRP6e3e4	HTFLTYDIN	GRITPRLGIANYA	CASYFGVMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATAYGSSSLNIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-B07	LRP6e3e4	YTFTGYYMH	GWINPNSGGTNYA	CVKDGGSFPLAYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-B06	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CAPALTDAGSFDYW	RVSQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-B08	LRP6e3e4	YTFTYRYLH	GGIIPVFGTADYA	CARDREQQILDYW	RASQGISNNLN	DASNLET	CQQSYTSRLTF
010S-C08	LRP6e3e4	FTFSTFGMH	STITSSGGSTYYA	CARAGIAAAPGSRNYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-C06	LRP6e3e4	YTFASYDIH	GWMNPNSGNTGYA	CARATGSGWYTDLGYW	RASRNINRYLN	AASSLLS	CQQSYNVPFTF
009S-D06	LRP6e3e4	FTFSSHSTH	STISDTNSGTYYA	CAKAQATGWSGYYTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-D08	LRP6e3e4	FTFSSSWMH	SAIGTGGGTYYA	CAKEDYDSSGYYYYYFQHW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-E06	LRP6e3e4	FTFTDYGLH	AVISYGGSNKYYA	CASGYSYGLYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-E08	LRP6e3e4	YSFTRTDMH	GYISAYTGHTSYA	CARDLGGTADYW	RASQSISSYLN	ZASSLQS	CQQSYSTPLTF
010S-F08	LRP6e3e4	LTFDDHAMH	SYISSSGRTIFYA	CVRGDSGWGILYYVMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-F06	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATEAALDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-G08	LRP6e3e4	YIFTDYYMH	GGFDPEDGETIYA	CARGGGPNEHDYYFDYW	RASQSVRSSDLA	GSSSRAT	CQQYGRSPRYSF
010S-H08	LRP6e3e4	FTFZNAWMS	SGISGSGGSTYYA	CARGRGKKNYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-A09	LRP6e3e4	FTFSTYYMS	SGISWNGGKTHYV	CARGGDFDYW	QASQDIANYLN	AASSLQS	CQQSYSTPYTF
010S-B09	LRP6e3e4	GTFSSYAIS	GWINPNSGDTNYA	CARGEQWLVWGFDPW	RASQSISRYLN	KASSLES	CQQSYDSPWTF
009S-G06	LRP6e3e4	YIFTDYYMH	GWINPNSGGTNYA	CARDFLGSTGDYW	RASQNIGLYLN	DASSLQR	CQQSYSTPYTF
010S-C09	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARDEVEGGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-H06	LRP6e3e4	FTFSSSAMH	SAIGTGGSTYYA	CAKGGDYFYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-D09	LRP6e3e4	GTFSSYTIS	GGIVPAYRRANYA	CAKGGYELDYW	QASQDISNYLN	AASSLQS	CQQIHSYPLTF
010S-E09	LRP6e3e4	GDLSIYTIN	GWINAGNGNTTYA	CARGGDSSGYYYYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATAYGSSSLNIDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-B07	LRP6e3e4	YTFTGYYMH	GWINPNSGGTNYA	CVKDGGSFPLAYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-D08	LRP6e3e4	YTFTSYDIN	GGIIPIFGTANYA	CARGPYYFDYW	RASQGISNNLN	DASSLES	CLQHNSYPFTF
010S-F09	LRP6e3e4	FTFDEYAMH	STISGSGGSTYYA	CASAKNDFWSGYFAFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-G09	LRP6e3e4	GTFNTHTIT	GWMNPNSGNTGYA	CARGNLDFDYW	QASQDISNYLN	DASNLET	CQQSYSTPLTF

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010S-H09	LRP6e3e4	FTFSDHYMS	SAISSGSDRTYYA	CARYSGYDFDYW	RASQGISNYLN	AASTLQS	CQQGYGTPPMF
010S-A10	LRP6e3e4	FSFSSYSMN	SYISSSSSTIYYA	CARGSGYYGPGYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-D07	LRP6e3e4	FPFRYYGMS	ARIGWNGGSIVYA	CARDYSDRSGIDYW	RSSQSLLHSNGYNYLD	LGSNRAS	CMQATQFPLTF
010S-B10	LRP6e3e4	FAFKDYYMT	SAIGAGGGTYYA	CARESALYSSSWYYYYYGMDVW	RASQSISSYLN	GTSSLHT	CQQANSFPFTF
010S-C10	LRP6e3e4	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSQSILSSSSNRDSLA	WASSRKS	CQQYYNIPYSF
009S-E07	LRP6e3e4	YTFTGYYIH	ZHVDPEDGETIYA	CARGPAAIGILGWFDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-D10	LRP6e3e4	YIFTDYYMH	GWMNPNSGNTGYA	CARTLSGYSSSWYVFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-E10	LRP6e3e4	FTFSSYSMN	SGISWNSGTTGYS	CARDHSSGWRHYFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-F10	LRP6e3e4	FTFSNSDMN	SYISGNSGYTNYA	CASGSYYSDFDYW	RASQSISNYLN	AASTLES	CQQANSFPPTF
010S-G10	LRP6e3e4	GTFSSYAIS	GRINPNGGGTIYA	CAREGGYYFDYW	RASQGISNYLA	AASSLQS	CQQSYSTPWTF
009S-F07	LRP6e3e4	GTFSSYAIS	GIINPSGGSTSYA	CARAAGNFWSGYYTFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-G07	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARGSYGMDVW	RASQGISNYLA	DASNLET	CLQDFSFPWTF
010S-H10	LRP6e3e4	YTFTSYYMH	GWINPNSGGTNYA	CAREAAEIPVGAFDIW	KSSHSLLYSSDNKNYLA	WSSTRES	CQQYYSTPQTF
010S-A11	LRP6e3e4	FTFSNSDMN	SYISGNSGYTNYA	CASGSYYSDFDYW	RASQSIZNYLN	ZASTLES	CQQANSFPPTF
010S-B11	LRP6e3e4	FTFRNYAIH	SAIGTGGDTYYA	CARDGGIRDFDYW	QASQDISNYLN	AASTLQS	CQQSYSTPLTF
010S-C11	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CAADDLGLELHYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-H07	LRP6e3e4	YTFTGYYMH	GWMNPNSGNTGYA	CASSVVPAGPAGVYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A08	LRP6e3e4	GTFSSHAIN	GWISANNGNTDYA	CARDQDYGDYGWYYYGMDVW	RASQGISNYLA	GSSTLQS	CQQTYSIPPTF
010S-D11	LRP6e3e4	YTFTYRYLH	GGIIPVFGTANYA	CATDEYSSSYAFDIW	RASQSVSSNLA	GASTRAT	CQQFDRSPLTF
010S-E11	LRP6e3e4	FTFSAHGMH	SGISESGGSTYYA	CARGRGYSYGYYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-F11	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CARDSDWGVVDPW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-G11	LRP6e3e4	YTFTYRYLH	GRIIPVLKITNYA	CAVVDDAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-H11	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CAKDGTDGRFDPW	RASQDISSYLA	SASTLQS	CQQSNSFPYTF
009S-B08	LRP6e3e4	FTFTSSAVQ	GWINAGNGNTTYA	CARRGGDVTVPAAYYAMDVW	RASQSISSYLN	ZASSLQS	CQQSYSTPLTF
010S-A12	LRP6e3e4	VTFSRYPIS	GGIIPIFGTANYA	CAKDSGNYGYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-B12	LRP6e3e4	FTFSSYDMH	SGITSNGGATYYA	CARGTTGKGYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-C12	LRP6e3e4	FTFSNYWIH	SAIGTGGGTYYA	CTTAGYKAARRSVYPRIFNFDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-D12	LRP6e3e4	YTFTYRYLH	GRIIPIFGTANYA	CAREEGVGGMDVW	RPSQSIGSWLA	DASNLQS	CQQSSSTPYTF
010S-E12	LRP6e3e4	FTFSSYAMH	SAIGAGGGTYYA	CARGVSSGYYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
010S-F12	LRP6e3e4	FTVSSNYMS	SAIGTGGGTYYA	CARAGTNWGGWYFDLW	RASQGISRDLA	AASTLQS	CQQSYSPPFTF
010S-G12	LRP6e3e4	FALSGYYMS	SSISSSSTYIRYA	CATVTGYSSAGAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-A01	LRP6e3e4	FTFSTHAFH	SAIRGSGERTYYA	CARDLRNWGSPYWYFDLW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-B01	LRP6e3e4	GTFSHYTIS	GWINAGNGNTKYS	CAKGGSLDMDVW	RASQGISNYLA	AASSLHS	CQQSYRTPLTF
011S-C01	LRP6e3e4	LTFTSHGMS	SYVSDSGSSVYYA	CARHPGSFGGYSYAWYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-D01	LRP6e3e4	GTISDYTVS	GIINPSGGSTSYA	CARGYYDFDYW	RASQGISNYLA	AASSLQS	CQQSYSTPLTF
009S-C08	LRP6e3e4	FSFNTFGIH	AVISYDGSNKYYA	CAKSIAAAGTGYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-E01	LRP6e3e4	FPFZYYSMN	SAISGRDGRTYYA	CAKDLGIQLPDYYFDYW	RASQGISSALA	AASTLQS	CQQSYSSPPTF
009S-D08	LRP6e3e4	YTFTSYDIN	GGIIPIFGTANYA	CARGPYYFDYW	RASQGISNNLN	DASSLES	CLQHNSYPFTF
011S-F01	LRP6e3e4	FSFSDYYMS	SGISESGGRTYYA	CASAADFDYW	RASQDISNYLN	AASSLQS	CLQDYSYPRTF
009S-E08	LRP6e3e4	YGFTGYYIH	GWMNPNSGNTGYA	CARGYGDYDLW	QASQDISNYLN	DASSLES	CQQSYRYPTF
009S-F08	LRP6e3e4	DTFANYGFS	GXVNAGNGNTTYA	CAKGWLDFDYW	QASQDISNYLN	DASSLES	CQQSYSTSITF
011S-G01	LRP6e3e4	YTFTYRYLH	GGIIPLFGTANYA	CTTDDYGDQYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-H01	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CTTDDYGDLTHLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF

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011S-A02	LRP6e3e4	GTFSSYAIS	GWMNPNSGNTGYA	CARDKGYAFDIW	RSSQSLLHSNGYNYLD	AASSLQS	CMQALQTPITF
011S-B02	LRP6e3e4	YSFTRTDMH	GYISAYTGHTSYA	CARDLGGTADYW	RZSQSZSZYLN	AASSLQS	CQQSYSTPLTF
011S-C02	LRP6e3e4	FTFSTYSMN	SGISWNSGRIGYA	CARDVGAFDIW	QASQDISNYLN	AASILQS	CQQSYSIPFTF
009S-G08	LRP6e3e4	FTFSDFAMT	SYISGDSGYTNYA	CARLGSYPGPYYYYMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-D02	LRP6e3e4	FTFSSYAMS	SSISGSGGVTYYA	CARGGNTYYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-H08	LRP6e3e4	YTFTDYFMN	GIINPSGDSTRFA	CARDDGLGGMDVW	QASQDISNYLA	AASSLQS	CQQSYSTPLTF
011S-E02	LRP6e3e4	YTFTYRYLH	GGIIPIFGTANYA	CATDYGDYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-A09	LRP6e3e4	YTFTYRYLH	GRIIPILGSTNYA	CTTDLWDYW	QASQGITNYLN	AASSLQS	CLQDYTDPFTF
011S-F02	LRP6e3e4	FTFSTYGMH	SSISVSSGTTHYA	CARGGSGSYYYAFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-G02	LRP6e3e4	YTFTSYAMN	GGIIPIFGTANYA	CARDASGGSTGWYYFDSW	RASQGISSYLA	AASSLQS	CQQAYSFPWTF
011S-H02	LRP6e3e4	YTFTNNFMH	GIINPSGGSTSYA	CARGLYKRYSYGYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
009S-B09	LRP6e3e4	FSFNTYAMN	AVTSYDGGKKNYA	CARDAGGDYDYW	QASQDISNYLN	AASSLQS	CQQSYNTPRTF
009S-C09	LRP6e3e4	GTFHTYGLS	GGIIPIFGTANYA	CARGSGWSGLDYW	QASQDISNYLN	DASNLET	CQQSYTTPFTF
011S-A03	LRP6e3e4	FTFSSYWMH	STISGSGGRTYYA	CATSPYGVFTLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-B03	LRP6e3e4	GTFSZYAIS	GIINPSGGSTNYA	CARAGYWSGYGYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-C03	LRP6e3e4	YTFSYRYLH	GGIIPIFGTANYA	CASTVTTDAFDIW	QASQDISNYLN	DASSLES	CQQSYSFPPFTF
011S-D03	LRP6e3e4	FSFDDYGMS	SVISSGGTIYYA	CARHLSSGYLSYYGMDVW	RASQSISSYLA	AASTLQS	CQQSYSTPLTF
009S-F09	LRP6e3e4	YSFTRTDMH	GYISAYTGHTSYA	CARDLGGTADYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-E03	LRP6e3e4	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSHSLLSTSTNRNQLA	WASSRKS	CQQYNNWPYTF
009S-G09	LRP6e3e4	FTFSRHSMN	SYSSGNSGYTNYA	CARGDLEFDYW	RASQGISNYLA	SASSLQS	CQQGYNTPRTF
011S-F03	LRP6e3e4	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSQSVLYTTTNRNHIA	WASSRKS	CQQYYSTPYTF
009S-H09	LRP6e3e4	FTFSSYAMS	SAISGSGGSTYYA	CAKGGRDGYKGYFDYW	KSSHSLLSTSTNRNHLA	WASSRKS	CQQYYNIPYSF
011S-G03	LRP6e3e4	YTFTYRYLH	GRIIPIHGIANYA	CAREYSYGYFRYW	RASQGISSYLA	DASNLET	CQQANSLFTF
009S-A10	LRP6e3e4	FTFTSSAMQ	GIINPSGGSTIYA	CASGDTYDLYSLDVW	RASQSISRWLA	AASSLQS	CQQAYSFPWTF
009S-B10	LRP6e3e4	YIFTDYYMH	GWINAGNGNTTYA	CAKVASGWSWPFDIW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-B04	LRP6e1e2	YTFTSYDIN	GIINPSGGSTSYA	CTREHSYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-C04	LRP6e1e2	GTFNSNAIS	GWMNPNSGNTGYA	CARDYYGSGSYNYGMDVW	GASQSVPRNSLA	GASQRAT	CQQYHNWPPEYTF
011S-D04	LRP6e1e2	YTFTSYDIN	GIINPSGGSTSYA	CAREAYYYYYGMDVW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-E04	LRP6e1e2	FTFSSZZMH	SAIGTGGGTZYA	CAKDLGRAAAGSMDVW	WASQSVRGNYVA	DASNRAA	CQHRSNWPLTF
011S-F04	LRP6e1e2	YIFTDYYMH	GRIIPILGRANYA	CARGGYSTLDYW	HGSQDISNYLN	DASNRQS	CQQSFSTPRTF
011S-H04	LRP6e1e2	YIFTDYYMH	GRIIPILGRANYA	CARGGYSTLDYW	QASQDISNYLN	AASTLQS	CQQSFSTPRTF
011S-A05	LRP6e1e2	FTFSSYAMH	SAIGTGGGTYYA	CAKDLGRAAAGSMDVW	WASQSVRGNYVA	DASNRAG	CQHRSNWPLTF
011S-B05	LRP6e1e2	YZFTDYYMH	GWMNPNSGNTGYA	CTRVAWGLDYW	RASQSISSYLN	AASSLQS	CQQSYSTPLTF
011S-C05	LRP6e1e2	FTFSSYAMH	SAIGTGGGTYYA	CAKDLGRAAAGSMDVW	WASQSVRGNYVA	DASNRAA	CQHRSNWPLTF

Table 2B. Anti-LRP5/6 Antibody Clone IDs, Heavy Chain (HC) Seq ID Nos, and Binding Characteristics.

Clone ID	HC Seq ID NO	Confirmed Binding
001S-F11	66	LRP6e1e2
009S-G02	67	LRP6e1e2
009S-A03	68	LRP6e1e2

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009S-D03	69	LRP6e1e2
009S-F03	70	LRP6e1e2
009S-H03	71	LRP6e1e2
009S-A04	72	LRP6e1e2
009S-B04	73	LRP6e3e4
009S-D04	74	LRP6e3e4
009S-E04	75	LRP6e3e4
009S-F04	76	LRP6e3e4
009S-G04	77	LRP6e3e4
009S-H04	78	LRP6e3e4
009S-A05	79	LRP6e3e4
013S-G04	80	LRP6e3e4
013S-H04	81	LRP6e3e4
013S-C05	82	LRP6e3e4
013S-D05	83	LRP6e3e4
013S-G04	84	LRP6e3e4
013S-H04	85	LRP6e3e4
013S-A05	86	LRP6e3e4
013S-C05	87	LRP6e3e4
013S-D05	88	LRP6e3e4
008S-D01	133	LRP5

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In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 with a K_D of less than or equal to about 1 x 10^{-4} M, less than or equal to about 1 x 10^{-5} M, less than or equal to about 1 x 10^{-6} M, less than or equal to about 1 x 10^{-7} M, less than or equal to about 1 x 10^{-8} M, less than or equal to about 1 x 10^{-9} M, or less than or equal to about 1 x 10^{-10} M in the context of a Wnt surrogate molecule. In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 with a K_D of greater than or equal to about 1 x 10^{-4} M, greater than or equal to about 1 x 10^{-5} M, greater than or equal to about 1 x 10^{-6} M, greater than or equal to about 1 x 10^{-7} M, greater than or equal to about 1 x 10^{-8} M, greater than or equal to about 1 x 10^{-9} M, or greater than about 1 x 10^{-10} M in the context of a Wnt surrogate molecule. In certain embodiment, the LRP5/6 binding domain may be selected from any binding domain that binds LRP5 or LRP6 at high affinity, e.g. a K_D of less than about 1 x 10^{-7} M, less than about 1 x 10^{-8} M, less than about 1 x 10^{-9} M, or less than about 1 x 10^{-10} M.

Other suitable LRP5/6 binding domains include, without limitation, de novo designed LRP5/6 binding proteins, antibody derived binding proteins, *e.g.* scFv, Fab, *etc.* and other portions of antibodies that specifically bind to one or more Fzd proteins; nanobody derived binding domains; knottin-based engineered scaffolds; naturally occurring LRP5/6, including without limitation, DKK1, DKK2, DKK3, DKK4, sclerostin; Wise; fusions proteins comprising any of the above; derivatives of any of the above; variants of any of the above; and biologically active fragments of any of the above, and the like. A LRP5/6 binding domain may be affinity selected to enhance binding.

Members of the Dickkopf (DKK) gene family (see Krupnik et al. (1999) Gene 238(2):301-13) include DKK-1, DKK-2, DKK-3, and DKK-4, and the DKK-3 related protein Soggy (Sgy). hDKKs 1-4 contain two distinct cysteine-rich domains in which the positions of 10 cysteine residues are highly conserved between family members. Exemplary sequences of human Dkk genes and proteins are publicly available, e.g., Genbank accession number

NM_014419 (soggy-1); NM_014420 (DKK4); AF177394 (DKK-1); AF177395 (DKK-2); NM_015881 (DKK3); and NM_014421 (DKK2). In some embodiments of the invention, the Lrp6 binding moiety is a DKK1 peptide, including without limitation the C-terminal domain of human DKK1. The C-terminal domain may comprise the sequence: KMYHTKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKG SHGLEIFQRCYCGEGLSCRIQKDHHQASNSSRLHTCQRH (see Genbank accession number NP_036374) or a biologically active fragment thereof.

Binding of DKK proteins to LRP5/6 are discussed, for example in Brott and Sokol Mol. Cell. Biol. 22 (17), 6100-6110 (2002); and Li et al. J. Biol. Chem. 277 (8), 5977-5981 (2002), each herein specifically incorporated by reference. The corresponding region of human DKK2 (Genbank reference NP_055236) may comprise the sequence: KMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGS HGLEIFQRCDCAKGLSCKVWKDATYSSKARLHVCQK or a biologically active fragment thereof.

Antibodies that specifically bind to LRP5 or LRP6 are known in the art and are commercially available, or can be generated de novo. LRP5, LRP6 or fragments thereof can be used as an immunogen or in screening assays to develop an antibody. Examples of known antibodies include, without limitation, those described in Gong et al. (2010) PLoS One. 5(9):e12682; Ettenberg et al. (2010) Proc Natl Acad Sci U S A. 107(35):15473-8; and those commercially available from, for example Santa Cruz biotechnology antibody clone 1A12, which was raised against synthetic LRP5/6 of human origin and binds to both the full length and proteolytic fragment of LRP6 and LRP5 of mouse and human origin; the monoclonal antibody 2B11; Cell Signaling Technology antibody specific for LRP5 (D80F2), catalog number 5731; etc.

In certain embodiments, Wnt surrogate molecules disclosed herein comprise one or more polypeptides comprising two or more binding regions. For example, the two or more binding regions may be two or more Fzd binding regions or two or more LRP5/6 binding regions, or they may comprise

one or more Fzd binding region and one or more LRP5/6 binding region. The binding regions may be directly joined or contiguous, or may be separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, etc. The length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate molecule. The enforced distance between binding domains can vary, but in certain embodiments may be less than about 100 angstroms, less than about 90 angstroms, less than about 80 angstroms, less than about 70 angstroms, less than about 60 angstroms, or less than about 50 angstroms. In some embodiments the linker is a rigid linker, in other embodiments the linker is a flexible linker. In certain embodiments where the linker is a peptide linker, it may be from about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more amino acids in length, and is of sufficient length and amino acid composition to enforce the distance between binding domains. In some embodiments, the linker comprises or consists of one or more glycine and/or serine residues.

In particular embodiments, a Wnt surrogate molecule comprises a polypeptide sequence having at least 90%, at least 95%, at least 98% or at least 99% identity to a polypeptide sequence disclosed in any of SEQ ID NOs:89-128 or 134-157, or having at least 90%, at least 95%, at least 98% or at least 99% identity to an antigen-binding fragment of a polypeptide sequence disclosed in any of SEQ ID NOs:89-128 or 134-157. In certain embodiments, the Wnt surrogate molecules comprises or consists of a polypeptide sequence set forth in any of SEQ ID NOs:89-128 or 134-157, or an antigen-binding fragment thereof. In particular embodiments, the antigen-binding fragment binds one or more Fzd receptors and also binds LRP5 and/or LRP6.

Wnt surrogate molecule can be multimerized, e.g. through an Fc domain, by concatenation, coiled coils, polypeptide zippers, biotin/avidin or streptavidin multimerization, and the like. The Wnt surrogate molecules can also be joined to a moiety such as PEG, Fc, etc., as known in the art to enhance stability in vivo.

In certain embodiments, a Wnt surrogate molecule directly activates canonical Wnt signaling through binding to one or more Fzd proteins and to LRP5/6, particularly by binding to these proteins on a cell surface, e.g., the surface of a human cell. The direct activation of Wnt signaling by a Wnt surrogate molecule is in contrast to potentiation of Wnt signaling, which enhances activity only when native Wnt proteins are present.

Wnt surrogate molecules may activate Wnt signaling, e.g., by mimicking the effect or activity of a Wnt protein binding to a frizzled protein. The ability of the Wnt surrogate molecules of the invention to mimic the activity of Wnt can be confirmed by a number of assays. The Wnt surrogate molecules typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the Wnt surrogate molecules of the invention enhance the canonical Wnt/β-catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of a Wnt surrogate molecule of the invention.

Various methods are known in the art for measuring the level of canonical Wnt/β-catenin signaling. These include, but are not limited to assays that measure: Wnt/β-catenin target gene expression; TCF reporter gene expression; β-catenin stabilization; LRP phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP. The canonical Wnt/β-catenin signaling pathway ultimately leads to changes in gene expression through the transcription factors TCF7, TCF7L1, TCF7L2 and LEF. The transcriptional response to Wnt activation has been characterized in a number of cells and tissues. As such, global transcriptional profiling by methods well known in the art can be used to assess Wnt/β-catenin signaling activation or inhibition.

Changes in Wnt-responsive gene expression are generally mediated by TCF and LEF transcription factors. A TCF reporter assay assesses changes in the transcription of TCF/LEF controlled genes to determine the level of Wnt/β-catenin signaling. A TCF reporter assay was first described by

Korinek, V. et al., 1997. Also known as TOP/FOP this method involves the use of three copies of the optimal TCF motif CCTTTGATC, or three copies of the mutant motif CCTTTGGCC, upstream of a minimal c-Fos promoter driving luciferase expression (pTOPFl_ASH and pFOPFl_ASH, respectively) to determine the transactivational activity of endogenous p-catenin/TCF4. A higher ratio of these two reporter activities (TOP/FOP) indicates higher β-catenin/TCF4 activity, whereas a lower ratio of these two reporter activities indicates lower β-catenin/TCF4 activity.

Various other reporter transgenes that respond to Wnt signals exist intact in animals and therefore, effectively reflect endogenous Wnt signaling. These reporters are based on a multimerized TCF binding site, which drives expression of LacZ or GFP, which are readily detectable by methods known in the art. These reporter genes include: TOP-GAL, BAT-GAL, ins-TOPEGFP, ins-TOPGAL, LEF-EGFP, Axin2-LacZ, Axin2-d2EGFP, Lgr5tm1 (cre/ERT2), TOPdGFP.

The recruitment of dephosphorylated β-catenin to the membrane, stabilization and phosphorylation status of β-catenin, and translocation of β-catenin to the nucleus (Klapholz- Brown Z et al., PLoS One. 2(9) e945, 2007), in some cases mediated by complex formation with TCF transcription factors and TNIK are key steps in the Wnt signaling pathway. Stabilization is mediated by Disheveled family proteins that inhibit the "destruction" complex so that degradation of intracellular β-catenin is reduced, and translocation of β-catenin to the nucleus follows thereafter. Therefore, measuring the level and location of β-catenin in a cell is a good reflection of the level of Wnt/β-catenin signaling. A non-limiting example of such an assay is the "BioImage β-Catenin Redistribution Assay" (Thermo Scientific) which provides recombinant U20S cells that stably express human β-catenin fused to the C-terminus of enhanced green fluorescent protein (EGFP). Imaging and analysis is performed with a fluorescence microscope or HCS platform allowing the levels and distribution of EGFP-β-catenin to be visualized.

Another way, in which the destruction complex is inhibited, is by removal of Axin by recruitment of Axin to the cytoplasmic tail of the Wnt co-receptor LRP. Axin has been shown to bind preferentially to a phosphorylated form of the LRP tail. Visualization of Axin translocation, for example with a GFP-Axin fusion protein, is therefore another method for assessing levels of Wnt/β-catenin signaling.

In certain embodiments, a Wnt surrogate molecule enhances or increases canonical Wnt pathway signaling, e.g., β-catenin signaling, by at least 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 150%, 200%, 250%, 300%, 400% or 500%, as compared to the β-catenin signaling induced by a neutral substance or negative control as measured in an assay described above, for example as measured in the TOPFlash assay. A negative control may be included in these assays. In particular embodiments, Wnt surrogate molecules may enhance β-catenin signaling by a factor of 2x, 5x, 10x, 100x, 1000x, 10000x or more as compared to the activity in the absence of the Wnt surrogate molecule when measured in an assay described above, for example when measured in the TOPFlash assay, or any of the other assays mentioned herein.

"Wnt gene product" or "Wnt polypeptide" when used herein encompass native sequence Wnt polypeptides, Wnt polypeptide variants, Wnt polypeptide fragments and chimeric Wnt polypeptides. In particular embodiments, a Wnt polypeptide is a native human full length mature Wnt protein.

For example, human native sequence Wnt proteins of interest in the present application include the following: Wnt-1 (GenBank Accession No. NM_005430); Wnt-2 (GenBank Accession No. NM_003391); Wnt-2B (Wnt-13) (GenBank Accession No. NM_004185 (isoform 1), NM_024494.2 (isoform 2)), Wnt-3 (RefSeq.: NM_030753), Wnt3a (GenBank Accession No. NM_033131), Wnt-4 (GenBank Accession No. NM_030761), Wnt-5A (GenBank Accession No. NM_003392), Wnt-5B (GenBank Accession No. NM_032642), Wnt-6 (GenBank Accession No. NM_006522), Wnt-7A (GenBank Accession No.

NM_004625), Wnt- 7B (GenBank Accession No. NM_058238), Wnt-8A (GenBank Accession No. NM_058244), Wnt-8B (GenBank Accession No. NM_003393), Wnt-9A (Wnt- 14) (GenBank Accession No. NM_003395), Wnt-9B (Wnt-15) (GenBank Accession No. NM_003396), Wnt-1 OA (GenBank Accession No. NM_025216), Wnt-10B (GenBank Accession No. NM_003394), Wnt-11 (GenBank Accession No. NM_004626), Wnt- 16 (GenBank Accession No. NM_016087)). Although each member has varying degrees of sequence identity with the family, all encode small (i.e., 39-46 kD), acylated, palmitoylated, secreted glycoproteins that contain 23-24 conserved cysteine residues whose spacing is highly conserved (McMahon, A P et al., Trends Genet. 1992; 8: 236-242; Miller, J R. Genome Biol. 2002; 3(1): 3001.1-3001.15). Other native sequence Wnt polypeptides of interest include orthologs of the above from any mammal, including domestic and farm animals, and zoo, laboratory or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, rats, mice, frogs, zebra fish, fruit fly, worm, etc.

"Wnt pathway signaling" or "Wnt signaling" is used herein to refer to the mechanism by which a biologically active Wnt exerts its effects upon a cell to modulate a cell's activity. Wnt proteins modulate cell activity by binding to Wnt receptors, including proteins from the Frizzled (Fzd) family of proteins, proteins from the ROR family of proteins, the proteins LRP5, LRP6 from the LRP family of proteins, the protein FRL1/crypto, and the protein Derailed/Ryk. Once activated by Wnt binding, the Wnt receptor(s) will activate one or more intracellular signaling cascades. These include the canonical Wnt signaling pathway; the Wnt/planar cell polarity (Wnt/PCP) pathway; the Wnt-calcium (Wnt/Ca^{2+}) pathway (Giles, RH et al. (2003) Biochim Biophys Acta 1653, 1-24; Peifer, M. et al. (1994) Development 120: 369-380; Papkoff, J. et al (1996) Mol. Cell Biol. 16: 2128-2134; Veeman, M. T. et al. (2003) Dev. Cell 5: 367-377); and other Wnt signaling pathways as is well known in the art.

For example, activation of the canonical Wnt signaling pathway results in the inhibition of phosphorylation of the intracellular protein β-catenin, leading to an accumulation of β- catenin in the cytosol and its subsequent

translocation to the nucleus where it interacts with transcription factors, e.g. TCF/LEF, to activate target genes. Activation of the Wnt/PCP pathway activates RhoA, c-Jun N-terminal kinase (JNK), and nemo-like kinase (NLK) signaling cascades to control such biological processes as tissue polarity and cell movement. Activation of the Wnt/Ca^{2+} by, for example, binding of Wnt-4, Wnt-5A or Wnt-11, elicits an intracellular release of calcium ions, which activates calcium sensitive enzymes like protein kinase C (PKC), calcium-calmodulin dependent kinase II (CamKII) or calcineurin (CaCN). By assaying for activity of the above signaling pathways, the biological activity of an antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate molecule, can be readily determined.

In certain embodiments, functional properties of Wnt surrogate molecules may be assessed using a variety of methods known to the skilled person, including e.g., affinity/binding assays (for example, surface plasmon resonance, competitive inhibition assays), cytotoxicity assays, cell viability assays, cell proliferation or differentiation assays in response to a Wnt, cancer cell and/or tumor growth inhibition using *in vitro* or *in vivo* models, including but not limited to any described herein. The Wnt surrogate molecules described herein may also be tested for effects on Fzd receptor internalization, *in vitro* and *in vivo* efficacy, *etc.* Such assays may be performed using well-established protocols known to the skilled person (see *e.g.*, Current Protocols in Molecular Biology (Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., NY, NY); Current Protocols in Immunology (Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober 2001 John Wiley & Sons, NY, NY); or commercially available kits.

In certain embodiments, a Fzd-binding region of a Wnt surrogate molecule (e.g., an antigen-binding fragment of an anti-Fzd antibody) comprises one or more of the CDRs of the anti-Fzd antibodies described herein. In certain embodiments, a LRP5/6-binding region of a Wnt surrogate molecule (e.g., an antigen-binding fragment of an anti-LRP5/6 antibody) comprises one or more of the CDRs of the anti-LRP5/6 antibodies described herein. In this regard, it has

been shown in some cases that the transfer of only the VHCDR3 of an antibody can be performed while still retaining desired specific binding (Barbas *et al.*, *PNAS* (1995) 92: 2529-2533). See also, McLane *et al.*, *PNAS* (1995) 92:5214-5218, Barbas *et al.*, *J. Am. Chem. Soc.* (1994) 116:2161-2162.

Also disclosed herein is a method for obtaining an antibody or antigen binding domain specific for a Fzd receptor, the method comprising providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VH domain set out herein or a VH domain which is an amino acid sequence variant of the VH domain, optionally combining the VH domain thus provided with one or more VL domains, and testing the VH domain or VH/VL combination or combinations to identify a specific binding member or an antibody antigen binding domain specific for one or more Fzd receptor and optionally with one or more desired properties. The VL domains may have an amino acid sequence which is substantially as set out herein. An analogous method may be employed in which one or more sequence variants of a VL domain disclosed herein are combined with one or more VH domains.

In particular embodiments, Wnt surrogate molecules are water soluble. By "water soluble" it is meant a composition that is soluble in aqueous buffers in the absence of detergent, usually soluble at a concentration that provides a biologically effective dose of the polypeptide. Compositions that are water soluble form a substantially homogenous composition that has a specific activity that is at least about 5% that of the starting material from which it was purified, usually at least about 10%, 20%, or 30% that of the starting material, more usually about 40%, 50%, or 60% that of the starting material, and may be about 50%, about 90% or greater. Wnt surrogate molecules disclosed herein typically form a substantially homogeneous aqueous solution at concentrations of at least 25 μM and higher, e.g. at least 25 μM, 40 μM, or 50 μM, usually at least 60 μM, 70 μM, 80 μM, or 90 μM, sometimes as much as 100 μM, 120 μM, or 150 μM. In other words, Wnt surrogate molecules disclosed herein typically

form a substantially homogeneous aqueous solution at concentrations of about 0.1 mg/ml, about 0.5 mg/ml, of about 1 mg/ml or more.

An antigen or epitope that "specifically binds" or "preferentially binds" (used interchangeably herein) to an antibody or antigen-binding fragment thereof is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule, e.g., a Wnt surrogate molecule, is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. A molecule or binding region thereof, e.g., a Wnt surrogate molecule or binding region thereof, "specifically binds" or "preferentially binds" to a target antigen, e.g., a Fzd receptor, if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, a Wnt surrogate molecule or binding region thereof that specifically or preferentially binds to the Fzd1 receptor is an antibody that binds to the Fzd1 receptor with greater affinity, avidity, more readily, and/or with greater duration than it binds to other Fzd receptors or non-Fzd proteins. It is also understood by reading this definition that, for example, a Wnt surrogate molecule or binding region thereof that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

In some embodiments, any of the one or more Fzd binding region of a Wnt surrogate molecule binds to one, two, three, four, five or more different frizzled proteins, e.g., one or more of human frizzled proteins Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, Fzd10. In some embodiments, any of the Fzd binding regions binds to Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8. In various embodiments, any of the Fzd binding regions binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii)

Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8. In some embodiments, the Fzd binding region is selective for one or more Fzd protein of interest, e.g. having a specificity for the one or more desired Fzd protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other Fzd proteins. In some embodiments, any of the one or more Fzd binding region of a Wnt surrogate molecule is monospecific and binds or specifically binds to only one of Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, or Fzd10.

In some embodiments, any of the one or more LRP5/6 binding region of a Wnt surrogate molecule binds to one or both of LRP5/6. For convenience, the term “LRP5/6” is used to refer collectively to either or both of LRP5 and/or LRP6.

Immunological binding generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific, for example by way of illustration and not limitation, as a result of electrostatic, ionic, hydrophilic and/or hydrophobic attractions or repulsion, steric forces, hydrogen bonding, van der Waals forces, and other interactions. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off} /K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d. See, generally, Davies *et al.* (1990) *Annual Rev. Biochem. 59*:439-473.

In certain embodiments, the Wnt surrogate molecules or binding regions thereof described herein have an affinity of less than about 10,000, less than about 1000, less than about 100, less than about 10, less than about 1 or less than about 0.1 nM, and in some embodiments, the antibodies may have even higher affinity for one or more Fzd receptor or LRP5 or LRP6 receptor.

The constant regions of immunoglobulins show less sequence diversity than the variable regions, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans, there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing features between these antibody classes are their constant regions, although subtler differences may exist in the V region.

The Fc region of an antibody interacts with a number of Fc receptors and ligands, imparting an array of important functional capabilities referred to as effector functions. For IgG, the Fc region comprises Ig domains CH2 and CH3 and the N-terminal hinge leading into CH2. An important family of Fc receptors for the IgG class are the Fc gamma receptors (FcγRs). These receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). In humans this protein family includes FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). These receptors typically have an extracellular domain that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils,

mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack.

The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ghetie *et al.*, 2000, Annu Rev Immunol 18:739-766; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). All FcγRs bind the same region on Fc, at the N-terminal end of the Cg2 (CH2) domain and the preceding hinge. This interaction is well characterized structurally (Sondermann *et al.*, 2001, J Mol Biol 309:737-749), and several structures of the human Fc bound to the extracellular domain of human FcγRIIIb have been solved (pdb accession code 1E4K) (Sondermann *et al.*, 2000, Nature 406:267-273.) (pdb accession codes 1IIS and 1IIX) (Radaev *et al.*, 2001, J Biol Chem 276:16469-16477.)

The different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4 (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). All FcγRs bind the same region on IgG Fc, yet with different affinities: the high affinity binder FcγRI has a K_d for IgG1 of 10^{-8} M^{-1}, whereas the low affinity receptors FcγRII and FcγRIII generally bind at 10^{-6} and 10^{-5} respectively. The extracellular domains of FcγRIIIa and FcγRIIIb are 96% identical; however,

FcγRIIIb does not have an intracellular signaling domain. Furthermore, whereas FcγRI, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex-triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM), FcγRIIb has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Thus the former are referred to as activation receptors, and FcγRIIb is referred to as an inhibitory receptor. The receptors also differ in expression pattern and levels on different immune cells. Yet another level of complexity is the existence of a number of FcγR polymorphisms in the human proteome. A particularly relevant polymorphism with clinical significance is V158/F158 FcγRIIIa. Human IgG1 binds with greater affinity to the V158 allotype than to the F158 allotype. This difference in affinity, and presumably its effect on ADCC and/or ADCP, has been shown to be a significant determinant of the efficacy of the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation). Subjects with the V158 allotype respond favorably to rituximab treatment; however, subjects with the lower affinity F158 allotype respond poorly (Cartron *et al.*, 2002, Blood 99:754-758). Approximately 10-20% of humans are V158/V158 homozygous, 45% are V158/F158 heterozygous, and 35-45% of humans are F158/F158 homozygous (Lehrnbecher *et al.*, 1999, Blood 94:4220-4232; Cartron *et al.*, 2002, Blood 99:754-758). Thus 80-90% of humans are poor responders, that is, they have at least one allele of the F158 FcγRIIIa.

The Fc region is also involved in activation of the complement cascade. In the classical complement pathway, C1 binds with its C1q subunits to Fc fragments of IgG or IgM, which has formed a complex with antigen(s). In certain embodiments of the invention, modifications to the Fc region comprise modifications that alter (either enhance or decrease) the ability of a Fzd-specific antibody as described herein to activate the complement system (see *e.g.*, U.S. Patent 7,740,847). To assess complement activation, a complement-dependent cytotoxicity (CDC) assay may be performed (See, *e.g.*, Gazzano-Santoro *et al.*, J. Immunol. Methods, 202:163 (1996)).

Thus in certain embodiments, the present invention provides anti-Fzd antibodies having a modified Fc region with altered functional properties, such as reduced or enhanced CDC, ADCC, or ADCP activity, or enhanced binding affinity for a specific FcγR or increased serum half-life. Other modified Fc regions contemplated herein are described, for example, in issued U.S. Patents 7,317,091; 7,657,380; 7,662,925; 6,538,124; 6,528,624; 7,297,775; 7,364,731; Published U.S. Applications US2009092599; US20080131435; US20080138344; and published International Applications WO2006/105338; WO2004/063351; WO2006/088494; WO2007/024249.

In certain embodiments, Wnt surrogate molecules comprise antibody variable domains with the desired binding specificities fused to immunoglobulin constant domain sequences. In certain embodiments, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. In particular embodiments, the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant effect on the yield of the desired chain combination.

Wnt surrogate molecules disclosed herein may also be modified to include an epitope tag or label, *e.g.*, for use in purification or diagnostic applications. There are many linking groups known in the art for making antibody conjugates, including, for example, those disclosed in U.S. Pat. No. 5,208,020 or EP Patent 0 425 235 B1, and Chari *et al.*, Cancer Research 52:

127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

In certain embodiments, anti-LRP5/6 antibodies and antigen-binding fragments thereof and/or anti-Fzd antibodies and antigen-binding fragments thereof present within a Wnt surrogate molecule are monoclonal. In certain embodiments, they are humanized.

The present invention further provides in certain embodiments an isolated nucleic acid encoding a polypeptide present in a Wnt surrogate molecule disclosed herein. Nucleic acids include DNA and RNA. These and related embodiments may include polynucleotides encoding antibody fragments that bind one or more Fzd receptors and/or LRP5 or LRP6 as described herein. The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin, or some combination thereof, which by virtue of its origin, the isolated polynucleotide: (1) is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature; (2) is linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence. An isolated polynucleotide may include naturally occurring and/or artificial sequences.

The term "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a transcription control sequence "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

The term "control sequence" as used herein refers to polynucleotide sequences that can affect expression, processing or intracellular localization of coding sequences to which they are ligated or operably linked. The nature of such control sequences may depend upon the host organism. In particular embodiments, transcription control sequences for prokaryotes may

include a promoter, ribosomal binding site, and transcription termination sequence. In other particular embodiments, transcription control sequences for eukaryotes may include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, transcription termination sequences and polyadenylation sequences. In certain embodiments, "control sequences" can include leader sequences and/or fusion partner sequences.

The term "polynucleotide" as referred to herein means single-stranded or double-stranded nucleic acid polymers. In certain embodiments, the nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine, ribose modifications such as arabinoside and 2',3'-dideoxyribose and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate. The term "polynucleotide" specifically includes single and double stranded forms of DNA.

The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" includes oligonucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. See, *e.g.*, LaPlanche *et al.*, 1986, Nucl. Acids Res., 14:9081; Stec *et al.*, 1984, J. Am. Chem. Soc., 106:6077; Stein *et al.*, 1988, Nucl. Acids Res., 16:3209; Zon *et al.*, 1991, Anti-Cancer Drug Design, 6:539; Zon *et al.*, 1991, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, pp. 87-108 (F. Eckstein, Ed.), Oxford University Press, Oxford England; Stec et al., U.S. Pat. No. 5,151,510; Uhlmann and Peyman, 1990, Chemical Reviews, 90:543, the disclosures of which are hereby incorporated by reference for any purpose. An oligonucleotide can include a

detectable label to enable detection of the oligonucleotide or hybridization thereof.

The term "vector" is used to refer to any molecule (*e.g.*, nucleic acid, plasmid, or virus) used to transfer coding information to a host cell. The term "expression vector" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control expression of inserted heterologous nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and RNA splicing, if introns are present.

As will be understood by those skilled in the art, polynucleotides may include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the skilled person.

As will be also recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide according to the present disclosure, and a polynucleotide may, but need not, be linked to other molecules and/or support materials. Polynucleotides may comprise a native sequence or may comprise a sequence that encodes a variant or derivative of such a sequence.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encodes an antibody as described herein. Some of these polynucleotides bear minimal sequence identity to the nucleotide sequence of the native or original polynucleotide sequence encoding a polypeptide within a Wnt surrogate molecule. Nonetheless, polynucleotides that vary due to

differences in codon usage are expressly contemplated by the present disclosure. In certain embodiments, sequences that have been codon-optimized for mammalian expression are specifically contemplated.

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, may be employed for the preparation of variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provide a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments, the inventors contemplate the mutagenesis of the polynucleotide sequences that encode a polypeptide present in a Wnt surrogate molecule, to alter one or more properties of the encoded polypeptide, such as the binding affinity, or the function of a particular Fc region, or the affinity of the Fc region for a particular FcγR. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phages are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

In many embodiments, one or more nucleic acids encoding a polypeptide of a Wnt surrogate molecule are introduced directly into a host cell, and the cell incubated under conditions sufficient to induce expression of the encoded polypeptides. The Wnt surrogate polypeptides of this disclosure may be prepared using standard techniques well known to those of skill in the art in combination with the polypeptide and nucleic acid sequences provided herein. The polypeptide sequences may be used to determine appropriate nucleic acid sequences encoding the particular polypeptide disclosed thereby. The nucleic acid sequence may be optimized to reflect particular codon "preferences" for various expression systems according to standard methods well known to those of skill in the art.

According to certain related embodiments there is provided a recombinant host cell which comprises one or more constructs as described herein, e.g., a vector comprising a nucleic acid encoding a Wnt surrogate molecule or polypeptide thereof; and a method of production of the encoded product, which method comprises expression from encoding nucleic acid therefor. Expression may conveniently be achieved by culturing under appropriate conditions recombinant host cells containing the nucleic acid. Following production by expression, an antibody or antigen-binding fragment thereof, may be isolated and/or purified using any suitable technique, and then used as desired.

Polypeptides, and encoding nucleic acid molecules and vectors, may be isolated and/or purified, *e.g.* 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 desired function. Nucleic acid may comprise DNA or RNA and may be wholly or partially synthetic. 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.

Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable host cells include bacteria, mammalian cells, 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, NSO mouse melanoma cells and many others. A common, preferred bacterial host is *E. coli*.

The expression of polypeptides, e.g., antibodies and antigen-binding fragments thereof, in prokaryotic cells such as *E. coli* is well established in the art. For a review, see for example Pluckthun, A. Bio/Technology 9: 545-551 (1991). Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production of antibodies or antigen-binding

fragments thereof, see recent reviews, for example Ref, M. E. (1993) Curr. Opinion Biotech. 4: 573-576; Trill J. J. *et al.* (1995) Curr. Opinion Biotech 6: 553-560.

Suitable vectors can be chosen or constructed, containing appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Vectors may be plasmids, viral *e.g.* phage, or phagemid, as appropriate. For further details see, for example, Molecular Cloning: a Laboratory Manual: 2nd edition, Sambrook *et al.*, 1989, Cold Spring Harbor Laboratory Press. Many known techniques and protocols for manipulation of nucleic acid, for example in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into cells and gene expression, and analysis of proteins, are described in detail in Current Protocols in Molecular Biology, Second Edition, Ausubel *et al.* eds., John Wiley & Sons, 1992, or subsequent updates thereto.

The term "host cell" is used to refer to a cell into which has been introduced, or which is capable of having introduced into it, a nucleic acid sequence encoding one or more of the herein described polypeptides, and which further expresses or is capable of expressing a selected gene of interest, such as a gene encoding any herein described polypeptide. The term includes the progeny of the parent cell, whether or not the progeny are identical in morphology or in genetic make-up to the original parent, so long as the selected gene is present. Accordingly there is also contemplated 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 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. In one embodiment, the nucleic acid is integrated into the genome (*e.g.* chromosome) of the host cell. Integration may be promoted by inclusion of sequences which promote recombination with the genome, in accordance-with standard techniques.

The present invention also provides, in certain embodiments, a method which comprises using a construct as stated above in an expression system in order to express a particular polypeptide such as a Wnyt mimetic molecule as described herein. The term "transduction" is used to refer to the transfer of genes from one bacterium to another, usually by a phage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by retroviruses. The term "transfection" is used to refer to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. See, *e.g.*, Graham *et al.*, 1973, Virology 52:456; Sambrook *et al.*, 2001, MOLECULAR CLONING, A LABORATORY MANUAL, Cold Spring Harbor Laboratories; Davis *et al.*, 1986, BASIC METHODS IN MOLECULAR BIOLOGY, Elsevier; and Chu *et al.*, 1981, Gene 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transfection or transduction, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, or may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is considered to have been stably transformed when the DNA is replicated with the division of the cell. The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like,

refers to materials which are found in nature and are not manipulated by a human. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by a human.

The terms "polypeptide" "protein" and "peptide" and "glycoprotein" are used interchangeably and mean a polymer of amino acids not limited to any particular length. The term does not exclude modifications such as myristylation, sulfation, glycosylation, phosphorylation and addition or deletion of signal sequences. The terms "polypeptide" or "protein" means one or more chains of amino acids, wherein each chain comprises amino acids covalently linked by peptide bonds, and wherein said polypeptide or protein can comprise a plurality of chains non-covalently and/or covalently linked together by peptide bonds, having the sequence of native proteins, that is, proteins produced by naturally-occurring and specifically non-recombinant cells, or genetically-engineered or recombinant cells, and comprise molecules having the amino acid sequence of the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms "polypeptide" and "protein" specifically encompass Wnt surrogate molecules, Fzd binding regions thereof, LRP5/6 binding regions thereof, antibodies and antigen-binding fragments thereof that bind to a Fzd receptor or a LRP5 or LRP6 receptor disclosed herein, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of any of these polyppetides. Thus, a "polypeptide" or a "protein" can comprise one (termed "a monomer") or a plurality (termed "a multimer") of amino acid chains.

The term "isolated protein," “isolated Wnt surrogate molecule or “isolated antibody” referred to herein means that a subject protein, Wnt surrogate molecule, or antibody: (1) is free of at least some other proteins with which it would typically be found in nature; (2) is essentially free of other proteins from the same source, *e.g.*, from the same species, (3) is expressed by a cell from a different species; (4) has been separated from at least about 50

percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature; (5) is not associated (by covalent or noncovalent interaction) with portions of a protein with which the "isolated protein" is associated in nature; (6) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature; or (7) does not occur in nature. Such an isolated protein can be encoded by genomic DNA, cDNA, mRNA or other RNA, or may be of synthetic origin, or any combination thereof. In certain embodiments, an isolated protein may comprise naturally-occurring and/or artificial polypeptide sequences. In certain embodiments, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its use (therapeutic, diagnostic, prophylactic, research or otherwise).

Amino acid sequence modification(s) of any of the polypeptides (e.g., Wnt surrogate molecules or Fzd binding regions or LRP5/6 binding regions thereof) described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the Wnt surrogate molecule. For example, amino acid sequence variants of a Wnt surrogate molecule may be prepared by introducing appropriate nucleotide changes into a polynucleotide that encodes the antibody, or a chain thereof, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution may be made to arrive at the final Wnt surrogate molecule, provided that the final construct possesses the desired characteristics (*e.g.*, high affinity binding to one or more Fzd and/or LRP5/6 receptor). The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites. Any of the variations and modifications described above for polypeptides of the present invention may be included in antibodies of the present invention.

The present disclosure provides variants of any of the polypeptides (e.g., Wnt surrogate molecules or Fzd binding regions or LRP5/6 binding regions thereof, or antibodies or antigen-binding fragments thereof) disclosed herein. In certain embodiments, a variant has at least 90%, at least 95%, at least 98%, or at least 99% identity to a polypeptide disclosed herein. In certain embodiments, such variant polypeptides bind to one or more Fzd receptor, and/or to one or more LRP5/6 receptor, at least about 50%, at least about 70%, and in certain embodiments, at least about 90% as well as a Wnt surrogate molecule specifically set forth herein. In further embodiments, such variant Wnt surrogate molecules bind to one or more Fzd receptor, and/or to one or more LRP5/6 receptor, with greater affinity than the Wnt surrogate molecules set forth herein, for example, that bind quantitatively at least about 105%, 106%, 107%, 108%, 109%, or 110% as well as an antibody sequence specifically set forth herein.

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or Nanobody® may comprise: a) a heavy chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and/or b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., one or more Fzd receptors or LRP5 or LRP6 receptors). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody or antigen-binding fragment thereof wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10,

11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See *e.g.*, Muller, 1998, Structure 6:1153-1167).

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or Nanobody®, may have: a) a heavy chain variable region having an amino acid sequence that is at least 80% identical, at least 95% identical, at least 90%, at least 95% or at least 98% or 99% identical, to the heavy chain variable region of an antibody or antigen-binding fragments thereof described herein; and/or b) a light chain variable region having an amino acid sequence that is at least 80% identical, at least 85%, at least 90%, at least 95% or at least 98% or 99% identical, to the light chain variable region of an antibody or antigen-binding fragments thereof described herein. The amino acid sequence of illustrative antigen-binding fragments thereof are set forth in SEQ ID NOs:1-128.

A polypeptide has a certain percent "sequence identity" to another polypeptide, meaning that, when aligned, that percentage of amino acids are the same when comparing the two sequences. Sequence similarity can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the world wide web at ncbi.nlm.nih.gov/BLAST/. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wis., USA, a wholly owned subsidiary of Oxford Molecular Group, Inc. Other techniques for alignment are described in Methods in Enzymology, vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. Of particular interest are alignment programs that permit gaps in the sequence. The Smith-Waterman is one type of algorithm that permits gaps in

sequence alignments. See Meth. Mol. Biol. 70: 173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. See J. Mol. Biol. 48: 443-453 (1970)

Of interest is the BestFit program using the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2: 482-489 (1981) to determine sequence identity. The gap generation penalty will generally range from 1 to 5, usually 2 to 4 and in many embodiments will be 3. The gap extension penalty will generally range from about 0.01 to 0.20 and in many instances will be 0.10. The program has default parameters determined by the sequences inputted to be compared. Preferably, the sequence identity is determined using the default parameters determined by the program. This program is available also from Genetics Computing Group (GCG) package, from Madison, Wis., USA.

Another program of interest is the FastDB algorithm. FastDB is described in Current Methods in Sequence Comparison and Analysis, Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp. 127-149, 1988, Alan R. Liss, Inc. Percent sequence identity is calculated by FastDB based upon the following parameters:
Mismatch Penalty: 1.00; Gap Penalty: 1.00; Gap Size Penalty: 0.33; and Joining Penalty: 30.0.

In particular embodiments, the Wnt surrogate molecule or a binding region thereof, e.g., a Fab, scFv, or Nanobody® may comprise: a) a heavy chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region

that is identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., a Fzd receptor, such as Fzd1). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10, 11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See *e.g.*, Muller, 1998, Structure 6:1153-1167).

Determination of the three-dimensional structures of representative polypeptides (*e.g.*, variant Fzd binding regions or LRP5/6 binding regions of Wnt surrogate molecules as provided herein) may be made through routine methodologies such that substitution, addition, deletion or insertion of one or more amino acids with selected natural or non-natural amino acids can be virtually modeled for purposes of determining whether a so derived structural variant retains the space-filling properties of presently disclosed species. *See,* for instance, Donate et al., 1994 *Prot. Sci.* 3:2378; Bradley et al., *Science* 309: 1868-1871 (2005); Schueler-Furman et al., *Science* 310:638 (2005); Dietz et al., *Proc. Nat. Acad. Sci. US*A 103:1244 (2006); Dodson et al., *Nature* 450:176 (2007); Qian et al., *Nature* 450:259 (2007); Raman *et al.* Science 327:1014-1018 (2010). Some additional non-limiting examples of computer algorithms that may be used for these and related embodiments, such as for rational design of binding regions include VMD which is a molecular visualization program for displaying, animating, and analyzing large biomolecular systems using 3-D graphics and built-in scripting (see the website for the Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champagne, at ks.uiuc.edu/Research/vmd/. Many other computer programs are known in the art and available to the skilled person and which allow for determining atomic dimensions from space-filling models (van

der Waals radii) of energy-minimized conformations; GRID, which seeks to determine regions of high affinity for different chemical groups, thereby enhancing binding, Monte Carlo searches, which calculate mathematical alignment, and CHARMM (Brooks et al. (1983) *J. Comput. Chem.* 4:187-217) and AMBER (Weiner et al (1981) *J. Comput. Chem*. 106: 765), which assess force field calculations, and analysis (see also, Eisenfield et al. (1991) *Am. J. Physiol.* 261:C376-386; Lybrand (1991) *J. Pharm. Belg.* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ. Health Perspect.* 61:185-190; and Kini et al. (1991) *J. Biomol. Struct. Dyn.* 9:475-488). A variety of appropriate computational computer programs are also commercially available, such as from Schrödinger (Munich, Germany).

Compositions

Pharmaceutical compositions comprising a Wnt surrogate molecule described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more Wnt polypeptides or Norrin polypeptides.

In further embodiments, pharmaceutical compositions comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more polynucleotides comprising a nucleic acid sequence encoding a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the

Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In further embodiments, pharmaceutical compositions comprising an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide, e.g., expression cassette.

The present invention further contemplates a pharmaceutical composition comprising a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid encoding a Wnt surrogate molecule and one or more pharmaceutically acceptable diluent, carrier, or excipient. In particular embodiments, the pharmaceutical composition further comprises a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid sequence encoding a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide, e.g., expression cassette and/or in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

The present disclosure contemplates pharmaceutical compositions comprising a first molecule for delivery of a Wnt surrogate molecule as a first active agent and a second molecule for delivery of a Wnt

polypeptide or Norrin polypeptide. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

The subject molecules, alone or in combination, can be combined with pharmaceutically-acceptable carriers, diluents, excipients and reagents useful in preparing a formulation that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for mammalian, e.g., human or primate, use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. Examples of such carriers, diluents and excipients include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Supplementary active compounds can also be incorporated into the formulations. Solutions or suspensions used for the formulations can include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates; detergents such as Tween 20 to prevent aggregation; and compounds 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. In particular embodiments, the pharmaceutical compositions are sterile.

Pharmaceutical compositions may further 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, or phosphate buffered saline (PBS). In some cases, the composition is sterile and should be fluid such that it can be drawn into a syringe or delivered to a subject from a syringe. In certain embodiments, it is stable under the conditions of manufacture and storage and is preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be, e.g., a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. 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, sodium chloride in the composition. Prolonged absorption of the internal compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile solutions can be prepared by incorporating the anti-Fzd antibody or antigen-binding fragment thereof (or encoding polynucleotide or cell comprising the same) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

In one embodiment, the pharmaceutical compositions are prepared with carriers that will protect the antibody or antigen-binding fragment thereof 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. The materials can also be obtained commercially. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art.

It may be advantageous to formulate the pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. 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 antibody or antigen-binding fragment thereof calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on the unique characteristics of the antibody or antigen-binding fragment thereof and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active antibody or antigen-binding fragment thereof for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser, e.g. syringe, e.g. a prefilled syringe, together with instructions for administration.

The pharmaceutical compositions of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal comprising a human, is capable of providing (directly or indirectly) the biologically active antibody or antigen-binding fragment thereof.

The present invention includes pharmaceutically acceptable salts of a Wnt surrogate molecule described herein. The term "pharmaceutically acceptable salt" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. A variety of pharmaceutically acceptable salts are known in the art and described, e.g., in "Remington's Pharmaceutical Sciences", 17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in J. Pharm. Sci. 66: 2 (1977). Also, for a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Metals used as cations comprise sodium, potassium, magnesium, calcium, and the like. Amines comprise N-N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., "Pharmaceutical Salts," J. Pharma Sci., 1977, 66, 119). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

In some embodiments, the pharmaceutical composition provided herein comprise a therapeutically effective amount of a Wnt surrogate molecule or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, diluent and/or excipient, for example

saline, phosphate buffered saline, phosphate and amino acids, polymers, polyols, sugar, buffers, preservatives and other proteins. Exemplary amino acids, polymers and sugars and the like are octylphenoxy polyethoxy ethanol compounds, polyethylene glycol monostearate compounds, polyoxyethylene sorbitan fatty acid esters, sucrose, fructose, dextrose, maltose, glucose, mannitol, dextran, sorbitol, inositol, galactitol, xylitol, lactose, trehalose, bovine or human serum albumin, citrate, acetate, Ringer's and Hank's solutions, cysteine, arginine, carnitine, alanine, glycine, lysine, valine, leucine, polyvinylpyrrolidone, polyethylene and glycol. Preferably, this formulation is stable for at least six months at 4º C.

In some embodiments, the pharmaceutical composition provided herein comprises a buffer, such as phosphate buffered saline (PBS) or sodium phosphate/sodium sulfate, tris buffer, glycine buffer, sterile water and other buffers known to the ordinarily skilled artisan such as those described by Good et al. (1966) Biochemistry 5:467. The pH of the buffer may be in the range of 6.5 to 7.75, preferably 7 to 7.5, and most preferably 7.2 to 7.4.

Methods of Use

The present disclosure also provides methods for using the Wnt surrogate molecules disclosed herein, e.g., to modulate a Wnt signaling pathway, e.g., to increase Wnt signaling, and the administration of a Wnt surrogate molecule disclosed herein in a variety of therapeutic settings. Provided herein are methods of treatment using a Wnt surrogate molecule. In one embodiment, a Wnt surrogate molecule is provided to a subject having a disease involving inappropriate or deregulated Wnt signaling, e.g., reduced Wnt signaling.

Increasing Wnt Pathway Signaling and Related Therapeutic Methods

In certain embodiments, a Wnt surrogate molecule may be used to increase Wnt signaling in a tissue or cell. Thus, in some aspects, the present invention provides a method for increasing Wnt signaling or enhancing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a Wnt surrogate molecule or pharmaceutically acceptable

salt thereof disclosed herein, wherein the a Wnt surrogate molecule is a Wnt signaling pathway agonist. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro. In certain embodiments, the method comprises further contacting the tissue or cell with one or more Wnt polypeptides or Norrin polypeptides.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a polynucleotide comprising a Wnt surrogate molecule disclosed herein. In certain embodiments, the target tissue or cell is also contacted with a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a vector comprising a nucleic acid sequence encoding a Wnt surrogate molecule. In certain embodiments, the tissue or cell is also contacted with a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding a Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin

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polypeptide are present in the same vector, e.g., in the same expression cassette.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue, comprising contacting the tissue with an effective amount of a cell comprising a nucleic acid sequence encoding a Wnt surrogate molecule of the present invention. In certain embodiments, the tissue is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the Wnt surrogate molecule or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Wnt surrogate molecules disclosed herein may be used in to treat a disease, disorder or condition, for example, by increasing Wnt signaling in a targeted cell, tissue or organ. Thus, in some aspects, the present invention provides a method for treating a disease or condition in a subject in need thereof, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting the subject with an effective amount of a composition of the present disclosure. In particular embodiments, the composition is a pharmaceutical composition comprising any of: a Wnt surrogate molecule; a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., a DNA or mRNA, optionally a modified mRNA; a vector comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., an expression vector or viral vector; or a cell comprising a nucleic acid sequence encoding a Wnt surrogate molecule, e.g., a cell transduced with an expression vector or viral vector encoding a Wnt surrogate molecule. In

particular embodiments, the disease or condition is a pathological disease or disorder, or an injury, e.g., an injury resulting from a wound. In certain embodiments, the wound may be the result of another therapeutic treatment. In certain embodiments, the disease or condition comprises impaired tissue repair, healing or regeneration, or would benefit from increased tissue repair, healing or regeneration. In some embodiments, contacting occurs in vivo, i.e., the subject composition is administered to a subject.

In certain embodiments, the method comprises further contacting the subject with a pharmaceutical composition comprising one or more Wnt polypeptides or Norrin polypeptides. The present disclosure contemplates contacting a subject with a first molecule for delivery of a Wnt surrogate molecule as a first active agent and a second molecule for delivery of a Wnt polypeptide or Norrin polypeptide. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence encoding a Wnt surrogate molecule disclosed herein. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA,

e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence encoding a Wnt surrogate molecule. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same vector, e.g., in the same expression cassette.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a cell comprising a nucleic acid sequence encoding a Wnt surrogate molecule. In certain embodiments, the subject is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the Wnt surrogate

molecule and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the Wnt surrogate molecule or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Wnt signaling plays key roles in the developmental process and maintenance of stem cells. Reactivation of Wnt signals is associated with regeneration and repair of most tissues after injuries and diseases. Wnt surrogate molecule molecules are expected to provide benefit of healing and tissue repair in response to injuries and diseases. Causes of tissue damage and loss include but are not limited to aging, degeneration, hereditary conditions, infection and inflammation, traumatic injuries, toxins/metabolic-induced toxicities, or other pathological conditions. Wnt signals and enhancers of Wnt signals have been shown to activate adult, tissue-resident stem cells. In some embodiments, the compounds of the invention are administered for use in treating diseased or damaged tissue, for use in tissue regeneration and for use in cell growth and proliferation, and/or for use in tissue engineering.

Human diseases associated with mutations of the Wnt pathway provide strong evidence for enhancement of Wnt signals in the treatment and prevention of diseases. Preclinical in vivo and in vitro studies provide additional evidence of involvement of Wnt signals in many disease conditions and further support utilization of a Wnt surrogate molecule in various human diseases. For example, compositions of the present invention may be used to promote or increase bone growth or regeneration, bone grafting, healing of bone fractures, treatment of osteoporosis and osteoporotic fractures, spinal fusion, osseointegration of orthopedic devices, tendon-bone integration, tooth growth and regeneration, dental implantation, periodontal diseases, maxillofacial reconstruction, and osteonecrosis of the jaw. They may also be used in the treatment of alopecia; enhancing regeneration of sensory organs, e.g.

treatment of hearing loss, treatment of vestibular hypofunction, treatment of macular degeneration, treatment of vitreoretinopathy, other diseases of retinal degeneration, Fuchs' dystrophy, other cornea disease, etc.; treatment of stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis and other conditions affecting the blood brain barrier; treatment of spinal cord injuries, other spinal cord diseases. The compositions of this invention may also be used in treatment of oral mucositis, treatment of short bowel syndrome, inflammatory bowel diseases (IBD), other gastrointestinal disorders; treatment of metabolic syndrome; treatment of diabetes, treatment of pancreatitis, conditions where exocrine or endocrine pancreas tissues are damaged; conditions where enhanced epidermal regeneration is desired, e.g., epidermal wound healing, treatment of diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, etc., conditions where angiogenesis is beneficial; treatment of myocardial infarction, coronary artery disease, heart failure; enhanced growth of hematopoietic cells, e.g. enhancement of hematopoietic stem cell transplants from bone marrow, mobilized peripheral blood, treatment of immunodeficiencies, graft versus host diseases, etc.; treatment of acute kidney injuries, chronic kidney diseases; treatment of lung diseases, chronic obstructive pulmonary diseases (COPD), enhanced regeneration of lung tissues. The compositions of the present invention may also be used in enhanced regeneration of liver cells, e.g. liver regeneration, treatment of cirrhosis, enhancement of liver transplantations, treatment of acute liver failure, treatment of chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, alcoholic liver diseases, non-alcoholic liver diseases with steatosis or steatohepatitis, and the like. The compositions of this invention may treat diseases and disorders including, without limitation, conditions in which regenerative cell growth is desired.

Human genetics involving loss-of-function or gain-of-function mutations in Wnt signaling components show strong evidence supporting enhancing Wnt signals for bone growth. Conditions in which enhanced bone growth is desired may include, without limitation, fractures, grafts, ingrowth

around prosthetic devices, osteoporosis, osteoporotic fractures, spinal fusion, osteonecrosis of the jaw, dental implantation, periodontal diseases, maxillofacial reconstruction, and the like. Wnt surrogate molecules enhance and promotes Wnt signals which are critical in promoting bone regeneration. Methods for regeneration of bone tissues benefit from administration of the compounds of the invention, which can be systemic or localized. In some embodiments, bone marrow cells are exposed to molecules of the invention, such that stem cells within that marrow become activated.

In some embodiments, bone regeneration is enhanced by contacting a responsive cell population, e.g. bone marrow, bone progenitor cells, bone stem cells, etc. with an effective dose of a Wnt surrogate molecule disclosed herein. Methods for regeneration of bone tissues benefit from administration of the Wnt surrogate molecule which can be systemic or localized. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include, without limitation, absorbable collagen sponges, ceramics, hydrogels, polymeric microspheres, nanoparticles, bone cements, and the like.

In particular embodiments, compositions comprising one or more Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to treat or prevent a bone disease or disorder, including but not limited to any of the following, or to treat or prevent an injury associated with, but not limited to, any of the following: osteoporosis, osteoporotic fractures, bone fractures, non-union fractures, delayed union fractures, spinal fusion, osteonecrosis, osteonecrosis of the jaw, hip, femoral head, etc., osseointegration of implants (e.g., to accelerate recovery following partial or total knee or hip replacement), osteogenesis imperfecta, bone grafts, tendon repair, maxillofacial surgery, dental implant, all other bone disorders or

defects resulting from genetic diseases, degeneration, aging, drugs, or injuries. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, and Fzd 7, and also LRP5 and/or LRP6, are used to treat or prevent any bone disease or disorder. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, Fzd 5, Fzd 7 and Fzd 8, and also LRP5 and/or LRP6, are used to treat or prevent any bone disease or disorder.

In particular embodiments, compositions and methods disclosed herein may be used to: increase bone mineral density, increase bone volume (e.g., tibia and/or femur bone volume), increase cortical thickness (e.g., in trabecular region or in femur mid-diaphysis), increase mineral apposition rate, increase the number of osteblasts and/or decrease the number of osteoclasts (e.g., in bone), increase bone stiffness, increase the ultimate load to fracture point, improve bone resistance to fracture, decrease bone loss associated with osteoporosis, or increase biochemical strength of bone, in a subject. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, and Fzd 7 are used for any of these indicated uses. In one embodiment, Wnt surrogate molecules that bind Fzd1, Fzd 2, Fzd 5, Fzd 7 and Fzd 8 are used for any of these indicated uses.

Compositions comprising one or more Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) can be used for the in vivo treatment of skeletal tissue deficiencies. By "skeletal tissue deficiency", it is meant a deficiency in bone or other skeletal connective tissue at any site where it is desired to restore the bone or connective tissue, no matter how the deficiency originated, e.g. whether as a result of surgical intervention, removal of tumor, ulceration, implant, fracture, or other traumatic or degenerative conditions. The compositions of the present invention can be used as part of a regimen for restoring cartilage function to a connective tissue, for the repair of defects or lesions in cartilage tissue such as degenerative wear and arthritis, trauma to the tissue, displacement of torn meniscus,

meniscectomy, a luxation of a joint by a torn ligament, malalignment of joints, bone fracture, or by hereditary disease.

A Wnt surrogate molecule may also be used for treatment of periodontal diseases. Periodontal diseases are a leading cause of tooth loss and are linked to multiple systemic conditions. In some embodiments, tooth or underlying bone regeneration is enhanced by contacting a responsive cell population. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo, with subsequent implantation of the activated stem or progenitor cells. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include, without limitation, absorbable collagen sponges, ceramics, hydrogels, bone cements, polymeric microspheres, nanoparticles, and the like.

Studies have shown that biology of Wnt signaling and R-spondins are capable of promoting sensory hair cell regeneration in the inner ear following injuries, aging, or degeneration. Loss of sensory hair cells in the inner ear involved in hearing loss or vestibular hypofunction may also benefit from the compositions of the invention. In the inner ear, the auditory organ houses mechanosensitive hair cells required for translating sound vibration to electric impulses. The vestibular organs, comprised of the semicircular canals (SSCs), the utricle, and the saccule, also contain sensory hair cells in order to detect head position and motion. Compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the ear for enhancement of auditory regeneration.

A Wnt surrogate molecule may also be used in regeneration of retinal tissue. In the adult mammalian retina, Muller glia cells are capable of regenerating retinal cells, including photoreceptors, for example after neurotoxic injury in vivo. Wnt signaling and enhancers of Wnt signals can promote proliferation of Muller glia-derived retinal progenitors after damage or during degeneration. The compositions of the invention may also be used in the

regeneration of tissues and other cell types in the eye. For examples age-related macular degeneration (AMD), other retina degenerative diseases, cornea diseases, Fuchs' dystrophy, vitreoretinopathy, hereditary diseases, etc. can benefit from the compositions of the present inventions. AMD is characterized by progressively decreased central vision and visual acuity. Fuchs' dystrophy is characterized by progressive loss of cornea endothelial cells. Wnt signal and enhancing of Wnt signal can promote regeneration of cornea endothelium, retina epithelium, etc. in the eye tissue. In other embodiments, compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the eye for retinal regeneration and treatment of macular degeneration.

Specific populations of proliferating cells for homeostatic renewal of hepatocytes have been identified through lineage tracing studies, for example Axin2-positive cells in peri-central region. Lineage tracing studies also identified additional potential liver progenitor cells, including but not limited to Lgr-positive cells. The self-renewing liver cells and other populations of potential progenitor cells, including Lgr5-positive and Axin2-positive cells, are identified to be capable of regeneration responding to Wnt signals and/or R-spondins following injuries. Numerous preclinical models of acute liver injury and failure and chronic liver diseases showed recovery and regeneration of hepatocytes benefit from enhancing Wnt signals.

In certain embodiments, compositions comprising a Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to promote liver regeneration, reduce fibrosis, and/or improve liver function. In certain embodiments, compositions and methods disclosed herein are used to: increase liver weight, increase the liver to body weight ratio, increase the number of PCNA and pH3 positive nuclei in liver, increase expression of Ki67 and/or Cyclin D1 in liver, increase liver cell proliferation and/or mitosis, decrease fibrosis following chronic liver injury, or increase hepatocyte function.

In particular embodiments, the compositions of this invention may be used in treatment of acute liver failure, acute alcoholic liver injuries, treatment of chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, chronic alcoholic liver diseases, non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis (NASH), treatment of cirrhosis and severe chronic liver diseases of all causes, and enhanced regeneration of liver cells. Methods for regeneration of liver tissue benefit from administration of the compounds of the invention, which can be systemic or localized. These include, but are not limited to, methods of systemic administration and methods of localized administration e.g. by injection into the liver tissue, by injection into veins or blood vessels leading into the liver, by implantation of a sustained release formulation, and the like.

In particular embodiments, compositions comprising a Wnt surrogate molecule disclosed herein (or a polynucleotide encoding a Wnt surrogate molecule, or a vector or cell comprising a polynucleotide encoding a Wnt surrogate molecule) are used to treat or prevent a liver disease or disorder, including but not limited to, or to treat or prevent a liver injury or disorder resulting from any of the following: acute liver failure (all causes), chronic liver failure (all causes), cirrhosis, liver fibrosis (all causes), portal hypertension, nonalcoholic steatohepatisis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, livery surgery, liver injury, liver transplantation, “small for size” syndrome in liver surgery and transplantation, congenital liver disease and disorders, any other liver disorder or detect resulting from genetic diseases, degeneration, aging, drugs, or injuries.

Wnt signals play an important role in regeneration of various epithelial tissues. Various epidermal conditions benefit from treatment with the compounds of the present invention. Mucositis occurs when there is a

breakdown of the rapidly divided epithelial cells lining the gastro-intestinal tract, leaving the mucosal tissue open to ulceration and infection. The part of the epithelial lining that covers the mouth, called the oral mucosa, is one of the most sensitive parts of the body and is particularly vulnerable to chemotherapy and radiation. Oral mucositis is probably the most common, debilitating complication of cancer treatments, particularly chemotherapy and radiation. In addition, the compositions of the invention may also benefit treatment of short bowel syndrome, inflammatory bowel diseases (IBD), or other gastrointestinal disorders. Other epidermal conditions include epidermal wound healing, diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, and the like. Molecules of the present invention may be used in all these conditions, where regenerative cells are contacted with compounds of the invention. Methods for regeneration of epithelial tissues benefit from administration of the compounds of the invention, which can be systemic or localized. Contacting can be, for example, topical, including intradermal, subdermal, in a gel, lotion, cream etc. applied at targeted site, etc.

In addition to skin and gastrointestinal tract, Wnt signals and enhancement and promotion of Wnt signals also play an important role in repair and regeneration of tissues including pancreas, kidney, and lung in preclinical models. A Wnt surrogate molecule may benefit various disease conditions involving exocrine and endocrine pancreas, kidney, or lung. The Wnt surrogate molecules may be used in treatment of metabolic syndrome; treatment of diabetes, treatment of acute or chronic pancreatitis, exocrine pancreatic insufficiency, treatment of acute kidney injuries, chronic kidney diseases, treatment of lung diseases, including but not limited to chronic obstructive pulmonary diseases (COPD), other conditions that cause loss of lung epithelial tissues. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

Epidermal Wnt signaling, in coordination with signaling via other development factors, is critical for adult hair follicle regeneration. Hair loss is a common problem, and androgenetic alopecia, often called male pattern

baldness, is the most common form of hair loss in men. In some embodiments, hair follicle regeneration is enhanced by contacting a responsive cell population with a molecule of the present invention. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo. The molecule may be localized to the site of action, e.g. topical lotions, gels, creams and the like.

Stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis and other conditions affecting the blood brain barrier (BBB) may be treated with a Wnt surrogate molecule. Angiogenesis is critical to ensure the supply of oxygen and nutrients to many tissues throughout the body, and is especially important for the CNS as the neural tissue is extremely sensitive to hypoxia and ischemia. CNS endothelial cells which form the BBB differ from endothelial cells in non-neural tissue, in that they are highly polarized cells held together by tight junctions and express specific transporters. Wnt signaling regulates CNS vessel formation and/or function. Conditions in which the BBB is compromised can benefit from administration of the compounds of the invention, which can be systemic or localized e.g. by direct injection, intrathecal administration, implantation of sustained release formulations, and the like. In addition, Wnt signal is actively involved in neurogenesis and plays a role of neuroprotection following injury. The compositions of the present invention may also be used in treatment of spinal cord injuries, other spinal cord diseases, stroke, traumatic brain injuries, etc.

Wnt signals also play a role in angiogenesis. A Wnt surrogate molecule may benefit conditions where angiogenesis is beneficial, treatment of myocardial infarction, coronary artery disease, heart failure, etc., and conditions from hereditary diseases. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

In certain embodiments, methods of the present invention promote tissue regeneration, e.g., in a tissue subjected to damage or tissue or cell reduction or loss. The loss or damage can be anything which causes the

cell number to diminish, including diseases or injuries. For example, an accident, an autoimmune disorder, a therapeutic side-effect or a disease state could constitute trauma. Tissue regeneration increases the cell number within the tissue and preferably enables connections between cells of the tissue to be re-established, and more preferably the functionality of the tissue to be regained.

The terms "administering" or "introducing" or “providing”, as used herein, refer to delivery of a composition to a cell, to cells, tissues and/or organs of a subject, or to a subject. Such administering or introducing may take place in vivo, in vitro or ex vivo.

In particular embodiments, a pharmaceutical composition is administered parenterally, e.g., intravenously, orally, rectally, or by injection. In some embodiments, it is administered locally, e.g., topically or intramuscularly. In some embodiments, a composition is administered to target tissues, e.g., to bone, joints, ear tissue, eye tissue, gastrointestinal tract, skin, a wound site or spinal cord. Methods of the invention may be practiced in vivo or ex vivo. In some embodiments, the contacting of a target cell or tissue with a Wnt surrogate molecule is performed ex vivo, with subsequent implantation of the cells or tissues, e.g., activated stem or progenitor cells, into the subject. The skilled artisan can determine an appropriate site of and route of administration based on the disease or disorder being treated.

The dose and dosage regimen may depend upon a variety of factors readily determined by a physician, such as the nature of the disease or disorder, the characteristics of the subject, and the subject's history. In particular embodiments, the amount of a Wnt surrogate molecule administered or provided to the subject is in the range of about 0.01 mg/kg to about 50 mg/kg, 0.1 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 50 mg/kg of the subject’s body weight.

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a

disease or symptom thereof, e.g. reducing the likelihood that the disease or symptom thereof occurs in the subject, and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent (e.g., a Wnt surrogate molecule) may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease. In some embodiments, the subject method results in a therapeutic benefit, e.g., preventing the development of a disorder, halting the progression of a disorder, reversing the progression of a disorder, etc. In some embodiments, the subject method comprises the step of detecting that a therapeutic benefit has been achieved. The ordinarily skilled artisan will appreciate that such measures of therapeutic efficacy will be applicable to the particular disease being modified, and will recognize the appropriate detection methods to use to measure therapeutic efficacy.

Other embodiments relate, in part, to the use of the Wnt surrogate molecules disclosed herein to promote or enhance the growth or proliferation of cells, tissues and organoids, for example, by contacting cells or tissue with one or more Wnt surrogate, optionally in combination with a Norrin or Rspondin polypeptide. In certain embodiments, the cells or tissue are contacted ex vivo, in vitro, or in vivo. Such methods may be used to generate cells, tissue or organoids for therapeutic use, e.g., to be transplanted or grafted into a subject. They may also be used to generate cells, tissue or organoids for research use.

The Wnt surrogate molecules have widespread applications in non-therapeutic methods, for example in vitro research methods.

The invention provides a method for tissue regeneration of damaged tissue, such as the tissues discussed above, comprising administering a Wnt surrogate molecule to cells. The Wnt surrogate molecule may be administered directly to the cells in vivo, administered to a subject orally, intravenously, or by other methods known in the art, or administered to ex vivo cells. In some embodiments where the Wnt surrogate molecule is administered to ex vivo cells, these cells may be transplanted into a subject before, after or during administration of the Wnt surrogate molecule.

Wnt signaling is a key component of stem cell culture. For example, the stem cell culture media as described in WO2010/090513, WO2012/014076, Sato et al., 2011 (GASTROENTEROLOGY 201 1; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5). The Wnt surrogate molecules disclosed herein are suitable alternatives to Rspondin for use in these stem cell culture media, or may be combined with Rspondin.

Accordingly, in one embodiment, the disclosure provides a method for enhancing the proliferation of stem cells comprising contacting stem cells with one or more Wnt surrogate molecules disclosed herein. In one embodiment, the disclosure provides a cell culture medium comprising one or more Wnt surrogate molecules disclosed herein. In some embodiments, the cell culture medium may be any cell culture medium already known in the art that normally comprises Wnt or Rspondin, but wherein the Wnt or Rspondin is replaced (wholly or partially) or supplemented by Wnt surrogate molecule(s) disclosed herein. For example, the culture medium may be as described in as described in WO2010/090513, WO2012/014076, Sato et al., 2011 (GASTROENTEROLOGY 201 1; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5), which are hereby incorporated by reference in their entirety.

Stem cell culture media often comprise additional growth factors. This method may thus additionally comprise supplying the stem cells with a growth factor. Growth factors commonly used in cell culture medium include

epidermal growth factor (EGF, (Peprotech), Transforming Growth Factor-alpha (TGF-alpha, Peprotech), basic Fibroblast Growth Factor (bFGF, Peprotech), brain-derived neurotrophic factor (BDNF, R&D Systems), Hepatocyte Growth Factor (HGF) and Keratinocyte Growth Factor (KGF, Peprotech, also known as FGF7). EGF is a potent mitogenic factor for a variety of cultured ectodermal and mesodermal cells and has a profound effect on the differentiation of specific cells in vivo and in vitro and of some fibroblasts in cell culture. The EGF precursor exists as a membrane-bound molecule which is proteolytically cleaved to generate the 53-amino acid peptide hormone that stimulates cells. EGF or other mitogenic growth factors may thus be supplied to the stem cells. During culturing of stem cells, the mitogenic growth factor may be added to the culture medium every second day, while the culture medium is refreshed preferably every fourth day. In general, a mitogenic factor is selected from the groups consisting of: i) EGF, TGF-alpha, and KGF, ii) EGF, TGF-alpha, and FGF7; iii) EGF, TGF-alpha, and FGF; iv) EGF and KGF; v) EGF and FGF7; vi) EGF and a FGF; vii) TGF-alpha and KGF; viii) TGF-alpha, and FGF7; ix) or from TGF-alpha and a FGF. In certain embdoiments, the disclosure includes a stem cell culture media comprising a Wnt surrogate molecule disclosed herein, e.g., optionally in combination with one or more of the growth factors or combinations thereof described herein.

These methods of enhancing proliferation of stem cells can be used to grow new organoids and tissues from stem cells, as for example described in WO2010/090513 WO2012/014076, Sato et al., 201 1 (GASTROENTEROLOGY 2011; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5).

In some embodiments, the Wnt surrogate molecules are used to enhance stem cell regeneration. Illustrative stem cells of interest include but are not limited to: muscle satellite cells; hematopoietic stem cells and progenitor cells derived therefrom (U.S. Pat. No. 5,061 ,620); neural stem cells (see Morrison et al. (1999) Cell 96: 737-749); embryonic stem cells; mesenchymal

stem cells; mesodermal stem cells; liver stem cells; adipose-tissue derived stem cells, etc.

Other embodiments of the present invention relate, in part, to diagnostic applications for detecting the presence of cells or tissues expressing one or more Fzd receptors or LRP5 or LRP6 receptors. Thus, the present disclosure provides methods of detecting one or more Fzd receptor or LRP5 or LRP6 receptor in a sample, such as detection of cells or tissues expressing Fzd1. Such methods can be applied in a variety of known detection formats, including, but not limited to immunohistochemistry (IHC), immunocytochemistry (ICC), *in situ* hybridization (ISH), whole-mount *in situ* hybridization (WISH), fluorescent DNA *in situ* hybridization (FISH), flow cytometry, enzyme immuno-assay (EIA), and enzyme linked immuno-assay (ELISA), e.g., by detecting binding of a Wnt surrogate molecule.

ISH is a type of hybridization that uses a labeled complementary DNA or RNA strand (*i.e.*, primary binding agent) to localize a specific DNA or RNA sequence in a portion or section of a cell or tissue (*in situ*), or if the tissue is small enough, the entire tissue (whole mount ISH). One having ordinary skill in the art would appreciate that this is distinct from immunohistochemistry, which localizes proteins in tissue sections using an antibody as a primary binding agent. DNA ISH can be used on genomic DNA to determine the structure of chromosomes. Fluorescent DNA ISH (FISH) can, for example, be used in medical diagnostics to assess chromosomal integrity. RNA ISH (hybridization histochemistry) is used to measure and localize mRNAs and other transcripts within tissue sections or whole mounts.

In various embodiments, the Wnt surrogate molecules described herein are conjugated to a detectable label that may be detected directly or indirectly. In this regard, an antibody "conjugate" refers to a Wnt surrogate molecule that is covalently linked to a detectable label. In the present invention, DNA probes, RNA probes, monoclonal antibodies, antigen-binding fragments thereof, and antibody derivatives thereof, such as a single-chain-variable-fragment antibody or an epitope tagged antibody, may all be covalently linked

to a detectable label. In “direct detection”, only one detectable antibody is used, *i.e.*, a primary detectable antibody. Thus, direct detection means that the antibody that is conjugated to a detectable label may be detected, per se, without the need for the addition of a second antibody (secondary antibody).

A "detectable label" is a molecule or material that can produce a detectable (such as visually, electronically or otherwise) signal that indicates the presence and/or concentration of the label in a sample. When conjugated to an antibody, the detectable label can be used to locate and/or quantify the target to which the specific antibody is directed. Thereby, the presence and/or concentration of the target in a sample can be detected by detecting the signal produced by the detectable label. A detectable label can be detected directly or indirectly, and several different detectable labels conjugated to different specific-antibodies can be used in combination to detect one or more targets.

Examples of detectable labels, which may be detected directly, include fluorescent dyes and radioactive substances and metal particles. In contrast, indirect detection requires the application of one or more additional antibodies, *i.e.*, secondary antibodies, after application of the primary antibody. Thus, the detection is performed by the detection of the binding of the secondary antibody or binding agent to the primary detectable antibody. Examples of primary detectable binding agents or antibodies requiring addition of a secondary binding agent or antibody include enzymatic detectable binding agents and hapten detectable binding agents or antibodies.

In some embodiments, the detectable label is conjugated to a nucleic acid polymer which comprises the first binding agent (*e.g.*, in an ISH, WISH, or FISH process). In other embodiments, the detectable label is conjugated to an antibody which comprises the first binding agent (*e.g.*, in an IHC process).

Examples of detectable labels which may be conjugated to Wnt surrogate molecules used in the methods of the present disclosure include fluorescent labels, enzyme labels, radioisotopes, chemiluminescent labels,

electrochemiluminescent labels, bioluminescent labels, polymers, polymer particles, metal particles, haptens, and dyes.

Examples of fluorescent labels include 5-(and 6)-carboxyfluorescein, 5- or 6-carboxyfluorescein, 6-(fluorescein)-5-(and 6)-carboxamido hexanoic acid, fluorescein isothiocyanate, rhodamine, tetramethylrhodamine, and dyes such as Cy2, Cy3, and Cy5, optionally substituted coumarin including AMCA, PerCP, phycobiliproteins including R-phycoerythrin (RPE) and allophycoerythrin (APC), Texas Red, Princeton Red, green fluorescent protein (GFP) and analogues thereof, and conjugates of R-phycoerythrin or allophycoerythrin, inorganic fluorescent labels such as particles based on semiconductor material like coated CdSe nanocrystallites.

Examples of polymer particle labels include micro particles or latex particles of polystyrene, PMMA or silica, which can be embedded with fluorescent dyes, or polymer micelles or capsules which contain dyes, enzymes or substrates.

Examples of metal particle labels include gold particles and coated gold particles, which can be converted by silver stains. Examples of haptens include DNP, fluorescein isothiocyanate (FITC), biotin, and digoxigenin. Examples of enzymatic labels include horseradish peroxidase (HRP), alkaline phosphatase (ALP or AP), β-galactosidase (GAL), glucose-6-phosphate dehydrogenase, β-N-acetylglucosamimidase, β-glucuronidase, invertase, Xanthine Oxidase, firefly luciferase and glucose oxidase (GO). Examples of commonly used substrates for horseradishperoxidase include 3,3'-diaminobenzidine (DAB), diaminobenzidine with nickel enhancement, 3-amino-9-ethylcarbazole (AEC), Benzidine dihydrochloride (BDHC), Hanker-Yates reagent (HYR), Indophane blue (IB), tetramethylbenzidine (TMB), 4-chloro-1-naphtol (CN), .alpha.-naphtol pyronin (.alpha.-NP), o-dianisidine (OD), 5-bromo-4-chloro-3-indolylphosp- hate (BCIP), Nitro blue tetrazolium (NBT), 2-(p-iodophenyl)-3-p-nitropheny- l-5-phenyl tetrazolium chloride (INT), tetranitro blue tetrazolium (TNBT), 5-bromo-4-chloro-3-indoxyl-beta-D-galactoside/ferro-ferricyanide (BCIG/FF).

Examples of commonly used substrates for Alkaline Phosphatase include Naphthol-AS-B 1-phosphate/fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-phosphate/- fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-phosphate/new fuschin (NABP/NF), bromochloroindolyl phosphate/nitroblue tetrazolium (BCIP/NBT), 5-Bromo-4-chloro-3-indolyl-b-- d-galactopyranoside (BCIG).

Examples of luminescent labels include luminol, isoluminol, acridinium esters, 1,2-dioxetanes and pyridopyridazines. Examples of electrochemiluminescent labels include ruthenium derivatives. Examples of radioactive labels include radioactive isotopes of iodide, cobalt, selenium, tritium, carbon, sulfur and phosphorous.

Detectable labels may be linked to the antibodies described herein or to any other molecule that specifically binds to a biological marker of interest, *e.g.*, an antibody, a nucleic acid probe, or a polymer. Furthermore, one of ordinary skill in the art would appreciate that detectable labels can also be conjugated to second, and/or third, and/or fourth, and/or fifth binding agents or antibodies, etc. Moreover, the skilled artisan would appreciate that each additional binding agent or antibody used to characterize a biological marker of interest may serve as a signal amplification step. The biological marker may be detected visually using, *e.g.*, light microscopy, fluorescent microscopy, electron microscopy where the detectable substance is for example a dye, a colloidal gold particle, a luminescent reagent. Visually detectable substances bound to a biological marker may also be detected using a spectrophotometer. Where the detectable substance is a radioactive isotope detection can be visually by autoradiography, or non-visually using a scintillation counter. See, *e.g.*, Larsson, 1988, Immunocytochemistry: Theory and Practice, (CRC Press, Boca Raton, Fla.); Methods in Molecular Biology, vol. 80 1998, John D. Pound (ed.) (Humana Press, Totowa, N.J.).

The invention further provides kits for detecting one or more Fzd or LRP5/6 receptor or cells or tissues expressing one or more Fzd or LRP5/6

receptors in a sample, wherein the kits contain at least one antibody, polypeptide, polynucleotide, vector or host cell as described herein. In certain embodiments, a kit may comprise buffers, enzymes, labels, substrates, beads or other surfaces to which the antibodies of the invention are attached, and the like, and instructions for use.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

EXAMPLES

Example 1

Illustrative Wnt surrogate Molecule Formats

Wnt surrogates having a variety of different formats disclosed herein were made. These included the following illustrative formats, each comprising a binding domain ("binder") that binds to one or more Fzd receptor and a binding domain ("binder") that binds to an LRP5 and/or LRP6 receptor.

As shown in Fig. 1A, if a binder to one receptor is a Fab and to the other receptor is a Nab or scFv, they can be put together in several different configurations. In certain instances, the Fab binder first can be reformatted to a full IgG format, then the Nab binder can be fused to any of the 4 available termini of the IgG. For example, the Nab can be fused to the N-terminus of the IgG light chain (LC, the fusion will be referred to as NL, shown in top left), N-terminus of the IgG heavy chain (HC, the fusion will be referred to as NH, shown in top right), the C-terminus of LC (the fusion will be referred to as CL, shown in middle right), and the C-terminus of HC (the fusion will be referred to

as CH, shown in middle left). The linkers and the length of the linkers between the IgG and the Nab can be varied. These four formats are bispecific and bivalent, they are bivalent binders toward each of the receptors. An alternative way to put the two binders together is the Hetero-Ig format where the Fab binder is presented as a half antibody, and the Nab is fused to the N-terminus of an Fc (shown in lower middle). The two halves may be brought together by mutations in the CH3 domain (such as the knobs-into-holes) that favor the formation of the heterodimer. The linker and its length between the Nab binder and the Fc can be varied. This format would be bispecific but monovalent toward each receptor. The Nab part of any of the formats described in this example can also be replaced by scFv fragments of binders as well.

As shown in Fig. 1B, if a binder to one receptor is a Fab and to the other receptor is also a Fab, they can be put together in several different configurations. In one approach, one Fab binder is first reformatted to a full IgG format (shown in top). The second Fab binder can be fused to the N-terminus of the IgG. The two HC can be fused together with a linker in between. The LCs can be fused or unfused. The linker and its length can be varied. This format is a bispecific and bivalent format. Alternatively, the second Fab binder LC can be fused to the HC of the IgG with a linker of various length in between. The second Fab binder HC can be fused or unfused to the LC of the IgG. A variation of this format has been called Fabs-in-tandem IgG (or FIT-Ig). In another approach, the two binders can be brought together as a Hetero-Ig by mutations in the CH3 domain that favors the heterodimer assembly, the two arms will each bind to one receptor (shown in bottom). This format is a bispecific and monovalent binder.

As shown in Fig. 1C, if a binder to one receptor is a Nab and to the other receptor is also a Nab, they can be put together in several different configurations. In the bispecific bivalent formats, in certain instances, the two Nab binders can be fused together in tandem (shown in top row) or fused to the two-different ends of the Fc (shown in middle row). The linker and its length between Nab and Nab or Nab and Fc can be varied. Alternatively, the two Nabs

can be assembled together as Hetero-Ig to generate a bispecific and monovalent format (shown in bottom row). Similar to Fig 1A, the Nab domains here can also be replaced by an scFv domain of a binder. In all the examples, the Nab and scFv can be mixed in certain combinations as well.

As shown in Fig. 1D, the binders against Fzd and LRP can also be linked together in a diabody (or DART) configuration. The diabody can also be in a single chain configuration. If the diabody is fused to an Fc, this will create a bivalent bispecific format. Without fusion to Fc, this would be a monovalent bispecific format.

A number of Wnt surrogates representing different configurations were produced. These included the Wnt surrogates described in Table 3. These illustrative Wnt surrogates include one, two or three polypeptides, the sequences of which are provided as Sequence 1, Sequence 2, and/or Sequence 3. The sequence may include a leader peptide sequence, a Nab sequence, a linker, and/or a heavy or light chain sequence. Annotated sequences are provided in FIG. 15, in which the leader peptide sequence is italicized, the linker sequence is underlined, the Nab sequence is shown in bold, and the remaining sequence is the heavy chain or light chain sequence. The Fzd binder IDs and LRP binder IDs correspond to the clone numbers provided in Tables 1A-B and 2A-B for various Fzd binding or LRP5/6 binding antibodies or antigen-binding fragments thereof.

The Wnt surrogates beginning with “R2M3” include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 001S-A04. The first six Wnt surrogates beginning with “18R5” in Table 3 include different LRP6 binding domains fused to the N-terminus of the anti-Fzd antibody or antigen-binding fragment thereof named 18R5. The Wnt surrogates beginning with “1R” include the anti-LRP6 antibody of antigen-binding fragment thereof named “009S-E04” fused to the N-terminus of different anti-Fzd antibodies or antigen-binding fragment thereof. For “R2M3-26CH,” the LRP6 binding region is fused to the C-terminus of the Fzd binding region. For “R2M3-26NH,” the LRP6 binding region

is fused to the N-terminus of the Fzd binding region. For "R2M3-26CL," the LRP6 binding region is fused to the C-terminus of the Fzd binding region. For "R2M3-26NL," the LRP6 binding region is fused to the N-terminus of the Fzd binding region. For "R2M3-26Fab" and "R2M3-32Fab," the LRP6 binding region is fused to the N-terminus of the Fzd binding region. For "Hetero-Ig," the LRP6 binding region is fused to the N-terminus of human Fc_hole, and paired with Fzd binder light chain and heavy chain human IgG1_knob. The Wnt surrogates beginning with "17SB9" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 017S-B09. The Wnt surrogates beginning with "1R-C07" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 001S-B03. The Wnt surrogates beginning with "R2M13" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 004S-G06. The Wnt surrogates beginning with "3SD10" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 003S-D10. The Wnt surrogates beginning with "4SD1" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 004S-D01. The Wnt surrogates beginning with "14SB6" include different LRP6 binding domains fused to the N-terminus of a light chain region of the anti-Fzd antibody or antigen-binding fragment thereof named 014S-B06.

Table 3. Wnt Surrogate Sequences

Name	Fzd binder ID	LRP binder ID	Sequence 1 SEQ ID NO	Sequence 2 SEQ ID NO	Sequence 3 SEQ ID NO
R2M3-23	001S-A04	009S-B04	89	95	N/A
R2M3-26	001S-A04	009S-E04	90	95	N/A
R2M3-28	001S-A04	009S-G04	91	95	N/A

R2M3-29	001S-A04	009S-H04	92	95	N/A
R2M3-31	001S-A04	013S-G04	93	95	N/A
R2M3-32	001S-A04	013S-H04	94	95	N/A
18R5-5	18R5	008S-G01	96	104	N/A
18R5-7	18R5	008S-C02	97	104	N/A
18R5-8	18R5	008S-D02	98	104	N/A
18R5-9	18R5	008S-E02	99	104	N/A
18R5-26	18R5	009S-E04	100	104	N/A
18R5-28	18R5	009S-G04	101	104	N/A
18R5-31	18R5	013S-G04	102	104	N/A
18R5-32	18R5	013S-H04	103	104	N/A
1R-B05-26	001S-E02	009S-E04	105	111	N/A
1R-C01-26	001S-B01	009S-E04	106	112	N/A
1R-C07-26	001S-B03	009S-E04	107	113	N/A
1R-E06-26	001S-H02	009S-E04	108	114	N/A
1R-G05-26	001S-G02	009S-E04	109	115	N/A
1R-G06-26	001S-A03	009S-E04	110	116	N/A
R2M3-26 CH	001S-A04	009S-E04	117	N/A	N/A
R2M3-26 NH	001S-A04	009S-E04	118	N/A	N/A
R2M3-26 CL	001S-A04	009S-E04	119	N/A	N/A
R2M3-26 NL	001S-A04	009S-E04	120	N/A	N/A
R2M3-26 Fab	001S-A04	009S-E04	121	122	N/A
R2M3-32 Fab	001S-A04	013S-H04	123	124	N/A
R2M3-26 Hetero-Ig	001S-A04	009S-E04	125	126	127

26-17SB9	017S-B09	009S-E04	128	N/A	N/A
1R-C07-3	001S-B03	008S-D01	134	113	N/A
1R-C07-36	001S-B03	013S-D05	135	113	N/A
R2M13-3	004S-G06	008S-D01	136	153	N/A
R2M13-26	004S-G06	009S-E04	137	153	N/A
R2M13-36	004S-G06	013S-D05	138	153	N/A
R2M3-3	001S-A04	008S-D01	139	95	N/A
R2M3-36	001S-A04	013S-D05	140	95	N/A
3SD10-3	003S-D10	008S-D01	141	154	N/A
3SD10-26	003S-D10	009S-E04	142	154	N/A
3SD10-36	003S-D10	013S-D05	143	154	N/A
4SD1-3	004S-D01	008S-D01	144	155	N/A
4SD1-26	004S-D01	009S-E04	145	155	N/A
4SD1-36	004S-D01	013S-D05	146	155	N/A
14SB6-3	014S-B06	008S-D01	147	156	N/A
14SB6-26	014S-B06	009S-E04	148	156	N/A
14SB6-36	014S-B06	013S-D05	149	156	N/A
R2M9-3	003S-E07	008S-D01	150	157	N/A
R2M9-26	003S-E07	009S-E04	151	157	N/A
R2M9-36	003S-E07	013S-D05	152	157	N/A

Example 2

Characterization of a Wnt Surrogate Molecule, R2M3-26

The R2M3-26 molecule consists of a Fzd binder (R2M3) and a LRP6 binder (26). The LRP6 binder 26 was fused to the N-terminus of R2M3

LC with a 5-amino acid linker as depicted in Fig. 2A. R2M3 was in the form of an IgG. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 2B. The ability of R2M3-26 to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cell line (293STF). The 293STF reporter activity traces across the SEC fractions were shown in Fig. 2B, the peak of the reporter activity correlated with the peak of the proteins. The peak fraction was further characterized by a dose response in 293STF cells in the absence and presence of R-spondin (Fig. 2D). R2M3-26 induced reporter activity in a dose dependent manner and was enhanced by the presence of R-spondin similar to a natural Wnt ligand, while R2M3 IgG alone without the attachment of the LRP binding arm did not induce reporter activity. The ability of R2M3-26 to interact with its target, a Fzd1 ECD, was performed in Octet interaction assay (Fig. 2C), and the results showed that the fusion of the LRP6 binding arm, 26, did not affect R2M3 interaction with its target, Fzd.

Example 3

Characterization of a Wnt Surrogate Molecule, R2M3-32

The R2M3-32 molecule consists of a Fzd binder (R2M3) and a LRP6 binder (32). The LRP6 binder 32 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 3A. R2M3 was in the form of an IgG. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 3B. The ability of R2M3-32 to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cell line (293STF). The 293STF reporter activity traces across the SEC fractions were shown in Fig. 3B, the peak of the reporter activity correlated with the peak of the proteins. The peak fraction was further characterized by a dose response in 293STF cells in the absence and presence of R-spondin (Fig. 3D). R2M3-32 induced reporter activity in a dose dependent manner and was

enhanced by the presence of R-spondin, while R2M3 IgG alone without the attachment of the LRP binding arm did not induce reporter activity. The ability of R2M3-32 to interact with its target, a Fzd1 extracellular domain (ECD), was performed in Octet interaction assay (Fig. 3C). The results showed that the fusion of the LRP6 binding arm, 32, did not affect R2M3 interaction with its target, Fzd.

Example 4

R2M3-26 and R2M3-32 Activities Can Be Inhibited by Soluble Fzd ECD and by R2M3 IgG Alone without the LRP Binding Arm

The ability of soluble Fzd extracellular domain (ECD) or R2M3 IgG alone to inhibit Wnt surrogates was determined using the 293STF reporter assay. The Fzd1ECD-Fc or R2M3 IgG was titrated into the 293STF reporter assay, at a fixed concentration of R2M3-26 or R2M3-32. In a dose dependent manner, both Fzd1ECD-Fc and R2M3 IgG inhibited R2M3-26 (Fig. 4A) and R2M3-32 (Fig. 4B) induced reporter signaling, while the negative control molecule, Fc alone had no impact.

Example 5

Characterization of R2M3-LRP6 Binder Fusions in 293, Huh7, A375, BNL.CL2 Wnt Dependent Reporter Assays

The Fzd binder, R2M3, was fused to additional LRP6 binders, 23, 25, 26, 27, 28, 29, 31, 32, 33, and 36. The LRP6 binders were Nab and were fused to the N-terminus of R2M3 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion proteins were tested in Wnt dependent reporter assays in 293, Huh7, A375, and BNL.CL2 cell lines, and activated Wnt signaling to various levels. R2M3 was also fused to two non-LRP6 binder Nabs, 24 and 34, in the same format as the Lrp6 binders. These two non-binders displayed no activity in Wnt dependent 293 reporter assay (Fig. 5), suggesting that Wnt activities observed with R2M3

fusions to 23, 25, 26, 27, 28, 29, 31, 32, 33, and 36 are dependent on the presence of both Fzd and Lrp mimicking the nature ligand function.

Example 6

Characterization of 18R5-LRP6 Binder Fusions in 293, A375, and BNL.CL2 Wnt Dependent Reporter Assays

The Fzd binder, 18R5, was fused to LRP6 binders, 26, 28, 31, 32. The LRP6 binders were Nab and were fused to the N-terminus of 18R5 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion proteins were tested in Wnt dependent reporter assays in 293, A375, and BNL.CL2 cell lines and demonstrated ability to activate Wnt signaling (Fig. 6).

Example 7

Characterization of 18R5-LRP5 Binder Fusions in 293 Wnt Dependent Reporter Assays

The Fzd binder, 18R5, was fused to LRP5 binders, 5, 7, 8, 9. The LRP5 binders were Nab and were fused to the N-terminus of 18R5 LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The fusion proteins were tested in a Wnt dependent reporter assays in 293 cells and were able to activate Wnt signaling (Fig. 7).

Example 8

Characterization of Various Fzd binders-LRP6 Binder 26 Fusions in 293 Wnt Dependent Reporter Assays

The various Fzd binders, 1R-B05, 1R-C01, 1R-C07, 1R-E01, 1R-E06, 1R-G05, 1R-G06, 1R-H04, in IgG format were fused to LRP6 binders, 26. The LRP6 binder Nab was fused to the N-terminus of various Fzd binder LC with a 5-amino acid linker. These proteins were purified by Protein A affinity column followed by a SEC step. The SDS-PAGE gel analysis of the SEC peak fractions were shown in Fig. 8A. The fusion proteins were tested in a Wnt

dependent reporter assays in 293 cells in the presence of Rspo and were able to activate Wnt signaling (Fig. 8B).

Example 9

SAR Analysis of the IgG-Nab Fusion Format

SAR analysis of the IgG-Nab fusions was performed by rotating the attachment location of the Nab to the different termini of the IgG HC or LC as depicted in Fig. 1A. CH indicates attaching the Nab to the C-terminus of heavy chain; NH indicates attaching the Nab to the N-terminus of heavy chain; CL indicates attaching the Nab to the C-terminus of light chain; NL indicates attaching the Nab to the N-terminus of light chain. Three pairs of IgG-Nab fusions SARs were shown, the pairs were between R2M3 and 26, between R2M3 and 32, and between 18R5 and 26. The assays were performed on Wnt responsive 293 reporter cells in the presence of Rspo and activated Wnt signaling to various levels (Fig. 9). These results demonstrate that the attachment location of the fusion and the geometry between the Fzd and LRP binding domains play roles in the ability of the Wnt surrogates to activate Wnt signaling.

Example 10

Characterization of R2M3-26 in the Fab Format

The molecule R2M3-26 Fab consists of a Fzd binder (R2M3) and a LRP6 binder (26). The LRP6 binder 26 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 10A. R2M3 was in the form of a Fab. The protein was purified by Ni-NTA affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions are shown in Fig. 10B. The ability of R2M3-26 as a Fab format to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cells (293STF). The 293STF reporter activity traces across the SEC fractions are shown in Fig. 10B. Unlike when R2M3 was in the IgG format shown in Fig. 2, the peak of the reporter activity from the

R2M3 in the Fab format did not correlate with the peak of the proteins. These results suggest that R2M3-26 fusion in the Fab format is ineffective in inducing canonical Wnt signaling as detected by a reporter assay.

Example 11

Characterization of R2M3-32 in the Fab Format

The molecule R2M3-32 Fab consists of a Fzd binder (R2M3) and a LRP6 binder (32). The Lrp6 binder 32 was fused to the N-terminus of R2M3 LC with a 5-amino acid linker as depicted in Fig. 11A. R2M3 was in the form of a Fab. The protein was purified by Ni-NTA affinity column followed by a size-exclusion-chromatography (SEC) step. The absorbance trace from the SEC and the SDS-PAGE gels of the SEC fractions were shown in Fig. 11B. The ability of R2M3-32 as a Fab format to activate canonical Wnt signaling was tested in a Wnt responding 293 reporter cells (293STF). The 293STF reporter activity traces across the SEC fractions are shown in Fig. 11B. Unlike when R2M3 was in the IgG format shown in Fig. 3, the peak of the reporter activity from the R2M3 in the Fab format did not correlate with the peak of the proteins. These results suggest that R2M3-32 fusion in the Fab format is ineffective in inducing canonical Wnt signaling as detected by a reporter assay.

Example 12

Characterization of R2M3-26 in the HeteroIg Format

The molecule R2M3-26 HeteroIg consists of a Fzd binder (R2M3) and a LRP6 binder (26) as depicted in Fig. 12A and described in Fig. 1A. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The peak fraction from the SEC column was tested in a dose response in the Wnt responsive 293STF reporter cells in the absence or presence of R-spondin (Fig. 12B). Compared to R2M3-26 in the IgG format (as described in Fig. 2), R2M3-26 HeteroIg was ineffective in inducing canonical Wnt signaling as detected in the 293 reporter assay.

Example 13

Characterization of 26-17SB9 in the Nab-Nab Format

The molecule 26-17SB9 Nab-Fc-Nab consists of a LRP6 binder (26) and a Fzd binder (17SB9) as depicted in Fig. 13A and described in Fig. 1C. The protein was purified by Protein A affinity column followed by a size-exclusion-chromatography (SEC) step. The peak fraction from the SEC column was tested in a dose response in the Wnt responsive 293STF reporter cells in the absence or presence of R-spondin (Fig. 13B). 26-17SB9 in the Nab-Fc-Nab format induced canonical Wnt signaling as detected in the 293 reporter assay.

Example 14

In Vivo PK/PD Characterization of R2M3-26

Six-week old C57Bl/6J male mice were obtained from Jackson Laboratories (Bar Harbor, ME, USA) and were housed 3 per cage. All animal experimentation was in accordance with the criteria of the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences. Protocols for animal experimentation were approved by the Surrozen Institutional Animal Care and Use Committee. Mice were acclimatized a minimum of two days prior to initiating experiments. Mice had unlimited access to purified, laboratory-grade acidified water and were fed *ad libitum* (2018 Teklad global 18% protein rodent diet) Mice were kept 12/12-hour light/dark cycle in a 30% to 70% humidity environment and room temperature ranging from 20°C to 26°C.

For the pharmacokinetic (PK) study (Fig. 14A), n=3 per group was used. Mice were dosed with R2M3-26 (with effectorless Fc mutations) at 1 mg/kg (10ml/kg in saline) either using intravenous (IV) or intraperitoneal (i.p.) injections. Mice were anesthetized with isoflurane and blood was removed from the retro-orbital plexus, tail vein or heart at 10 minutes, 30 minutes, 1, 4, 24, 72 or 144 hours after injection. Blood was allowed to coagulate at room temperature, followed by centrifugation for 7 minutes at 8,000 g. The serum

was removed and stored at -20° C until the measurement of serum R2M3-26 concentrations by ELISA.

For the pharmacodynamic (PD) study (Fig. 14B), n=6 per group was used. Mice were injected i.p. with R2M3-26 at the indicated doses (10ml/kg in saline). Control mice received saline only. Eight hours later, mice were anesthetized with isoflurane and the blood was collected by cardiac puncture. Blood was allowed to coagulate at room temperature, followed by centrifugation for 7 minutes at 10,000 g. The serum was removed and stored at -20oC until the measurement of serum R2M3-26 concentrations by ELISA. A portion of the left liver lobe was snap-frozen in liquid nitrogen and stored at -80°C for RNA analysis. RNA was extracted from liver samples using the MagMAX™ mirVana™ Total RNA Isolation Kit (ThermoFisher, A27828). cDNA was produced using the high-Capacity cDNA Reverse Transcription Kit (ThermoFisher, 43-688-14). Axin2 mRNA expression was measured by using TaqMan® Fast Advanced Master Mix (ThermoFisher, 4444963) and the Mm00443610_m1 Axin2 Probe (Thermofisher, 4331182).

These studies showed that R2M3-26 was stable, highly bioavailable and active in vivo, as shown by the induction of Axin2 mRNA expression.

Example 15

In Vivo Bone Model and Characterization of AAV-Delivered Wnt Surrogates

In vivo experiments were conducted by infecting mice with an AAV vector that expressed Flag- and His-tagged 18R5-DKK1c protein (AAV-18R5-DKK1c-FlagHis). 18R5-DKK1c is a fusion protein containing the frizzled binding antibody, 18R5, in scFv format, fused to DKK1c, as described in PCT Publication WO2016/040895, e.g., Fig. 5. Control mice were treated with vehicle only, romosozumab, an AAV vector that expressed green fluorescent protein (GFP) (AAV-CAG-GFP), or an AAV vector that expressed a fusion protein comprising an anti-GFP scFv fused to a mutant DKK1c (AAV-ScFv (anti-

GFP)-DKK1cF234K-Flag-His). 28 days after infection, animals were sacrificed and bone mineral density, bone volume and other characteristics were measured.

As shown in Figs. 16A-16E, systemic expression of 18R5-DKK1c resulted in significantly increased bone mineral density as early as 14 days of 18R5-DKK1c systemic expression, as determined by dual X-ray absorptiometry (DEXA) scan. Systemic expression of 18R5-DKK1c increased bone mineral density (BMD) as measured by DEXA scan (FIG. 16A) and increased levels of the serum P1NP bone formation marker in naïve mice (FIGS. 16C). Serum levels of AAV-ScFv (anti-GFP)-DKK1cF234K and 18R5-DKK1c were detected in the serum and found to be well above the in vitro determined EC50 (FIG. 16B). AAV-CAG-GFP and AAV-ScFv (anti-GFP)-DKK1cF234K were negative controls. Romosozumab was a positive control, and vehicle only was a negative control. 18R5-DKK1c also increase bone density in lumbar vertebra and whole body, as shown in FIGS. 16D and 16E, wherein * indicates P value <0.05 and ** indicates P value <0.0001.

18R5-DKK1c expression through AAV also increased bone volume in tibia and femur and cortical thickness in femur mid-diaphysis at 28 days after treatment in naïve mice as measured by micro CT, as shown in Figs. 17A-17D, wherein **** indicates P value <0.0001.

Systemic expression of 18R5-DKK1c resulted in significantly increased mineral apposition rate from baseline to single label in last 8 days, as shown in FIGS 18A and 18B.

Systemic expression of 18R5-DKK1c also resulted in increased osteoblast numbers and decreased osteoclast numbers, as shown in FIGS. 19A-19D.

18R5-DKK1c treatment increased bone stiffness and ultimate load to fracture in biomechanical testing, suggesting improved resistance to fracture, as shown in FIGS. 20A-20C.

These studies demonstrated that systemic expression of 18R5-DKK1c using AAV increased bone mineral density (BMD) as measured by

DEXA, and also showed that 18R5-DKK1c increased bone volume as measured by micro CT as early as 14 days of treatment. 18R5-DKK1c also increased cortical thickness 28 days after treatment. Systemic expression of 18R5-DKK1c resulted in significantly increased mineral apposition rate, increased osteoblast numbers, and decreased osteoclast numbers. It also increased bone stiffness and ultimate load to fracture, suggesting improved resistance to fracture.

Example 16

In Vivo Bone Model and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted by treating mice with recombinantly produced R2M3-26 protein at various dosages via i.p. injection. Control mice were treated with vehicle only (negative control), romosozumab (positive control), anti-Beta-Galactosidase (negative control), or IgG2-anti-GFP (negative control). Bone mineral density (BMD) measured by DEXA and bone volume measured by micro CT were monitored longitudinally at indicated time points. Four weeks after treatment, animals were sacrificed and bone characteristics were measured. For single injection of R2M3-26, the experimental data was monitored and is shown for two weeks after treatment.

Treatment with recombinant R2M3-26 induced rapid and sustained increase of bone mineral density (BMD) and bone volume in naive mice, as shown in FIGs. 21A-21D. Both bone volume and BMD increased rapidly, suggesting resistance to fracture.

Treatment with recombinant R2M3-26 treatment reversed bone loss in an ovariectomy-induced osteoporosis mouse model, as shown in FIGS. 22A-22C. Increased cortical thickness was observed in the trabecular regions, suggesting increased compressive strength. R2M3-26 treatment increased femur mid-diaphysis cortical bone thickness after 42 days as measured by micro CT, as shown by FIG. 22D. BMD was also increased by R2M3-26 as measured by DEXA, shown in FIG. 22E.

A single injection of R2M3-26 was sufficient to induce rapid bone formation and bone volume within one week, as shown in FIGS. 23A-23C, wherein * indicates P value <0.05.

High dose treatment with R2M3-26 and 1R-C07-26 rapidly and significantly increased bone volume and bone mineral density, and improved biomechanical strength of the bone (ultimate load to failure and stiffness), as shown in FIGS. 24A-24D. 1R-C07-26 showed a robust and significant effect on bone accrual which persisted through 28 days. Both R2M3-26 and 1R-C07-26 significantly increased the resistance to fracture after 28 days of treatment by biomechanical testing.

High does treatment with R2M3-26 and 1R-C07-3 rapidly and significantly increased bone volume, bone mineral density, and cortical thickness after only 14 days of treatment, as shown in FIG. 25A-E. 1R-C07-3 at 10 mpk appeared more effective at increasing bone mass than any other treatment tested in this preclinical model.

These studies demonstrate that recombinant protein treatment can induce rapid and sustained increase of bone mineral density and bone volume in naive mice and mouse osteoporosis model. Both bone volume and bone mineral density (BMD) increased rapidly, suggesting resistance to fracture. IgG2-anti-GFP is a negative control. Anti-Beta Galactosidase was a negative control.

Example 17

In Vivo Liver Regeneration Model and Characterization of AAV-Delivered Wnt Surrogates

In vivo experiments were conducted by infecting approximately 8-weeks old C57BL/6J mice with an AAV vector that expressed Flag- and His-tagged 18R5-DKK1c protein (AAV-18R5-DKK1c-FlagHis). 18R5-DKK1c is a fusion protein containing the frizzled binding antibody, 18R5, in scFv format, fused to DKK1c, as described in PCT Publication WO2016/040895, e.g., Fig. 5. Control mice were either injected sub-cutaneously with phosphate-buffered

saline (PBS) only or romosozumab (10mg/kg), or injected intravenously (IV) with an AAV vector that expressed green fluorescent protein (GFP) (AAV-CAG-GFP), or an AAV vector that expressed a fusion protein comprising an anti-GFP scFv fused to a mutant DKK1c (AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His). 28 days after infection, animals were weighed and sacrificed. The liver was weighed, and the liver to body weight ratio calculated. The content of the small intestine and colon was removed by flushing with phosphate-buffered saline and gentle pressure to expel the content. The small intestine and colon were then weighed.

Systemic expression of 18R5-DKK1c-FlagHis resulted in a significant liver weight increase (FIG. 26A). Systemic expression of the negative controls, eGFP or anti-eGFP-Dkk1cF234K, did not affect the liver to body weight ratio. Administration of the romosozumab recombinant protein or vehicle control, did not affect the liver to body weight ratio.

None of the treatments affected the small intestine (FIG. 26B) or colon (FIG. 26C) to body weight ratio.

These studies showed that 18R5-DKK1c-FlagHis increases liver weight, but not that of the small or large intestines. This suggests that 18R5-DKK1c-FlagHis can promote liver regeneration.

Example 18

In Vivo Liver Regeneration Model and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted by treating mice with recombinantly produced anti-eGFP, R2M3-26, 1R-C07-26, romosozumab or Rspo2 proteins at various dosages. The Rspo2 protein is a fusion protein between a short splice variant of the Rspo2 gene and a human Fc fragment.

In one study, mice were housed 4 per cage and n=8 per treatment group were used. Approximately 8-weeks old C57BL6/J mice were administered recombinant proteins, anti-eGFP (1 mg/kg), R2M3-26 (1 or 10 mg/kg) or 1R-C07-26 (1, 5 or 10 mg/kg), twice weekly intra-peritoneally (i.p.) for

four weeks. In addition, groups of mice were administered romosozumab (30 mg/kg) or PBS vehicle control, subcutaneously.

Mice were weighed at the beginning and throughout the treatment. None of the treatment with recombinant proteins affected total body weight significantly (FIG. 27A). On day 28, the liver was weighed, and the liver to body weight ratio calculated (FIG. 27B). The highest dose of R2M3-26 (10 mg/kg) resulted in a significant increase in liver to body weight ratio. None of the other treatment affected the liver weight significantly.

The increase in liver weight in response to R2M3-26 suggest that this recombinant protein can promote liver regeneration.

In another study, mice were housed 5 per cage and n=10 per treatment group were used. Approximately 8-weeks old C57BL/6J mice received a single i.p. injection containing anti-eGFP (0.56 mg/kg), R2M3-26 (0.3 mg/kg) or Rspo2 (0.46 mg/kg) alone, or with a combination of R2M3-26 (0.1 mg/kg) and Rspo2 (0.46mg/kg).

24 or 48 hours after injection, mice were euthanized. A portion of the left liver lobe was snap-frozen in liquid nitrogen and stored at -80^{o}C for RNA analysis. Cyclin D1 and Ki67 expression were measured by performing qPCR using the Mm00432359_m1 Ccnd1 probe and the Mm01278617_m1 Ki67 probe (Thermofisher, 4331182). An additional portion of the left liver lobe was fixed in formalin and embedded in paraffin for immunohistochemistry analysis. Sections were stained with the anti-proliferating cell nuclear antigen (PCNA) (Abcam, ab18197) or anti-phospho-histone H3 (pH3) rabbit antibodies (Abcam, ab47297). The number of positive nuclei were counted using the image processing software, Image J.

Rspo2 alone increased Ki67 (FIG. 28A) and CyclinD1 (FIG. 28B) mRNA expression. In combination with R2M3-26, Rspo2 increased Ki67 and CyclinD1 expression further than with Rspo2 alone at 24 and 48 hours after treatment with recombinant proteins. Rspo2 alone increased the number of PCNA (FIG. 28C) and pH3 (FIG. 28D) positive nuclei in liver sections. In combination with R2M3-26, Rspo2 increased the number of PCNA and pH3

positive nuclei further than with Rspo2 alone at 48 hours after treatment with recombinant proteins.

These studies show that the proliferation markers, Ki67 mRNA, CyclinD1 mRNA and PCNA-positive nuclei, and the pH3 mitotic marker are induced by the R2M3-26 and Rspo2 recombinant proteins and suggest that these recombinant proteins can promote liver regeneration.

Example 19

In Vivo Chronic Liver Injury Model and Characterization of AAV-Delivered Wnt Surrogates

Two in vivo experiments were conducted in two, thioacetamide (TAA)- and CCl4-induced, liver cirrhosis mouse models, thioacetamide (TAA)- and CCl4-induced, to test the effect of AAV vectors expressing 18R5-DKK1c-FlagHis or Rspo2 protein on chronic liver injury. TAA was added to the drinking water of 6 weeks old C57BL/6J mice at a concentration of 300 mg/L throughout the TAA treatment duration. Mice were housed 5 per cage and groups of n=10 were used, except for the control groups without TAA treatment where n=5 per group was used.

In Study 1 (FIGS. 29A, 29C, 29E, 29G-H), mice with (n=10) or without (n=5) TAA treatment were weighed and sacrificed after 9 weeks of TAA addition into the drinking water, to measure baseline values. Livers were weighed and liver samples were collected for mRNA and histological analysis. TAA supplementation was maintained in the drinking water of the remaining mice and they were injected IV with AAV vectors that expressed an enhanced green fluorescent protein (eGFP) (3e10 genomic particles (GC)), 18R5-DKK1c-FlagHis (3e10 or 1e11 GC) or Rspo2 protein (1e11 GC) or a combination of 18R5-DKK1c-FlagHis (3e10 GC) and Rspo2 (1e11 GC). 5 age-matched naïve animals (no TAA) were kept as a negative control. Three weeks after AAV injection, all mice were weighed and euthanized. Livers were weighed and liver samples were collected for mRNA and histological analysis.

Treatment with 18R5Dkk1FH or Rspo2 resulted in a significant increase of liver weight (FIG. 29C) and liver to body weight ratio (FIG. 29E) in mice undergoing a continuous exposure to TAA. Treatment with a combination of 18R5Dkk1FH and Rspo2 resulted in a further increase in liver weight and liver to body weight ratio beyond that observed with either treatment alone. The combination 18R5Dkk1FH and Rspo2 treatment resulted in a decrease of the fibrosis marker Col1a1 mRNA expression (FIG. 29G). Histological liver sections were stained with Sirius red to visualize the accumulation of collagen in fibrotic area (FIG. 29H). Quantification of the percentage of red are, using Image J analysis software, showed a significant increase of fibrotic area in TAA-treated mice. A combination of 18R5Dkk1FH and Rspo2 resulted in a reversal of fibrotic area increase when compared to mice treated with the eGFP negative control. Treatment with Rspo2 alone also resulted in a significant but smaller reversal than the combination treatment.

In Study 2, (FIGS. 29B, 29D, 29F), mice were exposed to TAA-supplemented water for 11 weeks, and were returned to standard drinking thereafter, two days prior to AAV treatment. At the start of AAV treatment, mice exposed to TAA (n=10) or not (n=5) were weighed and sacrificed to collect liver samples for baseline measurements. The remaining mice were injected with AAV vectors that expressed an enhanced green fluorescent protein (eGFP) (1.3e11 genomic particles (GC)), 18R5-DKK1c-FlagHis (3e10 or 1e11 GC) or Rspo2 protein (1e11 GC) or a combination of 18R5-DKK1c-FlagHis (3e10 GC) and Rspo2 (1e11 GC). 5 age-matched naïve animals (no TAA) were kept as a negative control. Three weeks after AAV injection, all mice were weighed and euthanized. Livers were weighed and liver samples were collected for mRNA and histological analysis.

A similar liver weight and liver to body weight increase was observed in mice treated with 18R5-Dkk1c-FlagHis and Rspo2 either alone or in combination than what was observed in Study 1 (FIGS. 29D, 29F).

These studies show that 18R5-Dkk1c-FlagHis and Rspo2 can increase liver weight in a TAA-induced liver cirrhosis model and reduce fibrosis

markers. These results suggest that 18R5-Dkk1c-FlagHis and Rspo2 can promote liver tissue repair after chronic liver injury.

Example 20

In Vivo Chronic Liver Injury Models and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted in thioacetamide (TAA)-induced and CCl_4-induced mouse models of liver cirrhosis by treating mice with recombinantly produced anti-eGFP, R2M3-26 and Rspo2 proteins.

In the TAA-induced cirrhosis model, six weeks old male mice were exposed to TAA-supplemented drinking water (300 mg/L) for approximately 22 weeks (FIG. 30A). TAA exposure was removed two days prior to beginning of treatment with recombinant proteins and mice were provided with fresh drinking water. Mice were housed 5 per cage and n=10 per treatment group were used. In a mono treatment study (FIGS. 30B, 30D, 30F, 30H, 30J, 30L), mice were injected i.p. with anti-eGFP (1 mg/kg) or Rspo2 (1 mg/kg) twice weekly. In a combination treatment study (FIGS. 30C, 30E, 30G, 30I, 30K, 30M), mice were injected i.p. with anti-eGFP (1.3mg/kg) or a combination of R2M3-26 (0.3 mg/kg) and Rspo2 (1 mg/kg) twice weekly. Mice were then weighed and sacrificed at day 3, 7 or 14 days after beginning of treatment. Groups of control mice without exposure to TAA (n=5 per group) were euthanized at day 0 and day 14 in both studies.

Treatment with Rspo2 protein alone or in combination with R2M3-26 resulted in an increase in liver to body weight ratio (FIGS. 30B and 30C) and a transient stimulation of the Wnt signaling pathway as shown by an increase in Axin2 expression (FIGS. 30D and 30E). Treatment with Rspo2 protein alone or in combination with R2M3-26 induced the following proliferation markers: cyclinD1 (FIGS. 30F, 30G) and Ki67 (FIGS. 30H and 30I) mRNA expression, PCNA (FIGS. 30J, 30K) and pH3 (FIGS. 30L, 30M) positive nuclei.

In an additional study, plasma was collected for prothrombin time measurement. Coagulation time is impaired in TAA-induced cirrhosis model as

exemplified by an increase in pro-thrombin (PT) test to normal value ratio in mice exposed to TAA when compared to normal mice without TAA exposure (FIG. 30N). Treatment with Rspo2 (1 mg/kg) and R2M3-26 (0.3 mg/kg) reversed the prolongation in PT time as shown by the decrease in PT_{test}/PT_{normal} ratio at day 7 and day 14 after biweekly Rspo2 and R2M3-26 treatment.

These studies show that Rspo2 and R2M3-26 can stimulate liver cell proliferation and improve hepatocytes functional activity such as pro-thrombin time in a TAA-induced liver cirrhosis model. These results suggest that Rspo2 and R2M3-26 can promote liver tissue repair in chronic liver disease.

In the CCl_4-induced cirrhosis model, six-weeks old C57BL/6J male mice were injected i.p. with 2 ml/kg CCl_4 in mineral oil, twice weekly for 8 weeks (FIG. 31A). 3 days after the last CCl_4 injection, mice were injected i.p. twice weekly with the following recombinant proteins: anti-β-galactosidase (10mg/kg), Rspo2 (1 or 10 mg/kg), or a combination of R2M3-26 (0.3mg/kg) and Rspo2 (1 mg/kg). Three additional control groups were included: one group injected with CCl_4 but no proteins, one group injected with mineral oil, and one untreated age-matched naïve group. n=8 were used for each group. After two weeks of treatment with recombinant proteins, mice were weighed and sacrificed. Plasma was collected for pro-thrombin time measurement. Livers were weighed and liver samples were collected for histological analysis.

Treatment with R2M3-26 and Rspo2 resulted in a significant increase in liver to body weight ratio when compared to treatment with anti-β-galactosidase negative control (FIG. 31B). Treatment with Rspo2 (10 mg/kg) or a combination of R2M3-26 and Rspo2 resulted in a significant decrease in prothrombin time (FIG. 31C). Treatment with Rspo2 (10 mg/kg) or a combination of R2M3-26 and Rspo2 resulted in a significant reversal in fibrotic area, induced by CCl_4 (FIG. 31D).

This study showed that Rspo2 and R2M3-26 can induce an increase in liver weight, improve hepatocytes functional activity such as pro-thrombin time and reduce fibrosis markers in a CCl_4-induced liver cirrhosis

model. These results suggest that Rspo2 and R2M3-26 can promote liver tissue repair in chronic liver disease.

Example 21

In Vivo Acute Liver Injury Model and Characterization of Recombinantly Produced Wnt Surrogates

In vivo experiments were conducted using acetaminophen-induced mouse models of acute liver injury by treating mice with recombinantly produced anti-eGFP, R2M3-26 and Rspo2 proteins.

Eight-weeks old C57BL/6 male mice were housed 5 per cage. n=10 were used per group. Mice were fasted overnight for 12 hours. Acetaminophen (APAP) was administered i.p. at a sublethal dose (300 mg/kg).

In a first study, anti-eGFP (0.3 mpk) or R2M3-26 (0.3 mpk) were injected i.p. either immediately after or 3 or 6 hours after APAP injection (FIG. 32). Serum samples were collected at 24 and 48 hours after APAP injection for ALT measurements. Mice were sacrificed 48 hours after APAP injection and liver samples were collected for mRNA analysis.

R2M3-26 treatment did not affect ALT level significantly (FIG. 32B). Treatment with R2M3-26 induced cyclinD1 (FIG. 32C) and Ki67 (FIG. 32D) mRNA significantly, beyond the level induced by APAP treatment alone.

In a second study, human Fc (0.46 mg/kg) or Rspo2 (0.46 mg/kg) were injected i.p. either immediately after or 3 or 6 hours after APAP injection (FIG. 33). Serum samples were collected at 24 and 48 hours after APAP injection. Liver samples were collected at 48 hours after APAP injection.

Rspo2 treatment did not affect ALT serum level significantly (FIG. 33B). Treatment with R2M3-26 induced cyclinD1 (FIG. 33C) and Ki67 (FIG. 33D) mRNA significantly, beyond the level induced by APAP treatment alone.

In a third study, anti-eGFP (0.56 mg/kg) or a combination of R2M3-26 (0.1 mg/kg) and Rspo2 (0.46 mg/kg) were injected i.p. 3 hours after APAP administration. Serum and liver samples were collected at 24, 36, 48 and 60 hours after APAP injection for ALT measurements and mRNA analysis.

R2M3-26 and Rspo2 combination treatment did not affect ALT level significantly (FIG. 34B). Treatment with R2M3-26 and Rspo2 induced cyclinD1 (FIG. 34C) and Ki67 (FIG. 34D) mRNA significantly, beyond the level induced by APAP treatment alone.

An additional study was performed to evaluate the effect of Rspo2 and R2M3-26 on the survival of mice treated with a dose of 600 mg/kg of acetaminophen (FIG. 35). Anti-eGFP (0.3 mg/kg), R2M3-26 (0.3 mg/kg), Rspo2 (0.46mg/kg) or a combination of R2M3-26 (0.1 mg/kg) and Rspo2 (0.46 mg/kg) were injected i.p. 3 hours after APAP administration. Mice were monitored several times daily over the next 96 hours. A consistent trend in improving survival was observed in groups treated with R2M3-26 (FIG. 35B), Rspo2 (FIG. 35C) or a combination of R2M3-26 and Rspo2 (FIG. 35D).

These studies show that Rspo2 and R2M3-26 can induce proliferation markers beyond that induced spontaneously in APAP-induced acute injury model. These results suggest that Rspo2 and R2M3-26 can enhance liver tissue repair after an acute liver injury.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description.

In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

What is claimed is:

1. A soluble, bivalent, bispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises: (i) one or more region that specifically binds to one or more Frizzled (Fzd) receptor (a Fzd binding region); and (ii) one or more region that specifically binds to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) (a LRP5/6 binding region).

2. The Wnt surrogate molecule of claim 1, comprising two or more Fzd binding regions and two or more LRP5/6 binding regions.

3. The Wnt surrogate molecule of claim 1, wherein the one or more Fzd binding regions comprise one or more antigen-binding fragments of an antibody.

4. The Wnt surrogate molecule of claim 3, wherein the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and Nanobodies®.

5. The Wnt surrogate molecule of any of claims 1-4, wherein the one or more Fzd antigen-binding fragments comprise: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Tables 1A or 1B; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Tables 1A or 1B, or a variant of said Fzd binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

6. The Wnt surrogate molecule of any of claims 3-5, wherein the one or more Fzd binding regions comprise an amino acid sequence having at least 90% identity to any of

the sequences set forth in SEQ ID NOs:1-65 or 129-132, or an antigen-binding fragment thereof.

7. The Wnt surrogate molecule of any of claims 1-6, wherein the one or more Fzd binding regions bind to one or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzle 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

8. The Wnt surrogate molecule of claim 7, wherein the one or more Fzd binding region binds to two or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

9. The Wnt surrogate molecule of claim 8, wherein the one or more Fzd binding region binds to: (i) Fzd1, Fzd2, Fzd7 and Fzd9; (ii) Fzd1, Fzd2 and Fzd7; (iii) Fzd5 and Fzd8; (iv) Fzd5, Fzd7 and Fzd8; (v) Fzd1, Fzd4, Fzd5 and Fzd8; (vi) Fzd1, Fzd2, Fzd5, Fzd7 and Fzd8; (vii) Fzd4 and Fzd9; (viii) Fzd9 and Fzd10; (ix) Fzd5, Fzd8 and Fzd10; or (x) Fzd4, Fzd5 and Fzd8; Fzd1, Fzd5, Fzd7 and Fzd8.

10. The Wnt surrogate molecule of any of claims 1-9, wherein the one or more LRP5/6 binding regions comprise one or more antigen-binding fragments of an antibody.

11. The Wnt surrogate molecule of claim 10, wherein the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and Nanobodies®.

12. The Wnt surrogate molecule of any of claims 1-11, wherein the one or more LRP5/6 binding regions or antigen-binding fragments comprise: (i) CDRH1, CDRH2 and

CDRH3 sequences set forth for any of the antibodies of Table 2; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2, or a variant of said LRP5/6 binding region comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

13. The Wnt surrogate molecule of any of claims 10-12, wherein the one or more LRP5/6 binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOs:66-88 or 133, or an antigen-binding fragment thereof.

14. The Wnt surrogate molecule of any of claims 1-13, wherein the Fzd binding region comprises a Fab, and the LRP5/6 binding region comprises a Nanobody® or a scFv.

15. The Wnt surrogate molecule of claim 14, wherein the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.

16. The Wnt surrogate molecule of claim 15, wherein the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the heavy chain.

17. The Wnt surrogate molecule of claim 15, wherein the LRP5/6 binding region is fused to the N-terminus or the C-terminus of the light chain.

18. The Wnt surrogate molecule of claim 16 or claim 17, wherein the LRP5/6 binding region is fused to the heavy chain or the light chain via one or more linker moiety.

19. The Wnt surrogate molecule of any of claims 1-13, wherein the Fzd binding region comprises a Nanobody® or scFv, and the LRP5/6 binding region comprises a Fab.

20. The Wnt surrogate molecule of claim 19, wherein the Fab is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.

21. The Wnt surrogate molecule of claim 20, wherein the Fzd binding region is fused to the N-terminus or the C-terminus of the heavy chain.

22. The Wnt surrogate molecule of claim 20, wherein the Fzd binding region is fused to the N-terminus or the C-terminus of the light chain.

23. The Wnt surrogate molecule of claim 21 or claim 22, wherein the Fzd binding region is fused to the heavy chain or the light chain via one or more linker moiety.

24. The Wnt surrogate molecule of any of claims 1-13, wherein the Fzd binding region comprises a Fab, and the LRP5/6 binding region comprises a Fab.

25. The Wnt surrogate molecule of claim 24, wherein the Fab of the Fzd binding region or the Fab of the LRP5/6 binding region is present within a full immunoglobulin (Ig), optionally an IgG, comprising a light chain and a heavy chain.

26. The Wnt surrogate molecule of claim 25, wherein only one of the Fab of the Fzd binding region or the Fab of the LRPp5/6 binding region is present within the full immunoglobulin (Ig).

27. The Wnt surrogate molecule of claim 26, wherein the Fab of the Fzd binding region is present within the full Ig.

28. The Wnt surrogate molecule of claim 27, wherein the Fab of the LRP5/6 binding region is fused to the N-terminus of the Ig, optionally the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig.

29. The Wnt surrogate molecule of claim 27, wherein the Fab of the LRP5/6 binding region is fused to the C-terminus of the Ig, optionally the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig.

30. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig.

31. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the LRP5/6 binding Fab is fused to the N-terminus of the variable light chain region of the full IgG.

32. The Wnt surrogate molecule of claim 26, wherein the Fab of the LRP5/6 binding region is present within the full Ig.

33. The Wnt surrogate molecule of claim 32, wherein the Fab of the Fzd binding region is fused to the N-terminus of the Ig, optionally the N-terminus of the heavy chain of the full Ig or the N-terminus of the light chain of the full Ig.

34. The Wnt surrogate molecule of claim 32, wherein the Fab of the Fzd binding region is fused to the C-terminus of the Ig, optionally the C-terminus of the heavy chain of the full Ig or the C-terminus of the light chain of the full Ig.

35. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig.

36. The Wnt surrogate molecule of claim 27, wherein the variable light chain region of the Fzd binding Fab is fused to the N-terminus of the variable heavy chain region of the full Ig, and the variable heavy chain region of the Fzd binding Fab is fused to the N-terminus of the variable light chain region of the full IgG.

37. The Wnt surrogate molecule of any of claims 1-13, wherein the Fzd binding region comprises a Nanobody® or scFv, and the LRP5/6 binding region comprises a Nanobody® or scFv.

38. The Wnt surrogate molecule of claim 37, wherein the Fzd binding region is fused to the Lrp5/6 binding region, and wherein the Fzd binding region or the LRP5/6 binding region is fused to an Fc region.

39. The Wnt surrogate molecule of claim 37, wherein the Fzd binding region is fused to the N-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the C-terminus of an Fc region.

40. The Wnt surrogate molecule of claim 37, wherein the Fzd binding region is fused to the C-terminus of an Fc region, and wherein the LRP5/6 binding region is fused to the N-terminus of an Fc region.

41. The Wnt surrogate molecule of any of claims 3-40, wherein the one or more antigen-binding fragment thereof, is humanized.

42. The Wnt surrogate molecule of any of claims 1-341, which binds to the one or more Fzd receptor with a KD of 50 μM or lower.

43. The Wnt surrogate molecule of any of claims 1-42, which binds to the one or more LRP5/6 receptor with a KD of 50 μM or lower.

44. The Wnt surrogate molecule of any of claims 1-43, which modulates a Wnt signaling pathway in a cell, optionally a mammalian cell.

45. The Wnt surrogate molecule of claim 44, which increases signaling via the Wnt signaling pathway in the cell.

46. The Wnt surrogate molecule of claim 44 or claim 45, wherein the Wnt signaling pathway is a canonical Wnt signaling pathway.

47. The Wnt surrogate molecule of claim 44 or claim 45, wherein the Wnt signaling pathway is a non-canonical Wnt signaling pathway.

48. An isolated polynucleotide encoding a polypeptide sequence comprising one or more of the Fzd binding regions and/or one or more of the LRP5/6 binding regions of a Wnt surrogate molecule of any of claims 1-47.

49. An expression vector comprising the isolated polynucleotide of claim 48.

50. An isolated host cell comprising the expression vector of claim 49.

51. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the Wnt surrogate

molecule according to any of claims 1-47, the polynucleotide of claim 48, the expression cell of claim 49, or the host cell of claim 50.

52. A method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell the Wnt surrogate molecule according to any of claims 1-47, the polynucleotide of claim 48, the expression cell of claim 49, or the host cell of claim 50, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

53. A method for treating a subject having a disease or disorder associated with reduced Wnt signaling, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 51, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

54. The method of claim 53, wherein the disease or disorder is a bone disease or disorder.

55. The method of claim 54, wherein the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6.

56. The method of claim 55, wherein the Wnt surrogate molecule also binds Fzd5 and Fzd8.

57. The method of claim 53, wherein the disease or disorder is selected from the group consisting of: bone fractures, stress fractures, vertebral compression fractures, osteoporosis, osteoporotic fractures, non-union fractures, delayed union fractures, spinal fusion, pre-operative optimization for spine surgeries, osteonecrosis, osseointegration of implants or orthopedic devices, osteogenesis imperfecta, bone grafts, tendon repair, tendon-bone integration, tooth growth and regeneration, maxillofacial surgery, dental implantation, periodontal diseases, maxillofacial

reconstruction, osteonecrosis of the jaw, hip or femoral head, avascular necrosis, alopecia, hearing loss, vestibular hypofunction, macular degeneration, age-related macular degeneration (AMD), vitreoretinopathy, retinopathy, diabetic retinopathy, diseases of retinal degeneration, Fuchs' dystrophy, cornea diseases, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, diseases affecting blood brain barrier (BBB), spinal cord injuries, spinal cord diseases, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), metabolic syndrome, diabetes, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, pressure sores, venous leg ulcers, epidermolysis bullosa, dermal hypoplasia, myocardial infarction, coronary artery disease, heart failure, hematopoietic cell disorders, immunodeficiencies, graft versus host diseases, acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, livery surgery, liver injury, liver transplantation, "small for size" syndrome in liver surgery and transplantation, congenital liver disease and disorders, any other liver disorder or detect resulting from genetic diseases, degeneration, aging, drugs, or injuries.

58. A method for increasing bone mineral density, increasing bone volume, increasing bone cortical thickness, increasing bone mineral apposition rate, increasing bone stiffness, increasing bone biomechanical strength, increasing resistance to bone fracture, or decreasing bone loss associated with osteoporosis, comprising providing to a subject an effective amount of the pharmaceutical composition of claim 51, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

59. The method of claim 57, wherein the Wnt surrogate molecule binds Fzd1, Fzd2, and FZD7, and binds LRP5 and/or LRP6.

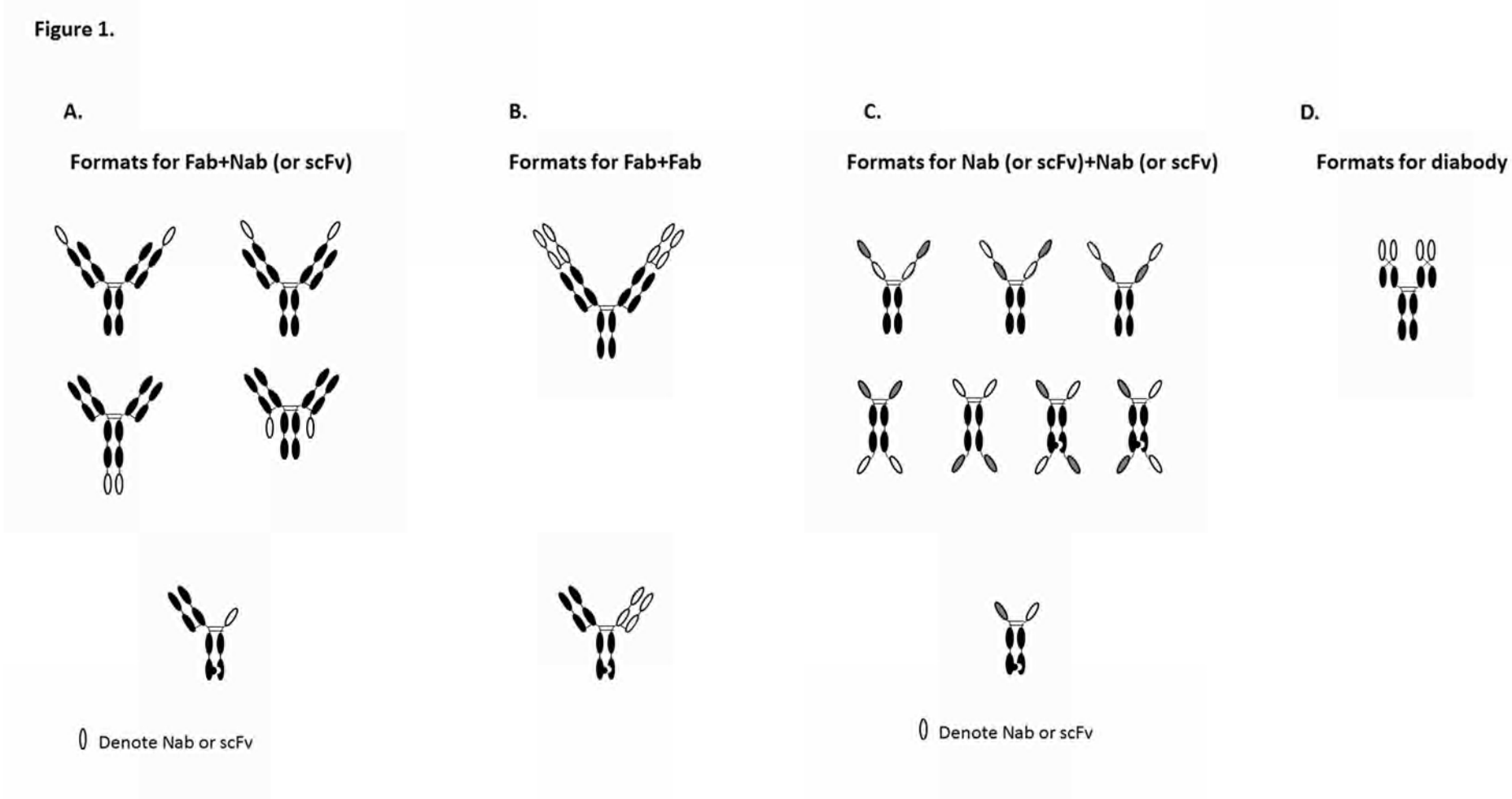
60. The method of claim 58, wherein the Wnt surrogate molecule also binds Fzd5 and Fzd8.

61. A method for increasing liver to body weight ratio, promoting liver regeneration, increasing liver cell proliferation or mitosis, decreasing liver fibrosis, optionally following a chronic liver injury, increasing hepatocyte function, or decreasing coagulation time in liver, comprising providing to a subject an effective amount of the pharmaceutical composition of claim 51, wherein the Wnt surrogate molecule is an agonist of a Wnt signaling pathway.

ABSTRACT OF THE DISCLOSURE

The present invention provides Wnt pathway agonists and related compositions, which may be used in any of a variety of therapeutic methods for the treatment of diseases.

Figure 1.



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Figure 2.

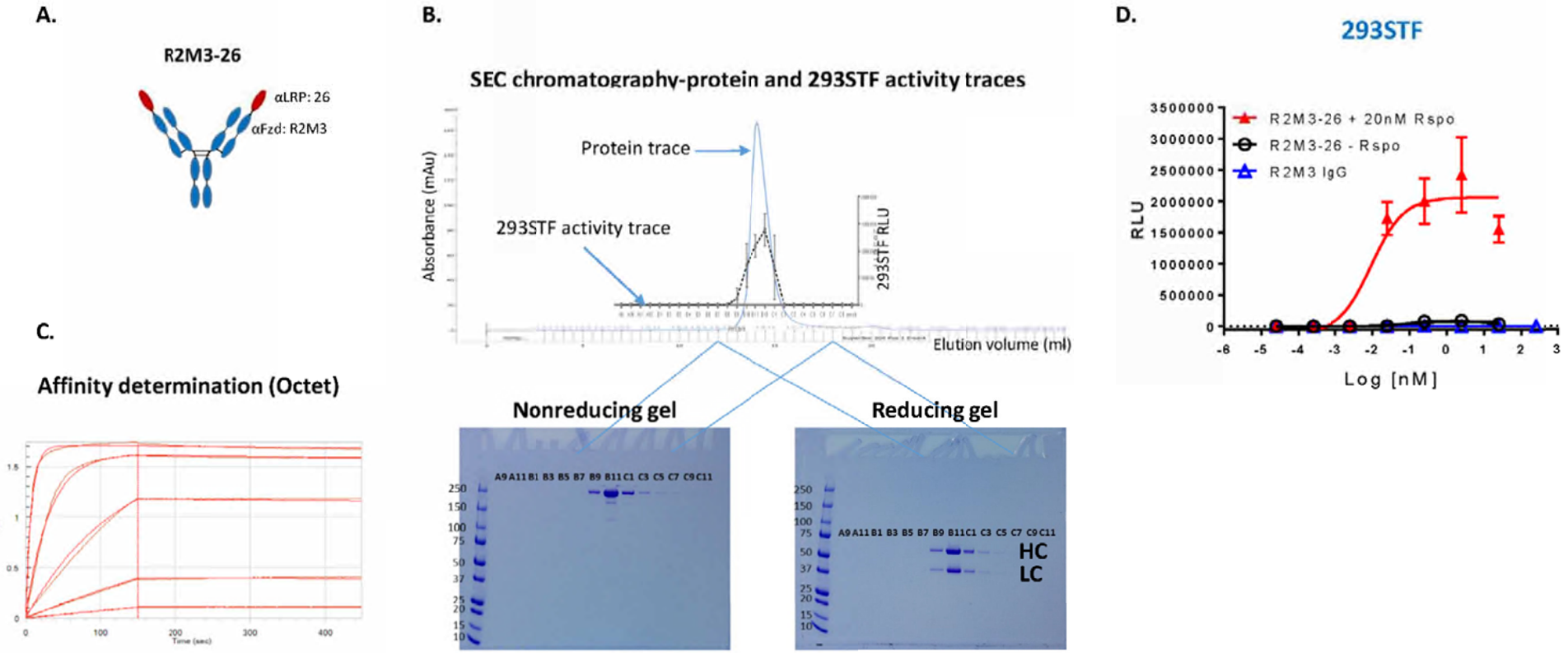

A.
R2M3-26
αLRP: 26
αFzd: R2M3
B.
SEC chromatography-protein and 293STF activity traces
Protein trace
293STF activity trace
Absorbance (mAu)
293STF RLU
Elution volume (ml)
Nonreducing gel
Reducing gel
HC
LC
C.
Affinity determination (Octet)
D.
293STF
R2M3-26 + 20nM Rspo
R2M3-26 - Rspo
R2M3 IgG
RLU
Log [nM]

Figure 3.

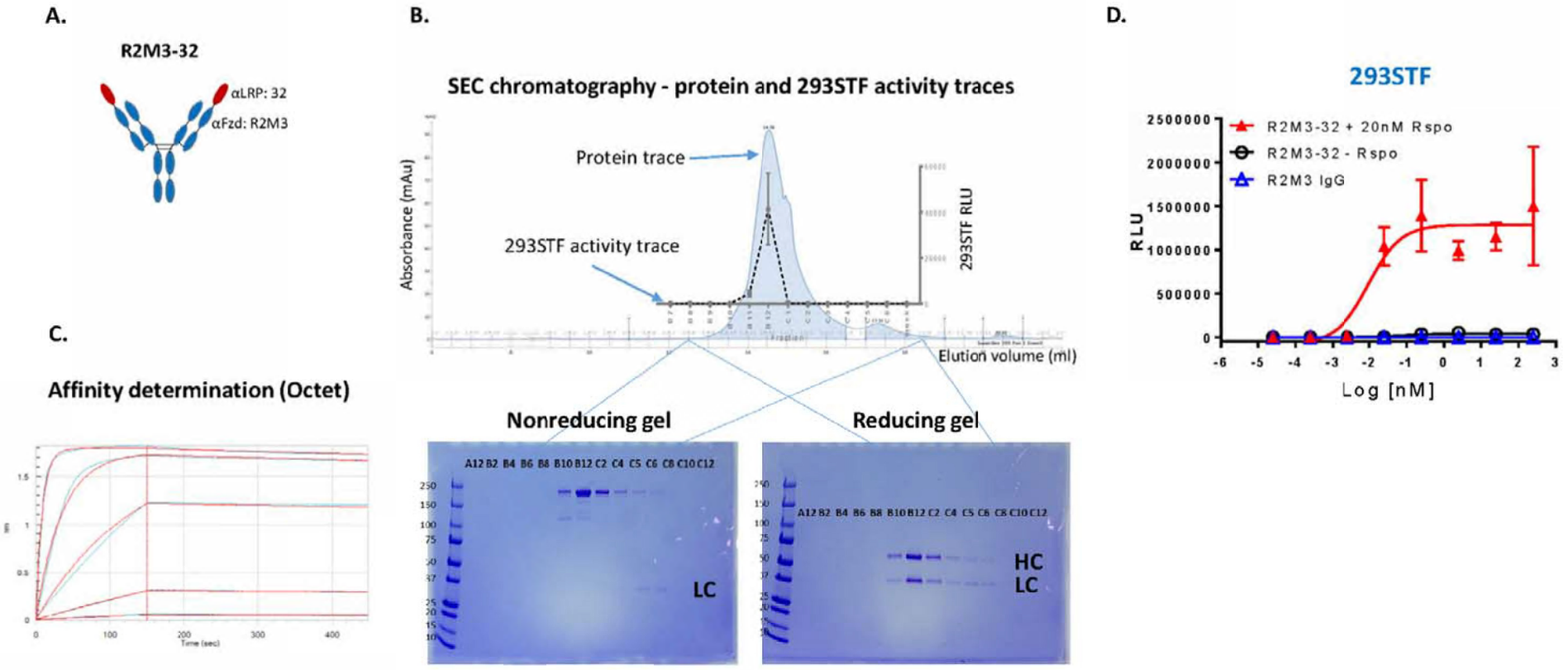

A.
R2M3-32
αLRP: 32
αFzd: R2M3
B.
SEC chromatography - protein and 293STF activity traces
Protein trace
293STF activity trace
Absorbance (mAu)
293STF RLU
Elution volume (ml)
Nonreducing gel
Reducing gel
A12 B2 B4 B6 B8 B10 B12 C2 C4 C5 C6 C8 C10 C12
LC
HC
LC
C.
Affinity determination (Octet)
Time (sec)
D.
293STF
R2M3-32 + 20nM Rspo
R2M3-32 - Rspo
R2M3 IgG
RLU
Log [nM]

Figure 4.

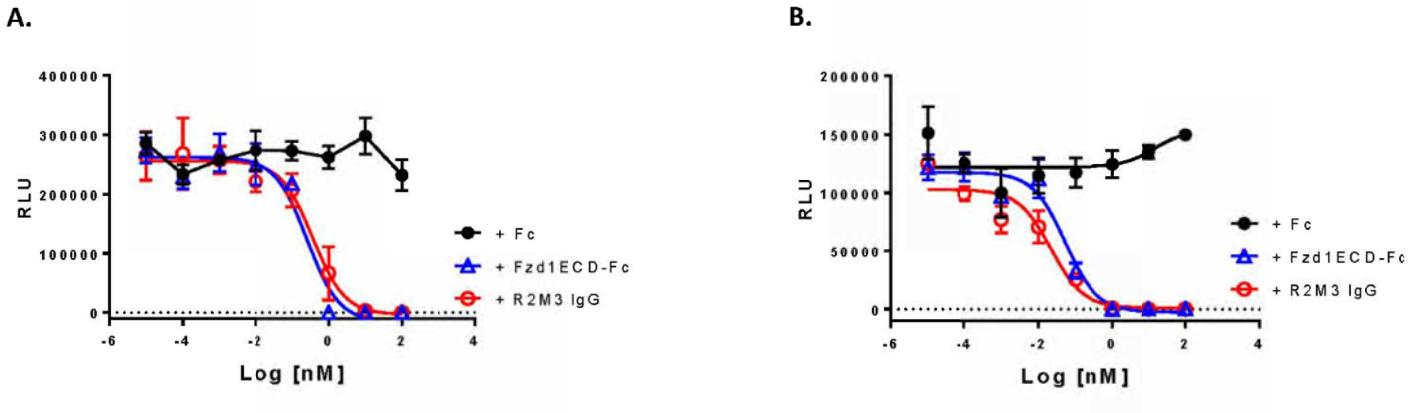

A.
400000
300000
200000
100000
0
RLU
-6
-4
-2
0
2
4
Log [nM]
+ Fc
+ Fzd1ECD-Fc
+ R2M3 IgG
B.
200000
150000
100000
50000
0
RLU
-6
-4
-2
0
2
4
Log [nM]
+ Fc
+ Fzd1ECD-Fc
+ R2M3 IgG

Figure 5.

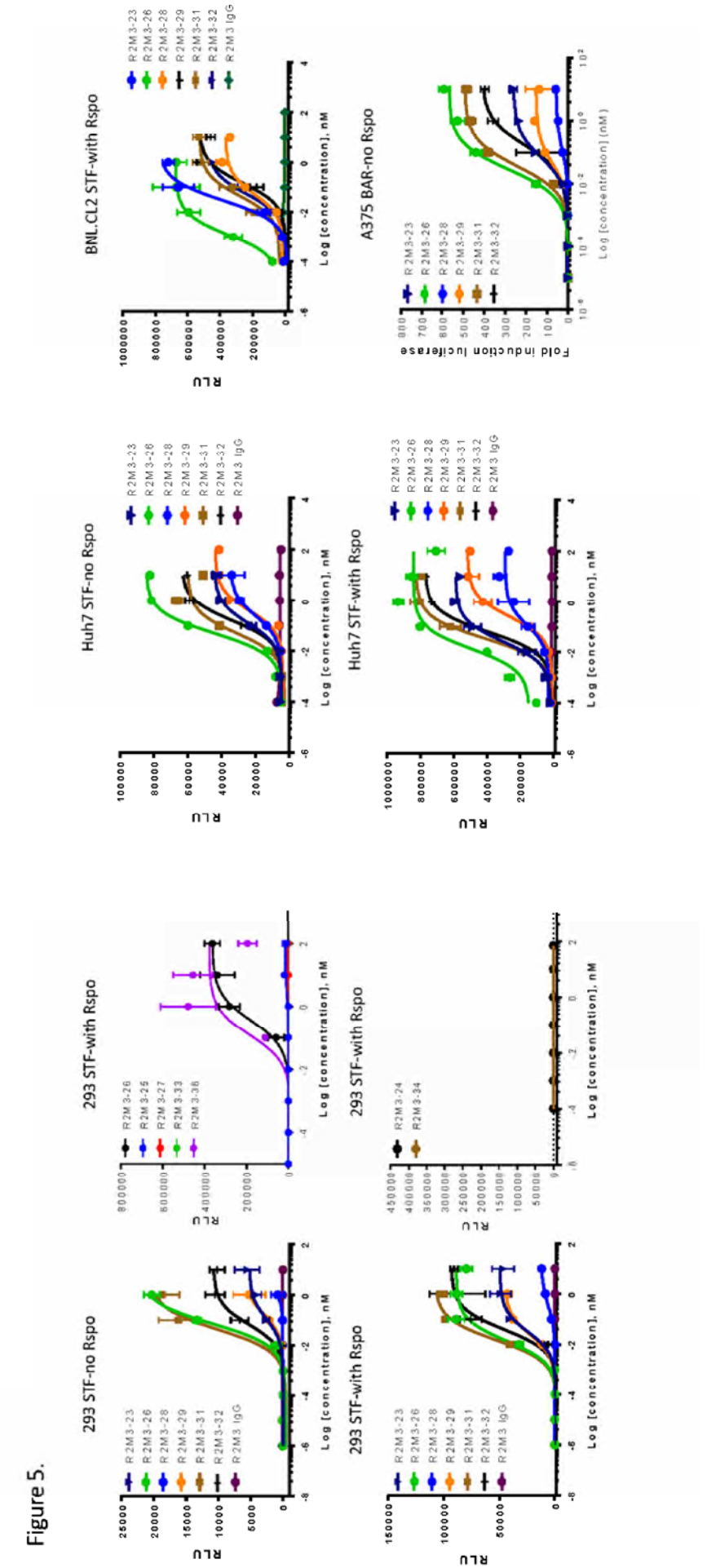
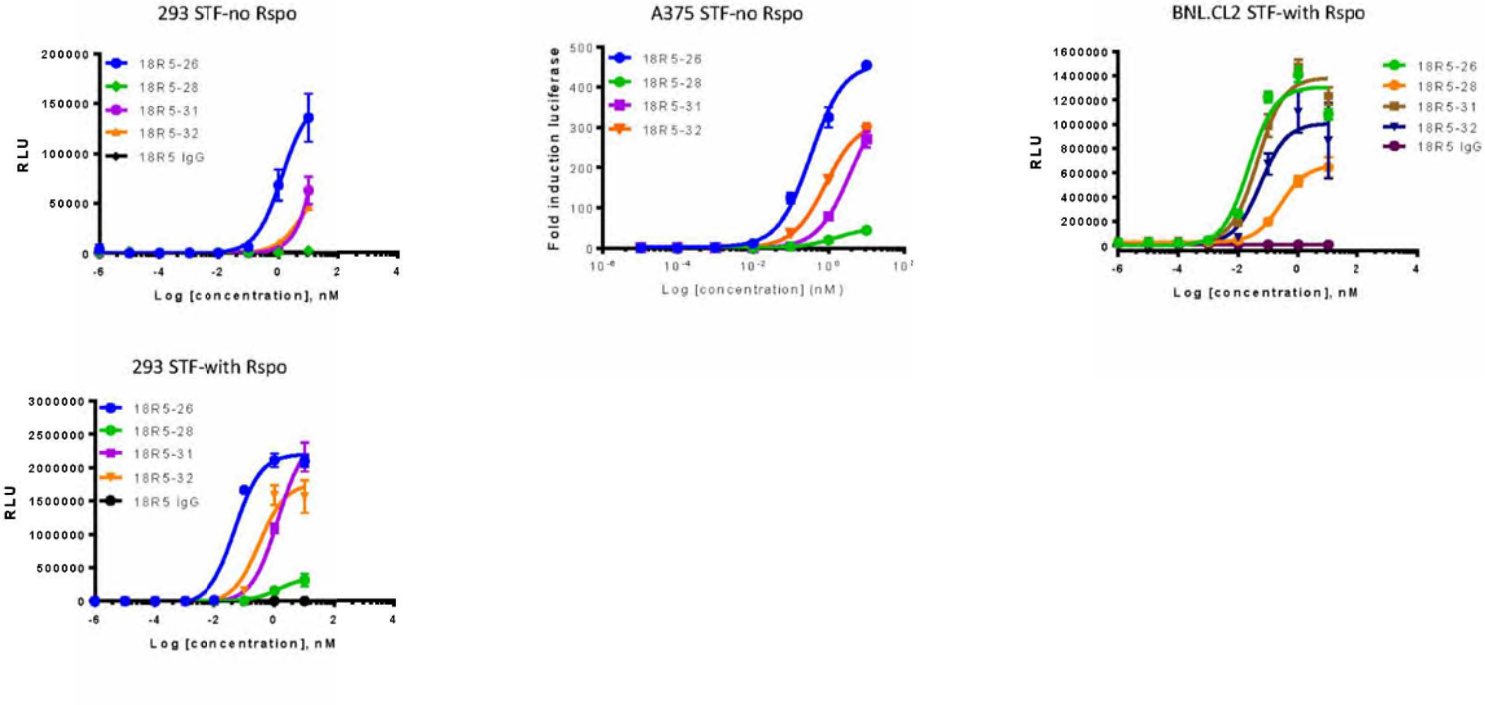

293 STF-no Rspo
293 STF-with Rspo
Huh7 STF-no Rspo
Huh7 STF-with Rspo
BNL.CL2 STF-with Rspo
A375 BAR-no Rspo
RLU
Fold induction luciferase
Log [concentration], nM
Log [concentration] (nM)
R2M3-23
R2M3-26
R2M3-28
R2M3-29
R2M3-31
R2M3-32
R2M3 IgG
R2M3-24
R2M3-34
R2M3-25
R2M3-27
R2M3-33
R2M3-36

Figure 6.


293 STF-no Rspo
RLU
Log [concentration], nM
18R5-26
18R5-28
18R5-31
18R5-32
18R5 IgG
A375 STF-no Rspo
Fold induction luciferase
Log [concentration] (nM)
BNL.CL2 STF-with Rspo
293 STF-with Rspo

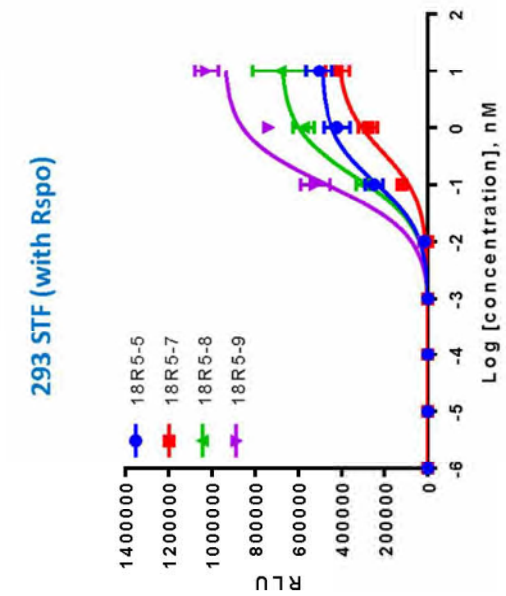
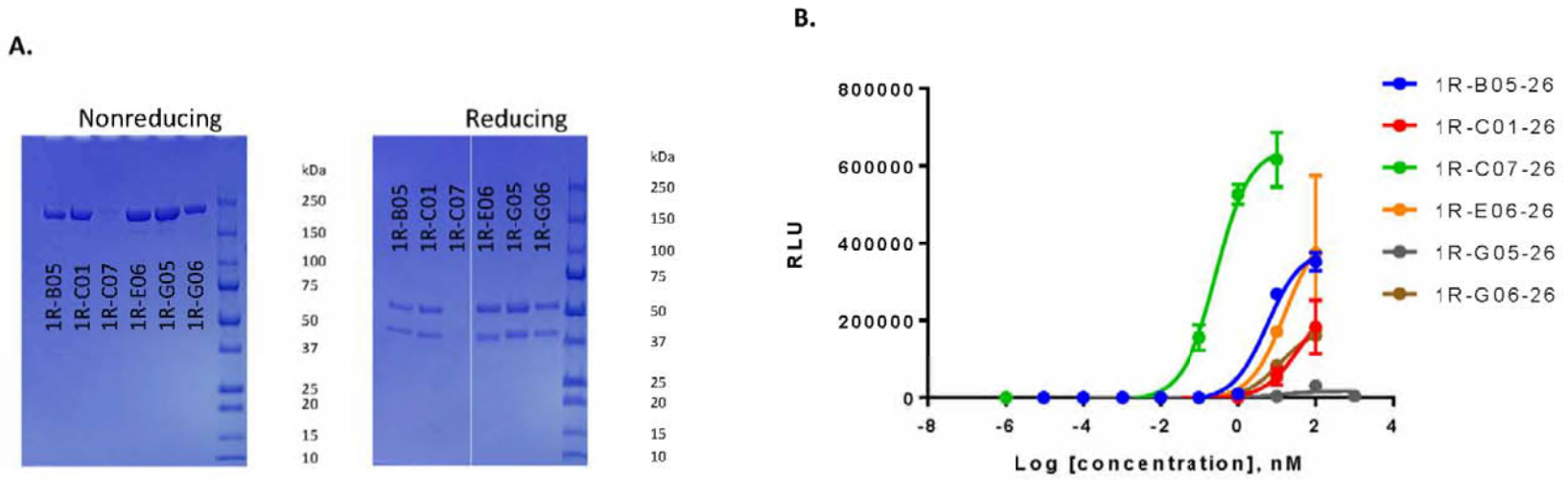

293 STF (with Rspo)
18R5-5
18R5-7
18R5-8
18R5-9
RLU
1400000
1200000
1000000
800000
600000
400000
200000
0
-6
-5
-4
-3
-2
-1
0
1
2
Log [concentration], nM

Figure 7.

Figure 8.


A.
Nonreducing
Reducing
1R-B05
1R-C01
1R-C07
1R-E06
1R-G05
1R-G06
kDa
250
150
100
75
50
37
25
20
15
10
B.
RLU
800000
600000
400000
200000
0
-8
-6
-4
-2
0
2
4
Log [concentration], nM
1R-B05-26
1R-C01-26
1R-C07-26
1R-E06-26
1R-G05-26
1R-G06-26

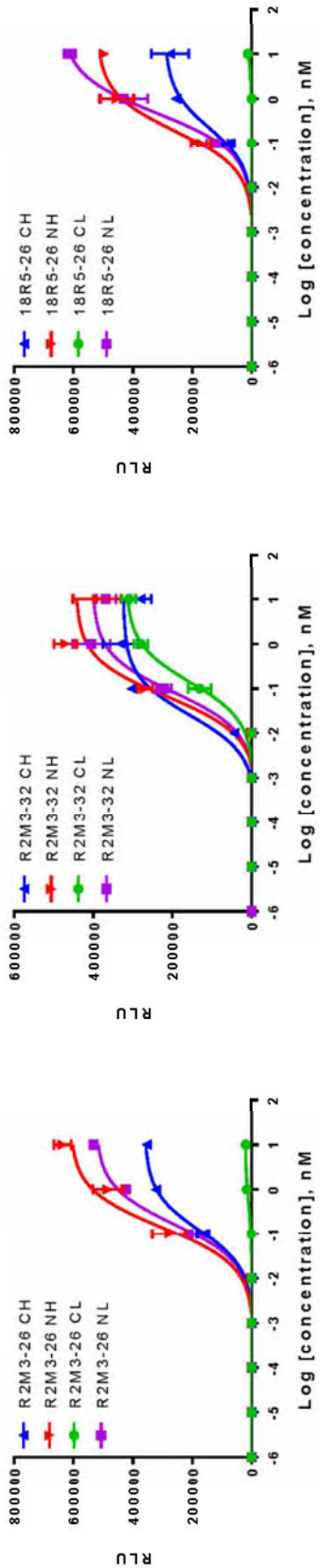

R2M3-26 CH
R2M3-26 NH
R2M3-26 CL
R2M3-26 NL
RLU
800000
600000
400000
200000
0
-6
-5
-4
-3
-2
-1
0
1
2
Log [concentration], nM
R2M3-32 CH
R2M3-32 NH
R2M3-32 CL
R2M3-32 NL
RLU
600000
400000
200000
0
-6
-5
-4
-3
-2
-1
0
1
2
Log [concentration], nM
18R5-26 CH
18R5-26 NH
18R5-26 CL
18R5-26 NL
RLU
800000
600000
400000
200000
0
-6
-5
-4
-3
-2
-1
0
1
2
Log [concentration], nM

Figure 9.

Figure 10.

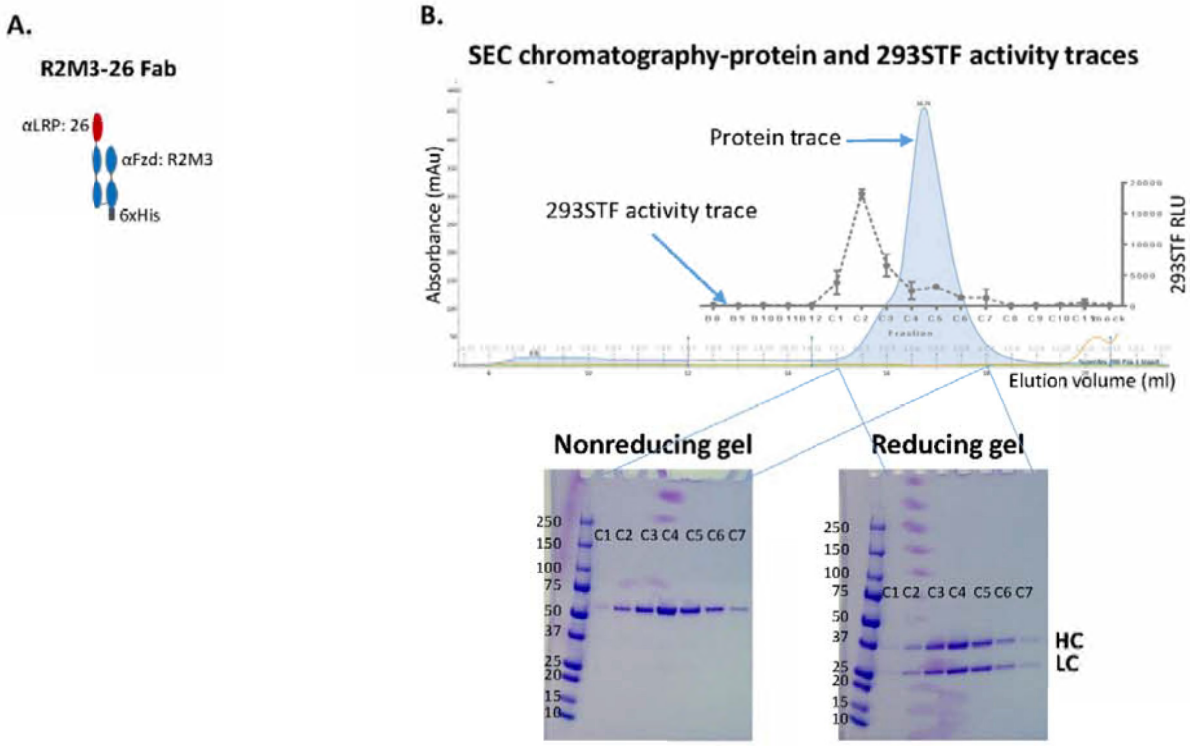

A.
R2M3-26 Fab
αLRP: 26
αFzd: R2M3
6xHis
B.
SEC chromatography-protein and 293STF activity traces
Protein trace
293STF activity trace
Absorbance (mAu)
293STF RLU
Elution volume (ml)
Nonreducing gel
Reducing gel
250
150
100
75
50
37
25
20
15
10
C1 C2 C3 C4 C5 C6 C7
HC
LC

Figure 11.

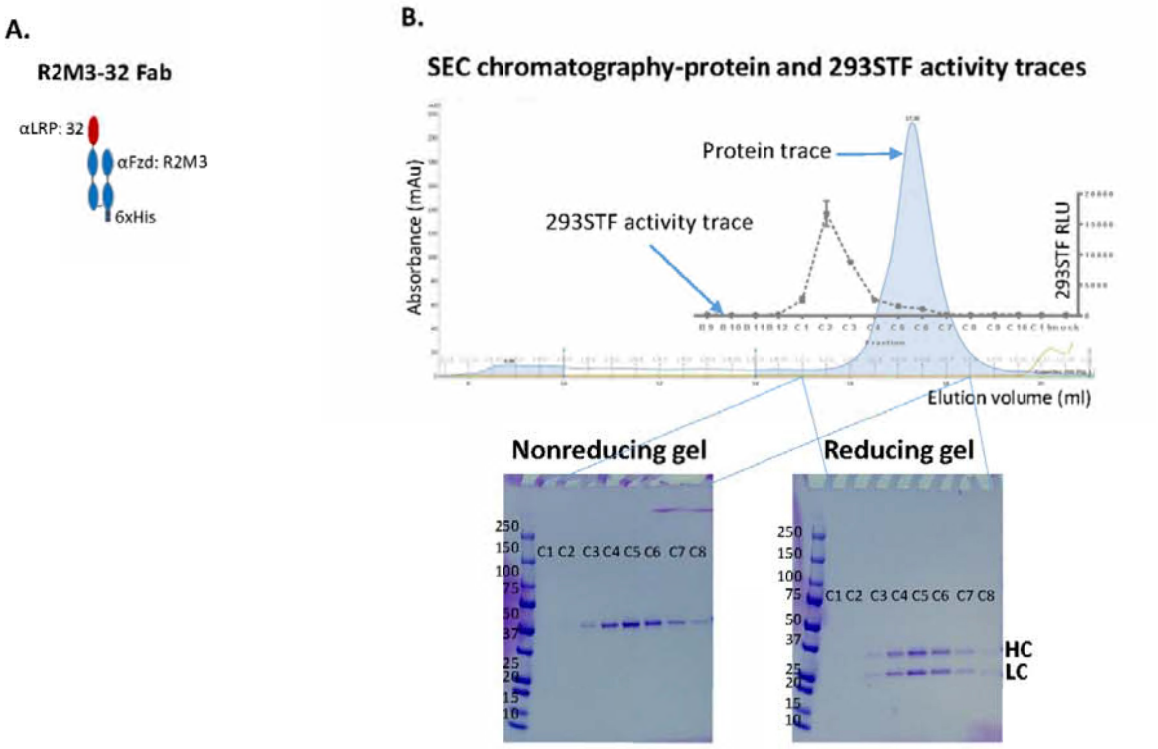
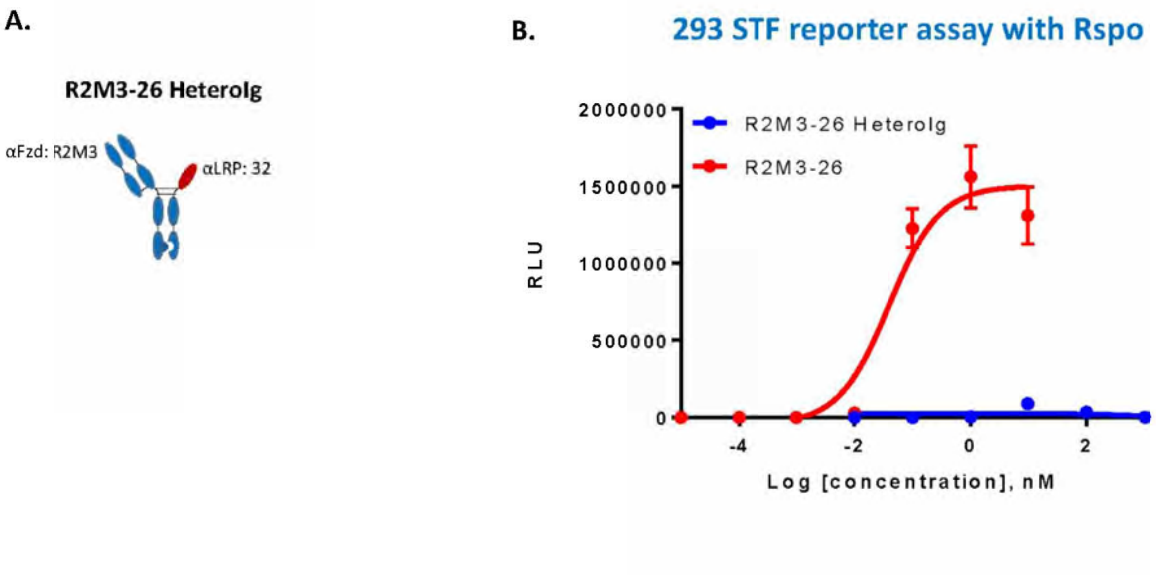
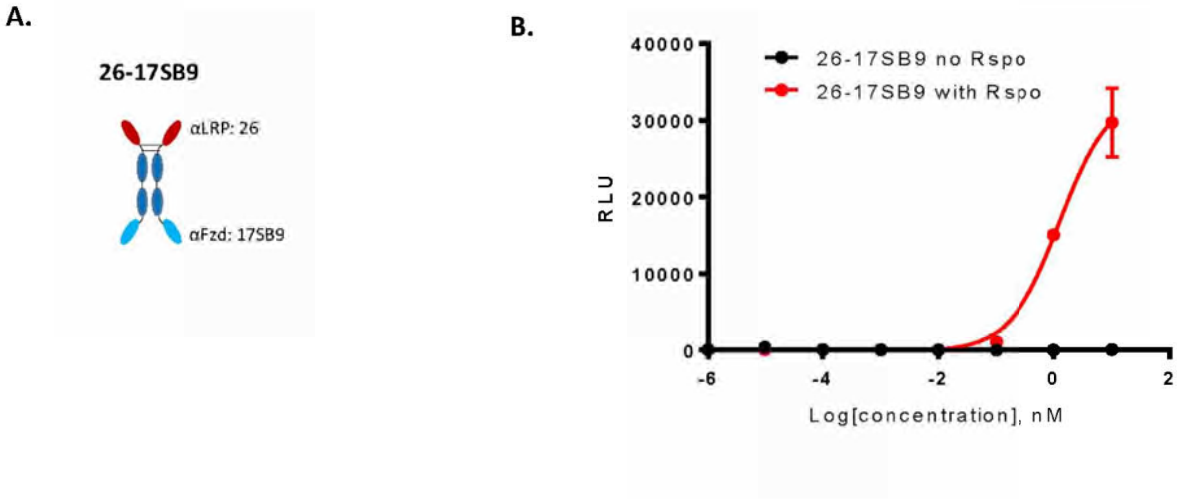

A.
R2M3-32 Fab
αLRP: 32
αFzd: R2M3
6xHis
B.
SEC chromatography-protein and 293STF activity traces
Protein trace
293STF activity trace
Absorbance (mAu)
293STF RLU
Elution volume (ml)
Nonreducing gel
Reducing gel
250
150
100
75
50
37
25
20
15
10
C1 C2 C3 C4 C5 C6 C7 C8
HC
LC

Figure 12.



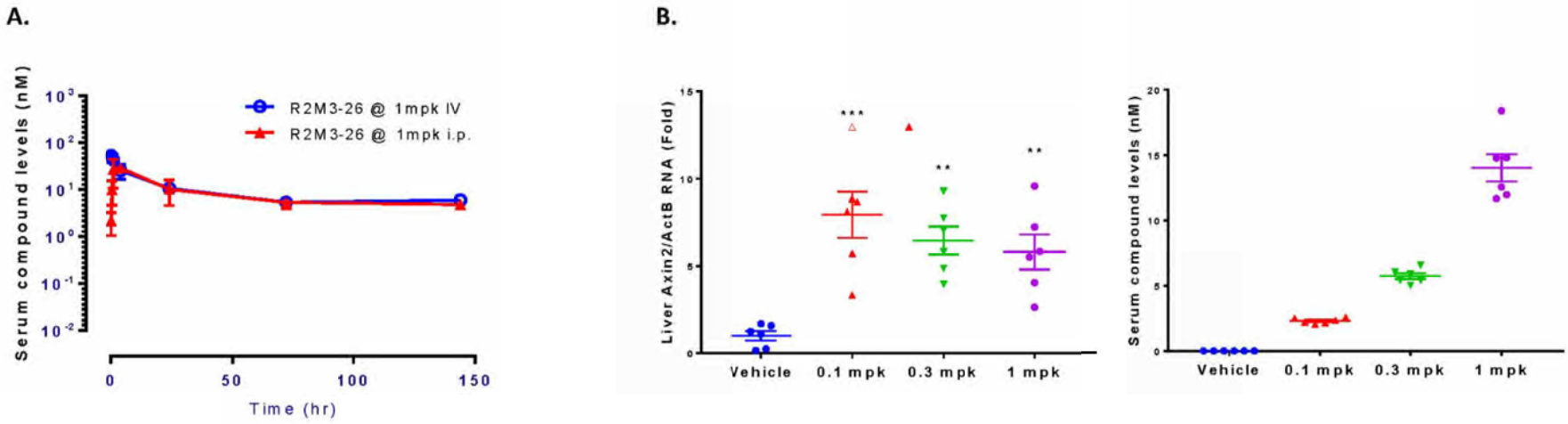
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Figure 13.



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Figure 14.



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FIG. 15

Leader = italics
Linker = underlined
Nab = bold

*MYRMQLLSCIALSLALVTNS***DVQLVESGGGLVQPGGSLRLSCAASGSIFMINTMAWYRQAPGNQRELV**
ATIRPVVSETTYADAVKGRFTISRDNAKNTVYLQMNSLKSEDTAIYYCNAKRPWGTRDEYWGQGTLVT
VSSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDVP
ERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS* (SEQ ID NO:89)

*MYRMQLLSCIALSLALVTNS***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRELVA**
MIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGTQVTV
SSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDVPE
RFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE
GSTVEKTVAPTECS* (SEQID NO:90)

*MYRMQLLSCIALSLALVTNS***EVQLVESGGGLVQAGGSLRVSCAASGGTFSRYHMGWFRQAPGKEREF**
VSAITWSGGRTYYADFVKGRFTISRDDARNTVYLQMSSLKPEDTAVYYCALTWAPTPTNRRSDYAYWG
QGTQVTVSSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNT
RSSDVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPS
SEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS
YSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:91)

*MYRMQLLSCIALSLALVTNS***EVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDMAWYRQAPGNQRELV**
ATIRPVVSETTYADAVKGRFTISRSNAMKTVYLQMNSLKSEDTAIYYCNAKRPWGTRDEYWGQGTLVT
VSSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDVP
ERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS* (SEQ ID NO:92)

*MYRMQLLSCIALSLALVTNS***AVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRQAPGNQRELVA**
TIRPVVSETTYADAVKGRFTISRSNAMKTVYLQMNSLKSEDTAIYYCNAKRPWGTRDEYWGQGTLVTV
SSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDVPE
RFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANK
ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE
GSTVEKTVAPTECS* (SEQ ID NO:93)

*MYRMQLLSCIALSLALVTNS***AVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKEREF**
VASIRWSSGNTWYADSMKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCYANIYYTRRAPEEYWGQGT
LVTVSSGSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSS
DVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS* (SEQ ID NO:94)

*MYRMQLLSCIALSLALVTNS*EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWM
GWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWGQGT
TVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN

NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:95)

*MYRMQLLSCIALSLALVTNS***EVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIAN MRGGGYMKYAGSLKGRFTMSTESAKNTLYLQMNSLKPEDTAVYYCYARTQRMGVVNSYWGQGTLVT VSS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFS GSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS* (SEQ ID NO:96)

*MYRMQLLSCIALSLALVTNS***QVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIA NMRGGGYMKYAGSLKGRFTMSTESAKNTLYLQMNSLKPEDTAVYFCNAVTYDGYTIRGQGTLVTVSS** GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS* (SEQ ID NO:97)

*MYRMQLLSCIALSLALVTNS***EVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIAN MRGGGYMKYADSVQGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAQFRNDYGLRYQSTNNYWGQ GTLVTVSS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGI PERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV THEGSTVEKTVAPTECS* (SEQ ID NO:98)

*MYRMQLLSCIALSLALVTNS***QVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRELIA NMRGGGYMKYAGSLKGRFTMSTESAKNTVYLQMNSLKPEDSAVYYCNANYRGNRYWGQGTLVTVSS** GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSGSN SGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS* (SEQ ID NO:99)

*MYRMQLLSCIALSLALVTNS***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRELVA MIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGTQVTV SS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSG SNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS* (SEQ ID NO:100)

*MYRMQLLSCIALSLALVTNS***EVQLVESGGGLVQAGGSLRVSCAASGGTFSRYHMGWFRQAPGKEREF VSAITWSGGRTYYADFVKGRFTISRDDARNTVYLQMSSLKPEDTAVYYCALTWAPTPTNRRSDYAYWG QGTQVTVSS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPS GIPERFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ VTHEGSTVEKTVAPTECS* (SEQ ID NO:101)

*MYRMQLLSCIALSLALVTNS***AVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRQAPGNQRELVA TIRPVVSETTYADAVKGRFTISRSNAMKTVYLQMNSLKSEDTAIYYCNAKRPWGTRDEYWGQGTLVTV SS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPERFSG SNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS* (SEQ ID NO:102)

*MYRMQLLSCIALSLALVTNS***AVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKEREF VASIRWSSGNTWYADSMKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCYANIYYTRRAPEEYWGQGT LVTVSS**GSGGSDIELTQPPSVSVAPGQTARISCSGDNIGSFYVHWYQQKPGQAPVLVIYDKSNRPSGIPE RFSGSNSGNTATLTISGTQAEDEADYYCQSYANTLSLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN

KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH
EGSTVEKTVAPTECS* (SEQ ID NO:103)

*MYRMQLLSCIALSLALVTNS*EVQLVESGGGLVQPGGSLRLSCAASGFTFSHYTLSWVRQAPGKGLEWVS
VISGDGSYTYYADSVKGRFTISSDNSKNTLYLQMNSLRAEDTAVYYCARNFIKYVFANWGQGTLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK
ALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:104)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGDVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSN
RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGTHWPYTFGQGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:105)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGDIVMTHTPLSLSVTPGEPASISCRSSRSLLDTDDGNTYLDWYLQKPGQSPQLLIHTLSH
RASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSIQLPWTFGQGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO:106)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQRPSGIP
VRFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQ
ANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQV
THEGSTVEKTVAPTECS* (SEQ ID NO:107)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGQSVVTQPPSVSGAPGQRVTISCTRSSSNIGAGYDVHWYQQHPGTAPKLLIFGNSIRPS
GVPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLSAWVFGGGTKLTVLGQPKAAPSVTLFPPSS
EELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY
SCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:108)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGEIVLTQSPATLSLSPGEGATLSCRASQSVGTYLTWYRQKPGQAPRLLIYDASNRATGIP
ARFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC* (SEQ ID NO:109)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE**
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSSGSGSGDIQLTQSPSSLSASVGDRVTITCRASRSISSYFNWYQQKPGKAPKLLIYAASSLQSGVP
SRFSGSRSGTDFTLTISSLQPEDFATYYCQQADTFPPTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC* (SEQ ID NO:110)

*MDMRVPAQLLGLLLLWLRGARC*QVQLQESGPGLVKPSETLSLTCTVSGGSISGNNYYWGWIRQPPGKG
LEWIGSIYFTGGTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVMLITDAFDIWGQGTMVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS

VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:111)

*MDMRVPAQLLGLLLLWLRGARC*QLQLQESGSGLVKPSQTLSLTCAVSGGSISSGGYSWSWIRQPPGKG
LEWIGSIYHSGSTYYNPSLKSRLTISVDTSKNQFSLKLSSVTAADTAVYYCARFYYDILTGYSYFDYWGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID
NO:112)

MDMRVPAQLLGLLLLWLRGARCQVQLQQWGAGLLKPSETLSLTCAVSGASFSGHYWTWIRQPPGKGLE
WIGEIDHTGSTNYEPSLRSRVTISVDTSKNQFSLNLKSVTAADTAVYYCARGGQGGYDWGHYHGLDVW
GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSGSGH
HHHHH* (SEQ ID NO:113)

*MDMRVPAQLLGLLLLWLRGARC*QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQHPGKG
LEWIGYIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARATYGGDAFDIWGQGTMV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:114)

*MDMRVPAQLLGLLLLWLRGARC*QVQLQESGPGLVKPSETLSLTCTVSGGAISGTSYFWGWIRQPPGKG
LEWIGSIYYTGNTYYNPSLKSRLTVSVDTSKNQFSLNLNSVTAADTATYYCARIGIAVAAPVDHWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:115)

*MDMRVPAQLLGLLLLWLRGARC*QLQLQESGPGLVKPSQTLSLTCTVSGGSISSGGYYWSWIRQHPGKG
LEWIGYIYYSGSTYYNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARVRDYYDSSGYYYDYFDY
WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP
KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ
ID NO:116)

MDMRVPAQLLGLLLLWLRGARCEVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLE
WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWG
QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGSGSG**D**

**VQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRELVAMIRPVVTEIDYADSVKGRFTIS
RNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGTQVTVSS*** (SEQ ID NO:117)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSS**GSGSGEVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNG
NTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWGQGTTVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEV
TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:118)

*MDMRVPAQLLGLLLLWLRGARC*QAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAP
RTLIYYTNTRSSDVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAP
SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE
QWKSHRSYSCQVTHEGSTVEKTVAPTECS**GSGSG*****DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDI
AWYRHPPGNQRELVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPW
GSRDEYWGQGTQVTVSS*** (SEQ ID NO:119)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSS**GSGSGQAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSS
DVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS* (SEQ ID NO:120)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSS**GSGSGQAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSS
DVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS* (SEQ ID NO:121)

*MDMRVPAQLLGLLLLWLRGARC*EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLE
WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWG
QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHHHHH* (SEQ ID NO:122)

*MYRMQLLSCIALSLALVTNS***AVQLVDSGGGLVQAGGSLRLSCAVSGRTFSMYDMGWFRQAPGKEREF
VASIRWSSGNTWYADSMKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCYANIYYTRRAPEEYWGQGT
LVTVSS**GSGGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSS
DVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL
QANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS* (SEQ ID NO:123)
*MDMRVPAQLLGLLLLWLRGARC*EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLE
WMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDVWG
QGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGSGSGHHHHHH* (SEQ ID NO:124)

*MDMRVPAQLLGLLLLWLRGARC*QAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAP
RTLIYYTNTRSSDVPERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAP
SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPE
QWKSHRSYSCQVTHEGSTVEKTVAPTECS* (SEQ ID NO:125)

*MDMRVPAQLLGLLLLWLRGARC***EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGL EWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCASSKEKATYYYGMDV WGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:126)

*MDMRVPAQLLGLLLLWLRGARCDVQLV*ESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQREL VAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGTQV TVSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGKGSGSGHHHHHH* (SEQ ID NO:127)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT QVTVSS**DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGKGGSGS**AVQQVESGGGLVQPGGSLRLSCAASGFTLDYYAISWF RQAPGKKRELVADITSGGSTNYADSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYFCNAVTYNGYTIW GQGTQVTVSS*** (SEQ ID NO:128)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV TVSS**GSGSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQRPSGIPVR FSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTH EGSTVEKTVAPTECS* (SEQ ID NO:134)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GS GSGSYVLTQPPSVSVSPGQTASITCSGDKVGHKYASWYQQKPGQSPVLVIYEDSQRPSGIPVRFSGSNS GNTATLTISGTQAMDEADYYCQAWDSSTDVVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVE KTVAPTECS* SEQ ID NO:135)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV TVSS**GGSGSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC* (SEQ ID NO:136)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT QVTVSS**GSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC* (SEQ ID NO:137)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GS GSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS

GTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC* (SEQ ID NO:138)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE
LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV
TVSS**GSGSGQAVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDV
PERFSGSIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQA
NKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVT
HEGSTVEKTVAPTECS* (SEQ ID NO:139)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER
EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GS
GGSQTVVLQEPSLSVSPGGTVTLTCGLSSGSVSTNYYPSWYQQTPGQAPRTLIYYTNTRSSDVPERFSG
SIVGNKAALTITGAQPDDESVYFCLLYLGRGIWVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV
CLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTV
EKTVAPTECS* (SEQ ID NO:140)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE
LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV
TVSS**GGSGSDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLLGGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQTYSTPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
SSPVTKSFNRGEC* (SEQ ID NO:141)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSS**GSGGSDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLLGGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQTYSTPWTFGQGTKVEIK* (SEQ ID NO:142)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER
EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GG
SGSDIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYAASNLLGGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQTYSTPWTFGQGTKVEIK* (SEQ ID NO:143)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE
LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV
TVSS**GGSGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK* (SEQ ID NO:144)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE
LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT
QVTVSS**GGSGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK* (SEQ ID NO:145)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER
EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GG
SGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK(SEQ ID NO:146)
MDMRVPAQLLGLLLLWLRGARCDVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQREL
IANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQVTV
SSGGSGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK* (SEQ ID NO:147)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT QVTVSS**GGSGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK* (SEQ ID NO:148)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GG SGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK* (SEQ ID NO:149)

*MDMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGKQRE LIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQV TVSS**GSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC* (SEQ ID NO:150)

M*DMRVPAQLLGLLLLWLRGARC***DVQLVESGGGLVQAGGSLRLACAGSGRIFAIYDIAWYRHPPGNQRE LVAMIRPVVTEIDYADSVKGRFTISRNNAMKTVYLQMNNLKPEDTAVYYCNAKRPWGSRDEYWGQGT QVTVSS**GSGSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ GLSSPVTKSFNRGEC* (SEQ ID NO:151)

*MDMRVPAQLLGLLLLWLRGARC***QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKER EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS**GS GSGDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYRTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC* (SEQ ID NO:152)

*MDMRVPAQLLGLLLLWLRGARC*EVQLLQSGAEVKKPGSSVKVSCKASGGTFTYRYLHWVRQAPGQGLE WMGGIIPIFGTGNYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCASSMVRVPYYYGMDVWGQG TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:153)

*MDMRVPAQLLGLLLLWLRGARC*EVQLVESGGGLVKPGGSLRLSCAASGFNFGIYSMTWVRQAPGKGLE WISYISGDSGYTNYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARVGPGGWFDPWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:154)

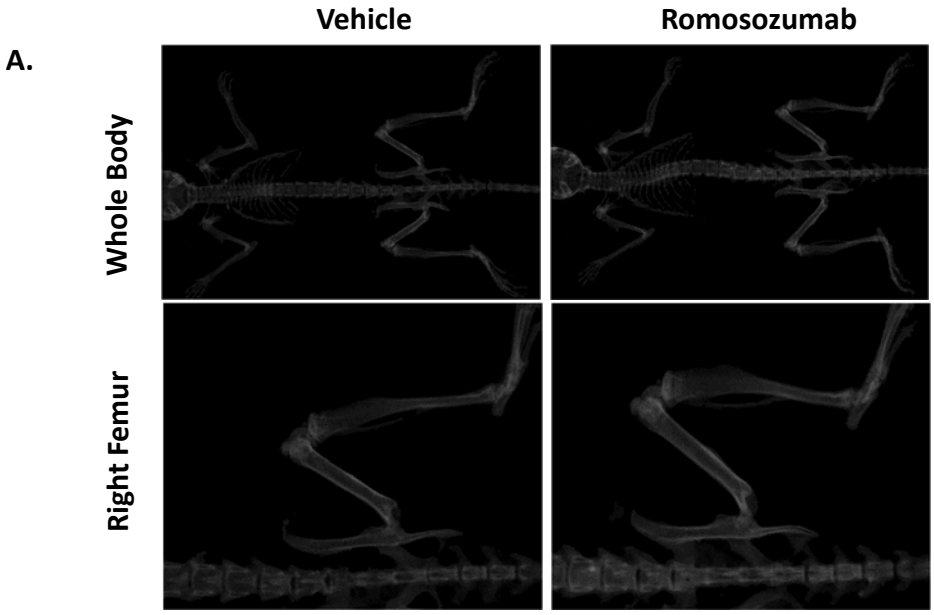
*MDMRVPAQLLGLLLLWLRGARC*EVQLVESGGGLVKPGGSLRLSCAASGFTFTNYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARATGFGTVVFDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN

YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:155)

*MDMRVPAQLLGLLLLWLRGARC*EVQLVQSGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGL EWVSYIENDGSITTYADSVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCARAPYYYGSGSLFRLDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK* (SEQ ID NO:156)

*MDMRVPAQLLGLLLLWLRGARC*QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNNFMHWVRQAPGQGL EWMGWINPNSGGTKYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSVGEVGATMLGIGVW YWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK * (SEQ ID NO:157)

FIG. 16


A.
Vehicle
Romosozumab
Whole Body
Right Femur

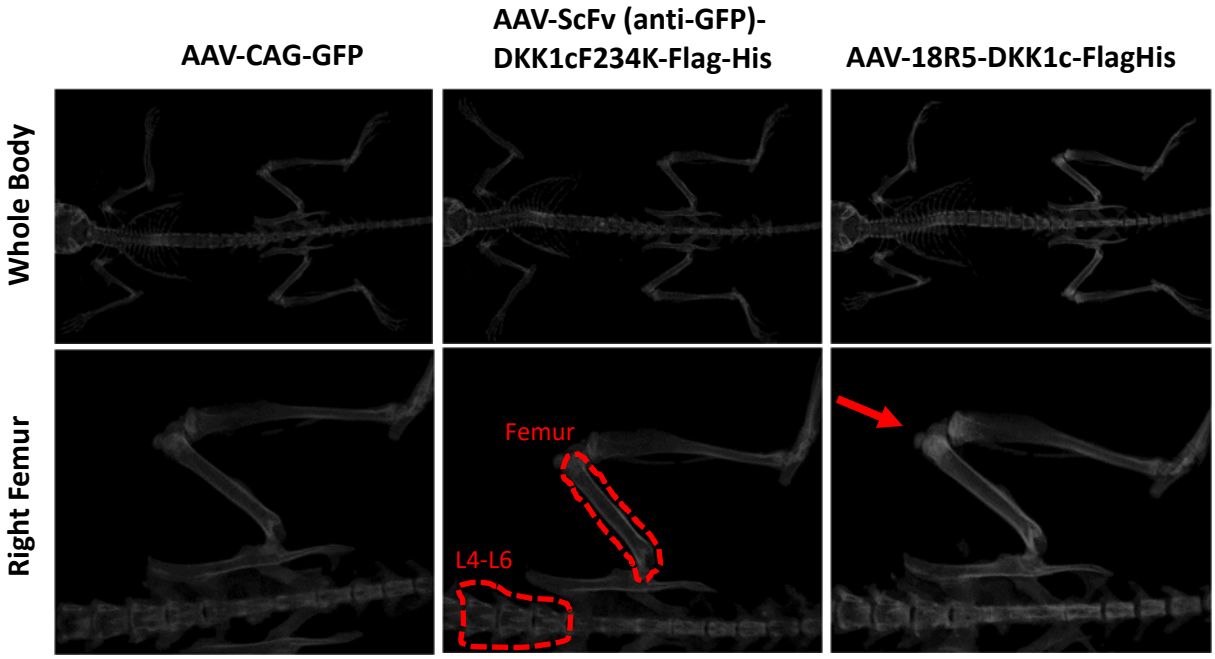
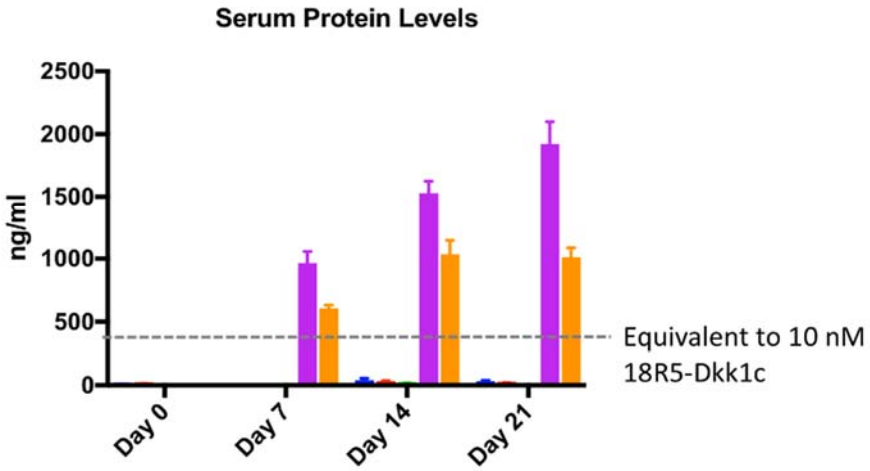
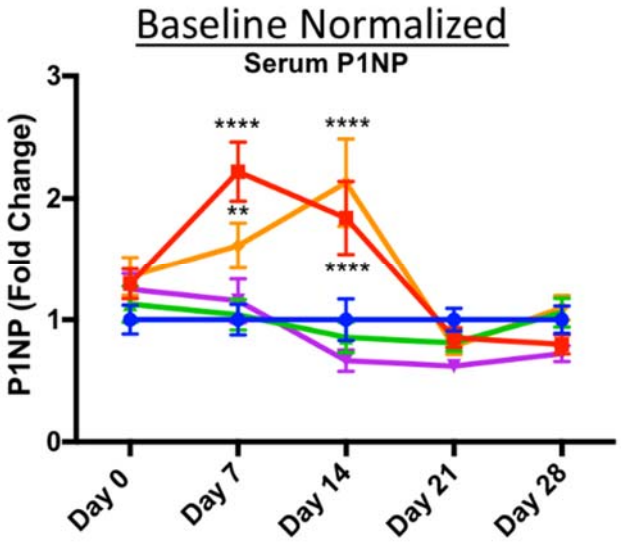

AAV-CAG-GFP
AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV-18R5-DKK1c-FlagHis
Whole Body
Right Femur
Femur
L4-L6

FIG. 16 (cont.)

B.



C.

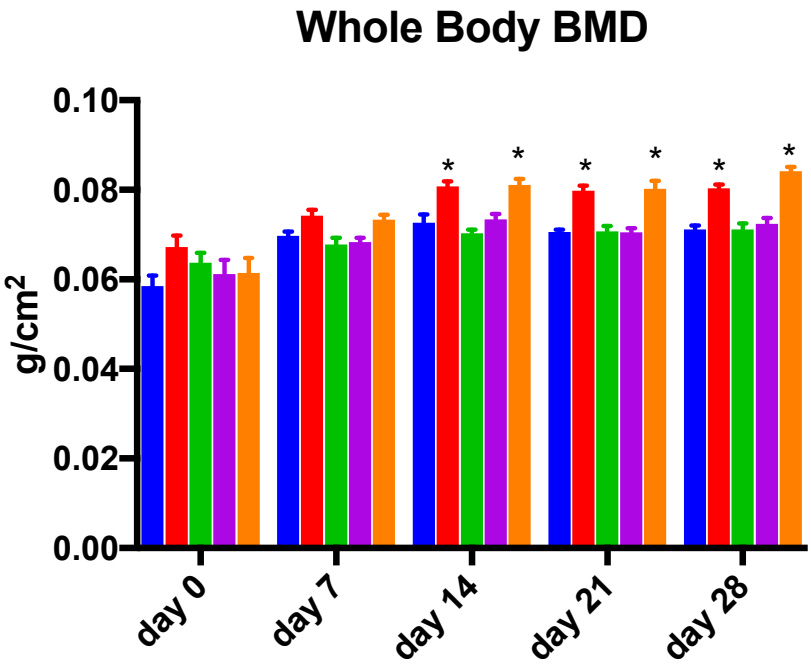


** P value <0.05

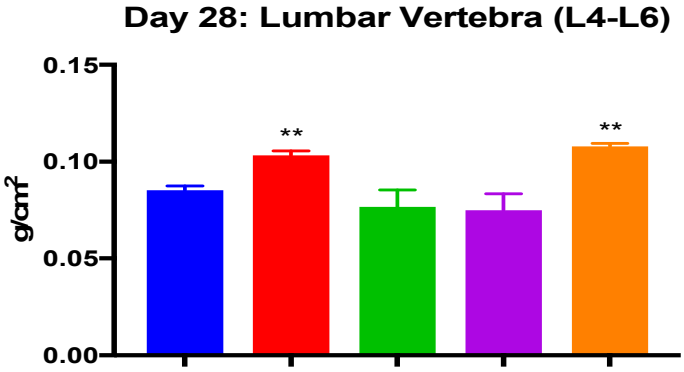
**** P value <0.0001

FIG. 16 (cont.)

D.



E.



Vehicle

Romosozumab

AAV ·CAG-GFP

AAV ·ScFv (anti-GFP)-DKK1cF234K-Flag-His

AAV ·18R5-DKK1c-FlagHis

** P value <0.05

**** P value <0.0001

FIG. 17

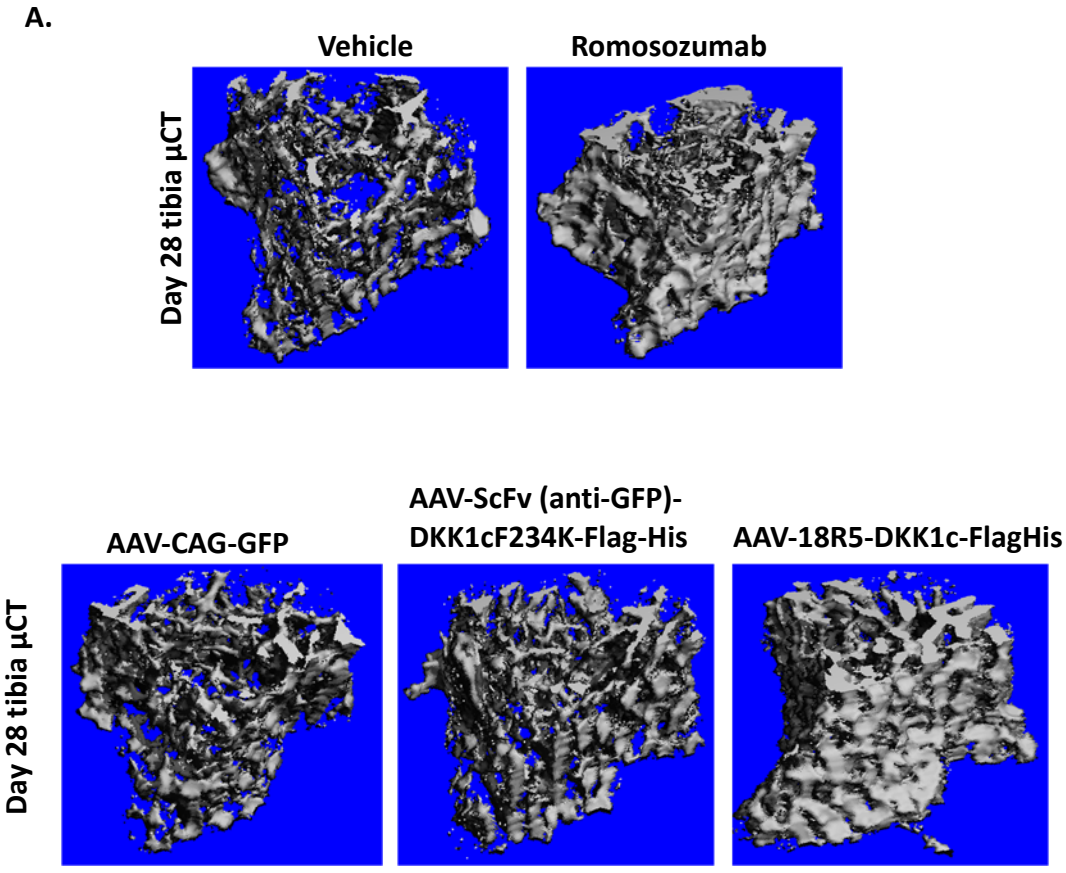
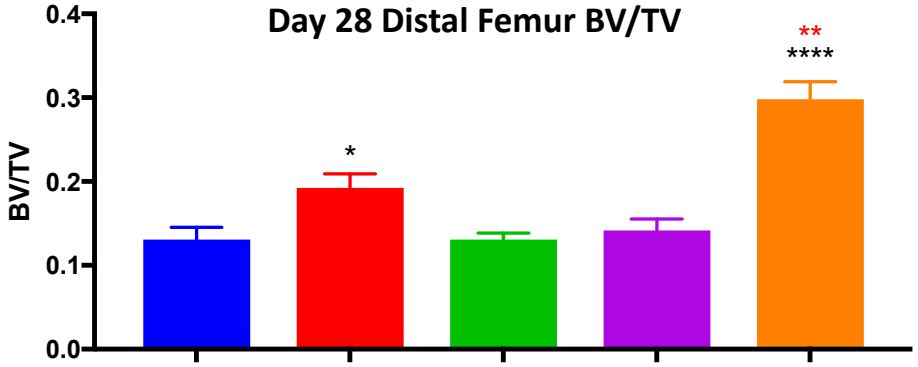
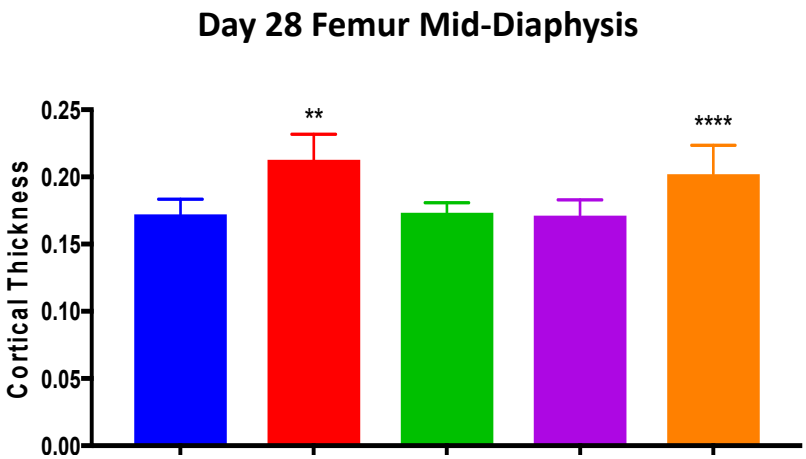

A.
Vehicle
Romosozumab
Day 28 tibia µCT
AAV-CAG-GFP
AAV-ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV-18R5-DKK1c-FlagHis
Day 28 tibia µCT

FIG. 17 (cont.)

B.





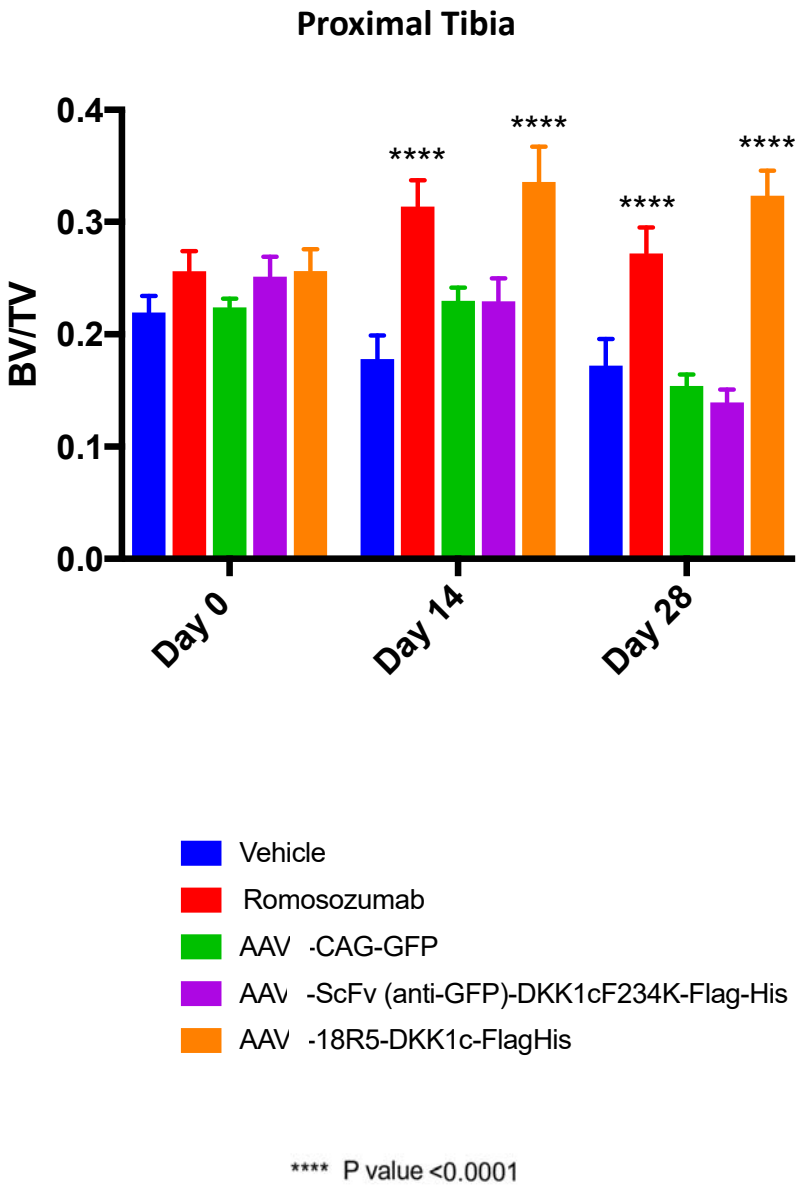
C.

Vehicle
Romosozumab
AAV -CAG-GFP
AAV -ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV -18R5-DKK1c-FlagHis

**** P value <0.0001

FIG. 17 (cont.)

D.



**** P value <0.0001

FIG. 18

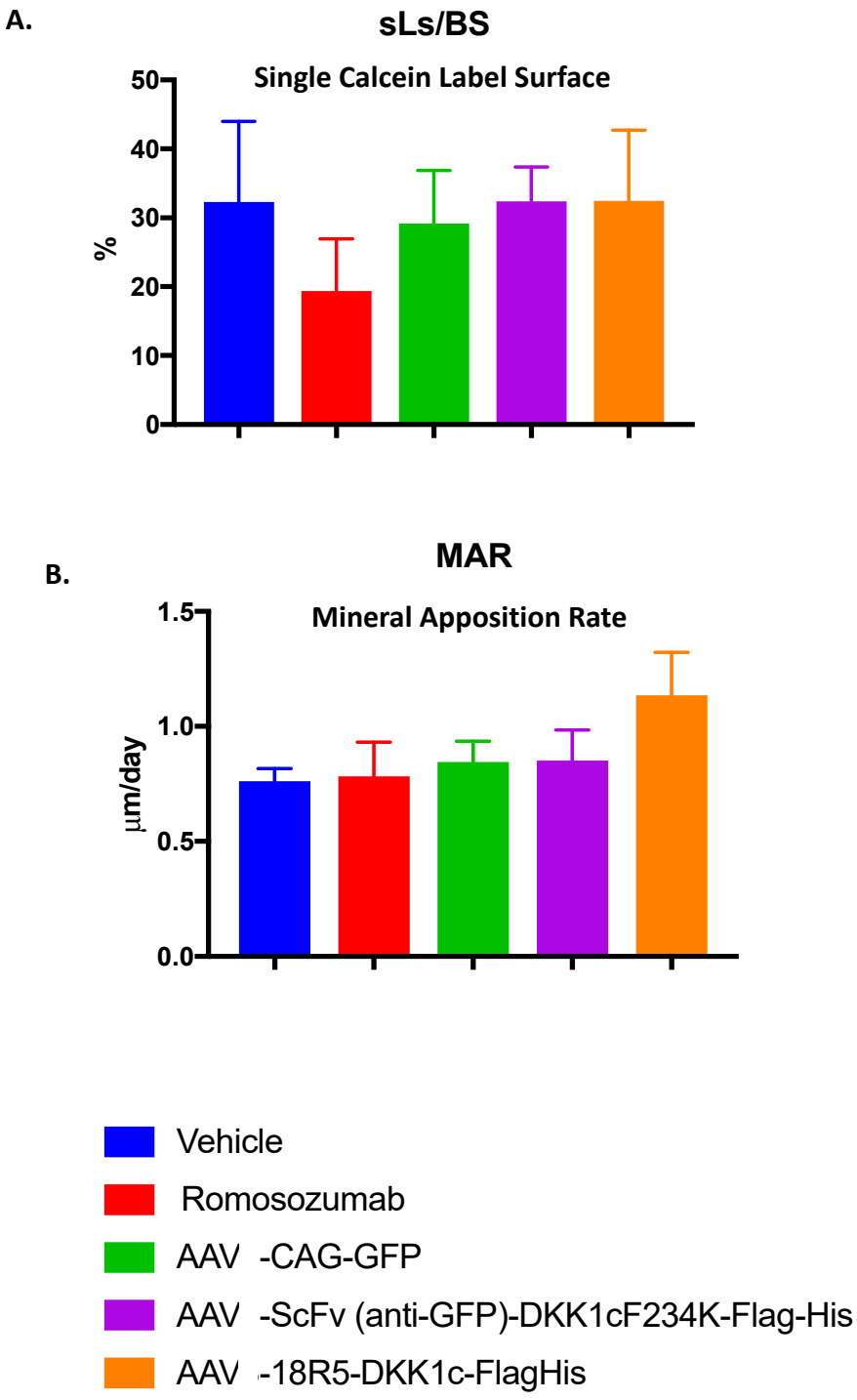
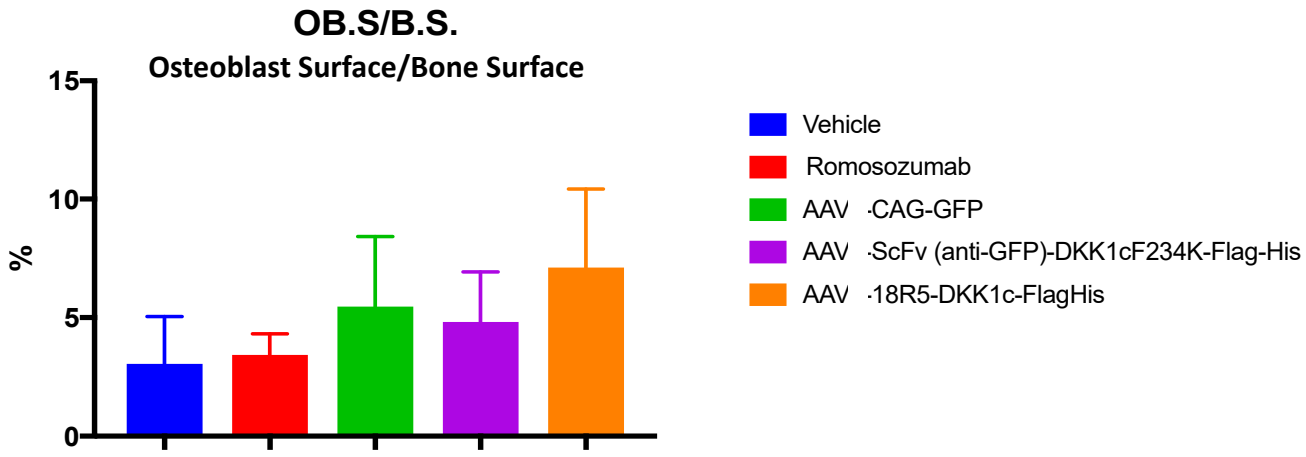
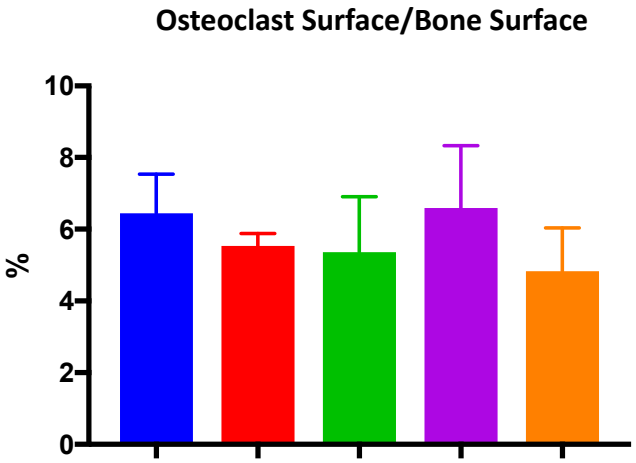

A.
sLs/BS
Single Calcein Label Surface
50
40
30
20
10
0
%
B.
MAR
Mineral Apposition Rate
1.5
1.0
0.5
0.0
µm/day
Vehicle
Romosozumab
AAV -CAG-GFP
AAV -ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV -18R5-DKK1c-FlagHis

FIG. 19

A.


OB.S/B.S.
Osteoblast Surface/Bone Surface
%
15
10
5
0
Vehicle
Romosozumab
AAV ·CAG-GFP
AAV ·ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV ·18R5-DKK1c-FlagHis

B.


Osteoclast Surface/Bone Surface
%
10
8
6
4
2
0

C.

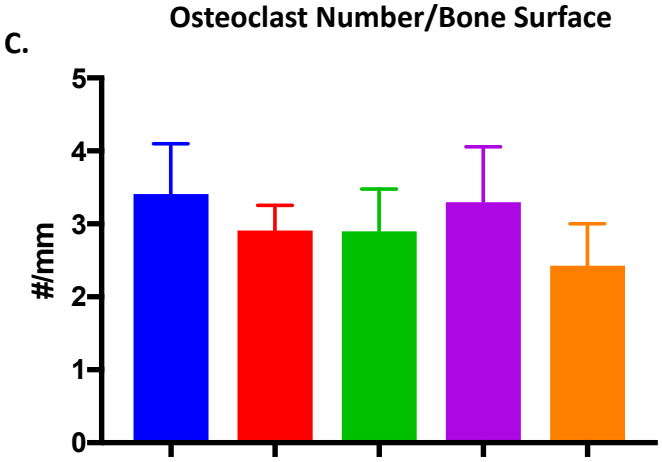

Osteoclast Number/Bone Surface
#/mm
5
4
3
2
1
0

FIG. 19 (cont.)

D.

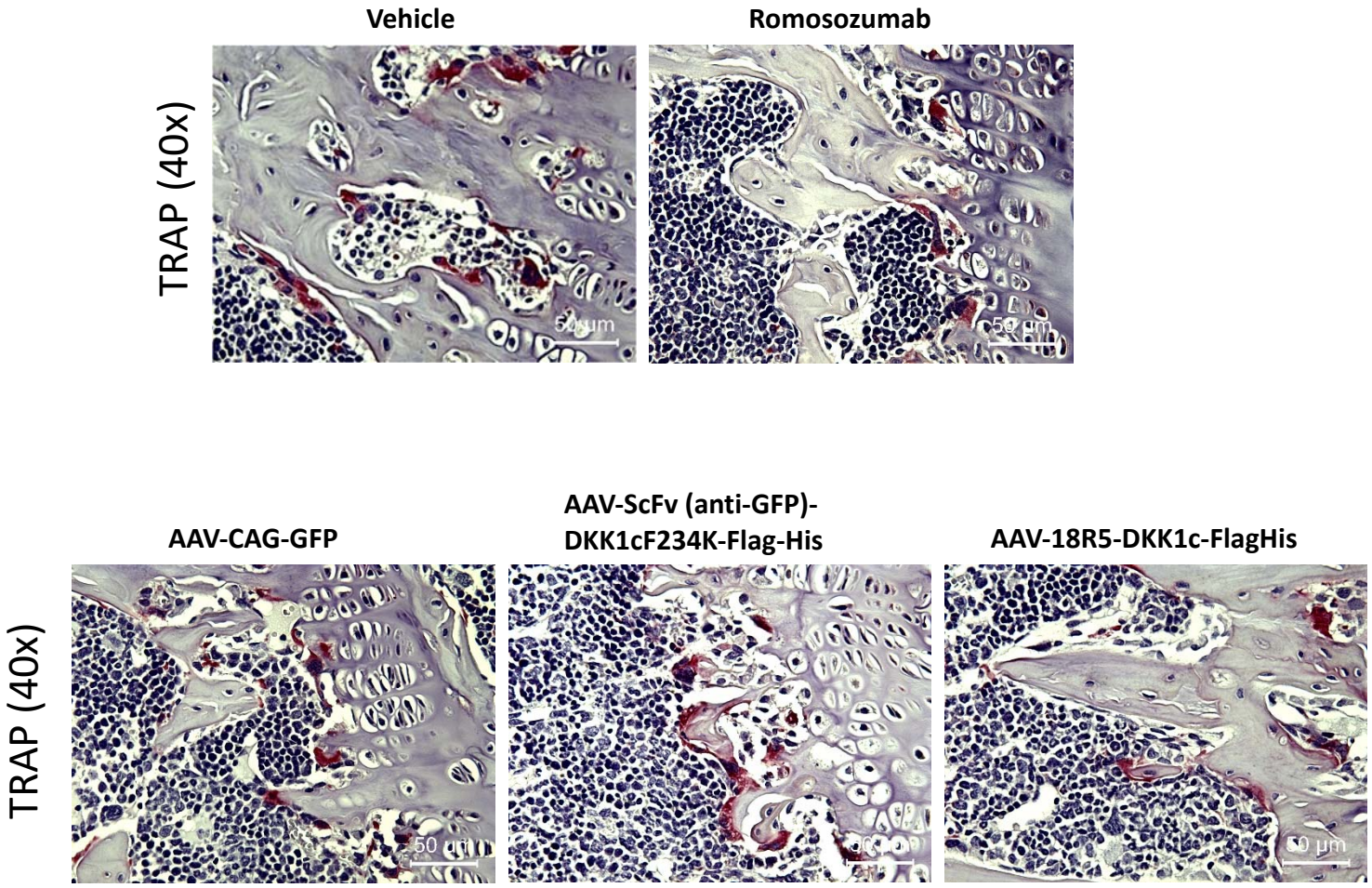
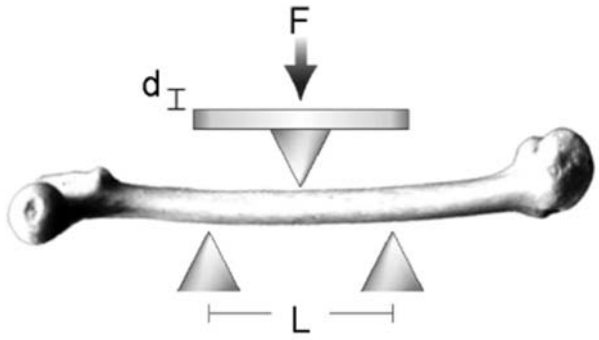
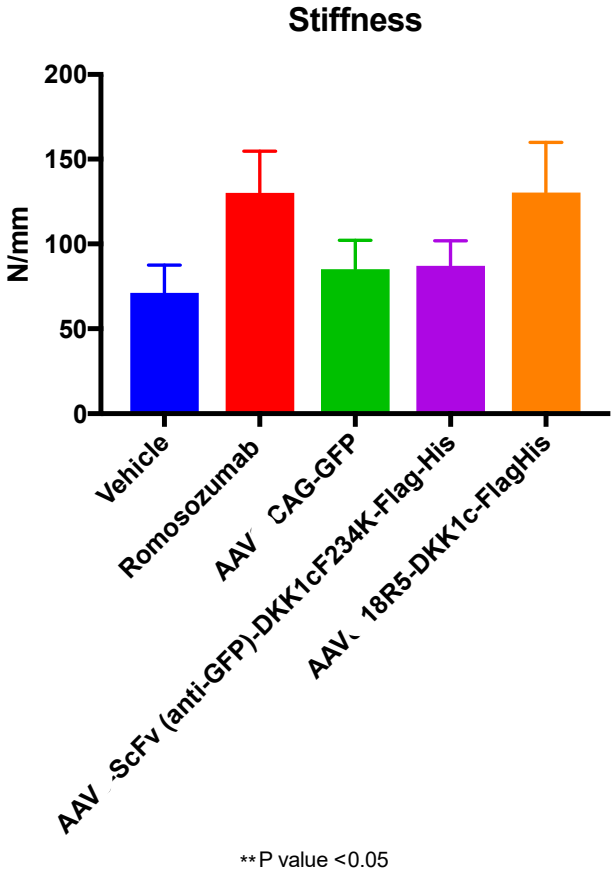

Vehicle
Romosozumab
TRAP (40x)
50 µm
50 µm
AAV-CAG-GFP
AAV-ScFv (anti-GFP)-
DKK1cF234K-Flag-His
AAV-18R5-DKK1c-FlagHis
TRAP (40x)
50 µm
50 µm

FIG. 20

A.



B.



**P value <0.05

FIG. 20 (cont.)

C.

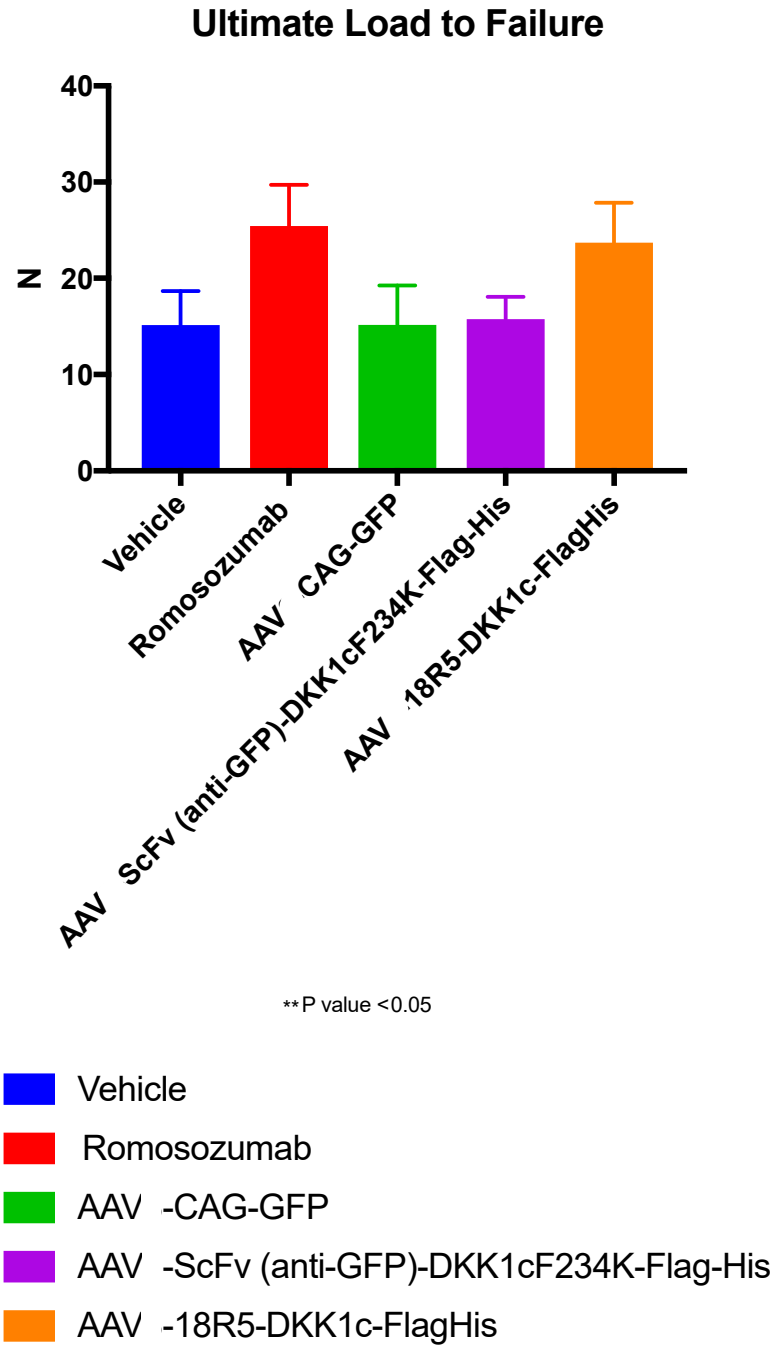

Ultimate Load to Failure
N
40
30
20
10
0
Vehicle
Romosozumab
AAV -CAG-GFP
AAV -ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV -18R5-DKK1c-FlagHis
**P value <0.05
Vehicle
Romosozumab
AAV -CAG-GFP
AAV -ScFv (anti-GFP)-DKK1cF234K-Flag-His
AAV -18R5-DKK1c-FlagHis

FIG. 21

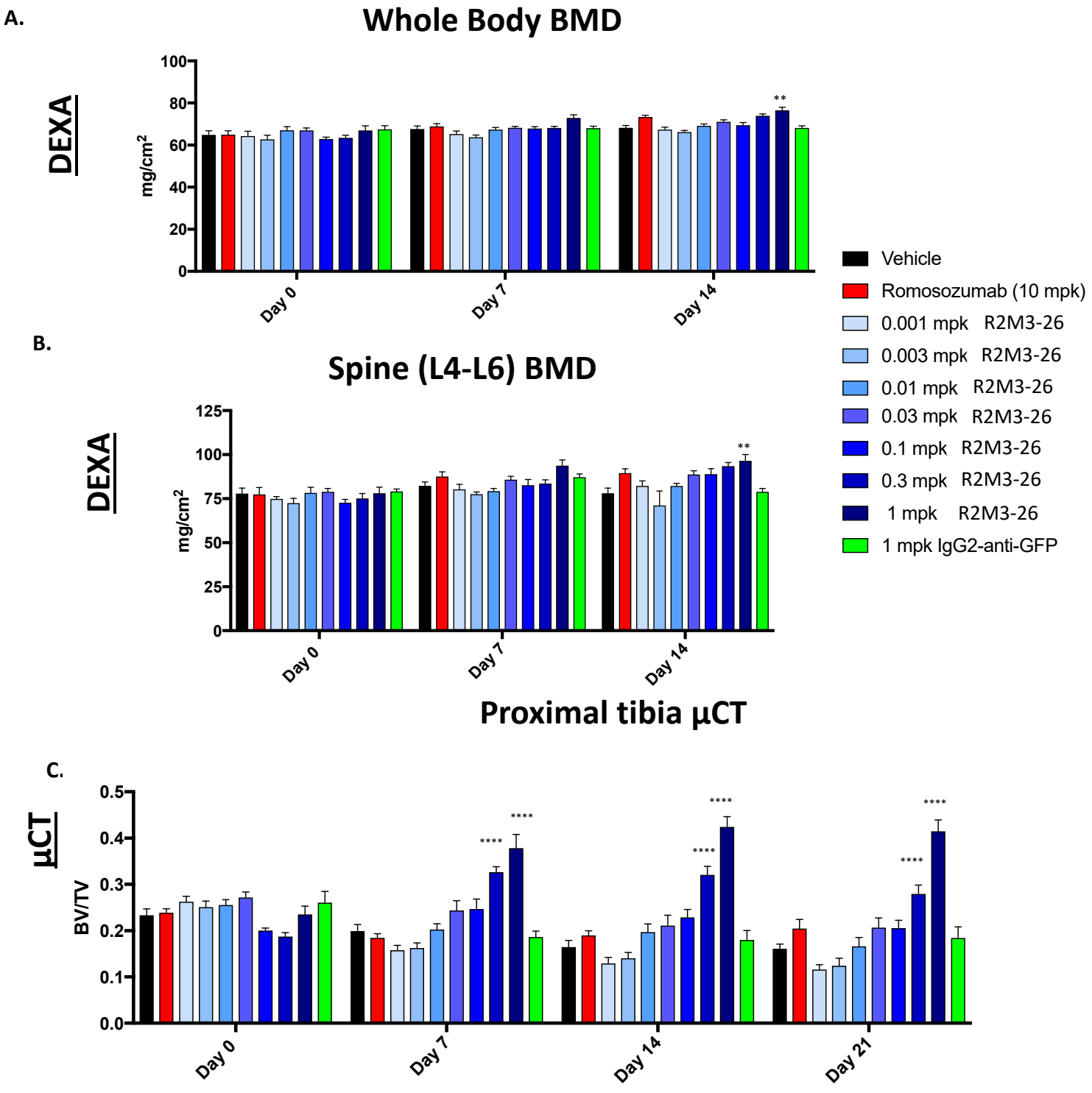

A.
Whole Body BMD
DEXA
mg/cm²
100
80
60
40
20
0
Day 0
Day 7
Day 14
**
B.
Spine (L4-L6) BMD
DEXA
mg/cm²
125
100
75
50
25
0
Day 0
Day 7
Day 14
**
Vehicle
Romosozumab (10 mpk)
0.001 mpk R2M3-26
0.003 mpk R2M3-26
0.01 mpk R2M3-26
0.03 mpk R2M3-26
0.1 mpk R2M3-26
0.3 mpk R2M3-26
1 mpk R2M3-26
1 mpk IgG2-anti-GFP
Proximal tibia µCT
C.
µCT
BV/TV
0.5
0.4
0.3
0.2
0.1
0.0
Day 0
Day 7
Day 14
Day 21
****

FIG. 21 (cont.)

D.

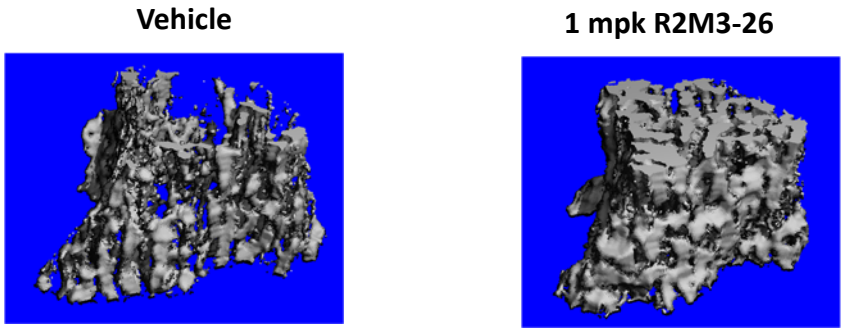


FIG. 22

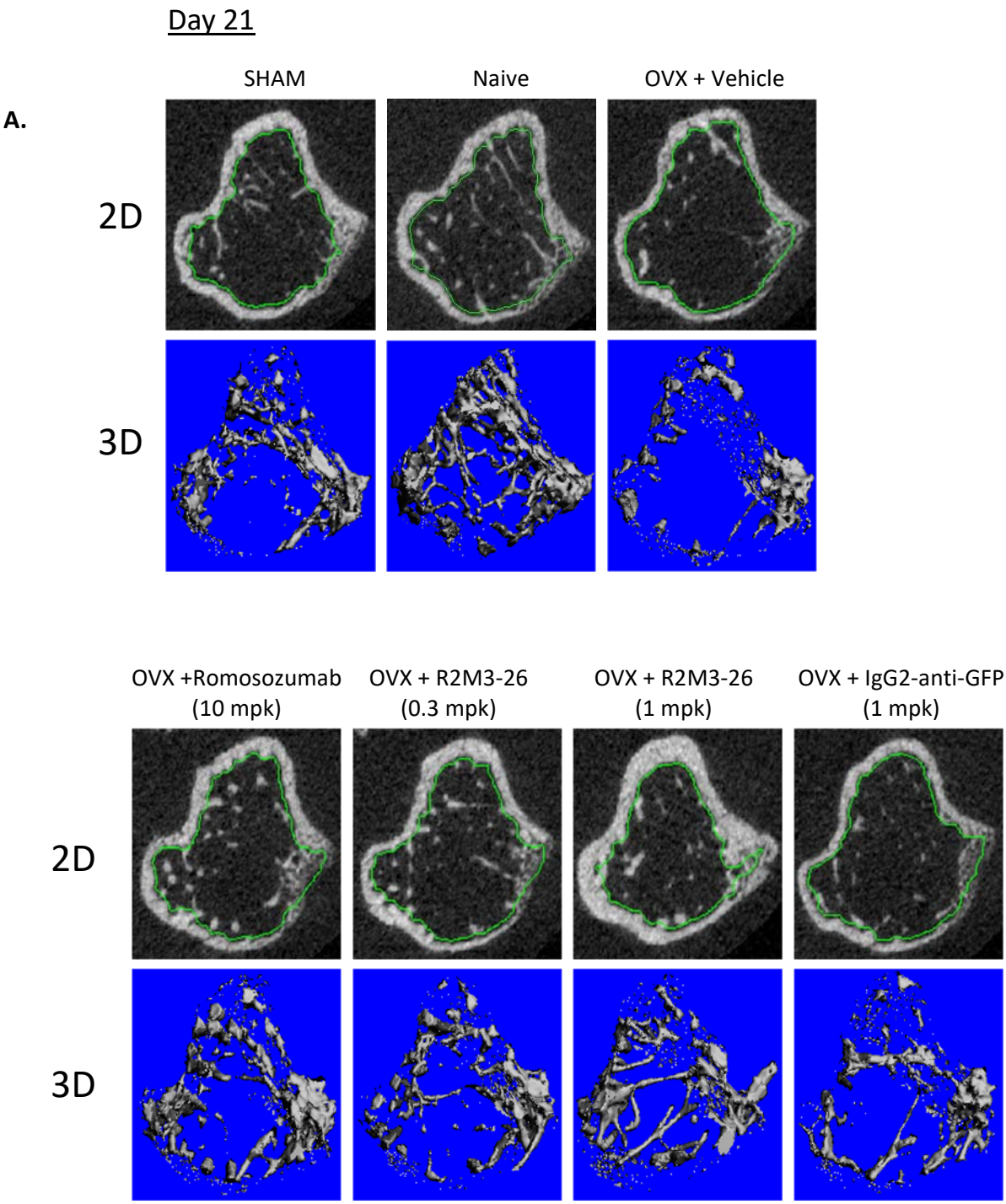
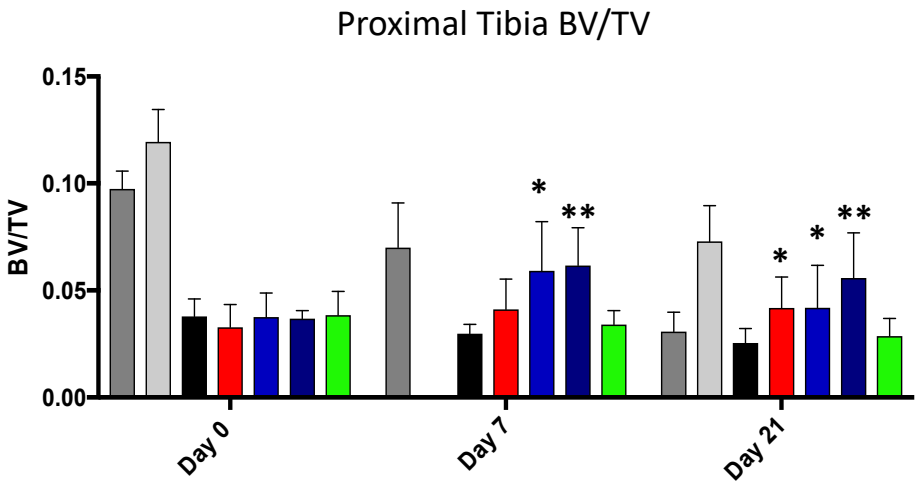
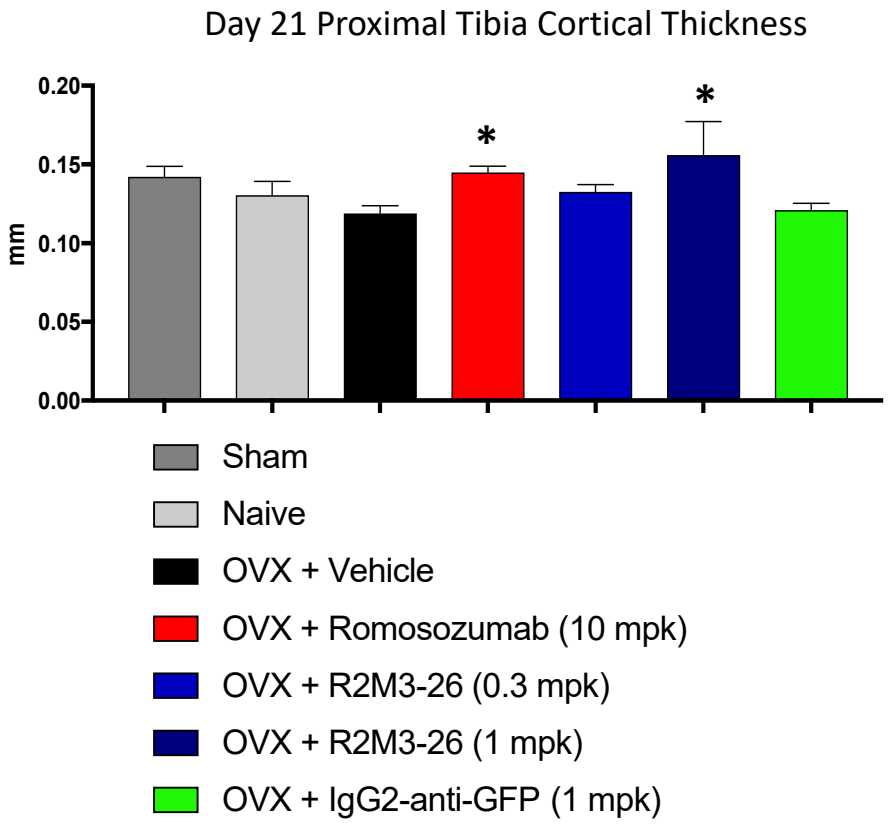

Day 21
A.
SHAM
Naive
OVX + Vehicle
2D
3D
OVX +Romosozumab (10 mpk)
OVX + R2M3-26 (0.3 mpk)
OVX + R2M3-26 (1 mpk)
OVX + IgG2-anti-GFP (1 mpk)
2D
3D

FIG. 22 (cont.)

B.



C.



*P value <0.05

** P value <0.0001 Compared to OVX + Veh

FIG. 23

A.

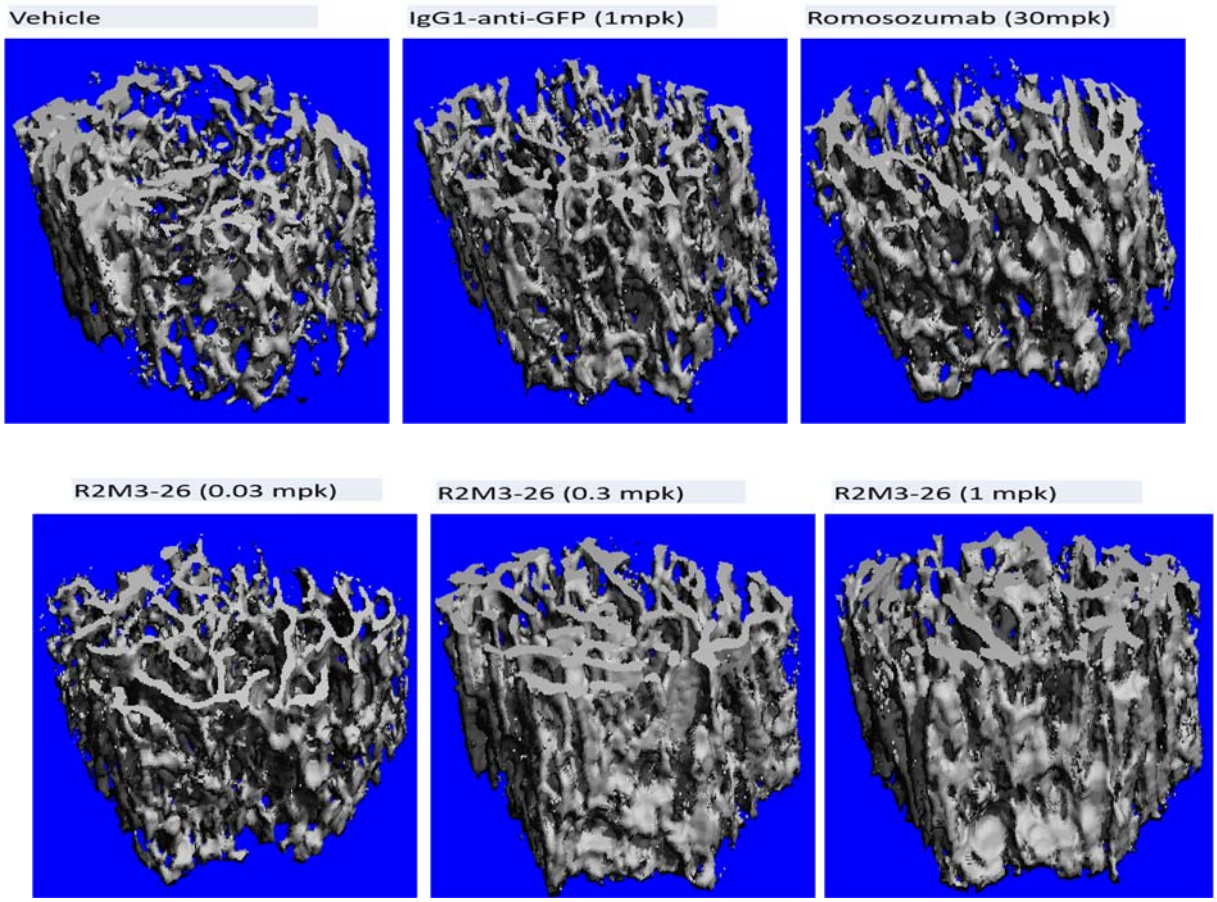
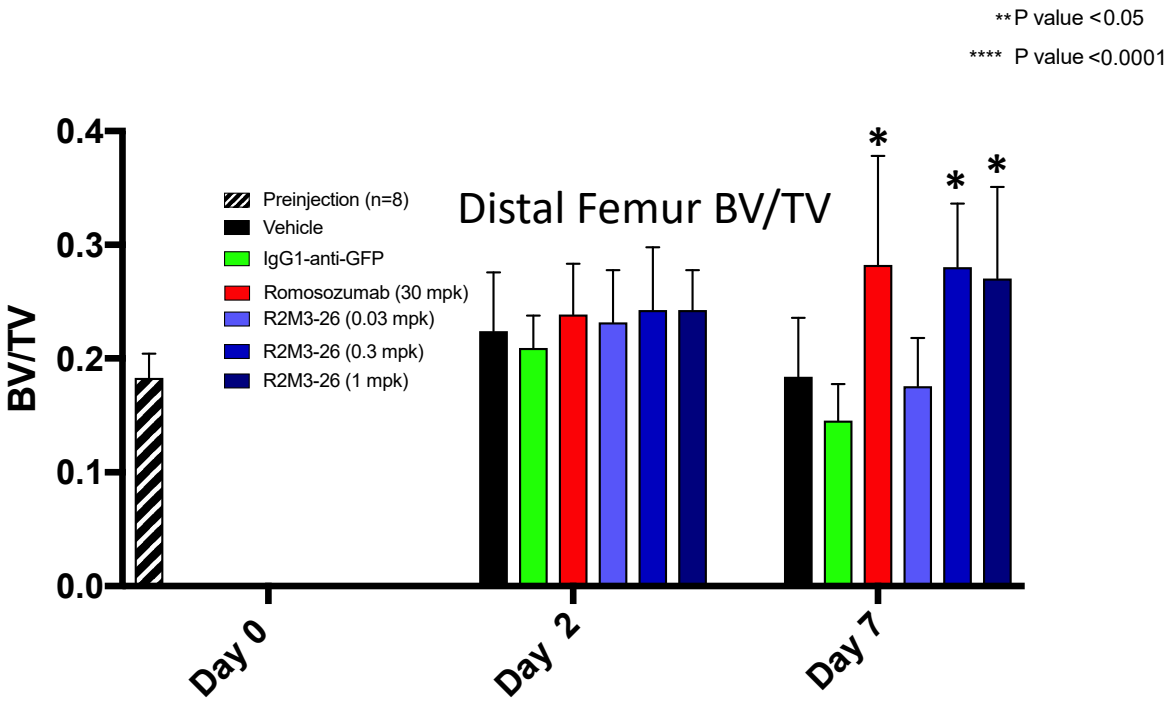

Vehicle
IgG1-anti-GFP (1mpk)
Romosozumab (30mpk)
R2M3-26 (0.03 mpk)
R2M3-26 (0.3 mpk)
R2M3-26 (1 mpk)

FIG. 23 (cont.)

B.



C.

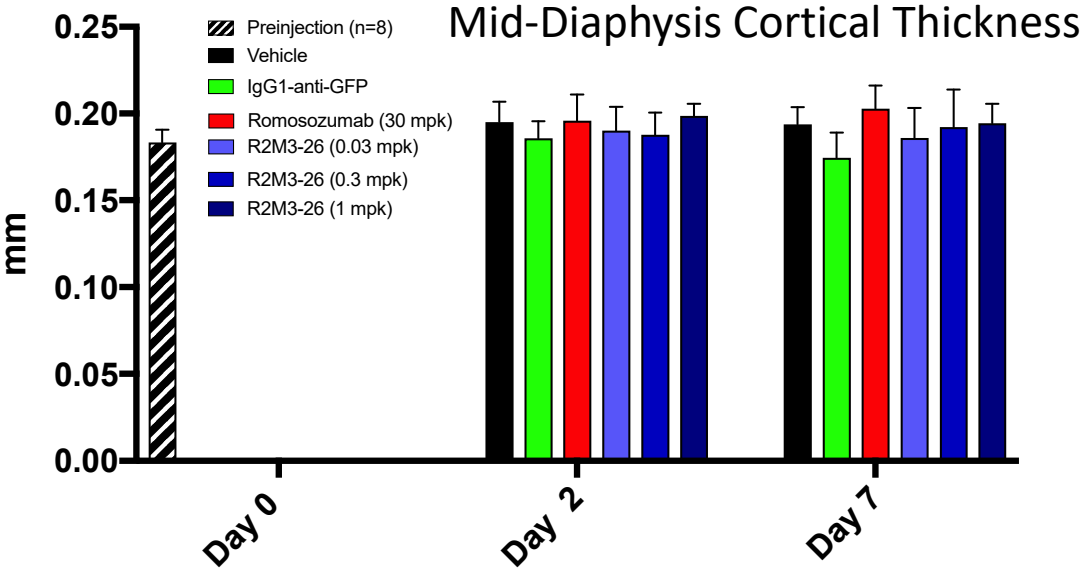


FIG. 24

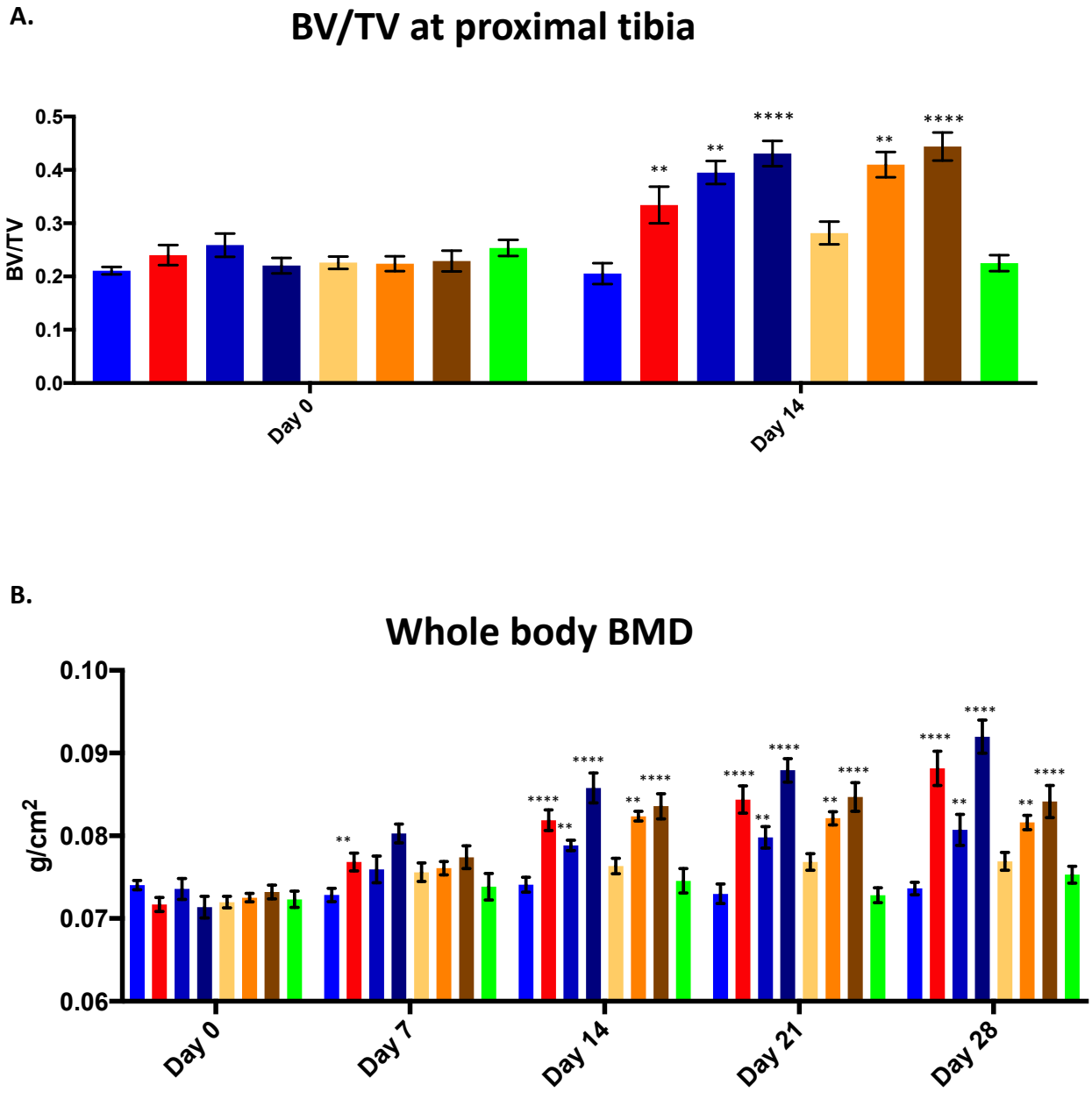
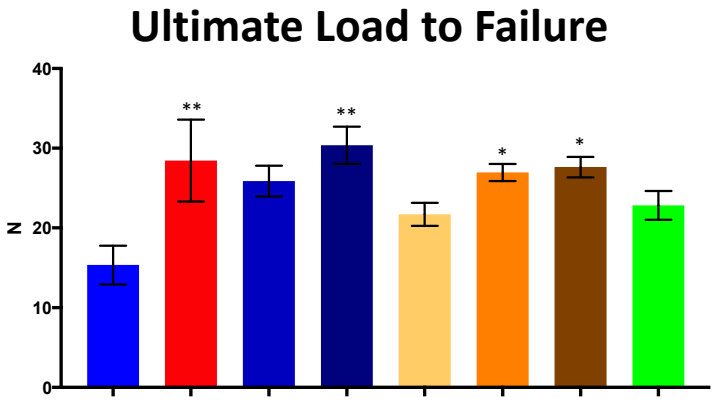
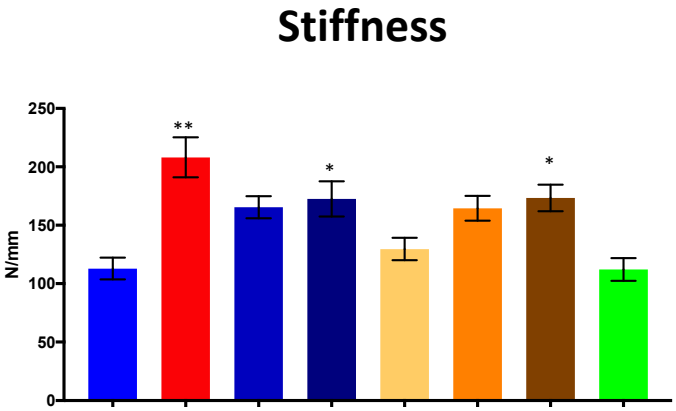

A.
BV/TV at proximal tibia
BV/TV
0.5
0.4
0.3
0.2
0.1
0.0
Day 0
Day 14
B.
Whole body BMD
g/cm2
0.10
0.09
0.08
0.07
0.06
Day 0
Day 7
Day 14
Day 21
Day 28

FIG. 24 (cont.)

C.



D.



Vehicle (PBS)
Romososzumab (30 MPK)
R2M3-26 (1MPK)
R2M3-26 (10 MPK)
1R-C07-26 (1 MPK)
1R-C07-26 (5 MPK)
1R-C07-26 (10 MPK)
Anti-GFP (1 MPK)

FIG. 25

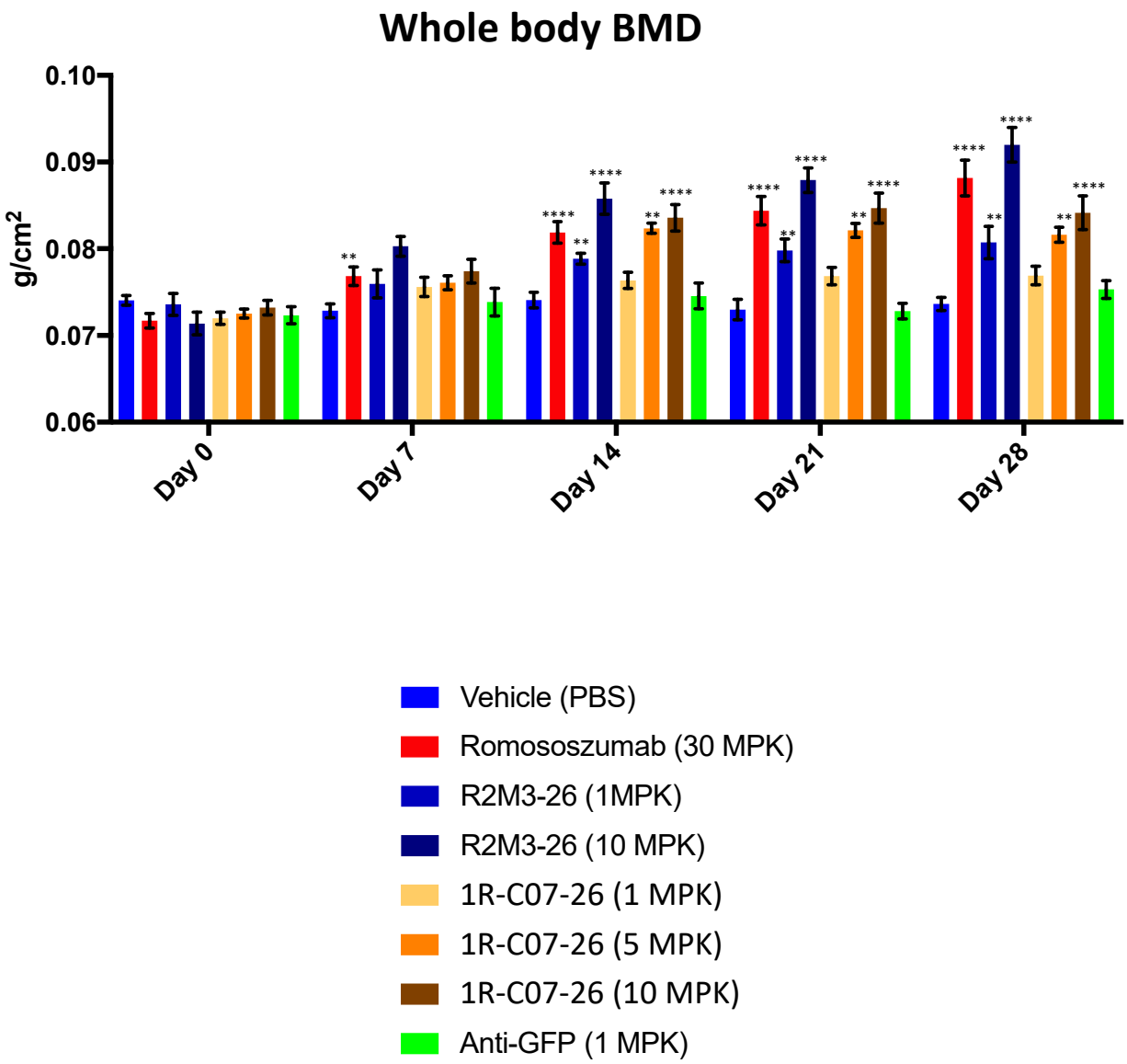

Whole body BMD
0.10
0.09
0.08
0.07
0.06
g/cm2
Day 0
Day 7
Day 14
Day 21
Day 28
Vehicle (PBS)
Romososzumab (30 MPK)
R2M3-26 (1MPK)
R2M3-26 (10 MPK)
1R-C07-26 (1 MPK)
1R-C07-26 (5 MPK)
1R-C07-26 (10 MPK)
Anti-GFP (1 MPK)

FIG. 26

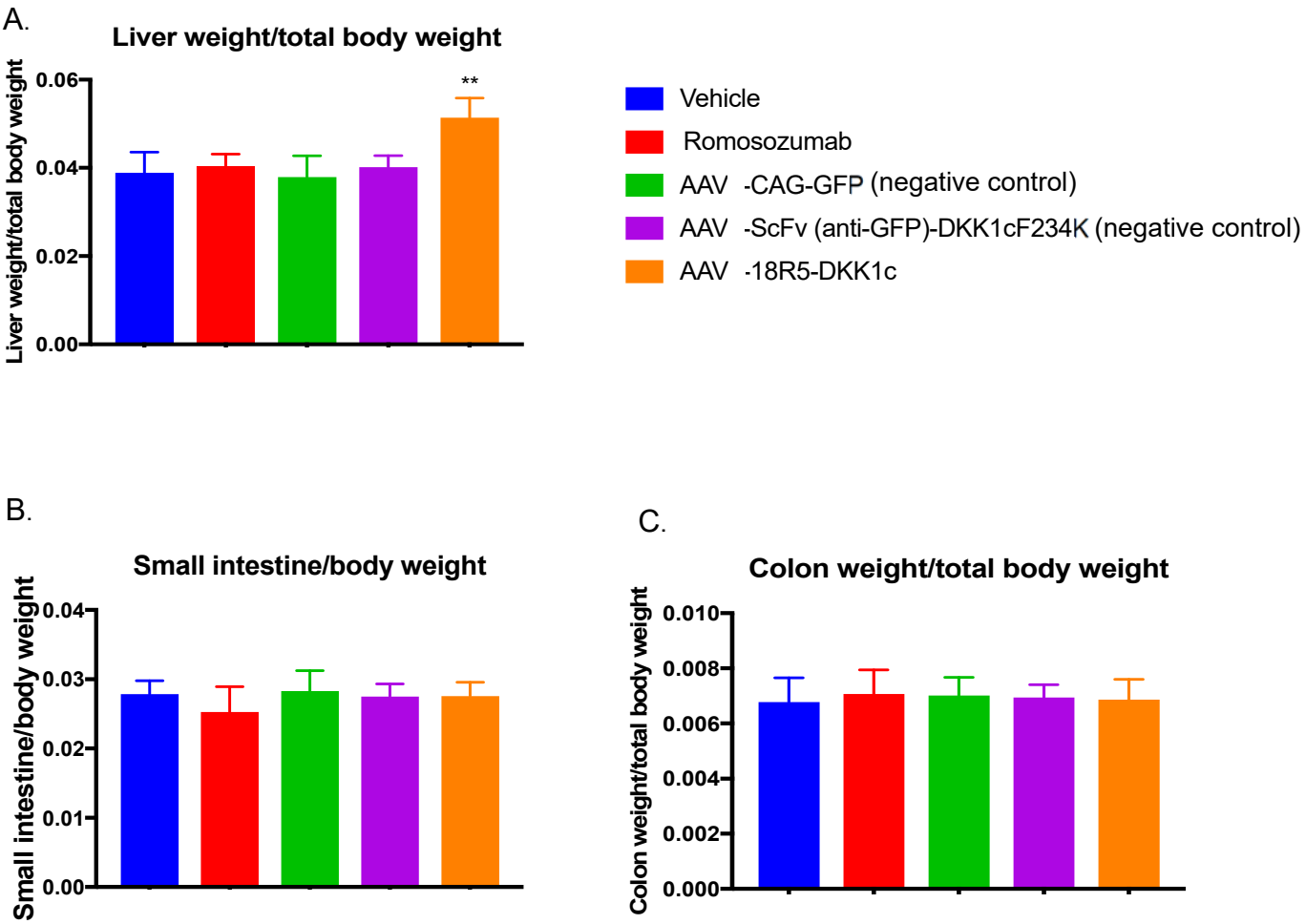
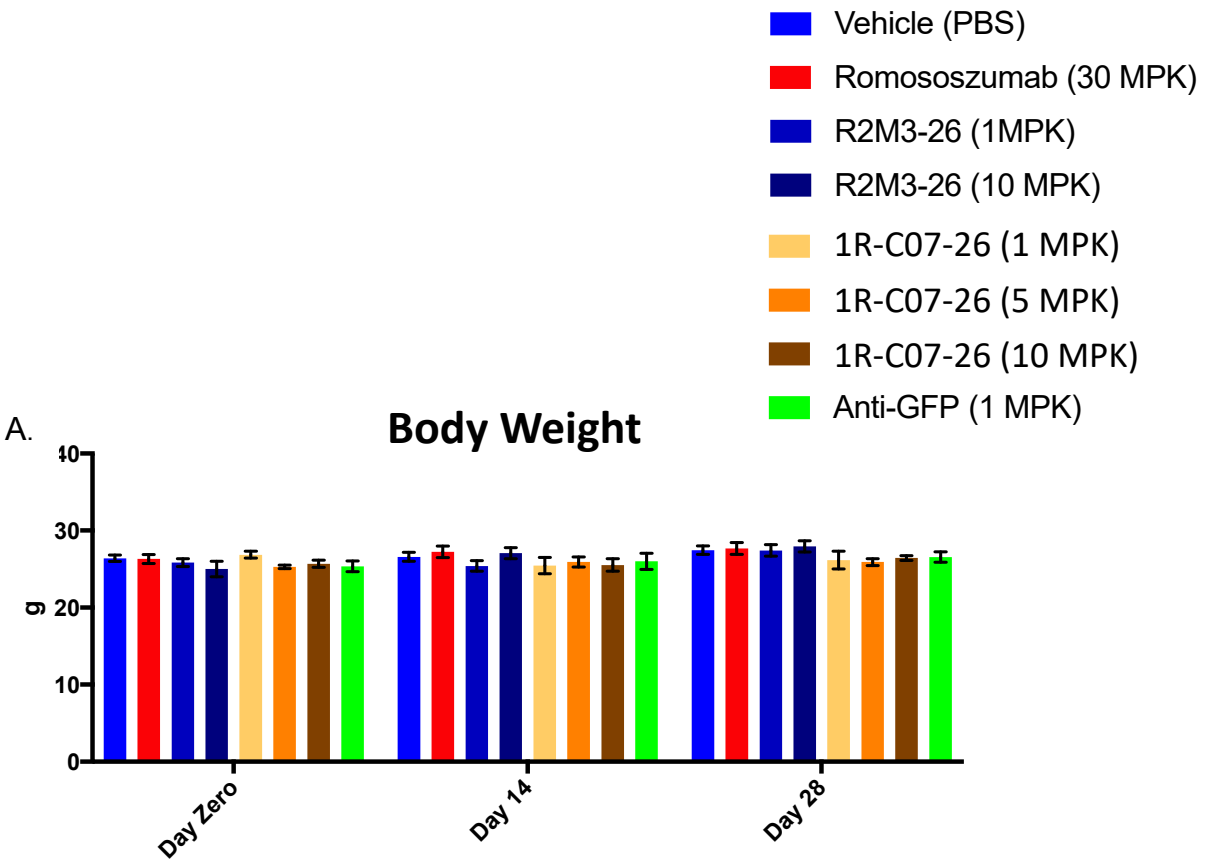

A.
Liver weight/total body weight
Liver weight/total body weight
0.06
0.04
0.02
0.00
**
Vehicle
Romosozumab
AAV -CAG-GFP (negative control)
AAV -ScFv (anti-GFP)-DKK1cF234K (negative control)
AAV -18R5-DKK1c
B.
Small intestine/body weight
Small intestine/body weight
0.04
0.03
0.02
0.01
0.00
C.
Colon weight/total body weight
Colon weight/total body weight
0.010
0.008
0.006
0.004
0.002
0.000

FIG. 27


Vehicle (PBS)
Romososzumab (30 MPK)
R2M3-26 (1MPK)
R2M3-26 (10 MPK)
1R-C07-26 (1 MPK)
1R-C07-26 (5 MPK)
1R-C07-26 (10 MPK)
Anti-GFP (1 MPK)
A.
Body Weight
g
40
30
20
10
0
Day Zero
Day 14
Day 28

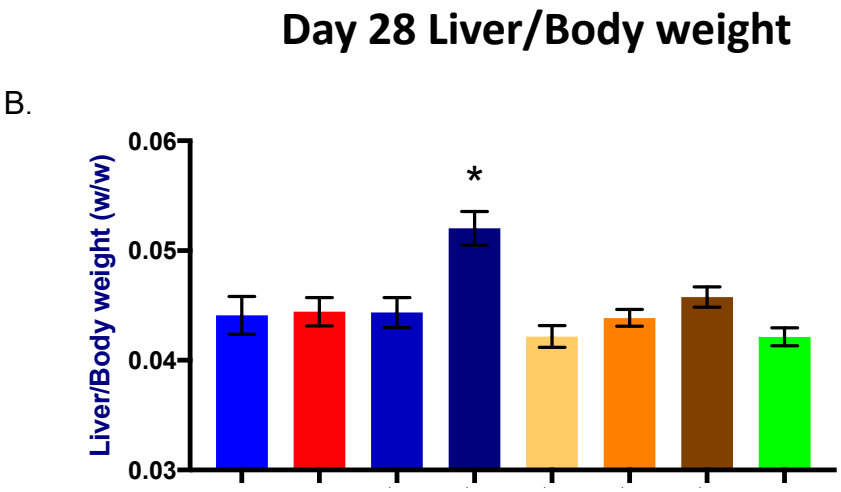

Day 28 Liver/Body weight
B.
Liver/Body weight (w/w)
0.06
0.05
0.04
0.03
*

FIG. 28

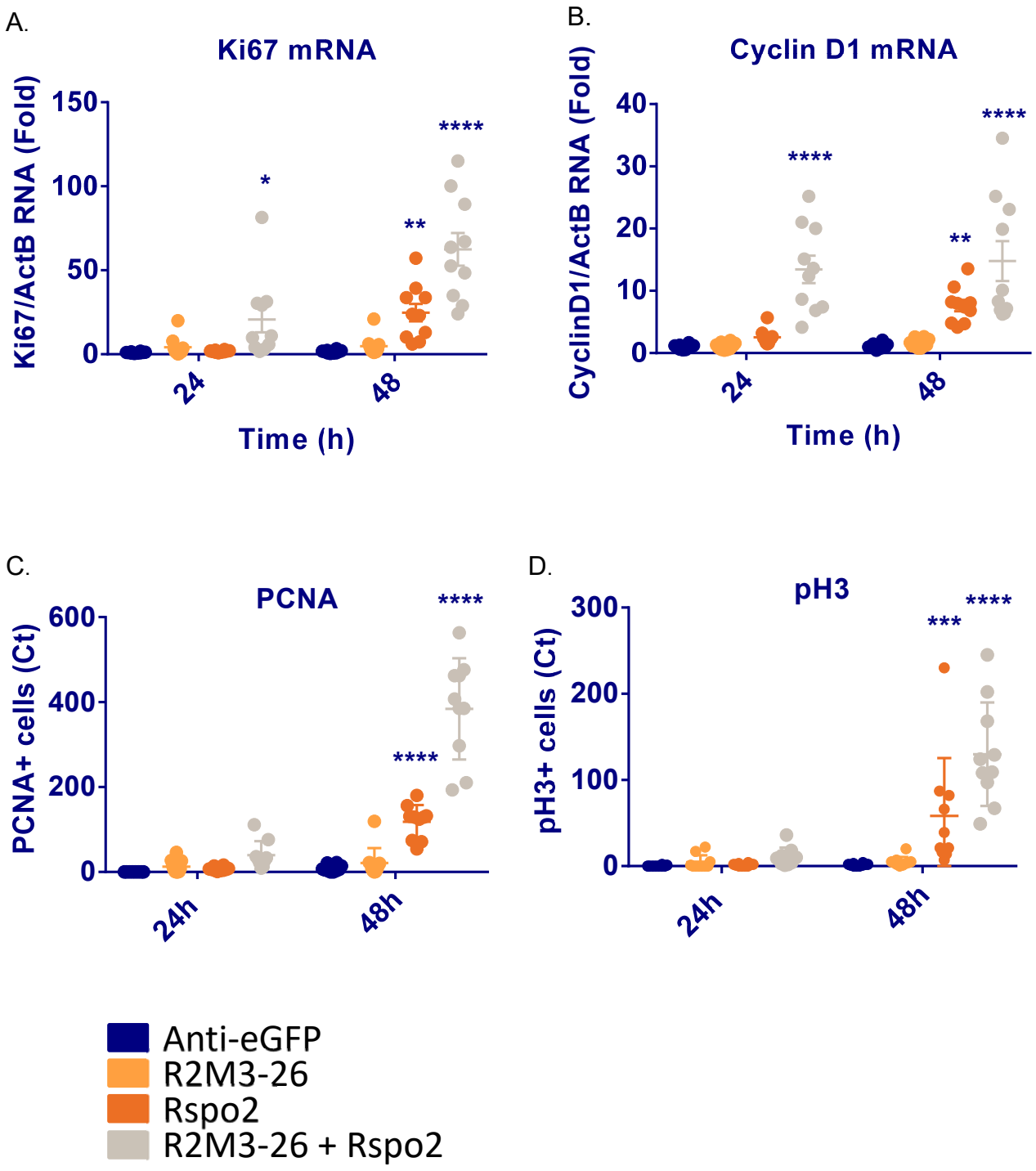
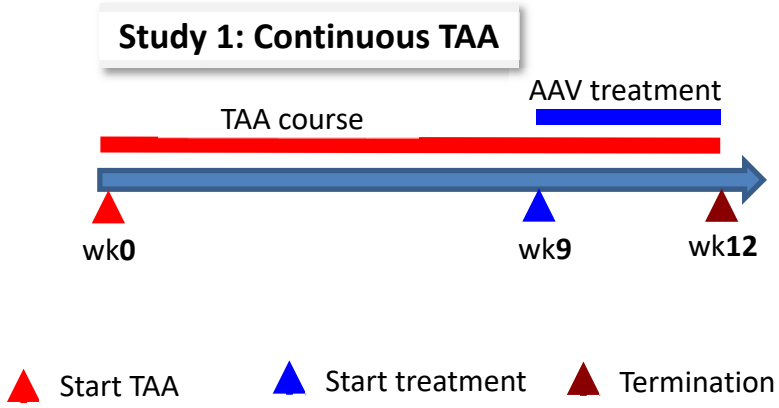

A.
Ki67 mRNA
Ki67/ActB RNA (Fold)
150
100
50
0
*
**
****
24
48
Time (h)
B.
Cyclin D1 mRNA
CyclinD1/ActB RNA (Fold)
40
30
20
10
0
****
**
****
24
48
Time (h)
C.
PCNA
PCNA+ cells (Ct)
600
400
200
0
****
****
24h
48h
D.
pH3
pH3+ cells (Ct)
300
200
100
0
***
****
24h
48h
Anti-eGFP
R2M3-26
Rspo2
R2M3-26 + Rspo2

FIG. 29

A.


Study 1: Continuous TAA
AAV treatment
TAA course
wk0
wk9
wk12
Start TAA
Start treatment
Termination

B.

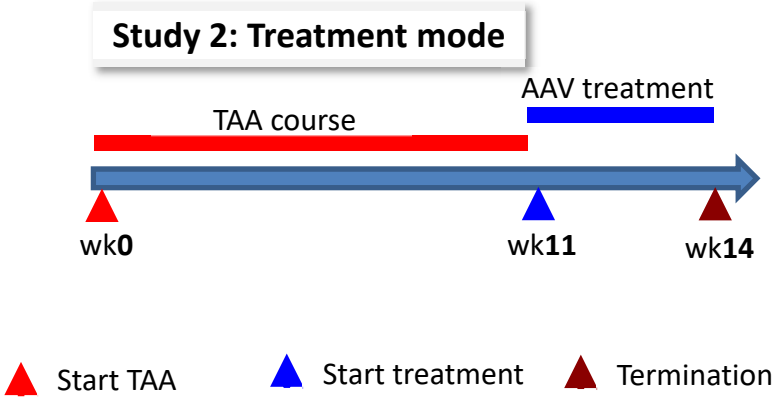

Study 2: Treatment mode
AAV treatment
TAA course
wk0
wk11
wk14
Start TAA
Start treatment
Termination

FIG. 29 (cont.)

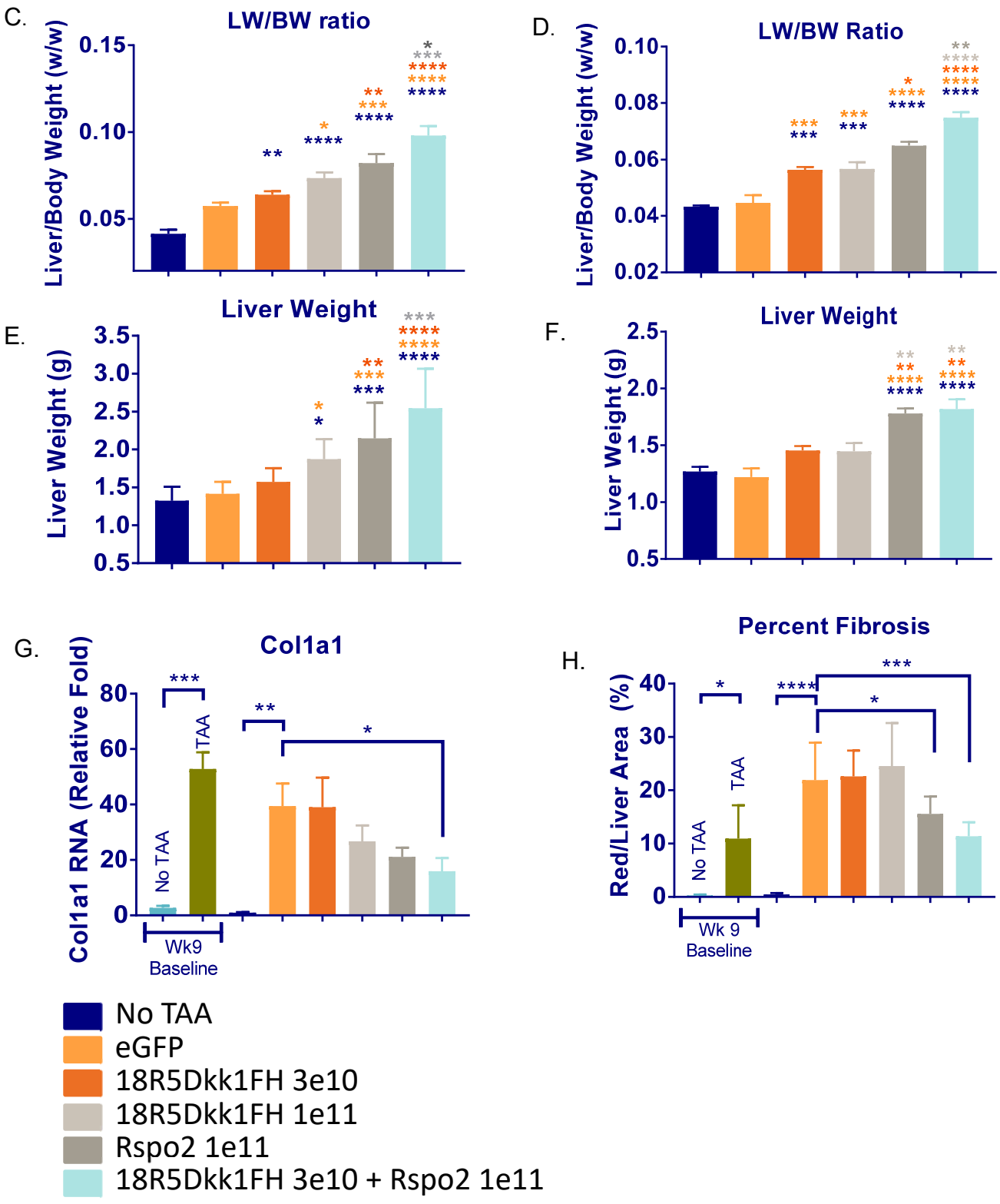

C.
LW/BW ratio
Liver/Body Weight (w/w)
0.15
0.10
0.05
D.
LW/BW Ratio
Liver/Body Weight (w/w)
0.10
0.08
0.06
0.04
0.02
E.
Liver Weight
Liver Weight (g)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
F.
Liver Weight
Liver Weight (g)
2.5
2.0
1.5
1.0
0.5
G.
Col1a1
Col1a1 RNA (Relative Fold)
80
60
40
20
0
No TAA
TAA
Wk9
Baseline
H.
Percent Fibrosis
Red/Liver Area (%)
40
30
20
10
0
No TAA
TAA
Wk 9
Baseline
No TAA
eGFP
18R5Dkk1FH 3e10
18R5Dkk1FH 1e11
Rspo2 1e11
18R5Dkk1FH 3e10 + Rspo2 1e11

FIG. 30

A.

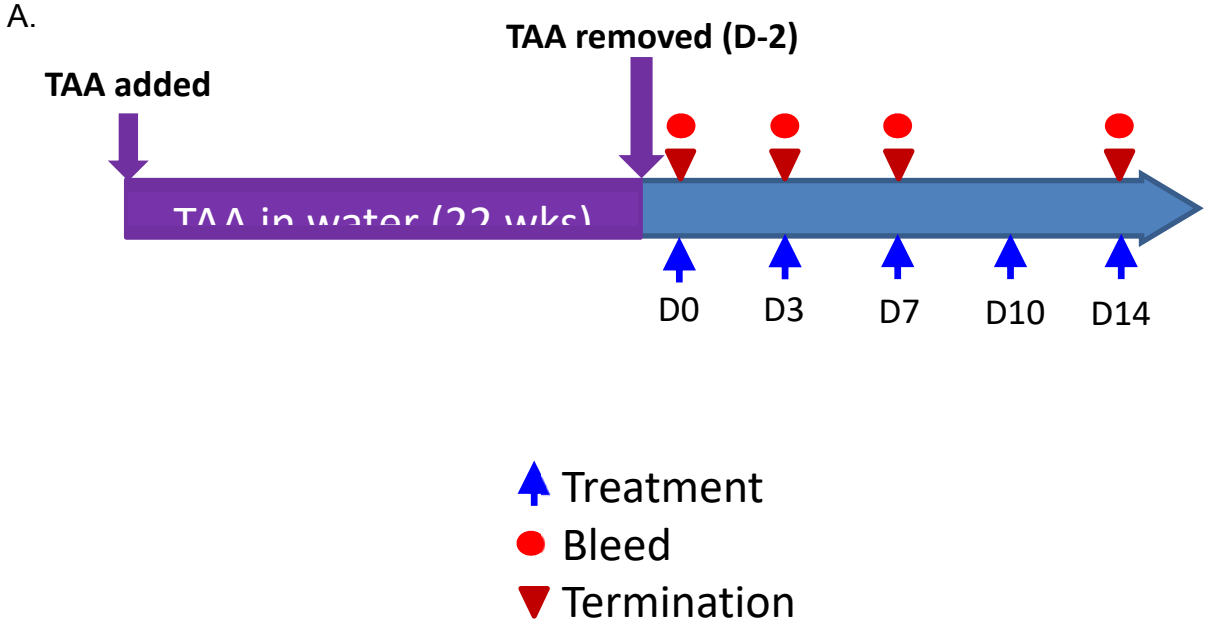

TAA added
TAA removed (D-2)
TAA in water (22 wks)
D0
D3
D7
D10
D14
Treatment
Bleed
Termination

FIG. 30 (cont.)

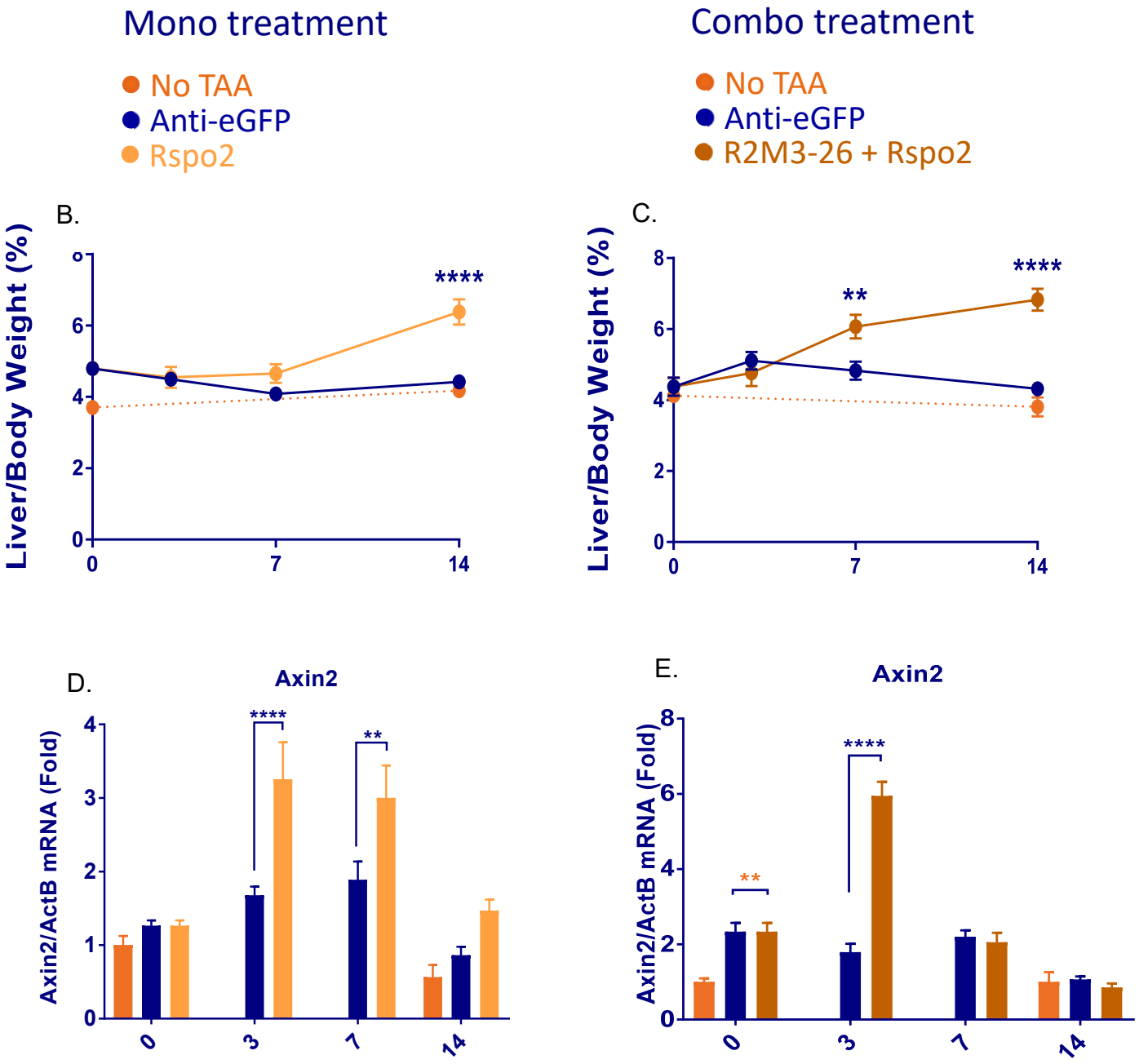

Mono treatment
No TAA
Anti-eGFP
Rspo2
Combo treatment
No TAA
Anti-eGFP
R2M3-26 + Rspo2
B.
C.
Liver/Body Weight (%)
****
**
D.
E.
Axin2
Axin2/ActB mRNA (Fold)
0
3
7
14

FIG. 30 (cont.)

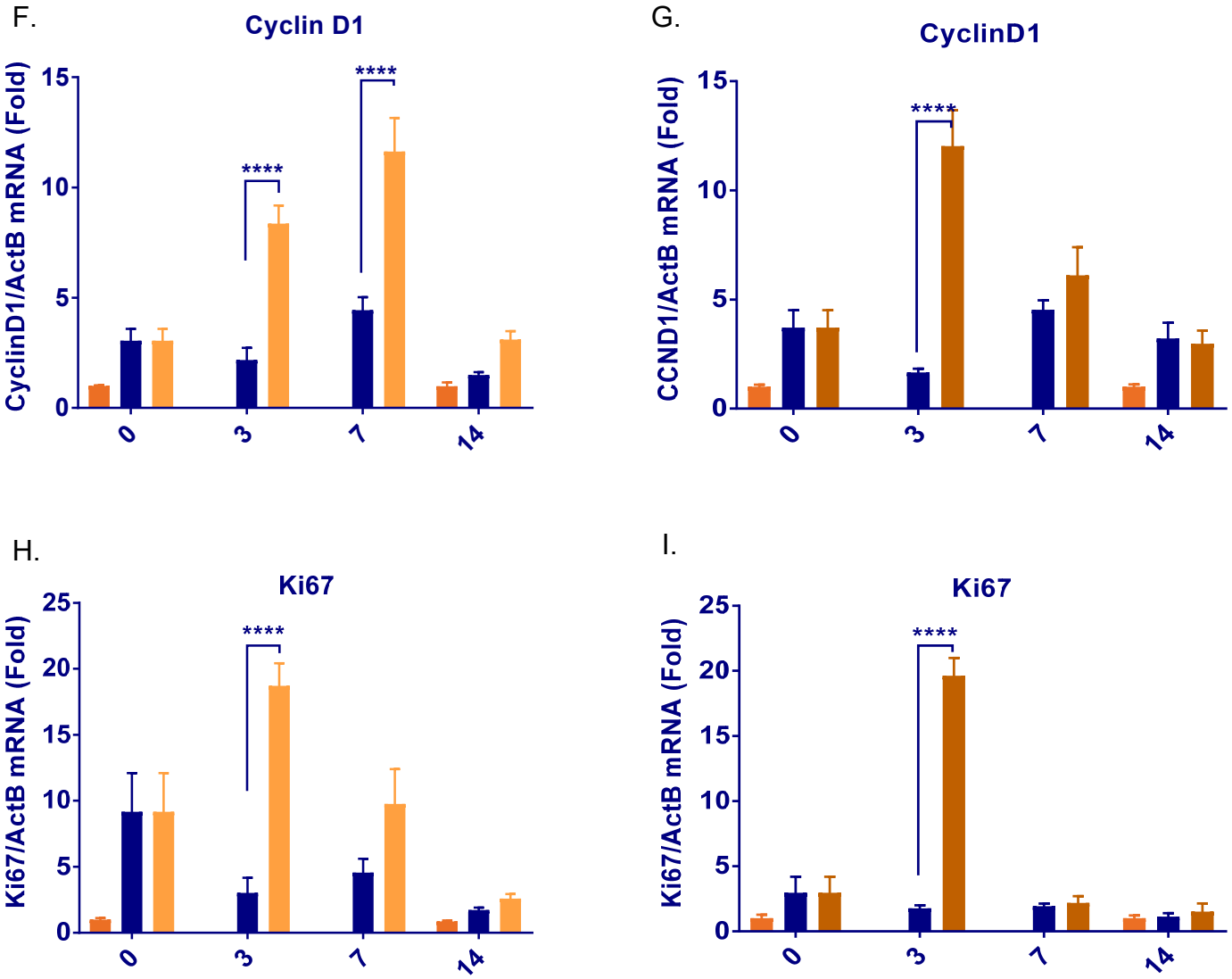

F.
Cyclin D1
CyclinD1/ActB mRNA (Fold)
15
10
5
0
****
****
0
3
7
14
G.
CyclinD1
CCND1/ActB mRNA (Fold)
15
10
5
0
****
0
3
7
14
H.
Ki67
Ki67/ActB mRNA (Fold)
25
20
15
10
5
0
****
0
3
7
14
I.
Ki67
Ki67/ActB mRNA (Fold)
25
20
15
10
5
0
****
0
3
7
14

FIG. 30 (cont.)

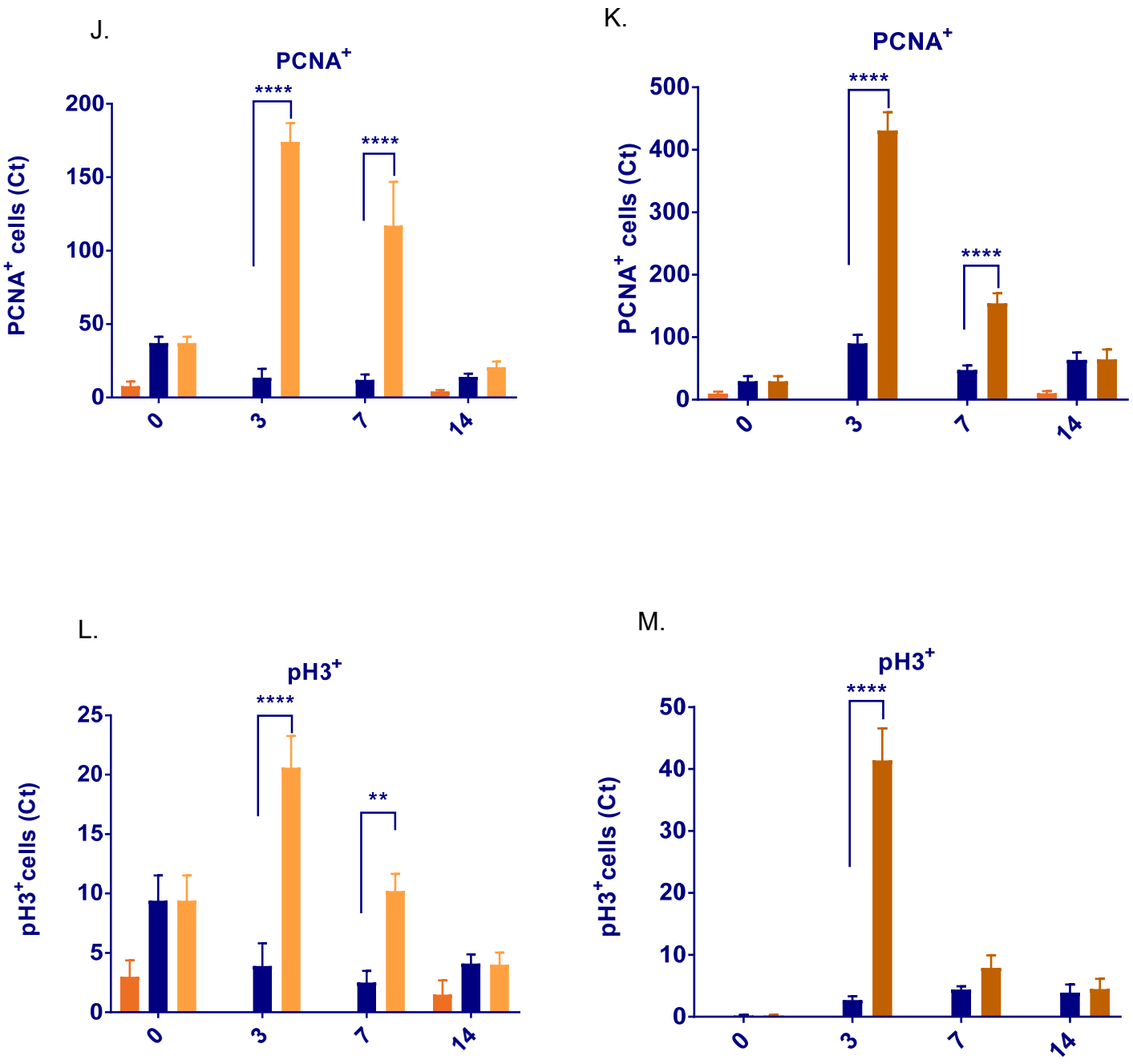

J.
PCNA+
PCNA+ cells (Ct)
200
150
100
50
0
****
****
0
3
7
14
K.
PCNA+
PCNA+ cells (Ct)
500
400
300
200
100
0
****
****
0
3
7
14
L.
pH3+
pH3+cells (Ct)
25
20
15
10
5
0
****
**
0
3
7
14
M.
pH3+
pH3+cells (Ct)
50
40
30
20
10
0
****
0
3
7
14

FIG. 30 (cont.)

N.

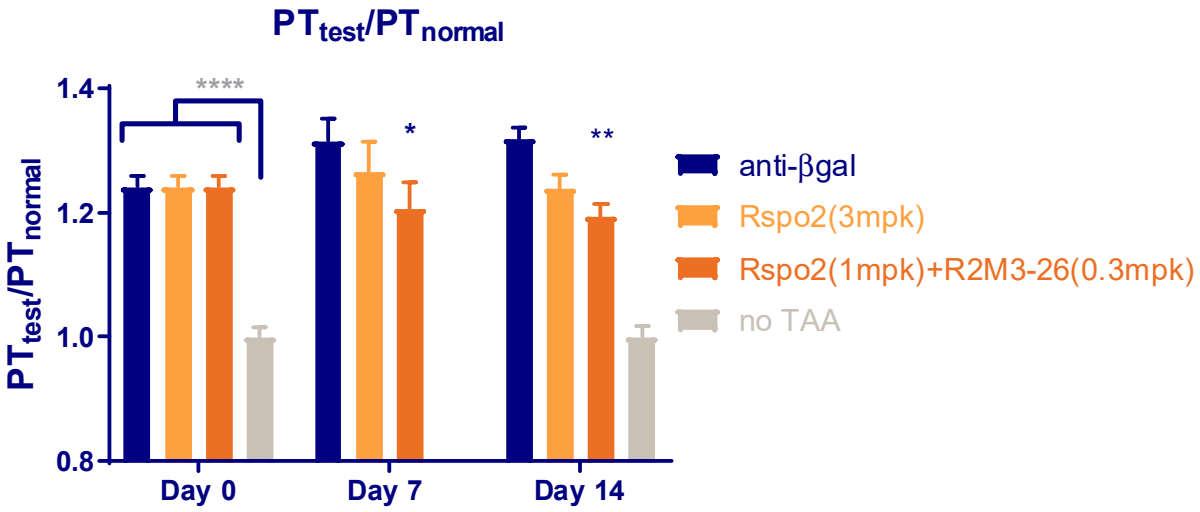

PTtest/PTnormal
PTtest/PTnormal
1.4
1.2
1.0
0.8
****
*
**
Day 0
Day 7
Day 14
anti-βgal
Rspo2(3mpk)
Rspo2(1mpk)+R2M3-26(0.3mpk)
no TAA

FIG. 31

A.

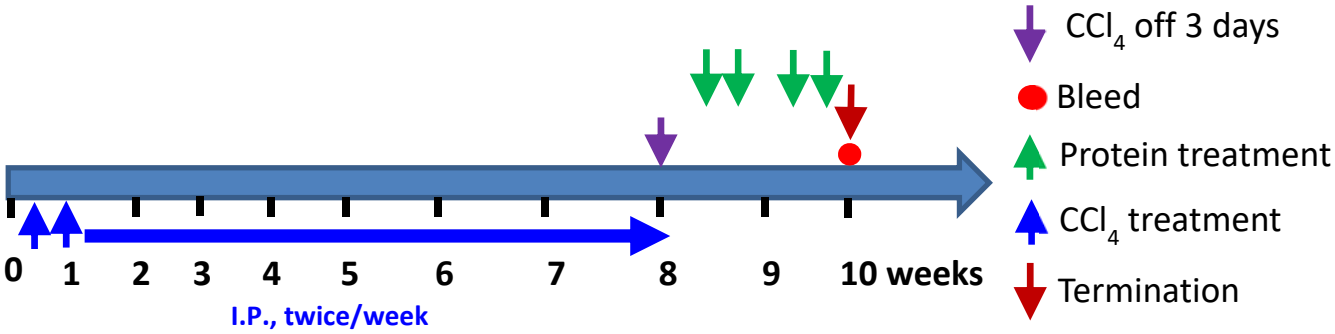
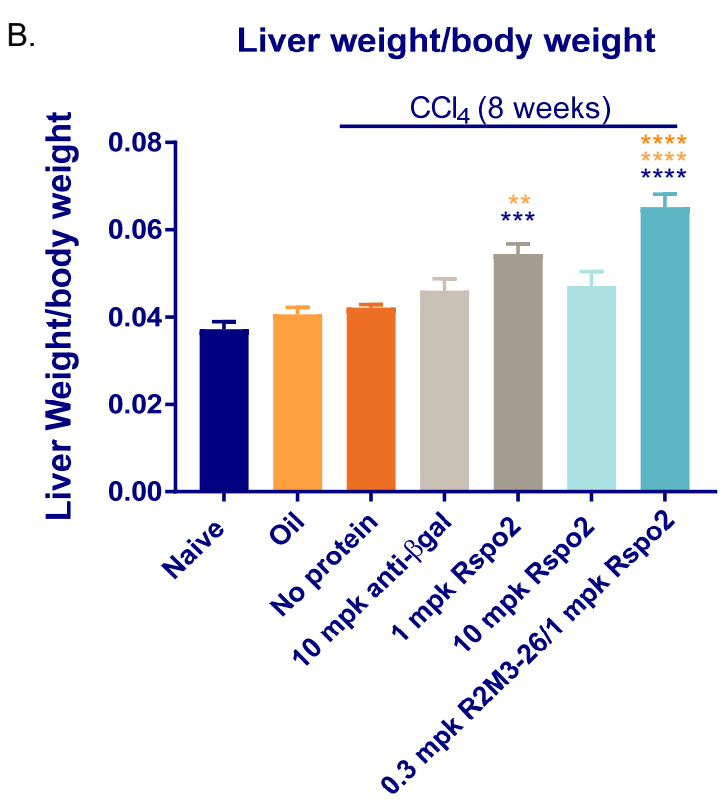
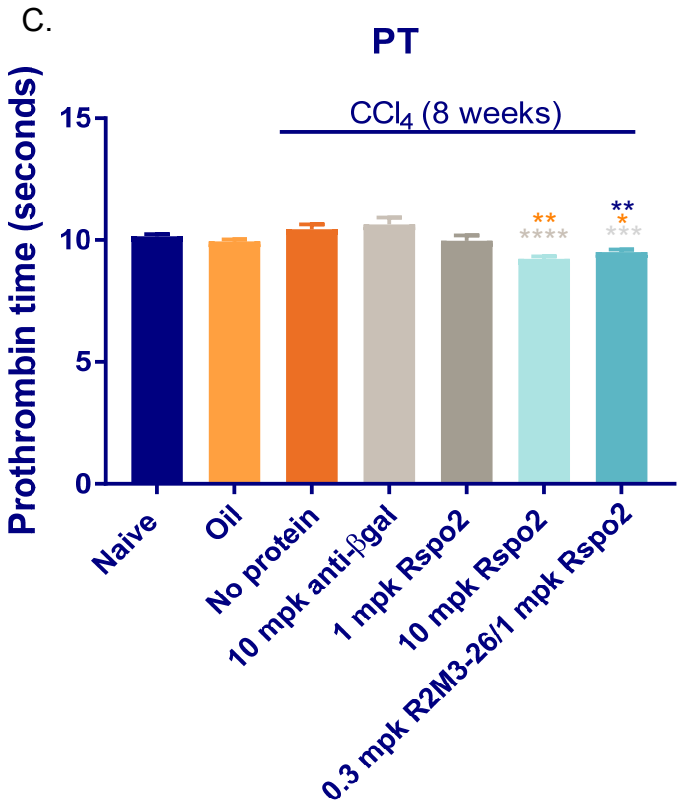
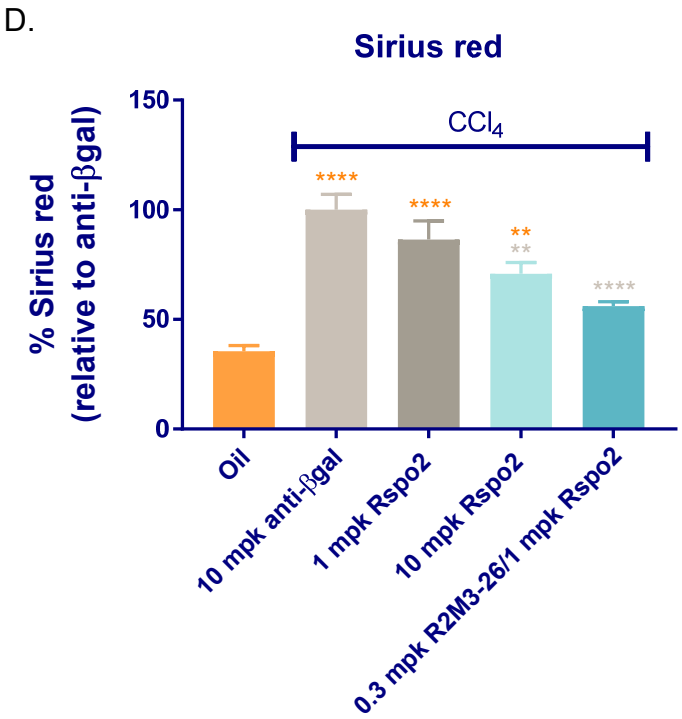

0
1
2
3
4
5
6
7
8
9
10 weeks
I.P., twice/week
CCl4 off 3 days
Bleed
Protein treatment
CCl4 treatment
Termination

FIG. 31 (cont.)


B.
Liver weight/body weight
CCl4 (8 weeks)
Liver Weight/body weight
0.08
0.06
0.04
0.02
0.00
Naive
Oil
No protein
10 mpk anti-βgal
1 mpk Rspo2
10 mpk Rspo2
0.3 mpk R2M3-26/1 mpk Rspo2


C.
PT
CCl4 (8 weeks)
Prothrombin time (seconds)
15
10
5
0
Naive
Oil
No protein
10 mpk anti-βgal
1 mpk Rspo2
10 mpk Rspo2
0.3 mpk R2M3-26/1 mpk Rspo2


D.
Sirius red
CCl4
% Sirius red
(relative to anti-βgal)
150
100
50
0
Oil
10 mpk anti-βgal
1 mpk Rspo2
10 mpk Rspo2
0.3 mpk R2M3-26/1 mpk Rspo2

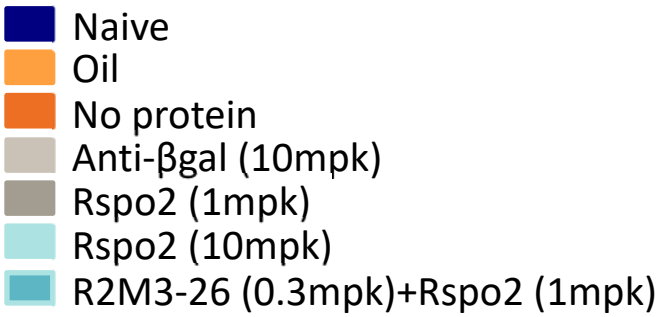
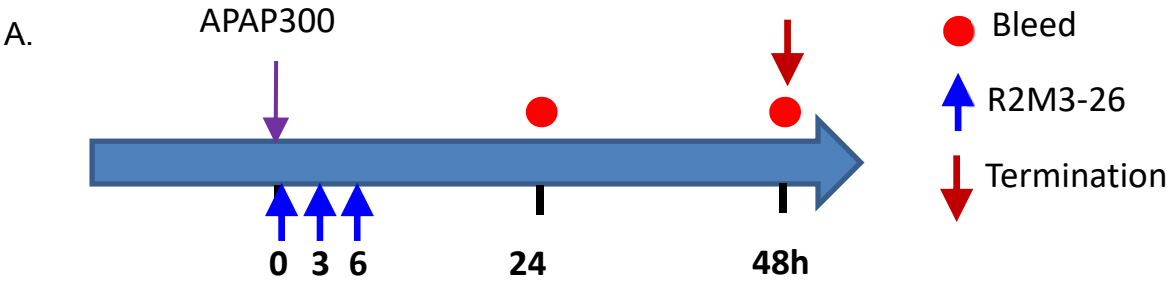
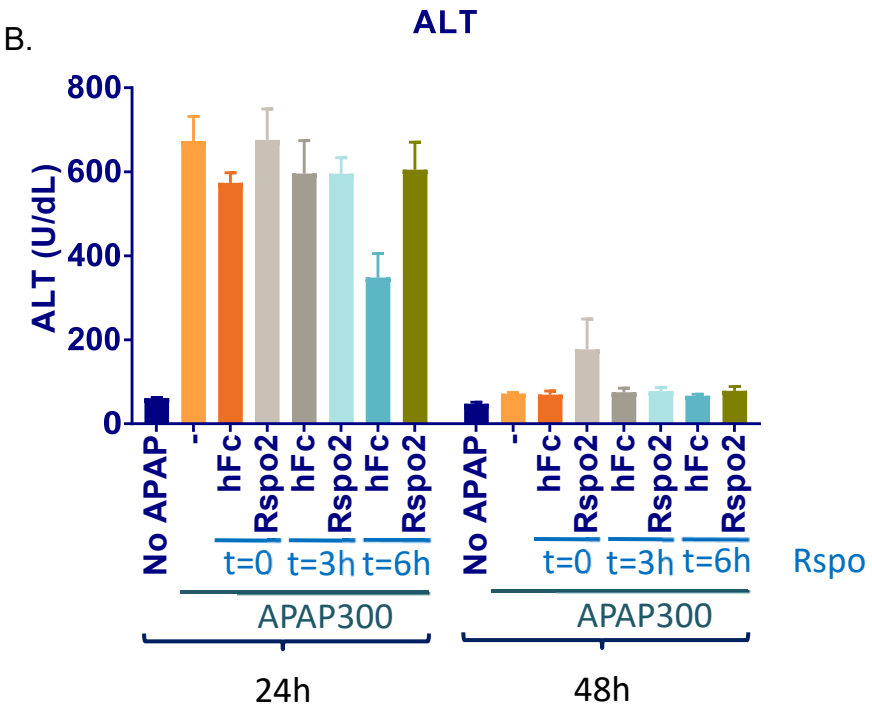
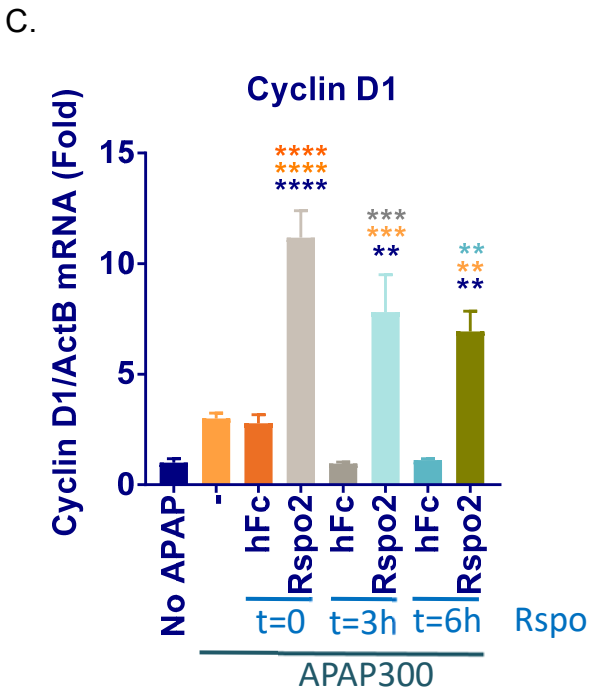

Naive
Oil
No protein
Anti-βgal (10mpk)
Rspo2 (1mpk)
Rspo2 (10mpk)
R2M3-26 (0.3mpk)+Rspo2 (1mpk)

FIG. 32


A.
APAP300
Bleed
R2M3-26
Termination
0 3 6
24
48h


B.
ALT
ALT (U/dL)
800
600
400
200
0
No APAP
-
hFc
Rspo2
t=0
t=3h
t=6h
Rspo
APAP300
24h
48h


C.
Cyclin D1
Cyclin D1/ActB mRNA (Fold)
15
10
5
0
No APAP
-
hFc
Rspo2
t=0
t=3h
t=6h
Rspo
APAP300

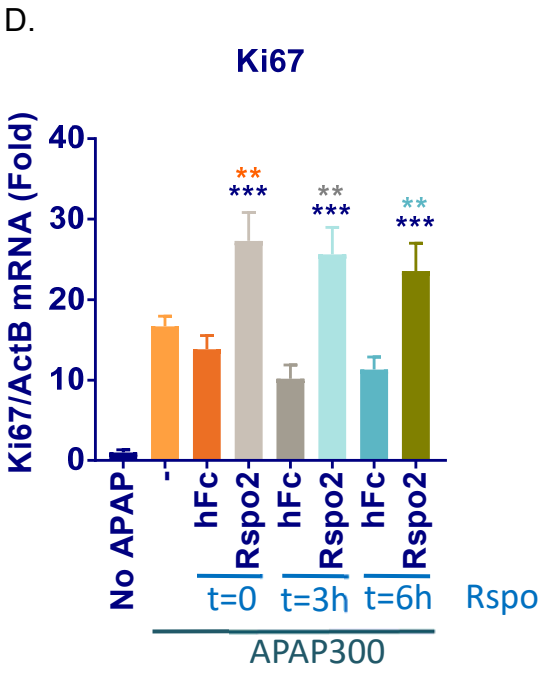

D.
Ki67
Ki67/ActB mRNA (Fold)
40
30
20
10
0
No APAP
-
hFc
Rspo2
t=0
t=3h
t=6h
Rspo
APAP300

FIG. 33

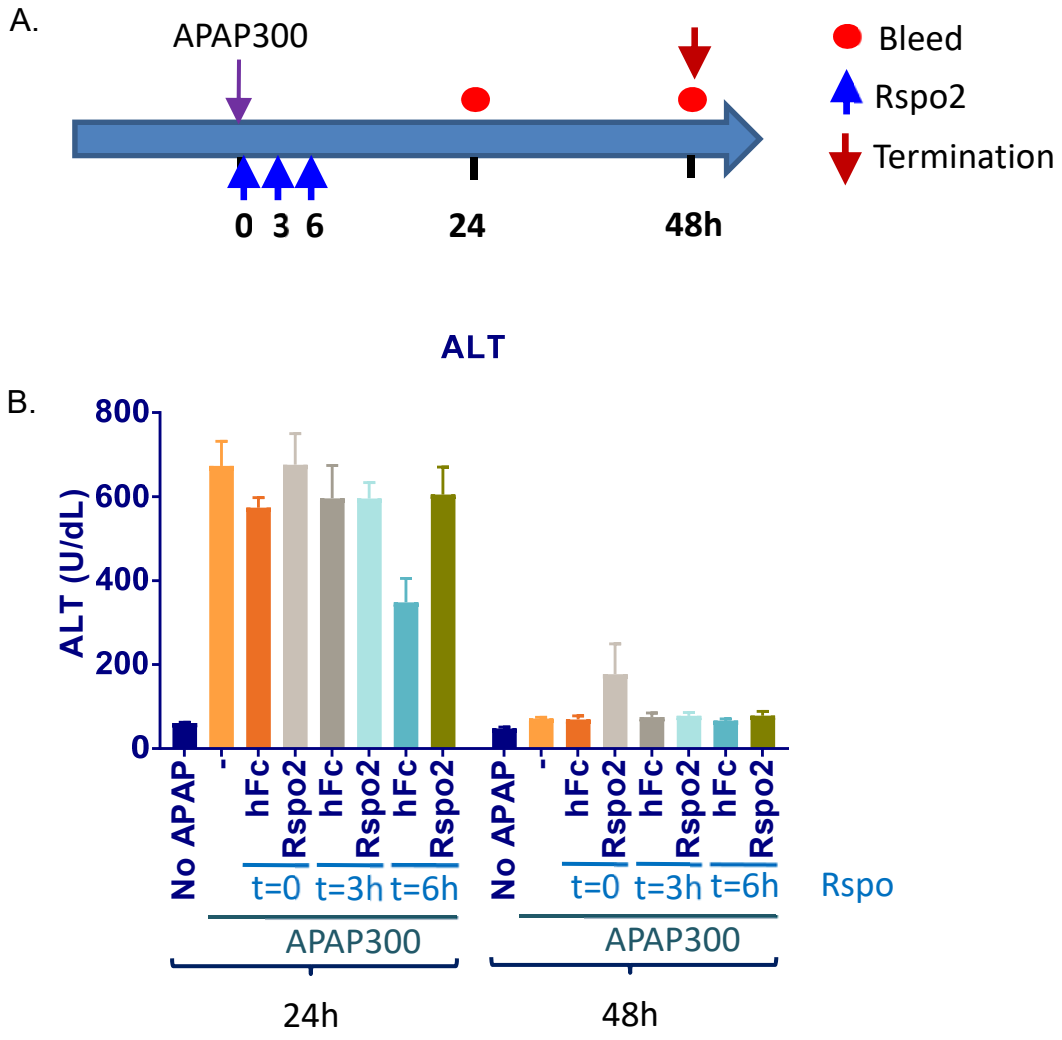
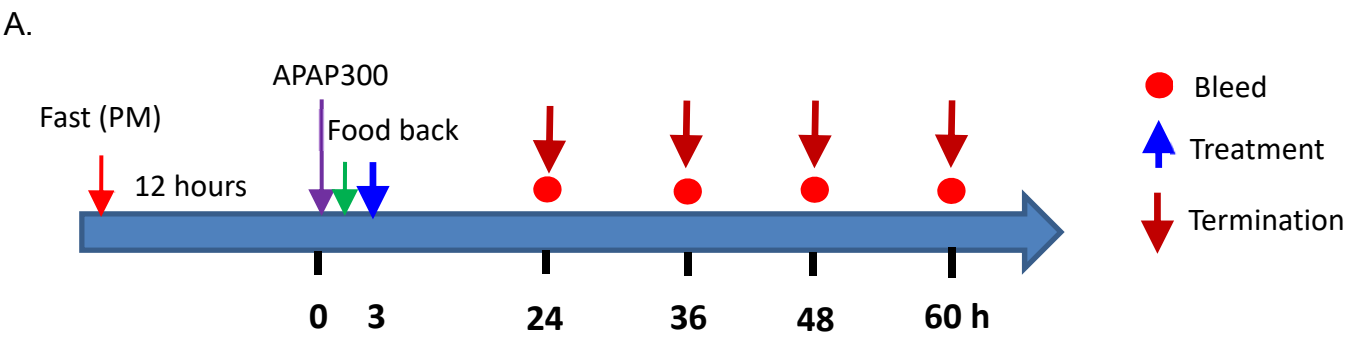
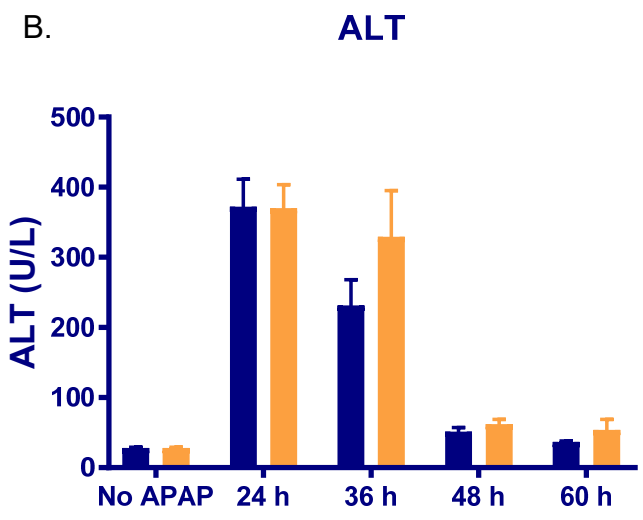
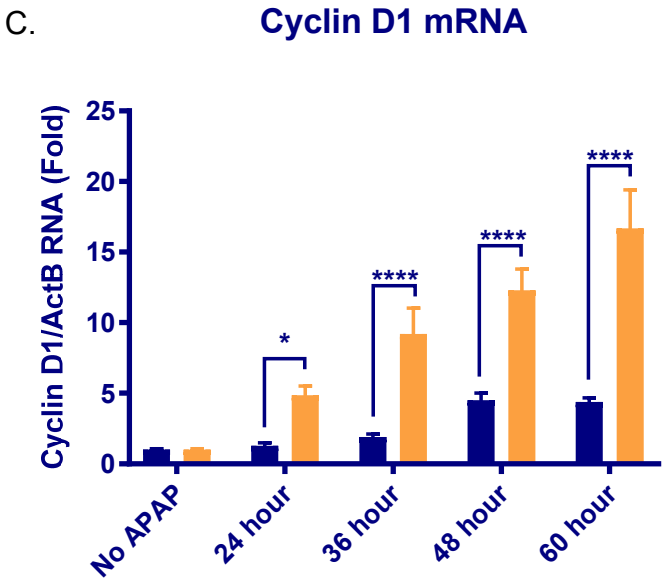
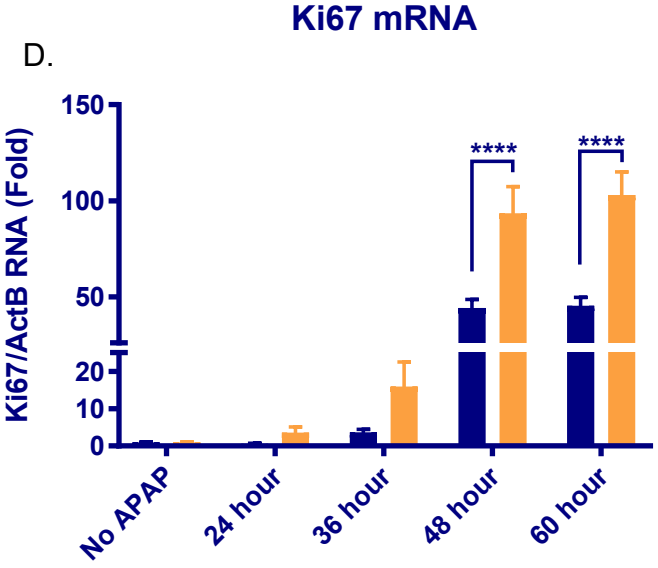

A.
APAP300
Bleed
Rspo2
Termination
0 3 6
24
48h
B.
ALT
ALT (U/dL)
800
600
400
200
0
No APAP
-
hFc
Rspo2
t=0
t=3h
t=6h
Rspo
APAP300
24h
48h
C.
Cyclin D1
Cyclin D1/ActB mRNA (Fold)
15
10
5
0
D.
Ki67
Ki67/ActB mRNA (Fold)
40
30
20
10
0

FIG. 34


A.
APAP300
Fast (PM)
Food back
12 hours
Bleed
Treatment
Termination
0
3
24
36
48
60 h


B.
ALT
ALT (U/L)
500
400
300
200
100
0
No APAP
24 h
36 h
48 h
60 h


C.
Cyclin D1 mRNA
Cyclin D1/ActB RNA (Fold)
25
20
15
10
5
0
*
****
****
****
No APAP
24 hour
36 hour
48 hour
60 hour


D.
Ki67 mRNA
Ki67/ActB RNA (Fold)
150
100
50
20
10
0
****
****
No APAP
24 hour
36 hour
48 hour
60 hour

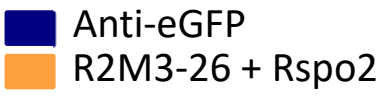
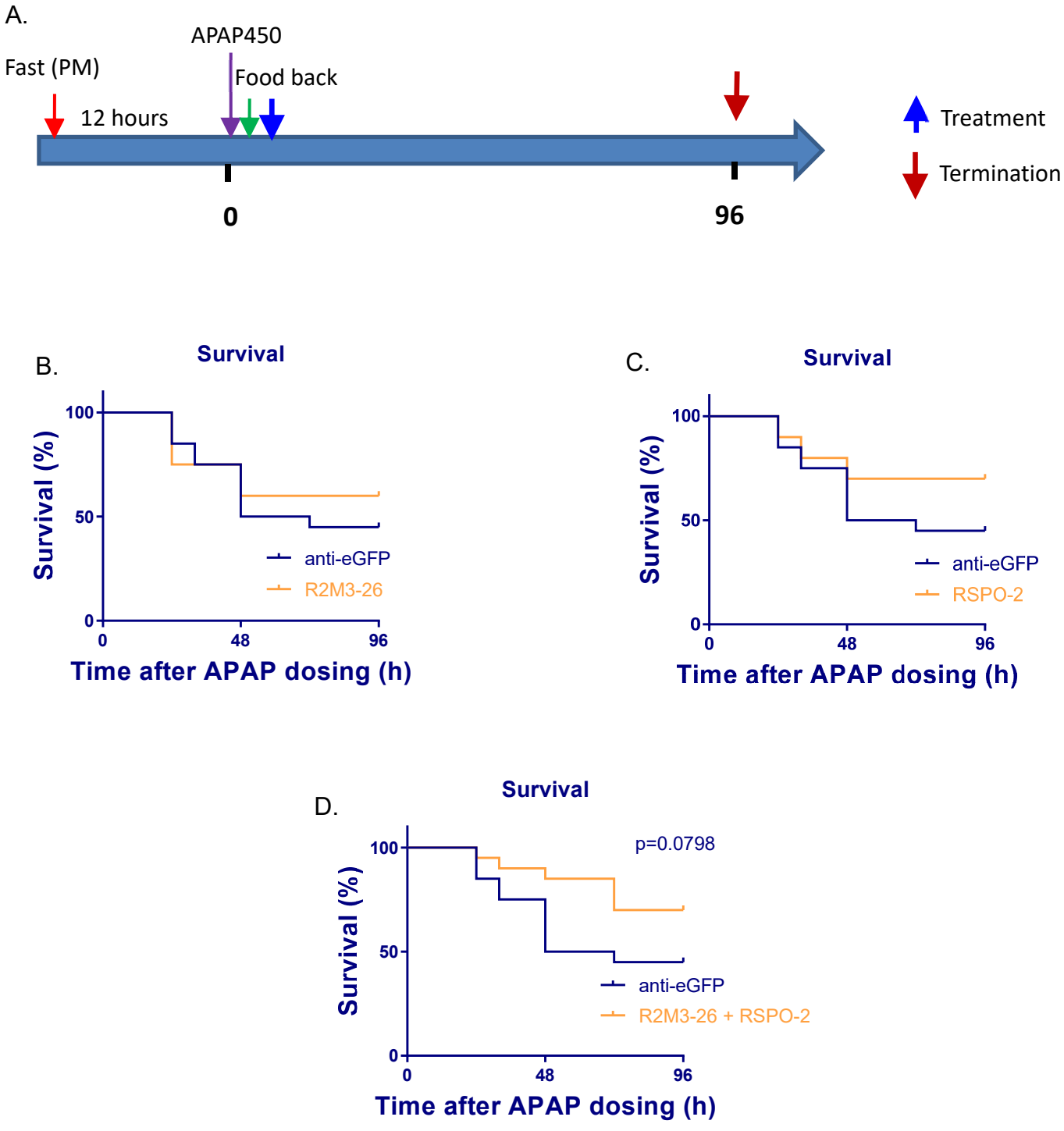

Anti-eGFP
R2M3-26 + Rspo2

FIG. 35


A.
APAP450
Fast (PM)
Food back
12 hours
0
96
Treatment
Termination
B.
Survival
Survival (%)
100
50
0
anti-eGFP
R2M3-26
0
48
96
Time after APAP dosing (h)
C.
Survival
Survival (%)
100
50
0
anti-eGFP
RSPO-2
0
48
96
Time after APAP dosing (h)
D.
Survival
p=0.0798
Survival (%)
100
50
0
anti-eGFP
R2M3-26 + RSPO-2
0
48
96
Time after APAP dosing (h)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	WNT SURROGATE MOLECULES AND USES THEREOF
First Named Inventor/Applicant Name:	Yang LI
Filer:	Carol Denise Laherty/John Oliver
Attorney Docket Number:	SRZN-006/02US 328202-2023

Filed as Small Entity

Filing Fees for Provisional

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PROVISIONAL APPLICATION FILING FEE	2005	1	140	140
Pages:				
PROVIS. APPL SIZE FEE PER 50 SHEETS >100	2085	2	200	400
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**540**

Electronic Acknowledgement Receipt

EFS ID:	32800895
Application Number:	62680522
International Application Number:	
Confirmation Number:	4895
Title of Invention:	WNT SURROGATE MOLECULES AND USES THEREOF
First Named Inventor/Applicant Name:	Yang LI
Customer Number:	58249
Filer:	Carol Denise Laherty/John Oliver
Filer Authorized By:	Carol Denise Laherty
Attorney Docket Number:	SRZN-006/02US 328202-2023
Receipt Date:	04-JUN-2018
Filing Date:	
Time Stamp:	20:43:50
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$540
RAM confirmation Number	060518INTEFSW00006496501283
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	SRZN-006_02US_ADS.pdf	1823025 f391fce731addb52f848902b288aa51d8c04f494	no	10
Warnings:					
Information:					
2		SRZN-006_02US_PROV_APP.pdf	897411 ebbebb6a72eef52062326201 60e81f671972b92b	yes	160

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	149
	Claims	150	159
	Abstract	160	160

Warnings:					
Information:					
3	Drawings-other than black and white line drawings	SRZN-006_02US_FIGS.pdf	3688894 2f7e68079e249d95461f13cd8981f18900f48fad	no	59
Warnings:					
Information:					
4	Sequence Listing (Text File)	SRZN_006_02US_ST25.txt	370426	no	-
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	31629 c140ffd6d533a078fe4c9fa026899897791d7c6f	no	2

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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.

DocCode – SCORE

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