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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 June 2018 (21.06.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/109174 A2

(51) International Patent Classification:
C07K 16/24 (2006.01)

(21) International Application Number:
PCT/EP2017/083051

(22) International Filing Date:
15 December 2017 (15.12.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1621446.2 16 December 2016 (16.12.2016) GB
1709535.7 15 June 2017 (15.06.2017) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

(54) Title: IL-11 ANTIBODIES

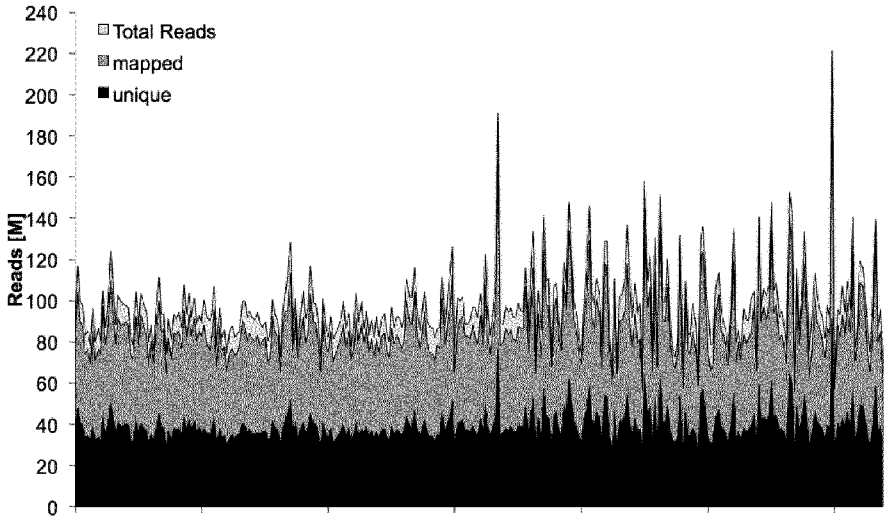

Figure 1

(57) Abstract: IL-11 antibodies are disclosed. Also disclosed are compositions comprising the IL-11 antibodies, and methods using the IL-11 antibodies.

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Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

IL-11 Antibodies

Field of the Invention

The present invention relates to antibodies that bind to interleukin 11 (IL-11).

Background to the Invention

Many fatal and incurable diseases are caused by organ failure due to excessive and maladaptive fibrosis (Rockey et al., 2015 Journal of Infectious Diseases 214, jiw176). Fibrotic disorders include both rare, genetically-driven diseases such as scleroderma, idiopathic pulmonary fibrosis and hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), and common diseases like atrial fibrillation, ventricular fibrillation, non-alcoholic fatty liver disease and diabetic kidney disease. Due to the significant impact on world-wide morbidity and mortality, there is a need to develop therapeutics to inhibit the fibrotic response (Nanthakumar et al., 2015 Nat Rev Drug Discov 14, 693–720).

A major hallmark of fibrosis is the pathologic activation of resident fibroblasts that drives their transition from a quiescent state to proliferating, secretory and contractile myofibroblasts (Hinz et al., 2010 Am J Pathology 170, 1807–1816). Stimuli such as mechanical stress and pro-fibrotic cytokines can activate fibroblasts. The TGFβ1 pathway is considered to be of central importance for the fibrotic response (Leask and Abraham, 2004 The FASEB Journal 18, 816–827) and its inhibition is a therapeutic strategy that is under investigation (Gourdie et al., 2016 Nature Reviews Drug Discovery 15, 620–638). However, direct inhibition of multi-functional TGFβ1 is associated with severe side effects such as inflammation and cancer susceptibility.

Summary of the Invention

In one aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, wherein the antibody or antigen binding fragment is a fully human antibody or antigen binding fragment and is capable of inhibiting IL-11 *trans* signalling.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: $X_1X_2DX_3GX_4YX_5Y$ (SEQ ID NO:239);
$X_6SNX_7GX_8X_9X_{10}$ (SEQ ID NO:240);
$QX_{11}X_{12}SSX_{13}$ (SEQ ID NO:241);
$X_{14}GX_{15}IASNX_{16}$ (SEQ ID NO:242);
QDVGRY (SEQ ID NO:101); or
SLRGYY (SEQ ID NO:161);

ii) LC-CDR2: DVX_{17} (SEQ ID NO:243);
$X_{18}NX_{19}$ (SEQ ID NO:244);
$X_{20}AS$ (SEQ ID NO:245);
$X_{21}DX_{22}$ (SEQ ID NO:246);
EVX_{23} (SEQ ID NO:247); or
$DX_{24}X_{25}$ (SEQ ID NO:248);

iii) LC-CDR3: $X_{26}SYTX_{27}X_{28}X_{29}X_{30}X_{31}VX_{32}$ (SEQ ID NO:249);
$X_{33}SYAX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO:250);
$X_{50}X_{51}WDX_{52}X_{53}LX_{54}X_{55}X_{56}V$ (SEQ ID NO:251);
$QQX_{57}X_{58}X_{59}PX_{60}X_{61}X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}$ (SEQ ID NO:252);
$QSYX_{73}X_{74}SX_{75}X_{76}X_{77}X_{78}$ (SEQ ID NO:253);
$X_{79}SYX_{80}SSX_{81}X_{82}X_{83}VX_{84}$ (SEQ ID NO:254);
NSYVTGNNWA (SEQ ID NO:169); or
DSRGRSGDHWL (SEQ ID NO:163);

iv) HC-CDR1: $GFTFSSYX_{85}$ (SEQ ID NO:255);
$GX_{86}X_{87}X_{88}X_{89}SYG$ (SEQ ID NO:256);
$X_{90}X_{91}X_{92}X_{93}X_{94}SYA$ (SEQ ID NO:257);
WIFLKSYA (SEQ ID NO:204);
VSSNSAAWN (SEQ ID NO:180);
GGSISSSNW (SEQ ID NO:220); or
GFTFSGAY (SEQ ID NO:183);

v) HC-CDR2: $ISYDGSX_{95}K$ (SEQ ID NO:258);
IIPIFGTA (SEQ ID NO:210);
YRSKWYN (SEQ ID NO:181);
ISAYNGNT (SEQ ID NO:229); or
IYHSGST (SEQ ID NO:221);

vi) HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);
$AKX_{96}X_{97}X_{98}GX_{99}X_{100}X_{101}X_{102}DY$ (SEQ ID NO:259);
$ARDX_{103}GYSSGWYFDY$ (SEQ ID NO:260);
$ARLX_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}X_{120}AFDI$ (SEQ ID NO:261);
ARIMGYDYGDYDVVDY (SEQ ID NO:199);
$ARIX_{121}X_{122}X_{123}X_{124}X_{125}X_{126}DX_{127}X_{128}X_{129}X_{130}$ (SEQ ID NO:262);
ARVGFSSWYPDLYYFDY (SEQ ID NO:205);
$X_{131}X_{132}X_{133}X_{134}RGYX_{135}DY$ (SEQ ID NO:263);
ARITHDYGDFSDAFDI (SEQ ID NO:194);
$ARX_{136}GVLX_{137}DY$ (SEQ ID NO:264);
AKGSYYFDY (SEQ ID NO:235);
ARLYSGYPSRYYYGMDV (SEQ ID NO:206);
ARVQSGEPESDY (SEQ ID NO:216);
AKIGATDPLDY (SEQ ID NO:187);
ARDLYAFDI (SEQ ID NO:185);
ARPDDDY (SEQ ID NO:203);
AKGGKSYYGFDY (SEQ ID NO:207);
ARADSSAGGGPYYYGMDV (SEQ ID NO:231);
ARVYYDSSGTQGDSFDY (SEQ ID NO:233);
ARVVAAARSYYYYMDV (SEQ ID NO:230);
ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

ARMVNLYYGDAFDI (SEQ ID NO:218);
ARGLITGTTP (SEQ ID NO:211);
ARGQNVDL (SEQ ID NO:198);
ARVQNLGGGSYYVGAFDY (SEQ ID NO:222); or
ARLVGATADDY (SEQ ID NO:219);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X_1 = S or I, X_2 = S or R, X_3 = V or I, X_4 = G, A or N, X_5 = N, E, K or D, X_6 = S or Y, X_7 = I or V, X_8 = S, N or Y, X_9 = N, Y or D, X_{10} = L, Y, T or A, X_{11} = G, S or I, X_{12} = S, I or V, X_{13} = Y or N, X_{14} = S or T, X_{15} = S or N, X_{16} = Y or R, X_{17} = S, T or G, X_{18} = R, I or G, X_{19} = N or D, X_{20} = A or G, X_{21} = E, D or N, X_{22} = N or D, X_{23} = S, F or N, X_{24} = N or V, X_{25} = H or T, X_{26} = S, N or G, X_{27} = S or T, X_{28} = S or G, X_{29} = S, N, G or I, X_{30} = T or S, X_{31} = W, L, V or Q, X_{32} = absent or V, X_{33} = C or S, X_{34} = G or D, X_{35} = S, Y, N or T, X_{36} = Y or N, X_{37} = T or N, X_{38} = W or F, X_{39} = V, G or L, X_{40} = absent or V, X_{41} = absent or R, X_{42} = absent or R, X_{43} = absent or R, X_{44} = absent or D, X_{45} = absent or R, X_{46} = absent or A, X_{47} = absent or D, X_{48} = absent or R, X_{49} = absent or P, X_{50} = A or G , X_{51} = A or T, X_{52} = D, G or S, X_{53} = S or G, X_{54} = S, K or N , X_{55} = G or A, X_{56} = W, G or H, X_{57} = S or Y, X_{58} = Y, R or N, X_{59} = S or N, X_{60} = T, A or W, X_{61} = L or T, X_{62} = Y, A, W or T, X_{63} = T, absent or F, X_{64} = absent or G, X_{65} = absent or G, X_{66} = absent or G, X_{67} = absent or T, X_{68} = absent or K, X_{69} = absent or V, X_{70} = absent or E, X_{71} = absent or F, X_{72} = absent or K, X_{73} = D or N, X_{74} = S or Y, X_{75} = K, S or N, X_{76} = V or L, X_{77} = I, V or W, X_{78} = absent or V, X_{79} = T or N, X_{80} = T or S, X_{81} = T or S, X_{82} = P or T, X_{83} = Y or L, X_{84} = absent or A, X_{85} = A or G, X_{86} = F or Y, X_{87} = S or T, X_{88} = L or F, X_{89} = G, R, T, S or N, X_{90} = G or I, X_{91} = G, F or L, X_{92} = T, S or P, X_{93} = F or S, X_{94} = S or D, X_{95} = N or D, X_{96} = L, F or D, X_{97} = Y, A or L, X_{98} = S or R, X_{99} = S, V or L, X_{100} = S, Y or P, X_{101} = N, L or I, X_{102} = F or I, X_{103} = S or V, X_{104} = H or A, X_{105} = S, Q or F, X_{106} = S or G, X_{107} = absent or Y, X_{108} = absent or S, X_{109} = absent, R or S, X_{110} = Q, N or S, X_{111} = W or Y, X_{112} = absent, Y or F, X_{113} = absent or E, X_{114} = absent or W, X_{115} = absent or E, X_{116} = absent or P, X_{117} = absent, G or S, X_{118} = absent, R or T, X_{119} = G, E or I, X_{120} = D or H, X_{121} = A or G, X_{122} = A or G, X_{123} = A or Y, X_{124} = D or absent, X_{125} = G or D, X_{126} = F, M or R, X_{127} = V, Y or A, X_{128} = absent or F, X_{129} = absent or D, X_{130} = absent or I, X_{131} = absent or A, X_{132} = absent or R, X_{133} = A or G, X_{134} = R or T, X_{135} = F or G, X_{136} = absent or S, X_{137} = absent or F.

In some embodiments, HC-CDR1 is one of VSSNSAAWN (SEQ ID NO:180), GFTFSGAY (SEQ ID NO:183), GFTFSSYG (SEQ ID NO:186), GFTFSSYA (SEQ ID NO:190), GFSFRSYG (SEQ ID NO:193), GFTFRSYG (SEQ ID NO:196), GFSFSSYA (SEQ ID NO:212), WIFLKSYA (SEQ ID NO:204), GFSLNSYG (SEQ ID NO:217), GGTFSSYA (SEQ ID NO:209), GGSISSSNW (SEQ ID NO:220), GFSLSSYG (SEQ ID NO:201), GGTFSSYA (SEQ ID NO:209), ILPSDSYA (SEQ ID NO:226), GYTFTSYG (SEQ ID NO:228), GFTFGSYG (SEQ ID NO:234) or GFSLGSYG (SEQ ID NO:238).

In some embodiments, HC-CDR2 is one of YRSKWYN (SEQ ID NO:181), ISYDGSNK (SEQ ID NO:184), ISYDGSDK (SEQ ID NO:188), IIPIFGTA (SEQ ID NO:210), IYHSGST (SEQ ID NO:221), or ISAYNGNT (SEQ ID NO:229).

In some embodiments, HC-CDR3 is one of ARGTRGYFDY (SEQ ID NO:182), ARDLYAFDI (SEQ ID NO:185), AKIGATDPLDY (SEQ ID NO:187), AKDLSGLPIIDY (SEQ ID NO:189),

ARRGYFDY (SEQ ID NO:191), ARIAAADGMDV (SEQ ID NO:192), ARITHDYGDFSDAFDI (SEQ ID NO:194), AKLYSGSSNFDY (SEQ ID NO:195), AKLSGPNGVDY (SEQ ID NO:197), ARGQNVDL (SEQ ID NO:198), ARIMGYDYGDYDVVDY (SEQ ID NO:199), ARRGYGDY (SEQ ID NO:213), ARVGFSSWYPDLYYFDY (SEQ ID NO:205), AKFARGVYLFDY (SEQ ID NO:215), ARVQSGEPESDY (SEQ ID NO:216), ARMVNLYYGDAFDI (SEQ ID NO:218), ARLVGATADDY (SEQ ID NO:219), AKLSGPNGVDY (SEQ ID NO:197), ARGLITGTTP (SEQ ID NO:211), ARVQNLGGGSYYVGAFDY (SEQ ID NO:222), ARLHFSQYFSTIDAFDI (SEQ ID NO:223), ARDVGYSSGWYFDY (SEQ ID NO:200), ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202), ARPDDDY (SEQ ID NO:203) AKLSGPNGVDY (SEQ ID NO:197), ARLYSGYPSRYYYGMDV (SEQ ID NO:206), AKGGKSYYGFDY (SEQ ID NO:207), ARLHSGRNWGDAFDI (SEQ ID NO:208), ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224), ARDSGYSSGWYFDY (SEQ ID NO:225), ARIAAAGRDAFDI (SEQ ID NO:227), ARVVAAARSYYYYMDV (SEQ ID NO:230), ARADSSAGGGPYYYGMDV (SEQ ID NO:231), ARIGGYDDFDY (SEQ ID NO:232), ARVYYDSSGTQGDSFDY (SEQ ID NO:233), AKGSYYFDY (SEQ ID NO:235), ARGVLFDY (SEQ ID NO:236) or ARSGVLDY (SEQ ID NO:237).

In some embodiments, LC-CDR1 is one of QDVGRY (SEQ ID NO:101), TGNIASNR (SEQ ID NO:104), SSDVGGYNY (SEQ ID NO:107), SSDVGAYNY (SEQ ID NO:110), SSDIGAYNY (SEQ ID NO:114), SSNIGSNY (SEQ ID NO:116), ISDVGGYNY (SEQ ID NO:122), SSNIGNNL (SEQ ID NO:126), SSDVGGYDY (SEQ ID NO:128), QSVSSN (SEQ ID NO:137), SSNIGNNY (SEQ ID NO:140), YSNVGSNL (SEQ ID NO:144), SSNIGSNT (SEQ ID NO:147), SRDVGGYNY (SEQ ID NO:150), SGSIASNY (SEQ ID NO:152), QIISSY (SEQ ID NO:155), SSDVGGYEY (SEQ ID NO:159), SLRGYY (SEQ ID NO:161), SSNIGSYY (SEQ ID NO:164), SSDVGAYNY (SEQ ID NO:167), SSNIGYDA (SEQ ID NO:170), QGSSSY (SEQ ID NO:173), SSDVGGYKY (SEQ ID NO:175) or SSDVGNYKY (SEQ ID NO:178).

In some embodiments, LC-CDR2 is one of AAS (SEQ ID NO:102), DNH (SEQ ID NO:105), DVS (SEQ ID NO:108), EVS (SEQ ID NO:111), RNN (SEQ ID NO:117), DVT (SEQ ID NO:123), DVH (SEQ ID NO:129), DVG (SEQ ID NO:133), EVN (SEQ ID NO:135), DVT (SEQ ID NO:123), GAS (SEQ ID NO:138), DNT (SEQ ID NO:141), EDD (SEQ ID NO:145), INN (SEQ ID NO:148), DDN (SEQ ID NO:153), EDN (SEQ ID NO:157), GNN (SEQ ID NO:162), RND (SEQ ID NO:165), EVF (SEQ ID NO:168) or NDN (SEQ ID NO:171).

In some embodiments, LC-CDR3 is one of QQYRSAPLA (SEQ ID NO:103), QSYDYSSVI (SEQ ID NO:106), SSYTSSSSWV (SEQ ID NO:109), SSYTSSNTLV (SEQ ID NO:112), SSYTSSSTVV (SEQ ID NO:113), SSYTTSSTVV (SEQ ID NO:115), AAWDGSLSGWV (SEQ ID NO:118), SSYTSSSTWV (SEQ ID NO:119), CSYAGSYTFV (SEQ ID NO:120), NSYTSSTPYV (SEQ ID NO:121), SSYAGSYTWV (SEQ ID NO:124), GSYTSSNTQV (SEQ ID NO:125), AAWDDSLSAGV (SEQ ID NO:127), SSYTSSITWV (SEQ ID NO:130), CSYAGSYTWV (SEQ ID NO:131), GSYTSSSTWV (SEQ ID NO:132), SSYTSGSTWV (SEQ ID NO:134), SSYAGTNNFVV (SEQ ID NO:136), QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139), GTWDSSLSGGV (SEQ ID NO:142), SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143), AAWDDSLKGHV (SEQ ID NO:146), AAWDDSLNGWV (SEQ ID NO:149), CSYADYYTWV (SEQ ID NO:151), QSYDSSNLWV (SEQ ID NO:154), QQSYSTPTWT (SEQ ID NO:156), QSYNSSKVV (SEQ ID NO:158), NSYTSSGTLVV (SEQ ID NO:160), DSRGRSGDHWL (SEQ ID NO:163), ATWDDGLSGWV (SEQ ID NO:166), NSYVTGNNWA (SEQ ID

NO:169), AAWDDSLSGWV (SEQ ID NO:172), QQSYSTPLYT (SEQ ID NO:174), CSYAGNYTWL (SEQ ID NO:176), TSYSSSSTLVA (SEQ ID NO:177) or SSYTSSSTLVV (SEQ ID NO:179).

In some embodiments, the antibody or antigen binding fragment has at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: VSSNSAAWN (SEQ ID NO:180)
HC-CDR2: YRSKWYN (SEQ ID NO:181)
HC-CDR3: ARGTRGYFDY (SEQ ID NO:182);

or

HC-CDR1: GFTFSGAY (SEQ ID NO:183)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDLYAFDI (SEQ ID NO:185);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSDK (SEQ ID NO:188)
HC-CDR3: AKDLSGLPIIDY (SEQ ID NO:189);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYFDY (SEQ ID NO:191);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAADGMDV (SEQ ID NO:192);

or

HC-CDR1: GFSFRSYG (SEQ ID NO:193)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFRSYG (SEQ ID NO:196)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGQNVDL (SEQ ID NO:198);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFSFSSYA (SEQ ID NO:212)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYGDY (SEQ ID NO:213);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVQSGEPESDY (SEQ ID NO:216);

or

HC-CDR1: GFSLNSYG (SEQ ID NO:217)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARMVNLYYGDAFDI (SEQ ID NO:218);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLVGATADDY (SEQ ID NO:219);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGLITGTTP (SEQ ID NO:211);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGSISSSNW (SEQ ID NO:220)
HC-CDR2: IYHSGST (SEQ ID NO:221)
HC-CDR3: ARVQNLGGGSYYVGAFDY (SEQ ID NO:222);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHFSQYFSTIDAFDI (SEQ ID NO:223);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDVGYSSGWYFDY (SEQ ID NO:200);

or

HC-CDR1: GFSLSSYG (SEQ ID NO:201)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARPDDDY (SEQ ID NO:203);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLYSGYPSRYYYGMDV (SEQ ID NO:206);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHSGRNWGDAFDI (SEQ ID NO:208);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: ILPSDSYA (SEQ ID NO:226)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAAGRDAFDI (SEQ ID NO:227);

or

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: ISAYNGNT (SEQ ID NO:229)
HC-CDR3: ARVVAAARSYYYYMDV (SEQ ID NO:230);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARADSSAGGGPYYYGMDV (SEQ ID NO:231);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIGGYDDFDY (SEQ ID NO:232);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVYYDSSGTQGDSFDY (SEQ ID NO:233);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFSLGSYG (SEQ ID NO:238)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGVLFDY (SEQ ID NO:236);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARSGVLDY (SEQ ID NO:237).

In some embodiments, the antibody or antigen binding fragment has at least one light chain variable region incorporating the following CDRs:

LC-CDR1: QDVGRY (SEQ ID NO:101)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQYRSAPLA (SEQ ID NO:103);

or

LC-CDR1: TGNIASNR (SEQ ID NO:104)
LC-CDR2: DNH (SEQ ID NO:105)
LC-CDR3: QSYDYSSVI (SEQ ID NO:106);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVS (SEQ ID NO:111)
LC-CDR3: SSYTSSNTLV (SEQ ID NO:112);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113);

or

LC-CDR1: SSDIGAYNY (SEQ ID NO:114)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTTSSTVV (SEQ ID NO:115);

or

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTFV (SEQ ID NO:120);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSTPYV (SEQ ID NO:121);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)

LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSNTQV (SEQ ID NO:125);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVH (SEQ ID NO:129)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSSTWV (SEQ ID NO:132);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: SSYTSGSTWV (SEQ ID NO:134);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: EVN (SEQ ID NO:135)
LC-CDR3: SSYAGTNNFVV (SEQ ID NO:136);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: QSVSSN (SEQ ID NO:137)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139);

or

LC-CDR1: SSNIGNNY (SEQ ID NO:140)
LC-CDR2: DNT (SEQ ID NO:141)
LC-CDR3: GTWDSSLSGGV (SEQ ID NO:142);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143);

or

LC-CDR1: YSNVGSNL (SEQ ID NO:144)
LC-CDR2: EDD (SEQ ID NO:145)
LC-CDR3: AAWDDSLKGHV (SEQ ID NO:146);

or

LC-CDR1: SSNIGSNT (SEQ ID NO:147)
LC-CDR2: INN (SEQ ID NO:148)
LC-CDR3: AAWDDSLNGWV (SEQ ID NO:149);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYADYYTWV (SEQ ID NO:151);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)

LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SGSIASNY (SEQ ID NO:152)
LC-CDR2: DDN (SEQ ID NO:153)
LC-CDR3: QSYDSSNLWV (SEQ ID NO:154);

or

LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SGSIASNY (SEQ ID NO:152)
LC-CDR2: EDN (SEQ ID NO:157)
LC-CDR3: QSYNSSKVV (SEQ ID NO:158);

or

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160);

or

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SLRGYY (SEQ ID NO:161)
LC-CDR2: GNN (SEQ ID NO:162)
LC-CDR3: DSRGRSGDHWL (SEQ ID NO:163);

or

LC-CDR1: SSNIGSYY (SEQ ID NO:164)
LC-CDR2: RND (SEQ ID NO:165)
LC-CDR3: ATWDDGLSGWV (SEQ ID NO:166);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVF (SEQ ID NO:168)
LC-CDR3: NSYVTGNNWA (SEQ ID NO:169);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGYDA (SEQ ID NO:170)
LC-CDR2: NDN (SEQ ID NO:171)
LC-CDR3: AAWDDSLSGWV (SEQ ID NO:172);

or

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174);

or

LC-CDR1: SSDVGGYKY (SEQ ID NO:175)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGNYTWL (SEQ ID NO:176);

or

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS(SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: TSYSSSSTLVA (SEQ ID NO:177);

or

LC-CDR1: SSDVGNYKY (SEQ ID NO:178)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTLVV (SEQ ID NO:179).

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, having at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: VSSNSAAWN (SEQ ID NO:180)
HC-CDR2: YRSKWYN (SEQ ID NO:181)
HC-CDR3: ARGTRGYFDY (SEQ ID NO:182);

or

HC-CDR1: GFTFSGAY (SEQ ID NO:183)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDLYAFDI (SEQ ID NO:185);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSDK (SEQ ID NO:188)
HC-CDR3: AKDLSGLPIIDY (SEQ ID NO:189);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYFDY (SEQ ID NO:191);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAADGMDV (SEQ ID NO:192);

or

HC-CDR1: GFSFRSYG (SEQ ID NO:193)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFRSYG (SEQ ID NO:196)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGQNVDL (SEQ ID NO:198);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFSFSSYA (SEQ ID NO:212)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYGDY (SEQ ID NO:213);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVQSGEPESDY (SEQ ID NO:216);

or

HC-CDR1: GFSLNSYG (SEQ ID NO:217)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARMVNLYYGDAFDI (SEQ ID NO:218);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLVGATADDY (SEQ ID NO:219);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)

HC-CDR3: ARGLITGTTP (SEQ ID NO:211);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGSISSSNW (SEQ ID NO:220)
HC-CDR2: IYHSGST (SEQ ID NO:221)
HC-CDR3: ARVQNLGGGSYYVGAFDY (SEQ ID NO:222);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHFSQYFSTIDAFDI (SEQ ID NO:223);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDVGYSSGWYFDY (SEQ ID NO:200);

or

HC-CDR1: GFSLSSYG (SEQ ID NO:201)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARPDDDY (SEQ ID NO:203);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLYSGYPSRYYYGMDV (SEQ ID NO:206);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHSGRNWGDAFDI (SEQ ID NO:208);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: ILPSDSYA (SEQ ID NO:226)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAAGRDAFDI (SEQ ID NO:227);

or

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: ISAYNGNT (SEQ ID NO:229)
HC-CDR3: ARVVAAARSYYYYMDV (SEQ ID NO:230);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARADSSAGGGPYYYGMDV (SEQ ID NO:231);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIGGYDDFDY (SEQ ID NO:232);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: ARVYYDSSGTQGDSFDY (SEQ ID NO:233);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFSLGSYG (SEQ ID NO:238)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: ARGVLFDY (SEQ ID NO:236);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: ARSGVLDY (SEQ ID NO:237); and

having at least one light chain variable region arrived at following light chain shuffling.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of $X_1X_2DX_3GX_4YX_5Y$ (SEQ ID NO:239), $X_6SNX_7GX_8X_9X_{10}$ (SEQ ID NO:240), $QX_{11}X_{12}SSX_{13}$ (SEQ ID NO:241), $X_{14}GX_{15}IASNX_{16}$ (SEQ ID NO:242), QDVGRY (SEQ ID NO:101), or SLRGYY (SEQ ID NO:161); LC-CDR2: one of DVX_{17} (SEQ ID NO:243), $X_{18}NX_{19}$ (SEQ ID NO:244), $X_{20}AS$ (SEQ ID NO:245), $X_{21}DX_{22}$ (SEQ ID NO:246), EVX_{23} (SEQ ID NO:247), or $DX_{24}X_{25}$ (SEQ ID NO:248); LC-CDR3: one of $X_{26}SYTX_{27}X_{28}X_{29}X_{30}X_{31}VX_{32}$ (SEQ ID NO:249), $X_{33}SYAX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO:250), $X_{50}X_{51}WDX_{52}X_{53}LX_{54}X_{55}X_{56}V$ (SEQ ID NO:251), $QQX_{57}X_{58}X_{59}PX_{60}X_{61}X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}$ (SEQ ID NO:252), $QSYX_{73}X_{74}SX_{75}X_{76}X_{77}X_{78}$ (SEQ ID NO:253), $X_{79}SYX_{80}SSX_{81}X_{82}X_{83}VX_{84}$ (SEQ ID NO:254), NSYVTGNNWA (SEQ ID NO:169), or DSRGRSGDHWL (SEQ ID NO:163); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: one of $GFTFSSYX_{85}$ (SEQ ID NO:255), $GX_{86}X_{87}X_{88}X_{89}SYG$ (SEQ ID NO:256), $X_{90}X_{91}X_{92}X_{93}X_{94}SYA$ (SEQ ID NO:257), WIFLKSYA (SEQ ID NO:204), VSSNSAAWN (SEQ ID NO:180), GGSISSSNW (SEQ ID NO:220), or GFTFSGAY (SEQ ID NO:183); HC-CDR2: one of $ISYDGSX_{95}K$ (SEQ ID NO:258), IIPIFGTA (SEQ ID NO:210), YRSKWYN (SEQ ID NO:181), ISAYNGNT (SEQ ID NO:229), or IYHSGST (SEQ ID NO:221); HC-CDR3: one of AKLSGPNGVDY (SEQ ID NO:197),

$AKX_{96}X_{97}X_{98}GX_{99}X_{100}X_{101}X_{102}DY$ (SEQ ID NO:259), $ARDX_{103}GYSSGWYFDY$ (SEQ ID NO:260), $ARLX_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}X_{120}AFDI$ (SEQ ID NO:261), ARIMGYDYGDYDVVDY (SEQ ID NO:199), $ARIX_{121}X_{122}X_{123}X_{124}X_{125}X_{126}DX_{127}X_{128}X_{129}X_{130}$ (SEQ ID NO:262), ARVGFSSWYPDLYYFDY (SEQ ID NO:205), $X_{131}X_{132}X_{133}X_{134}RGYX_{135}DY$ (SEQ ID NO:263), ARITHDYGDFSDAFDI (SEQ ID NO:194), $ARX_{136}GVLX_{137}DY$ (SEQ ID NO:264), AKGSYYFDY (SEQ ID NO:235), ARLYSGYPSRYYYGMDV (SEQ ID NO:206), ARVQSGEPESDY (SEQ ID NO:216), AKIGATDPLDY (SEQ ID NO:187), ARDLYAFDI (SEQ ID NO:185), ARPDDDY (SEQ ID NO:203), AKGGKSYYGFDY (SEQ ID NO:207), ARADSSAGGGPYYYGMDV (SEQ ID NO:231), ARVYYDSSGTQGDSFDY (SEQ ID NO:233), ARVVAAARSYYYYMDV (SEQ ID NO:230), ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224), ARMVNLYYGDAFDI (SEQ ID NO:218), ARGLITGTTP (SEQ ID NO:211), ARGQNVDL (SEQ ID NO:198), ARVQNLGGGSYYVGAFDY (SEQ ID NO:222), or ARLVGATADDY (SEQ ID NO:219);

wherein X_1 = S or I, X_2 = S or R, X_3 = V or I, X_4 = G, A or N, X_5 = N, E, K or D, X_6 = S or Y, X_7 = I or V, X_8 = S, N or Y, X_9 = N, Y or D, X_{10} = L, Y, T or A, X_{11} = G, S or I, X_{12} = S, I or V, X_{13} = Y or N, X_{14} = S or T, X_{15} = S or N, X_{16} = Y or R, X_{17} = S, T or G, X_{18} = R, I or G, X_{19} = N or D, X_{20} = A or G, X_{21} = E, D or N, X_{22} = N or D, X_{23} = S, F or N, X_{24} = N or V, X_{25} = H or T, X_{26} = S, N or G, X_{27} = S or T, X_{28} = S or G, X_{29} = S, N, G or I, X_{30} = T or S, X_{31} = W, L, V or Q, X_{32} = absent or V, X_{33} = C or S , X_{34} = G or D, X_{35} = S, Y, N or T, X_{36} = Y or N, X_{37} = T or N, X_{38} = W or F, X_{39} = V, G or L, X_{40} = absent or V, X_{41} = absent or R, X_{42} = absent or R, X_{43} = absent or R, X_{44} = absent or D, X_{45} = absent or R, X_{46} = absent or A, X_{47} = absent or D, X_{48} = absent or R, X_{49} = absent or P, X_{50} = A or G , X_{51} = A or T, X_{52} = D, G or S, X_{53} = S or G, X_{54} = S, K or N , X_{55} = G or A, X_{56} = W, G or H, X_{57} = S or Y, X_{58} = Y, R or N, X_{59} = S or N, X_{60} = T, A or W, X_{61} = L or T, X_{62} = Y, A, W or T, X_{63} = T, absent or F, X_{64} = absent or G, X_{65} = absent or G, X_{66} = absent or G, X_{67} = absent or T, X_{68} = absent or K, X_{69} = absent or V, X_{70} = absent or E, X_{71} = absent or F, X_{72} = absent or K, X_{73} = D or N, X_{74} = S or Y, X_{75} = K, S or N, X_{76} = V or L, X_{77} = I, V or W, X_{78} = absent or V, X_{79} = T or N, X_{80} = T or S, X_{81} = T or S, X_{82} = P or T, X_{83} = Y or L, X_{84} = absent or A, X_{85} = A or G, X_{86} = F or Y, X_{87} = S or T, X_{88} = L or F, X_{89} = G, R, T, S or N, X_{90} = G or I, X_{91} = G, F or L, X_{92} = T, S or P, X_{93} = F or S, X_{94} = S or D, X_{95} = N or D, X_{96} = L, F or D, X_{97} = Y, A or L, X_{98} = S or R, X_{99} = S, V or L, X_{100} = S, Y or P, X_{101} = N, L or I, X_{102} = F or I, X_{103} = S or V, X_{104} = H or A, X_{105} = S, Q or F, X_{106} = S or G, X_{107} = absent or Y, X_{108} = absent or S, X_{109} = absent, R or S, X_{110} = Q, N or S, X_{111} = W or Y, X_{112} = absent, Y or F, X_{113} = absent or E, X_{114} = absent or W, X_{115} = absent or E, X_{116} = absent or P, X_{117} = absent, G or S, X_{118} = absent, R or T, X_{119} = G, E or I, X_{120} = D or H, X_{121} = A or G, X_{122} = A or G, X_{123} = A or Y, X_{124} = D or absent, X_{125} = G or D, X_{126} = F, M or R, X_{127} = V, Y or A, X_{128} = absent or F, X_{129} = absent or D, X_{130} = absent or I, X_{131} = absent or A, X_{132} = absent or R, X_{133} = A or G, X_{134} = R or T, X_{135} = F or G, X_{136} = absent or S, X_{137} = absent or F.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs:1 to 50, and;

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs:51 to 100.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, which is capable of inhibiting IL-11 *trans* signalling, optionally wherein the antibody or antigen binding fragment is an antibody or antigen binding fragment according to the present invention.

In some embodiments in accordance with the various aspects of the present invention, the antibody or antigen binding fragment is conjugated to a drug moiety or a detectable moiety.

In another aspect, the present invention provides a complex, optionally an *in vitro* complex and/or optionally isolated, comprising an antibody or antigen binding fragment according to the present invention bound to IL-11.

In another aspect, the present invention provides a composition comprising the antibody or antigen binding fragment according to the present invention, and at least one pharmaceutically-acceptable carrier.

In another aspect, the present invention provides an isolated nucleic acid encoding the antibody or antigen binding fragment according to the present invention.

In some embodiments, the nucleic acid comprises a sequence having at least 60%, 70%, 80%, 90%, 95%, or greater sequence identity to one of SEQ ID NOs:476 to 539, or an equivalent sequence as a result of codon degeneracy. In some embodiments, the nucleic acid comprises a sequence having at least 60%, 70%, 80%, 90%, 95%, or greater sequence identity to one of SEQ ID NOs:571 to 580, or an equivalent sequence as a result of codon degeneracy.

In another aspect, the present invention provides a vector comprising the nucleic acid according to the present invention.

In another aspect, the present invention provides a host cell comprising the vector according to the present invention.

In another aspect, the present invention provides a method for making an antibody or antigen binding fragment according to the present invention, comprising culturing the host cell according to the present invention under conditions suitable for the expression of the antibody or antigen binding fragment, and recovering the antibody or antigen binding fragment.

In another aspect, the present invention provides an antibody, antigen binding fragment, or composition according to the present invention for use in therapy, or in a method of medical treatment.

In another aspect, the present invention provides an antibody, antigen binding fragment, or composition according to the present invention for use in the treatment or prevention of fibrosis, or a disease/disorder characterised by fibrosis.

In another aspect, the present invention provides an antibody, antigen binding fragment, or composition according to the present invention for use in the treatment of a cancer.

In another aspect, the present invention provides the use of an antibody, antigen binding fragment, or composition according to the present invention in the manufacture of a medicament for use in the treatment or prevention of fibrosis or a disease/disorder characterised by fibrosis.

In another aspect, the present invention provides the use of an antibody, antigen binding fragment, or composition according to the present invention in the manufacture of a medicament for use in the treatment or prevention of a cancer.

In another aspect, the present invention provides a method of treating fibrosis comprising administering an antibody, antigen binding fragment, or composition according to the present invention to a subject suffering from fibrosis or a disease/disorder characterised by fibrosis.

In another aspect, the present invention provides a method of treating cancer comprising administering an antibody, antigen binding fragment, or composition according to the present invention to a subject suffering from a cancer.

In another aspect, the present invention provides an antibody or antigen binding fragment for use in a method of treating a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

In another aspect, the present invention provides the use of an antibody or antigen binding fragment in the manufacture of a medicament for use in the treatment of a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

In another aspect, the present invention provides a method of treating a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, comprising administering an antibody or antigen binding fragment to a subject suffering from the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

In another aspect, the present invention provides a method comprising contacting a sample containing, or suspected to contain, IL-11 with an antibody or antigen binding fragment according to the present invention and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

In another aspect, the present invention provides a method of diagnosing a disease or condition in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding fragment according to the present invention and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

In another aspect, the present invention provides a method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with the antibody or antigen binding fragment according to the present invention and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

In another aspect, the present invention provides the use of an antibody or antigen binding fragment according to the present invention for the detection of IL-11 *in vitro* or *in vivo*.

In another aspect, the present invention provides the use of an antibody or antigen binding fragment according to the present invention as an *in vitro* or *in vivo* diagnostic or prognostic agent.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: $X_{138}X_{139}$DVGGY$X_{140}X_{141}$ (SEQ ID NO:393), SSDV$X_{142}X_{143}$YX_{144}Y (SEQ ID NO:394), $X_{145}X_{146}$DX_{147}GAYNY (SEQ ID NO:395), SSDIGX_{148}YNY (SEQ ID NO:396), X_{149}SDVGAYDY (SEQ ID NO:397), SGDVGTYX_{150}Y (SEQ ID NO:398), QX_{151}IX_{152}SY (SEQ ID NO:399), QSX_{153}SSSY (SEQ ID NO:400), RX_{154}DX_{155}GGYDX_{156} (SEQ ID NO:401), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:349) or QSVNSAY (SEQ ID NO:359);

ii) LC-CDR2: DVX_{157} (SEQ ID NO:402) or X_{158}AS (SEQ ID NO:403);

iii) LC-CDR3: X_{159}SYAG$X_{160}X_{161}X_{162}$WX_{163} (SEQ ID NO:404), SSYT$X_{164}X_{165}X_{166}X_{167}$WV (SEQ ID NO:405), QQSYSX_{168}PX_{169}WT (SEQ ID NO:406), SSF$X_{170}X_{171}$S$X_{172}X_{173}$WV (SEQ ID NO:407), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357), or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282);

iv) HC-CDR1: GFTFX_{174}SYX_{175} (SEQ ID NO:409);

v) HC-CDR2: ISYDGSNX_{176} (SEQ ID NO:410);

vi) HC-CDR3: AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKLSGPNGVDY (SEQ ID NO:197) or AKG$X_{177}X_{178}$SYYX_{179}FDY (SEQ ID NO:411);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X_{138} = S, N or I, X_{139} = S or R, X_{140} = N, E or D, X_{141} = Y or F, X_{142} = G or A, X_{143} = D, G or T, X_{144} = N or D, X_{145} = S or N, X_{146} = N, T or S, X_{147} = V or I, X_{148} = V or G, X_{149} = S or G, X_{150} = N or D, X_{151} = A or I, X_{152} = N or S, X_{153} = F or V, X_{154} = S or R, X_{155} = I or V, X_{156} = Y or F, X_{157} = S, T, N, G, V or D, X_{158} = A or G, X_{159} = C, S, A or N, X_{160} = S, R, N, G, T or F, X_{161} = Y or H, X_{162} = T, N, I, S or V, X_{163} = V, M or I, X_{164} = S or N, X_{165} = S or N, X_{166} = T, I, S or R, X_{167} = T or S, X_{168} = T or D, X_{169} = S, R or T, X_{170} = T or A, X_{171} = T or S, X_{172} = I or T, X_{173} = A or T, X_{174} = S or G, X_{175} = G or A, X_{176} = K or R, X_{177} = absent or G, X_{178} = absent or K, and X_{179} = absent or G.

In some embodiments HC-CDR1 is one of GFTFSSYG (SEQ ID NO:186), GFTFSSYA (SEQ ID NO:190) or GFTFGSYG (SEQ ID NO:234).

In some embodiments HC-CDR2 is one of ISYDGSNK (SEQ ID NO:184) or ISYDGSNR (SEQ ID NO:381).

In some embodiments HC-CDR3 is one of AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKGGKSYYGFDY (SEQ ID NO:207), AKGSYYFDY (SEQ ID NO:235) or AKLSGPNGVDY (SEQ ID NO:197).

In some embodiments LC-CDR1 is one of SSDVGGYNF (SEQ ID NO:294), SSDVGGYEY (SEQ ID NO:159), SRDVGGYNY (SEQ ID NO:150), NSDVGGYNY (SEQ ID NO:300), SSDVGGYDY (SEQ ID NO:128), SSDVGGYNY (SEQ ID NO:107), ISDVGGYNY (SEQ ID NO:122), SSDVGDYDY (SEQ ID NO:317), SSDVAGYNY (SEQ ID NO:330), SSDVGTYNY (SEQ ID NO:344), NTDVGAYNY (SEQ ID NO:272), SNDIGAYNY (SEQ ID NO:306), SSDVGAYNY (SEQ ID NO:110), SSDIGVYNY (SEQ ID NO:347), SSDIGGYNY (SEQ ID NO:326), SSDVGAYDY (SEQ ID NO:333), GSDVGAYDY (SEQ ID NO:322), SGDVGTYNY (SEQ ID NO:298), SGDVGTYDY (SEQ ID NO:302), QAINSY (SEQ ID NO:352), QIISSY (SEQ ID NO:155), QSFSSSY (SEQ ID NO:356), QSVSSSY (SEQ ID NO:367), RSDIGGYDY (SEQ ID NO:290), RRDVGGYDF (SEQ ID NO:339), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:349) or QSVNSAY (SEQ ID NO:359).

In some embodiments LC-CDR2 is one of DVS (SEQ ID NO:108), DVV (SEQ ID NO:275), DVT (SEQ ID NO:123), DVD (SEQ ID NO:295), DVN (SEQ ID NO:291), DVG (SEQ ID NO:133), AAS (SEQ ID NO:102) or GAS (SEQ ID NO:138).

In some embodiments LC-CDR3 is one of CSYAGSYTWV (SEQ ID NO:131), SSYAGSYTWV (SEQ ID NO:124), CSYAGSYSWV (SEQ ID NO:273), CSYAGGYTWV (SEQ ID NO:276), NSYAGSYTWV (SEQ ID NO:278), CSYAGSYVWV (SEQ ID NO:285), CSYAGRYTWI (SEQ ID NO:296), CSYAGRYTWM (SEQ ID NO:336), CSYAGTYTWV (SEQ ID NO:340), CSYAGFYTWV (SEQ ID NO:345), CSYAGSHIWV (SEQ ID NO:308), CSYAGRYTWV (SEQ ID NO:313), CSYAGNYTWM (SEQ ID NO:315), CSYAGSYTWI (SEQ ID NO:324), ASYAGNYNWV (SEQ ID NO:304), SSYAGGYTWV (SEQ ID NO:364), SSYTNSRTWV (SEQ ID NO:292), SSYTSNTTWV (SEQ ID NO:311), SSYTSSTTWV (SEQ ID NO:320), SSYTSSSSWV (SEQ ID NO:109), SSYTSSISWV (SEQ ID NO:288), SSYTSSITWV (SEQ ID NO:130), QQSYSTPSWT (SEQ ID NO:354), QQSYSDPRWT (SEQ ID NO:360), QQSYSTPTWT (SEQ ID NO:156), SSFTTSIAWV (SEQ ID NO:268), SSFTSSTTWV (SEQ ID NO:281), SSFATSISWV (SEQ ID NO: 408), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357) or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282).

In some embodiments the antibody or antigen binding fragment has at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNR (SEQ ID NO:381)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197).

In some embodiments the antibody or antigen binding fragment has at least one light chain variable region incorporating the following CDRs:

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTTSIAWV (SEQ ID NO:268);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: NTDVGAYNY (SEQ ID NO:272)
LC-CDR2: DVS (SEQ ID NO:108)

LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVV (SEQ ID NO:275)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);

or

LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTSSTTWV (SEQ ID NO:281);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282);

or

LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYVWV (SEQ ID NO:285);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSISWV (SEQ ID NO:288);

or

LC-CDR1: RSDIGGYDY (SEQ ID NO:290)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTNSRTWV (SEQ ID NO:292);

or

LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVD (SEQ ID NO:295)
LC-CDR3: CSYAGRYTWI (SEQ ID NO:296);

or

LC-CDR1: SGDVGTYNY (SEQ ID NO:298)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);

or

LC-CDR1: NSDVGGYNY (SEQ ID NO:300)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SGDVGTYDY (SEQ ID NO:302)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);

or

LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: ASYAGNYNWV (SEQ ID NO:304);

or

LC-CDR1: SNDIGAYNY (SEQ ID NO:306)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSHIWV (SEQ ID NO:308);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);

or

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYTSNTTWV (SEQ ID NO:311);

or

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGRYTWV (SEQ ID NO:313);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)

LC-CDR3: CSYAGNYTWM (SEQ ID NO:315);

or

LC-CDR1: SSDVGDYDY (SEQ ID NO:317)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSTTWV (SEQ ID NO:320);

or

LC-CDR1: GSDVGAYDY (SEQ ID NO:322)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSFATSISWV (SEQ ID NO: 408);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWI (SEQ ID NO:324);

or

LC-CDR1: SSDIGGYNY (SEQ ID NO:326)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);

or

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVAGYNY (SEQ ID NO:330)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGAYDY (SEQ ID NO:333)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: ASYTRSSVWV (SEQ ID NO:334);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGRYTWM (SEQ ID NO:336);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: RRDVGGYDF (SEQ ID NO:339)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGTYNY (SEQ ID NO:344)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGFYTWV (SEQ ID NO:345);

or

LC-CDR1: SSDIGVYNY (SEQ ID NO:347)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: GSNVGGYNY (SEQ ID NO:349)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109);

or

LC-CDR1: QAINSY (SEQ ID NO:352)
LC-CDR2: AAS (SEQ ID NO:102)

LC-CDR3: QQSYSTPSWT (SEQ ID NO:354);

or

LC-CDR1: QSFSSSY (SEQ ID NO:356)

LC-CDR2: GAS (SEQ ID NO:138)

LC-CDR3: QQSSTSPTWA (SEQ ID NO:357);

or

LC-CDR1: QSVNSAY (SEQ ID NO:359)

LC-CDR2: GAS (SEQ ID NO:138)

LC-CDR3: QQSYSDPRWT (SEQ ID NO:360);

or

LC-CDR1: QIISSY (SEQ ID NO:155)

LC-CDR2: AAS (SEQ ID NO:102)

LC-CDR3: QQSYSTPTWT (SEQ ID NO:156);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)

LC-CDR2: DVN (SEQ ID NO:291

LC-CDR3: NSYTSGSTWV (SEQ ID NO:362);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)

LC-CDR2: DVT (SEQ ID NO:123)

LC-CDR3: SSYAGGYTWV (SEQ ID NO:364);

or

LC-CDR1: QIISSY (SEQ ID NO:155)

LC-CDR2: AAS (SEQ ID NO:102);

or

LC-CDR1: QSVSSSY (SEQ ID NO:367)

LC-CDR2: GAS (SEQ ID NO:138)

LC-CDR3: QQSYSTPTWT (SEQ ID NO:156).

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of $X_{138}X_{139}$DVGGY$X_{140}X_{141}$ (SEQ ID NO:393), SSDV$X_{142}X_{143}$YX_{144}Y (SEQ ID NO:394), $X_{145}X_{146}$DX_{147}GAYNY (SEQ ID NO:395), SSDIGX_{148}YNY (SEQ ID NO:396), X_{149}SDVGAYDY (SEQ ID NO:397), SGDVGTYX_{150}Y (SEQ ID NO:398), QX_{151}IX_{152}SY (SEQ ID NO:399), QSX_{153}SSSY (SEQ ID NO:400), RX_{154}DX_{155}GGYDX_{156} (SEQ ID NO:401), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:214) or QSVNSAY (SEQ ID NO:359); LC-CDR2: one of DVX_{157} (SEQ ID NO:402) or X_{158}AS (SEQ ID NO:403); LC-CDR3: one of X_{159}SYAG$X_{160}X_{161}X_{162}$WX_{163} (SEQ ID NO:404), SSYT$X_{164}X_{165}X_{166}X_{167}$WV (SEQ ID NO:405), QQSYSX_{168}PX_{169}WT (SEQ ID NO:406), SSF$X_{170}X_{171}$S$X_{172}X_{173}$WV (SEQ ID NO:407), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357), or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: GFTFX$_{174}$SYX$_{175}$ (SEQ ID NO:409); HC-CDR2: ISYDGSNX$_{176}$ (SEQ ID NO:410); HC-CDR3: AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKLSGPNGVDY (SEQ ID NO:197) or AKGX$_{177}$X$_{178}$SYYX$_{179}$FDY (SEQ ID NO:411);

wherein X$_{138}$ = S, N or I, X$_{139}$ = S or R, X$_{140}$ = N, E or D, X$_{141}$ = Y or F, X$_{142}$ = G or A, X$_{143}$ = D, G or T, X$_{144}$ = N or D, X$_{145}$ = S or N, X$_{146}$ = N, T or S, X$_{147}$ = V or I, X$_{148}$ = V or G, X$_{149}$ = S or G, X$_{150}$ = N or D, X$_{151}$ = A or I, X$_{152}$ = N or S, X$_{153}$ = F or V, X$_{154}$ = S or R, X$_{155}$ = I or V, X$_{156}$ = Y or F, X$_{157}$ = S, T, N, G, V or D, X$_{158}$ = A or G, X$_{159}$ = C, S, A or N, X$_{160}$ = S, R, N, G, T or F, X$_{161}$ = Y or H, X$_{162}$ = T, N, I, S or V, X$_{163}$ = V, M or I, X$_{164}$ = S or N, X$_{165}$ = S or N, X$_{166}$ = T, I, S or R, X$_{167}$ = T or S, X$_{168}$ = T or D, X$_{169}$ = S, R or T, X$_{170}$ = T or A, X$_{171}$ = T or S, X$_{172}$ = I or T, X$_{173}$ = A or T, X$_{174}$ = S or G, X$_{175}$ = G or A, X$_{176}$ = K or R, X$_{177}$ = absent or G, X$_{178}$ = absent or K, and X$_{179}$ = absent or G.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs: 267, 269, 270, 271, 274, 277, 279, 280, 540, 283, 286, 287, 289, 353, 293, 297, 299, 301, 303, 305, 307, 309, 310, 312, 314, 316, 318, 319, 321, 323, 325, 327, 328, 329, 331, 332, 335, 337, 338, 341, 342, 343, 346, 348, 214, 350, 13, 3, 351, 355, 358, 35, 361, 363, 365, 366, or 20; and

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs: 53, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 85, 390, 73, 391, or 392.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising an amino acid sequence having at least 85% sequence identity to the sequence of one of SEQ ID NOs: 412 to 475.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565);

ii) LC-CDR2: X$_{184}$AS (SEQ ID NO:569);

iii) LC-CDR3: X$_{185}$QX$_{186}$X$_{187}$SX$_{188}$X$_{189}$X$_{190}$T (SEQ ID NO:570);

iv) HC-CDR1: GYTFTX$_{180}$YX$_{181}$ (SEQ ID NO:567);

v) HC-CDR2: INPX$_{182}$NGGX$_{183}$ (SEQ ID NO:568) or IYPRSSNT (SEQ ID NO:552);

vi) HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X$_{180}$ = D or S, X$_{181}$ =N or G, X$_{182}$ = H, D or N, X$_{183}$ = P, T or I, X$_{184}$ = G, Y or W, X$_{185}$ = Q or G X$_{186}$ = Y, G or S, X$_{187}$ = Y, N or S, X$_{188}$ = Y or W, X$_{189}$ = P or absent, and X$_{190}$ = L, Y or R.

In some embodiments HC-CDR1 is one of GYTFTDYN (SEQ ID NO:542) or GYTFTSYG (SEQ ID NO:228).

In some embodiments HC-CDR2 is one of INPHNGGP (SEQ ID NO:543), INPDNGGT (SEQ ID NO:546), INPNNGGI (SEQ ID NO:549) or IYPRSSNT (SEQ ID NO:552).

In some embodiments HC-CDR3 is one of ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553).

In some embodiments LC-CDR1 is one of ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565).

In some embodiments LC-CDR2 is one of GAS (SEQ ID NO:138), YAS (SEQ ID NO:559) or WAS (SEQ ID NO:563).

In some embodiments LC-CDR3 is one of GQGYSYPYT (SEQ ID NO:556), QQSNSWPLT (SEQ ID NO:560), QQYYSYPLT (SEQ ID NO:563) or QQYSSYRT (SEQ ID NO:566).

In some embodiments the antibody or antigen binding fragment has at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPHNGGP (SEQ ID NO:543)
HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544);
or
HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPDNGGT (SEQ ID NO:546)
HC-CDR3: AREGPYGYTWFAY (SEQ ID NO:547);
or
HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPNNGGI (SEQ ID NO:549)
HC-CDR3: ARNPSLYDGYLDC (SEQ ID NO:550);
or
HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: IYPRSSNT (SEQ ID NO:552)
HC-CDR3: ARANWVGYFDV (SEQ ID NO:553).

In some embodiments the antibody or antigen binding fragment has at least one heavy chain variable region incorporating the following CDRs:

LC-CDR1: ENVVTY (SEQ ID NO:555)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: GQGYSYPYT (SEQ ID NO:556);
or
LC-CDR1: QSIGTS (SEQ ID NO:558)
LC-CDR2: YAS (SEQ ID NO:559)
LC-CDR3: QQSNSWPLT (SEQ ID NO:560);
or
LC-CDR1: QSLLYNSSQKNY (SEQ ID NO:562)
LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYYSYPLT (SEQ ID NO:581);

or

LC-CDR1: QDVGTA (SEQ ID NO:565)
LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYSSYRT (SEQ ID NO:566).

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565); LC-CDR2: X_{184}AS (SEQ ID NO:569); LC-CDR3: $X_{185}QX_{186}X_{187}SX_{188}X_{189}X_{190}T$ (SEQ ID NO:570); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: $GYTFTX_{180}YX_{181}$ (SEQ ID NO:567); HC-CDR2: one of $INPX_{182}NGGX_{183}$ (SEQ ID NO:568) or IYPRSSNT (SEQ ID NO:552); HC-CDR3: one of ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553);

wherein X_{180} = D or S, X_{181} =N or G, X_{182} = H, D or N, X_{183} = P, T or I, X_{184} = G, Y or W, X_{185} = Q or G X_{186} = Y, G or S, X_{187} = Y, N or S, X_{188} = Y or W, X_{189} = P or absent, and X_{190} = L, Y or R.

In another aspect, the present invention provides an antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs:554, 557, 561 or 564; and

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs:541, 545, 548 or 551.

Description

The present invention relates to antibodies with specificity for interleukin-11 (IL-11). The present disclosure describes the identification of IL-11/IL-11R signalling as a key mediator of fibrosis, and the generation and functional characterisation of anti-IL-11 antibodies. Therapeutic and diagnostic uses of the antibodies is also described.

IL-11 and IL-11 mediated signalling

The antibodies and fragments of the present invention bind to interleukin 11. Interleukin 11 (IL-11), also known as adipogenesis inhibitory factor, is a pleiotropic cytokine and a member of the IL-6 family of cytokines that includes IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF) and neuropoetin (NP-1).

IL-11 is transcribed with a canonical signal peptide that ensures efficient secretion from cells. The immature form of human IL-11 is a 199 amino acid polypeptide whereas the mature form of IL-11 encodes a protein of 178 amino acid residues (Garbers and Scheller., Biol. Chem. 2013; 394(9):1145-1161). The human IL-11

amino acid sequence is available under UniProt accession no. P20809 (P20809.1 GI:124294). Recombinant human IL-11 (oprelvekin) is also commercially available. IL-11 from other species, including mouse, rat, pig, cow, several species of bony fish and primates, have also been cloned and sequenced.

In this specification "IL-11" refers to an IL-11 from any species and includes isoforms, fragments, variants or homologues of an IL-11 from any species.

In some embodiments, the IL-11 is mammalian IL-11 (e.g. cynomolgous, human and/or rodent (e.g. rat and/or murine) IL-11). Isoforms, fragments, variants or homologues of an IL-11 may optionally be characterised as having at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of immature or mature IL-11 from a given species, e.g. human. Isoforms, fragments, variants or homologues of an IL-11 may optionally be characterised by ability to bind IL-11Rα (preferably from the same species) and stimulate signal transduction in cells expressing IL-11Rα and gp130 (e.g. as described in Curtis et al. Blood, 1997, 90(11); or Karpovich et al. Mol. Hum. Reprod. 2003 9(2): 75-80). A fragment of IL-11 may be of any length (by number of amino acids), although may optionally be at least 25% of the length of mature IL-11 and may have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of mature IL-11. A fragment of IL-11 may have a minimum length of 10 amino acids, and a maximum length of one of 15, 20, 25, 30, 40, 50, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 195 amino acids.

IL-11 signals through a homodimer of the ubiquitously expressed β-receptor glycoprotein 130 (gp130; also known as glycoprotein 130, IL-6ST, IL-6-beta or CD130). Gp130 is a transmembrane protein that forms one subunit of the type I cytokine receptor with the IL-6 receptor family. Specificity is gained through an individual IL-11 α-receptor (IL-11Rα), which does not directly participate in signal transduction, although the initial cytokine binding event to the α-receptor leads to the final complex formation with the β-receptors. IL-11 activates a downstream signalling pathway, which is predominantly the mitogen-activated protein kinase (MAPK)-cascade and the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway (Garbers and Scheller, *supra*).

Human IL-11Rα is a 422 amino acid polypeptide (Genbank accession no. NP_001136256.1 GI:218505839) and shares ~85% nucleotide and amino acid sequence identity with the murine IL-11Rα (Du and Williams., Blood Vol, 89, No,11, June 1, 1997). Two isoforms of IL-11Rα have been reported, which differ in the cytoplasmic domain (Du and Williams, *supra*). In some embodiments as used herein, the IL-11Rα may be IL-11Rα isoform 1 or IL-11Rα isoform 2.

The IL-11 receptor α-chain (IL-11Rα) shares many structural and functional similarities with the IL-6 receptor α-chain (IL-6Rα). The extracellular domain shows 24% amino acid identity including the characteristic conserved Trp-Ser-X-Trp-Ser (WSXWS) motif. The short cytoplasmic domain (34 amino acids) lacks the Box 1 and 2 regions that are required for activation of the JAK/STAT signalling pathway.

IL-11Rα binds its ligand with a low affinity (Kd ~10 nmol/L) and alone is insufficient to transduce a biological signal. The generation of a high affinity receptor (Kd ~400 to 800 pmol/L) capable of signal transduction requires co-expression of the IL-11Rα and gp130 (Curtis et al (Blood 1997 Dec 1;90 (11):4403-12; Hilton et al., EMBO J 13:4765, 1994; Nandurkar et al., Oncogene 12:585, 1996). Binding of IL-11 to cell-surface IL-11Rα induces heterodimerization, tyrosine phosphorylation, activation of gp130 and MAPK and/or Jak/STAT signalling as described above.

The receptor binding sites on murine IL-11 have been mapped and three sites – sites I, II and III - identified. Binding to gp130 is reduced by substitutions in the site II region and by substitutions in the site III region. Site III mutants show no detectable agonist activity and have IL-11Rα antagonist activity (Cytokine Inhibitors Chapter 8; edited by Gennaro Ciliberto and Rocco Savino, Marcel Dekker, Inc. 2001).

In principle, a soluble IL-11Rα can also form biologically active soluble complexes with IL-11 (Pflanz et al., 1999 FEBS Lett, 450, 117-122) raising the possibility that, similar to IL-6, IL-11 may in some instances bind soluble IL-11Rα prior to binding cell-surface gp130 (Garbers and Scheller, *supra*). Curtis et al (Blood 1997 Dec 1;90 (11):4403-12) describe expression of a soluble murine IL-11 receptor alpha chain (sIL-11Rα) and examined signalling in cells expressing gp130. In the presence of gp130 but not transmembrane IL-11R the sIL-11R mediated IL-11 dependent differentiation of M1 leukemic cells and proliferation in Ba/F3 cells and early intracellular events including phosphorylation of gp130, STAT3 and SHP2 similar to signalling through transmembrane IL-11R.

Activation of signalling through cell-membrane bound gp130 by IL-11 bound to soluble IL-11Rα has recently been demonstrated (Lokau et al., 2016 Cell Reports 14, 1761–1773). This so-called IL-11 *trans* signalling may be a very important component of IL-11 mediated signalling, and may even be the most common form of IL-11 mediated signalling, because whilst the expression of IL-11Rα is restricted to a relatively small subset of cell types, gp130 is expressed on a wide range of cell types.

As used herein, 'IL-11 *trans* signalling' is used to refer to signalling which is triggered by binding of IL-11 bound to IL-11Rα, to gp130. The IL-11 may be bound to IL-11Rα as a non-covalent complex. The gp130 is membrane-bound and expressed by the cell in which signalling occurs following binding of the IL-11:IL-11Rα complex to gp130. In some embodiments the IL-11Rα may be a soluble IL-11Rα. In some embodiments, the soluble IL-11Rα is a soluble (secreted) isoform of IL-11Rα (e.g. lacking a transmembrane domain). In some embodiments, the soluble IL-11Rα is the liberated product of proteolytic cleavage of the extracellular domain of cell membrane bound IL-11Rα. In some embodiments, the IL-11Rα may be cell membrane-bound, and signalling through gp130 may be triggered by binding of IL-11 bound to cell-membrane-bound IL-11Rα.

In this specification an IL-11 receptor (IL-11R) refers to a polypeptide capable of binding IL-11 and inducing signal transduction in cells expressing gp130. An IL-11 receptor may be from any species and includes isoforms, fragments, variants or homologues of an IL-11 receptor from any species. In preferred embodiments the species is human (*Homo sapiens*). In some embodiments the IL-11 receptor may be IL-11Rα. Isoforms, fragments, variants or homologues of an IL-11Rα may optionally be characterised as having

at least 70%, preferably one of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity to the amino acid sequence of IL-11Rα from a given species, e.g. human. Isoforms, fragments, variants or homologues of an IL-11Rα may optionally be characterised by ability to bind IL-11 (preferably from the same species) and stimulate signal transduction in cells expressing IL-11Rα and gp130 (e.g. as described in Curtis et al. Blood, 1997, 90(11) or Karpovich et al. Mol. Hum. Reprod. 2003 9(2): 75-80). A fragment of an IL-11 receptor may be of any length (by number of amino acids), although may optionally be at least 25% of the length of the mature IL-11Rα and have a maximum length of one of 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the length of the mature IL-11Rα. A fragment of an IL-11 receptor fragment may have a minimum length of 10 amino acids, and a maximum length of one of 15, 20, 25, 30, 40, 50, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 400, or 415 amino acids.

TGFβ1 has been shown to induce IL-11 expression in fibroblasts (Elias et al., 1994 J. Immunol. 152, 2421–2429).

IL-11 has been proposed to function mainly as a thrombopoietic growth factor, which underpinned the use of recombinant IL-11 (Neumega (Oprelvekin)) as a therapeutic agent to increase platelet count.

The role of IL-11 in fibrosis is not clear. The majority of studies suggest an anti-fibrotic function for IL-11 in the heart (Obana et al., 2010 Circulation 121, 684–691; Obana et al., 2012 Heart and Circulatory Physiology 303, H569–77) and kidney (Ham et al., 2013 Anesthesiology 119, 1389–1401; Stangou et al., 2011 J. Nephrol. 24, 106–111). Kurahara et al., J. Smooth Muscle Res. 2016; 52: 78–92 describes IL-11 as an anti-fibrotic cytokine, and suggests that IL-11 supresses αSMA expression.

IL-11 has also been suggested to be an anti-inflammatory factor in several tissues and chronic inflammatory diseases (Trepicchio and Dorner, 1998 Expert Opin Investig Drugs 7, 1501–1504; Zhu et al., 2015 PLoS ONE 10, e0126296). These studies suggest that the observed secretion of IL-11 in response to TGFβ1 is a protective mechanism.

On the other hand, it has been suggested that IL-11 signalling may be involved in pathology of diseases of the lung. Inhibition of IL-11 either via antibodies or a mutated recombinant IL-11 in a model of tuberculosis revealed a positive feedback loop *in vivo* and diminished histopathology of the lung (Kapina et al., 2011 PLoS ONE 6, e21878; Shepelkova et al., 2016 Journal of Infectious Diseases 214, jiw176), fibrosis of the murine airway has been associated with IL-11 expression (Tang et al., 1996 The Journal of Clinical Investigation 98, 2845–2853). When the pro-fibrotic function of IL-13 in lung tissue was investigated in IL-11RA -/- mice, IL-11 signalling was implicated in the mechanism (Chen et al., 2005 J. Immunol. 174, 2305–2313).

IL-11 was also found to be elevated in the airway of patients with severe asthma (Minshall et al., 2000 Respiratory Research 14, 1–14), is overexpressed in the lungs of IPF patients (Lindahl et al., 2013 Respiratory Research 14, 1–14) and is elevated in skin lesions in atopic dermatitis patients (Toda et al., 2003 J Allergy Clin Immun 111, 875–881). It is uncertain whether these associations are due to increased IL-

11 gene/protein expression as a response to disease processes, or whether IL-11 is an effector of disease processes.

Antibodies and antigen-binding fragments

Antibodies and antigen-binding fragments according to the present invention bind to IL-11 (interleukin 11). In some embodiments, the antibody/fragment binds to human IL-11. In some embodiments, the antibody/fragment binds to non-human primate IL-11. In some embodiments, the antibody/fragment binds to murine IL-11.

By “antibody” we include fragments and derivatives thereof, or a synthetic antibody or synthetic antibody fragment. As used herein, an antibody is a polypeptide capable of binding specifically to the relevant target molecule (i.e. the antigen for which the antibody is specific). Antibodies according to the present invention may be provided in isolated form.

In view of contemporary techniques in relation to monoclonal antibody technology, antibodies can be prepared to most antigens. The antigen-binding portion may be a part of an antibody (for example a Fab fragment) or a synthetic antibody fragment (for example a single chain Fv fragment [ScFv]). Suitable monoclonal antibodies to selected antigens may be prepared by known techniques, for example those disclosed in "Monoclonal Antibodies: A manual of techniques ", H Zola (CRC Press, 1988) and in "Monoclonal Hybridoma Antibodies: Techniques and Applications ", J G R Hurrell (CRC Press, 1982). Chimeric antibodies are discussed by Neuberger et al (1988, 8th International Biotechnology Symposium Part 2, 792-799).

Monoclonal antibodies (mAbs) are useful in the methods of the invention and are a homogenous population of antibodies specifically targeting a single epitope on an antigen.

Antigen binding fragments of antibodies, such as Fab and Fab_2 fragments may also be used/provided as can genetically engineered antibodies and antibody fragments. The variable heavy (V_H) and variable light (V_L) domains of the antibody are involved in antigen recognition, a fact first recognised by early protease digestion experiments. Further confirmation was found by "humanisation" of rodent antibodies. Variable domains of rodent origin may be fused to constant domains of human origin such that the resultant antibody retains the antigenic specificity of the rodent parent antibody (Morrison et al (1984) Proc. Natl. Acad. Sd. USA 81, 6851-6855).

In some embodiments, the antibody/fragment is a fully human antibody/fragment. A fully human antibody/fragment is encoded by human nucleic acid sequence(s). Fully human antibodies/fragments are devoid of non-human amino acid sequences.

The two most commonly employed techniques to the production of fully human antibodies are (i) phage display, in which human antibody genes are expressed in phage display libraries, and (ii) production of antibodies in transgenic mice engineered to have human antibody genes (described in Park and Smolen Advances in Protein Chemistry (2001) 56: 369-421). Briefly, in the human antibody gene-phage display

technique, genes encoding the VH and VL chains are generated by PCR amplification and cloning from "naive" human lymphocytes, and assembled into a library from which they can be expressed either as disulfide-linked Fab fragments or as single-chain Fv (scFv) fragments. The Fab- or scFv-encoding genes are fused to a surface coat protein of filamentous bacteriophage and Fab or scFv capable of binding to the target of interest can then be identified by screening the library with antigen. Molecular evolution or affinity maturation procedures can be employed to enhance the affinity of the Fab/scFv fragment. In the transgenic mouse technique, mice in which the endogenous murine Ig gene loci have been replaced by homologous recombination with their human homologues are immunized with antigen, and monoclonal antibody is prepared by conventional hybridoma technology, to yield fully human monoclonal antibody.

In some embodiments, the antibody/fragment according to the present invention is a murine antibody/fragment. The antibody/fragment may be prepared by phage display using a human naïve antibody gene library.

In some embodiments, the antibody/fragment is a mouse/human chimeric antibody/fragment (e.g., an antibody/antigen binding fragment comprising murine variable domains and human constant regions). In some embodiments, the antibody/fragment is a humanised antibody/fragment (e.g., an antibody/antigen binding fragment comprising murine CDRs and human framework and constant regions).

A mouse/human chimeric antibody/antigen binding fragment can be prepared from a mouse monoclonal antibody by the process of chimerisation, e.g. as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 8 thereof, in particular section 3 of Chapter 8.

A humanised antibody/antigen binding fragment can be prepared from a mouse antibody by the process of chimerisation, e.g. as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 7 thereof, in particular section 3.1 of Chapter 7 entitled ‘Antibody Humanization’.

That antigenic specificity is conferred by variable domains and is independent of the constant domains is known from experiments involving the bacterial expression of antibody fragments, all containing one or more variable domains. These molecules include Fab-like molecules (Better et al (1988) Science 240, 1041); Fv molecules (Skerra et al (1988) Science 240, 1038); single-chain Fv (ScFv) molecules where the V_H and V_L partner domains are linked via a flexible oligopeptide (Bird et al (1988) Science 242, 423; Huston et al (1988) Proc. Natl. Acad. Sd. USA 85, 5879) and single domain antibodies (dAbs) comprising isolated V domains (Ward et al (1989) Nature 341, 544). A general review of the techniques involved in the synthesis of antibody fragments which retain their specific binding sites is to be found in Winter & Milstein (1991) Nature 349, 293-299.

By "ScFv molecules" we mean molecules wherein the V_H and V_L partner domains are covalently linked, e.g. by a flexible oligopeptide.

Fab, Fv, ScFv and dAb antibody fragments can all be expressed in and secreted from E. coli, thus allowing the facile production of large amounts of the said fragments.

Whole antibodies, and $F(ab')_2$ fragments are "bivalent". By "bivalent" we mean that the said antibodies and $F(ab')_2$ fragments have two antigen combining sites. In contrast, Fab, Fv, ScFv and dAb fragments are monovalent, having only one antigen combining site.

The present invention provides an antibody or antigen binding fragment which is capable of binding to IL-11. In some embodiments, the antibody or antigen binding fragment may be isolated.

An antigen-binding fragment according to the present invention may be any fragment of a polypeptide which is capable of binding to an antigen.

In some embodiments, an antigen binding fragment comprises at least three light chain CDRs (i.e. LC-CDR1, LC-CDR2 and LC-CDR3; also referred to herein as LC-CDRs 1-3) and three heavy chain CDRs (i.e. HC-CDR1, HC-CDR2 and HC-CDR3; also referred to herein as HC-CDRs 1-3) which together define the antigen binding region of an antibody or antigen binding fragment. In some embodiments, an antigen binding fragment may comprise the light chain variable domain and heavy chain variable domain of an antibody or antigen binding fragment. In some embodiments, an antigen binding fragment may comprise the light chain polypeptide and heavy chain polypeptide of an antibody or antigen binding fragment.

The present invention also provides a chimeric antigen receptor (CAR) capable of binding to IL-11, comprising one or more antigen binding fragments or polypeptides according to the present invention. Chimeric Antigen Receptors (CARs) are recombinant receptors that provide both antigen-binding and T cell activating functions. CAR structure and engineering is reviewed, for example, in Dotti et al., Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. Antigen-binding fragments according to the present invention are provided herein as the antigen-binding domain of a chimeric antigen receptor (CAR). In some embodiments, the CAR comprises a VL domain and a VH domain according to any embodiment of an antibody, antigen binding fragment or polypeptide described herein. CARs may be combined with costimulatory ligands, chimeric costimulatory receptors or cytokines to further enhance T cell potency, specificity and safety (Sadelain et al., The basic principles of chimeric antigen receptor (CAR) design. Cancer Discov. 2013 April; 3(4): 388–398. doi:10.1158/2159-8290.CD-12-0548, specifically incorporated herein by reference). Also provided is a cell comprising a CAR according to the invention. The CAR according to the present invention may be used to generate T cells. Engineering of CARs into T cells may be performed during culture, *in vitro*, for transduction and expansion, such as happens during expansion of T cells for adoptive T cell therapy.

Also provided in the present invention are bispecific antibodies and bispecific antigen binding fragments comprising an antibody or antigen binding fragment according to the present invention. The bispecific antibodies or bispecific antigen binding fragments may comprise (i) an antibody or antigen binding fragment according to the present invention, and (ii) an antibody or antigen binding fragment specific for a target other than IL-11.

Bispecific antibodies/fragments may be provided in any suitable format, such as those formats described in Kontermann MAbs 2012, 4(2): 182-197, which is hereby incorporated by reference in its entirety. For example, a bispecific antibody or bispecific antigen binding fragment may be a bispecific antibody conjugate (e.g. an IgG2, $F(ab')_2$ or CovX-Body), a bispecific IgG or IgG-like molecule (e.g. an IgG, $scFv_4$-Ig, IgG-scFv, scFv-IgG, DVD-Ig, IgG-sVD, sVD-IgG, 2 in 1-IgG, mAb^2, or Tandemab common LC), an asymmetric bispecific IgG or IgG-like molecule (e.g. a kih IgG, kih IgG common LC, CrossMab, kih IgG-scFab, mAb-Fv, charge pair or SEED-body), a small bispecific antibody molecule (e.g. a Diabody (Db), dsDb, DART, scDb, tandAbs, tandem scFv (taFv), tandem dAb/VHH, triple body, triple head, Fab-scFv, or $F(ab')_2$-$scFv_2$), a bispecific Fc and C_H3 fusion protein (e.g. a taFv-Fc, Di-diabody, scDb-C_H3, scFv-Fc-scFv, HCAb-VHH, scFv-kih-Fc, or scFv-kih-C_H3), or a bispecific fusion protein (e.g. a $scFv_2$-albumin, scDb-albumin, taFv-toxin, DNL-Fab_3, DNL-Fab_4-IgG, DNL-Fab_4-IgG-$cytokine_2$). See in particular Figure 2 of Kontermann MAbs 2012, 4(2): 182-19.

Methods for producing bispecific antibodies include chemically crosslinking of antibodies or antibody fragments, e.g. with reducible disulphide or non-reducible thioether bonds, for example as described in Segal and Bast, 2001. Production of Bispecific Antibodies. Current Protocols in Immunology. 14:IV:2.13:2.13.1–2.13.16, which is hereby incorporated by reference in its entirety. For example, *N*-succinimidyl-3-(-2-pyridyldithio)-propionate (SPDP) can be used to chemically crosslink e.g. Fab fragments via hinge region SH- groups, to create disulfide-linked bispecific $F(ab)_2$ heterodimers. Other methods include fusing antibody-producing hybridomas e.g. with polyethylene glycol, to produce a quadroma cell capable of secreting bispecific antibody, for example as described in D. M. and Bast, B. J. 2001. Production of Bispecific Antibodies. Current Protocols in Immunology. 14:IV:2.13:2.13.1–2.13.16. Bispecific antibodies and bispecific antigen binding fragments can also be produced recombinantly, by expression from e.g. a nucleic acid construct encoding polypeptides for the antigen binding molecules, for example as described in Antibody Engineering: Methods and Protocols, Second Edition (Humana Press, 2012), at Chapter 40: Production of Bispecific Antibodies: Diabodies and Tandem scFv (Hornig and Färber-Schwarz), or French, How to make bispecific antibodies, Methods Mol. Med. 2000; 40:333-339, the entire contents of both of which are hereby incorporated by reference.

Antibodies may be produced by a process of affinity maturation in which a modified antibody is generated that has an improvement in the affinity of the antibody for antigen, compared to an unmodified parent antibody. Affinity-matured antibodies may be produced by procedures known in the art, e.g., Marks *et al.,Rio/Technology* 10:779-783 (1992); Barbas *et al. Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier *et al. Gene* 169:147-155 (1995); Yelton *et al. J. Immunol.* 155:1994-2004 (1995); Jackson *et al., J. Immunol.* 154(7):331 0-15 9 (1995); and Hawkins *et al, J. Mol. Biol.* 226:889-896 (1992).

The present invention provides antibodies described herein which have further undergone the process of chain shuffling, e.g. light chain shuffling and/or heavy chain shuffling. Chain shuffling to improve antibody affinity is described in detail in Marks, Antibody Affinity Maturation by Chain Shuffling, Antibody Engineering Methods and Protocols, Humana Press (2004) Vol. 248, pp327-343, which is hereby incorporated by reference in its entirety – in particular, light chain shuffling is described in detail at sections 3.1 and 3.2

thereof. In light chain shuffling, heavy chain variable regions of antibodies are combined with a repertoire of light chain variable region partners to identify new VL/VH combinations having high affinity for the target protein of interest. In this way, the antibody/fragment is optimised for very high binding affinity.

In some aspects, the antibody/fragment of the present invention comprises the CDRs (i.e. CDRs 1-3) of the VH and/or VL domains of an IL-11-binding antibody clone described herein, or a variant thereof. In some embodiments, the antibody/fragment of the present invention comprises HC-CDRs 1-3 of an IL-11-binding antibody clone described herein, or a variant thereof. In some embodiments, the antibody/fragment of the present invention comprises LC-CDRs 1-3 of an IL-11-binding antibody clone described herein, or a variant thereof.

HC-CDRs 1-3 and LC-CDRs 1-3 of the antibody clones of the present disclosure are defined according to VBASE2, as described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674, which is hereby incorporated by reference in its entirety.

As used herein, a variant of a CDR may comprise e.g. 1 or 2 or 3 substitutions in the amino acid sequence of the CDR. As used herein, a variant of a VL or VH domain may comprise e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 substitutions in the amino acid sequence of the domain.

In some embodiments, the antibody/fragment of the present invention comprises HC-CDRs 1-3 of an IL-11-binding antibody clone described herein, or a variant thereof, and LC-CDRs 1-3 of an IL-11-binding antibody clone described herein, or a variant thereof.

In some aspects, the antibody/fragment of the present invention comprises the CDRs of the VH and/or VL domains of an IL-11-binding antibody clone described herein, or a variant thereof. In some aspects, the antibody/fragment of the present invention comprises the VH and/or VL domains of an IL-11-binding antibody clone described herein, or a variant thereof.

In some aspects, the antibody/fragment of the present invention comprises the CDRs of the VH and/or VL domains of a clone, or a variant thereof, selected from YU33-A2, YU33-B3/H3, YU33-B4/YU45-G2/A3, YU33-E3, YU33-E6, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-B2, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-H8, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4, YU45-C3/A6, YU45-D1, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU45-B8, YU45-C1, YU46-G1, YU46-A2, YU46-A8, YU46-B2, YU46-B6, YU46-C1, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7 or YU46-D3; e.g. selected from YU45-C11/A10, YU45-G1, YU45-E3, YU45-F8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-G7, YU45-B6, YU45-C1, YU46-B6, YU46-E3, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-H11/D12, YU45-G1, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-F8, YU45-H10, YU46-A10, YU45-A8/C6, YU45-D9/D3, YU45-B6, YU45-C1, YU46-A8, YU46-C1, YU46-H8, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-E3, YU45-F2, YU45-F5, YU46-A8 or YU46-G8.

In some aspects, the antibody/fragment of the present invention comprises the VH and/or VL domains of a clone, or a variant thereof, selected from YU33-A2, YU33-B3/H3, YU33-B4/YU45-G2/A3, YU33-E3, YU33-E6, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-B2, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-H8, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4, YU45-C3/A6, YU45-D1, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU45-B8, YU45-C1, YU46-G1, YU46-A2, YU46-A8, YU46-B2, YU46-B6, YU46-C1, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7 or YU46-D3; e.g. selected from YU45-C11/A10, YU45-G1, YU45-E3, YU45-F8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-G7, YU45-B6, YU45-C1, YU46-B6, YU46-E3, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-H11/D12, YU45-G1, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-F8, YU45-H10, YU46-A10, YU45-A8/C6, YU45-D9/D3, YU45-B6, YU45-C1, YU46-A8, YU46-C1, YU46-H8, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-E3, YU45-F2, YU45-F5, YU46-A8 or YU46-G8.

In some aspects, the antibody/fragment of the present invention comprises the CDRs of the VH and/or VL domains of a clone, or a variant thereof, selected from BSN-1H2, BSN-1H7, BSN-2E1, BSN-2F5, BSN-2G6, BSN-3C6, BSN-3C11, BSN-5A6, BSN-5B8, BSN-5F6, BSN-6F3, BSN-7D4, BSN-7E4, BSN-7F9, BSN-8C4 or BSN-8H11, e.g. selected from one of BSN-2E1, BSN-2G6, BSN-3C6, BSN-5A6 or BSN-5B8; or selected from one of BSN-2G6, BSN-3C6, BSN-5B8 or BSN-7D4; or BSN-3C6.

In some aspects, the antibody/fragment of the present invention comprises the VH and/or VL domains of a clone, or a variant thereof, selected from BSN-1H2, BSN-1H7, BSN-2E1, BSN-2F5, BSN-2G6, BSN-3C6, BSN-3C11, BSN-5A6, BSN-5B8, BSN-5F6, BSN-6F3, BSN-7D4, BSN-7E4, BSN-7F9, BSN-8C4 or BSN-8H11, e.g. selected from one of BSN-2E1, BSN-2G6, BSN-3C6, BSN-5A6 or BSN-5B8; or selected from one of BSN-2G6, BSN-3C6, BSN-5B8 or BSN-7D4; or BSN-3C6.

In some aspects, the antibody/fragment of the present invention comprises HC-CDRs 1-3 of the VH domain of an IL-11-binding antibody clone described herein, or a variant thereof. In some aspects, the antibody/fragment of the present invention comprises the VH domain of a clone, or a variant thereof.

In some aspects, the antibody/fragment of the present invention comprises LC-CDRs 1-3 of the VL domain of an IL-11-binding antibody clone described herein, or a variant thereof. In some aspects, the antibody/fragment of the present invention comprises the VL domain of a clone, or a variant thereof.

In some embodiments the antibody/fragment of the present invention comprises HC-CDRs 1-3 of the VH domain, or the VH domain, of an IL-11-binding antibody clone selected from YU33-A2, YU33-B3/H3, YU33-B4/YU45-G2/A3, YU33-E3, YU33-E6, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-B2, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-H8, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4,

YU45-C3/A6, YU45-D1, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU45-B8, YU45-C1, YU46-G1, YU46-A2, YU46-A8, YU46-B2, YU46-B6, YU46-C1, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7 or YU46-D3; e.g. selected from YU45-C11/A10, YU45-G1, YU45-E3, YU45-F8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-G7, YU45-B6, YU45-C1, YU46-B6, YU46-E3, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-H11/D12, YU45-G1, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-F8, YU45-H10, YU46-A10, YU45-A8/C6, YU45-D9/D3, YU45-B6, YU45-C1, YU46-A8, YU46-C1, YU46-H8, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-E3, YU45-F2, YU45-F5, YU46-A8 or YU46-G8. In some embodiments, the antibody/fragment comprises a VL domain which is arrived at following light chain shuffling.

In some embodiments the antibody/fragment of the present invention comprises LC-CDRs 1-3 of the VL domain, or the VL domain, of an IL-11-binding antibody clone selected from YU33-A2, YU33-B3/H3, YU33-B4/YU45-G2/A3, YU33-E3, YU33-E6, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-B2, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-H8, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4, YU45-C3/A6, YU45-D1, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU45-B8, YU45-C1, YU46-G1, YU46-A2, YU46-A8, YU46-B2, YU46-B6, YU46-C1, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7 or YU46-D3; e.g. selected from YU45-C11/A10, YU45-G1, YU45-E3, YU45-F8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-G7, YU45-B6, YU45-C1, YU46-B6, YU46-E3, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-H11/D12, YU45-G1, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-F8, YU45-H10, YU46-A10, YU45-A8/C6, YU45-D9/D3, YU45-B6, YU45-C1, YU46-A8, YU46-C1, YU46-H8, YU46-G8 or YU46-D3; or selected from YU33-B4/YU45-G2/A3, YU45-E3, YU45-F2, YU45-F5, YU46-A8 or YU46-G8. In some embodiments, the antibody/fragment comprises a VH domain which is arrived at following heavy chain shuffling.

The amino acid sequences of the VL domains of the human anti-human IL-11-binding antibody clones YU33-A2, YU33-B3/H3, YU33-B4/YU45-G2/A3, YU33-E3, YU33-E6, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-B2, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-B3, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-H8, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4, YU45-C3/A6, YU45-D1, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU45-B8, YU45-C1, YU46-G1, YU46-A2, YU46-A8, YU46-B2, YU46-B6, YU46-C1, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7 and YU46-D3 are shown in Figure 15, as are the LC-CDRs 1-3, defined using VBASE2 (described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674). The amino acid sequences of the VH domains for these human anti-human IL-11-binding antibody clones are shown in Figure 16, as are the HC-CDRs 1-3, defined using VBASE2.

In some aspects, the antibody/fragment of the present invention comprises the CDRs of the VH and/or VL domains of a clone, or a variant thereof, selected from YU100-A10, YU100-A11, YU100-A12, YU100-B01, YU100-B03, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-B12, YU100-C02, YU100-C04, YU100-C05, YU100-C10, YU100-C11, YU100-C12, YU100-D01, YU100-D02, YU100-D05, YU100-D07, YU100-D11, YU100-E01, YU100-E04, YU100-E05, YU100-E06, YU100-E07, YU100-E08, YU100-E09, YU100-E10, YU100-E11, YU100-E12, YU100-F01, YU100-F02, YU100-F05, YU100-F06, YU100-F07, YU100-F11, YU100-G01, YU100-G07, YU100-G08, YU100-G09, YU100-G10, YU100-G11, YU100-H01, YU100-H02, YU100-H04, YU100-H05, YU100-H06, YU100-H09, YU100-H11, YU112-A07, YU112-B06, YU112-C03, YU112-C05, YU112-C09, YU112-D08, YU112-E07, YU112-E08, YU112-F05, YU112-G01, YU112-G06, YU112-G09, YU112-H01 or YU112-H02. The amino acid sequences of the VL domains and LC-CDRs 1-3 (defined using VBASE2) for these human anti-human IL-11-binding antibody clones are shown in Figure 44, and the amino acid sequences of the VH domains and HC-CDRs 1-3 (defined using VBASE2) for these human anti-human IL-11-binding antibody clones are shown in Figure 45.

Antibodies according to the present invention may comprise VL and/or VH chains comprising an amino acid sequence that has a high percentage sequence identity to one or more of the VL and/or VH amino acid sequences described herein. For example, antibodies according to the present invention include antibodies that bind IL-11 and have a VL chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VL chain amino acid sequence of one of SEQ ID NOs:1 to 50. Antibodies according to the present invention include antibodies that bind IL-11 and have VH chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VH chain amino acid sequence of one of SEQ ID NOs:51 to 100.

Antibodies according to the present invention include antibodies that bind IL-11 and have a VL chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VL chain amino acid sequence of one of SEQ ID NOs: 267, 269, 270, 271, 274, 277, 279, 280, 540, 283, 286, 287, 289, 353, 293, 297, 299, 301, 303, 305, 307, 309, 310, 312, 314, 316, 318, 319, 321, 323, 325, 327, 328, 329, 331, 332, 335, 337, 338, 341, 342, 343, 346, 348, 214, 350, 13, 3, 351, 355, 358, 35, 361, 363, 365, 366, or 20. Antibodies according to the present invention include antibodies that bind IL-11 and have VH chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VH chain amino acid sequence of one of SEQ ID NOs: 53, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 85, 390, 73, 391, or 392.

In some embodiments the antibody/fragment of the present invention comprises HC-CDRs 1-3 of the VH domain, or the VH domain, of an IL-11-binding antibody clone selected from BSN-2E1, BSN-3C6, BSN-5A6_1 BSN-2G6, BSN-5A6_2 or BSN-5B8; e.g. BSN-3C6.

In some embodiments the antibody/fragment of the present invention comprises LC-CDRs 1-3 of the VL domain, or the VL domain, of an IL-11-binding antibody clone selected from BSN-2E1, BSN-3C6, BSN-5A6_1 BSN-2G6, BSN-5A6_2 or BSN-5B8; e.g. BSN-3C6.

The amino acid sequences of the VH domains of the anti-human IL-11-binding antibody clones BSN-2E1, BSN-3C6, BSN-5A6_1 BSN-2G6, BSN-5A6_2 and BSN-5B8 are shown in Figure 68, as are the HC-CDRs 1-3, defined using VBASE2 (described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674). The amino acid sequences of the VL domains for these anti-human IL-11-binding antibody clones are shown in Figure 69, as are the LC-CDRs 1-3, defined using VBASE2.

In some aspects, the antibody/fragment of the present invention comprises the CDRs of the VH and/or VL domains of a clone, or a variant thereof, selected from BSN-2E1, BSN-3C6, BSN-5A6_1 BSN-2G6, BSN-5A6_2 or BSN-5B8; e.g. BSN-3C6.

Antibodies according to the present invention include antibodies that bind IL-11 and have a VL chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VL chain amino acid sequence of one of SEQ ID NOs:554, 557, 561 or 564. Antibodies according to the present invention include antibodies that bind IL-11 and have VH chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VH chain amino acid sequence of one of SEQ ID NOs: 541, 545, 548 or 551.

The light and heavy chain CDRs disclosed herein may also be particularly useful in conjunction with a number of different framework regions. Accordingly, light and/or heavy chains having LC-CDR1-3 or HC-CDR1-3 may possess an alternative framework region. Suitable framework regions are well known in the art and are described for example in M. Lefranc & G. Le:franc (2001) "The Immunoglobulin FactsBook", Academic Press, incorporated herein by reference.

Antibodies according to the present invention may be detectably labelled or, at least, capable of detection. For example, the antibody may be labelled with a radioactive atom or a coloured molecule or a fluorescent molecule or a molecule which can be readily detected in any other way. Suitable detectable molecules include fluorescent proteins, luciferase, enzyme substrates, radiolabels and binding moieties. Labelling may be by conjugation to the antibody/fragment. The antigen binding molecule may be directly labelled with a detectable label or it may be indirectly labelled. In some embodiments, the label may be selected from: a radio-nucleotide, positron-emitting radionuclide (e.g. for positron emission tomography (PET)), MRI contrast agent or fluorescent label.

Antibodies and antigen binding fragments according to the present invention may be conjugated to a drug moiety, e.g. a cytotoxic small molecule. Such conjugates are useful for the targeted killing of cells expressing the antigen molecule.

Also provided by the present invention are isolated heavy chain variable region polypeptides, and isolated light chain variable region polypeptides.

In some aspects an isolated heavy chain variable region polypeptide is provided, comprising the HC-CDRs 1-3 of any one of the anti-IL-11 antibody clones described herein. In some aspects an isolated heavy chain variable region polypeptide is provided, comprising an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of the heavy chain variable region of any one of the anti-IL-11 antibody clones described herein.

In some aspects an isolated light chain variable region polypeptide is provided, comprising the LC-CDRs 1-3 of any one of the anti-IL-11 antibody clones described herein. In some aspects an isolated light chain variable region polypeptide is provided, comprising an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of the light chain variable region of any one of the anti-IL-11 antibody clones described herein.

Antibodies according to the present invention include antibodies that bind IL-11 and comprise an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of one of SEQ ID NOs: 412 to 475.

Functional properties of the antibodies/fragments

The IL-11 antibodies and fragments of the present invention may be characterised by reference to certain functional properties. In particular, an IL-11 antibody or antigen binding fragment according to the present invention may possess one or more of the following properties:

a) Specific binding to IL-11 (e.g. human IL-11 and/or mouse IL-11);
b) Binding to IL-11 (e.g. human IL-11) with an affinity of binding of EC50 = less than 1000 ng/ml, e.g. as determined by ELISA;
c) Inhibition of interaction between IL-11 and IL-11Rα;
d) Inhibition of interaction between IL-11 and gp130;
e) Inhibition of interaction between IL-11 and IL-11Rα:gp130 receptor complex;
f) Inhibition of interaction between IL-11:IL-11Rα complex and gp130;
g) Inhibition of signalling mediated by IL-11;
h) Inhibition of signalling mediated by binding of IL-11 to IL-11Rα:gp130 receptor complex;
i) Inhibition of signalling mediated by binding of IL-11:IL-11Rα complex to gp130 (i.e. IL-11 *trans* signalling);
j) Inhibition of fibroblast proliferation;
k) Inhibition of myofibroblast generation from fibroblasts;
l) Inhibition of a pathological process mediated by IL-11;
m) Inhibition of fibrosis;

n) Inhibition of gene or protein expression in fibroblasts of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2, e.g. following stimulation with a profibrotic factor;
o) Inhibition of extracellular matrix production by fibroblasts
p) Inhibition of proliferation and/or survival of cells of a cancer;
q) Inhibition of tumour growth.

Herein, 'inhibition' refers to a reduction, decrease or lessening relative to a control condition. For example, inhibition of a process by an antibody/fragment refers to a reduction, decrease or lessening of the extent/degree of that process in the absence of the antibody/fragment, and/or in the presence of an appropriate control antibody/fragment.

Inhibition may herein also be referred to as neutralisation or antagonism. That is, an IL-11 binding antibody/fragment which is capable of inhibiting a function or process (e.g. interaction, signalling or other activity mediated by IL-11 or an IL-11-containing complex) may be said to be a 'neutralising' or 'antagonist' antibody/fragment with respect to the relevant function or process. For example, antibody/fragment which is capable of inhibiting IL-11 mediated signalling may be referred to as an antibody/fragment which is capable of neutralising IL-11 mediated signalling, or may be referred to as an antagonist of IL-11 mediated signalling.

The skilled person is able to identify an appropriate control condition for a given assay. For example, a control antibody/fragment may be an antibody/fragment directed against a target protein which is known not to have a role involved in the property being investigated in the assay. A control antibody/fragment may be of the same isotype as the ant-IL-11 antibody/fragment being analysed, and may e.g. have the same constant regions.

An antibody/fragment that specifically binds to a target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other, non-target molecules. In some embodiments the present antibodies/fragments may bind with greater affinity to IL-11 than to one or more members of the IL-6 cytokine family. In some embodiments the present antibodies/fragments may bind with greater affinity to IL-11 than to one or more of IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), and cardiotrophin-like cytokine (CLC).

In some embodiments, the extent of binding of an antibody to an non-target is less than about 10% of the binding of the antibody to the target as measured, e.g., by ELISA, SPR, Bio-Layer Interferometry (BLI), MicroScale Thermophoresis (MST), or by a radioimmunoassay (RIA). Alternatively, the binding specificity may be reflected in terms of binding affinity, where the anti-IL-11 antibody/fragment of the present invention binds to IL-11 with a K_D that is at least 0.1 order of magnitude (i.e. 0.1 x 10^n, where n is an integer representing the order of magnitude) greater than the K_D towards another, non-target molecule. This may optionally be one of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, or 2.0.

Binding affinity of an antibody or antigen-binding fragment for its target is often described in terms of its dissociation constant (K_D). Binding affinity can be measured by methods known in the art, such as by ELISA, Surface Plasmon Resonance (SPR; see e.g. Hearty et al., Methods Mol Biol (2012) 907:411-442; or Rich et

al., Anal Biochem. 2008 Feb 1; 373(1):112-20), Bio-Layer Interferometry (see e.g. Lad et al., (2015) J Biomol Screen 20(4): 498-507; or Concepcion et al., Comb Chem High Throughput Screen. 2009 Sep; 12(8):791-800), MicroScale Thermophoresis (MST) analysis (see e.g. Jerabek-Willemsen et al., Assay Drug Dev Technol. 2011 Aug; 9(4): 342–353), or by a radiolabelled antigen binding assay (RIA) performed with the Fab version of the antibody and antigen molecule.

In some embodiments, the antibody/fragment according to the present invention binds to IL-11 with a K_D of 5 μM or less, preferably one of ≤1 μM, ≤500 nM, ≤100 nM, ≤75 nM, ≤50 nM, ≤40 nM, ≤30 nM, ≤20 nM, ≤15 nM, ≤12.5 nM, ≤10 nM, ≤9 nM, ≤8 nM, ≤7 nM, ≤6 nM, ≤5 nM, ≤4 nM ≤3 nM, ≤2 nM, ≤1 nM, ≤500 pM.

In some embodiments, the antibody/fragment according to the present invention binds to IL-11 with an affinity of binding (e.g. as determined by ELISA) of EC50 = 1000 ng/ml or less, preferably one of ≤900 ng/ml, ≤800 ng/ml, ≤700 ng/ml, ≤600 ng/ml, ≤500 ng/ml, ≤400 ng/ml, ≤300 ng/ml, ≤200 ng/ml, ≤100 ng/ml, ≤90 ng/ml, ≤80 ng/ml, ≤70 ng/ml, ≤60 ng/ml, ≤50 ng/ml, ≤40 ng/ml, ≤30 ng/ml, ≤20 ng/ml, ≤15 ng/ml, ≤10 ng/ml, ≤7.5 ng/ml, ≤5 ng/ml, ≤2.5 ng/ml, or ≤1 ng/ml.

Affinity of binding to IL-11 by an antibody/fragment may be analysed *in vitro* by ELISA assay. Suitable assays are well known in the art and can be performed by the skilled person, for example, as described in Antibody Engineering, vol. 1 (2nd Edn), Springer Protocols, Springer (2010), Part V, pp657-665. For example, the affinity of binding to IL-11 by an antibody/fragment may be analysed according to the methodology described herein in the experimental examples.

The ability of an antibody/fragment to inhibit interaction between two proteins can be determined for example by analysis of interaction in the presence of, or following incubation of one or both of the interaction partners with, the antibody/fragment. An example of a suitable assay to determine whether a given antibody/fragment is capable of inhibiting interaction between two interaction partners is a competition ELISA assay.

An antibody/fragment which is capable of inhibiting a given interaction (e.g. between IL-11 and IL-11Rα, or between IL-11 and gp130, or between IL-11 and IL-11Rα:gp130, or between IL-11:IL-11Rα and gp130) is identified by the observation of a reduction/decrease in the level of interaction between the interaction partners in the presence of – or following incubation of one or both of the interaction partners with – the antibody/fragment, as compared to the level of interaction in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). Suitable analysis can be performed *in vitro*, e.g. using recombinant interaction partners or using cells expressing the interaction partners. Cells expressing interaction partners may do so endogenously, or may do so from nucleic acid introduced into the cell. For the purposes of such assays, one or both of the interaction partners and/or the antibody/fragment may be labelled or used in conjunction with a detectable entity for the purposes of detecting and/or measuring the level of interaction.

Ability of an antibody/fragment to inhibit interaction between two binding partners can also be determined by analysis of the downstream functional consequences of such interaction, e.g. receptor signalling. For example, downstream functional consequences of interaction between IL-11 and IL-11Rα:gp130 or between

IL-11:IL-11Rα and gp130 may include proliferation of fibroblasts, myofibroblast generation from fibroblasts, or gene or protein expression of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2.

Fibroblasts according to the present disclosure may be derived from any tissue, including liver, lungs, kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. In particular embodiments, for the purposes of analysis of the antibody/fragment, the fibroblasts may be cardiac fibroblasts (e.g. atrial fibroblasts), skin fibroblasts, lung fibroblasts, kidney fibroblasts or liver fibroblasts. Fibroblasts may be characterised by gene or protein expression of one or more of COL1A, ACTA2, prolyl-4-hydroxylase, MAS516, and FSP1.

Gene expression can be measured by various means known to those skilled in the art, for example by measuring levels of mRNA by quantitative real-time PCR (qRT-PCR), or by reporter-based methods. Similarly, protein expression can be measured by various methods well known in the art, e.g. by antibody-based methods, for example by western blot, immunohistochemistry, immunocytochemistry, flow cytometry, ELISA, ELISPOT, or reporter-based methods.

In some embodiments, the antibody/fragment according to the present invention may inhibit protein expression of one or more markers of fibrosis, e.g. protein expression of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2.

The ability of an antibody/fragment to inhibit interaction between IL-11 and IL-11Rα:gp130 can, for example, be analysed by stimulating fibroblasts with TGFβ1, incubating the cells in the presence of the antibody/fragment and analysing the proportion of cells having αSMA-positive phenotype after a defined period of time. In such example, inhibition of interaction between IL-11 and IL-11Rα:gp130 can be identified by observation of a lower proportion of cells having an αSMA-positive phenotype as compared to positive control condition in which cells are treated with TGFβ1 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment), or in the presence of an appropriate control antibody/fragment.

Such assays are also suitable for analysing the ability of antibody/fragment to inhibit IL-11-mediated signalling.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and IL-11Rα to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and IL-11Rα in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and IL-11Rα to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3

times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of interaction between IL-11 and IL-11Rα in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and gp130 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and gp130 to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of interaction between IL-11 and gp130 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and IL-11Rα:gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11 and IL-11Rα:gp130 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11 and IL-11Rα:gp130 to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of interaction between IL-11 and IL-11Rα:gp130 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting interaction between IL-11:IL-11Rα complex and gp130 to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of interaction between IL-11:IL-11Rα complex and gp130 in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of inhibiting interaction between IL-11:IL-11Rα complex and gp130 to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of interaction between IL-11:IL-11Rα complex and gp130 in the absence of the antibody/fragment.

Inhibition of IL-11 mediated signalling can also be analysed using ^{3}H-thymidine incorporation and/or Ba/F3 cell proliferation assays such as those described in e.g. Curtis et al. Blood, 1997, 90(11) and Karpovich et al. Mol. Hum. Reprod. 2003 9(2): 75-80. Ba/F3 cells co-express IL-11Rα and gp130.

As used herein, IL-11 mediated signalling and/or processes mediated by IL-11 includes signalling mediated by fragments of IL-11 and polypeptide complexes comprising IL-11 or fragments thereof. IL-11 mediated signalling may be signalling mediated by human IL-11 and/or mouse IL-11. Signalling mediated by IL-11 may occur following binding of IL-11 or an IL-11 containing complex to a receptor to which IL-11 or said complex binds.

In some embodiments, antibodies and fragments according to the present invention are capable of inhibiting the biological activity of IL-11 or an IL-11-containing complex. In some embodiments, the antibody/fragment binds to IL-11 or the IL-11-containing complex in a region which is important for binding to a receptor for the IL-11 or IL-11-containing complex, e.g. gp130 or IL-11Rα, and thereby disrupts binding to and/or signalling through the receptor.

In some embodiments, the antibody/fragment according to the present invention is an antagonist of one or more signalling pathways which are activated by signal transduction through receptors comprising IL-11Rα and/or gp130, e.g. IL-11Rα:gp130. In some embodiments, the antibody/fragment is capable of inhibiting signalling through one or more immune receptor complexes comprising IL-11Rα and/or gp130, e.g. IL-11Rα:gp130.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting IL-11-mediated signalling to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of signalling in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing IL-11 mediated signalling to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of signalling in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the IL-11 mediated signalling may be signalling mediated by binding of IL-11 to IL-11Rα:gp130 receptor. Such signalling can be analysed e.g. by treating cells expressing IL-11Rα and gp130 with IL-11, or by stimulating IL-11 production in cells which express IL-11Rα and gp130.

The IC_{50} for antibody/fragment for inhibition of IL-11 mediated signalling may be determined, e.g. by culturing Ba/F3 cells expressing IL-11Rα and gp130 in the presence of human IL-11 and the IL-11 binding agent, and measuring ^{3}H-thymidine incorporation into DNA.

In some embodiments, the antibody/fragment of the present invention may exhibit an IC_{50} of 10 µg/ml or less, preferably one of ≤ 5 µg/ml, ≤ 4 µg/ml, ≤ 3.5 µg/ml, ≤ 3 µg/ml, ≤ 2 µg/ml, ≤ 1 µg/ml, ≤ 0.9 µg/ml, ≤ 0.8 µg/ml, ≤ 0.7 µg/ml, ≤ 0.6 µg/ml, or ≤ 0.5 µg/ml in such an assay.

In some embodiments, the IL-11 mediated signalling may be signalling mediated by binding of IL-11:IL-11Rα complex to gp130. In some embodiments, the IL-11:IL-11Rα complex may be soluble, e.g. complex of extracellular domain of IL-11Rα and IL-11, or complex of soluble IL-11Rα isoform/fragment, and IL-11. In some embodiments, the soluble IL-11Rα is a soluble (secreted) isoform of IL-11Rα, or is the liberated product of proteolytic cleavage of the extracellular domain of cell membrane bound IL-11Rα.

In some embodiments, the IL-11:IL-11Rα complex may be cell-bound, e.g. complex of cell-membrane bound IL-11Rα and IL-11. Signalling mediated by binding of IL-11:IL-11Rα complex to gp130 can be analysed by treating cells expressing gp130 with IL-11:IL-11Rα complex, e.g. recombinant fusion protein comprising IL-11 joined by a peptide linker to the extracellular domain of IL-11Rα (e.g. hyper IL-11 as described herein).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting signalling mediated by binding of IL-11:IL-11Rα complex to gp130, and is also capable of inhibiting signalling mediated by binding of IL-11 to IL-11Rα:gp130 receptor.

In some embodiments, the antibody/fragment is capable of inhibiting fibroblast proliferation. Proliferation of fibroblasts can be determined by analysing cell division over a period of time. Cell division for a given population of fibroblasts can be analysed, for example, by *in vitro* analysis of incorporation of ^{3}H-thymidine or by CFSE dilution assay, e.g. as described in Fulcher and Wong, Immunol Cell Biol (1999) 77(6): 559-564, hereby incorporated by reference in entirety. Proliferating cells (e.g. proliferating fibroblasts) may also be identified by analysis of incorporation of 5-ethynyl-2′-deoxyuridine (EdU) by an appropriate assay, as described e.g. in Buck et al., Biotechniques. 2008 Jun; 44(7):927-9, and Sali and Mitchison, PNAS USA 2008 Feb 19; 105(7): 2415–2420, both hereby incorporated by reference in their entirety.

Fibroblasts according to the present disclosure may be derived from any tissue, including liver, lungs, kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. In particular embodiments, for the purposes of analysis of the antibody/fragment, the fibroblasts may be cardiac fibroblasts (e.g. atrial fibroblasts), skin fibroblasts, lung fibroblasts, kidney fibroblasts or liver fibroblasts.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting fibroblast proliferation to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of fibroblast proliferation in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing fibroblast proliferation to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45

times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of fibroblast proliferation in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting a pathological process mediated by IL-11, e.g. following stimulation with a profibrotic factor (e.g. TGFβ1). Pathological processes mediated by IL-11 include fibrosis, and can be evaluated either *in vitro* or *in vivo*.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting fibrosis. Fibrosis may be of a particular tissue or several tissues, e.g. liver, lung, kidney, heart, blood vessel, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, or bone marrow. Fibrosis may be measured by means well known to the skilled person, for example by analysing gene or protein expression of one or more myofibroblast markers and/or gene or protein expression of one or more markers of fibrosis in a given tissue or tissues.

Myofibroblast markers may include one or more of increased αSMA, vimentin, palladin, cofilin or desmin. Markers of fibrosis include increased level of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1 and MMP2, extracellular matrix components, number/proportion of myofibroblasts, and organ weight.

Inhibition of fibrosis can be measured *in vitro* or *in vivo*. For example, whether an antibody/fragment is capable of inhibiting fibrosis in a given tissue can be analysed *in vitro* by treating fibroblasts derived from that tissue with a profibrotic stimulus, and then analysing whether the antibody can reduce myofibroblast generation from the fibroblasts (or e.g. some other marker of fibrosis). Whether an antibody/fragment is capable of inhibiting fibrosis can be analysed *in vivo*, for example, by administering the antibody/fragment to a subject (e.g. a subject that has been exposed to a profibrotic stimulus), and analysing tissue(s) for one or more markers of fibrosis.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting fibrosis to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of fibrosis in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing fibrosis to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of fibrosis in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting myofibroblast generation from fibroblasts, e.g. following exposure of the fibroblasts to profibrotic factor. Myofibroblast generation from fibroblasts can be investigated by analysis for myofibroblast markers. A

profibrotic factor according to the present disclosure may be e.g. TGFβ1, IL-11, IL-13, PDGF, ET-1, oncostatin M (OSM) or ANG2 (AngII).

In some embodiments, the antibody/fragment is capable of inhibiting gene or protein expression in fibroblasts, or fibroblast-derived cells (e.g. myofibroblasts), of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2, e.g. following stimulation with a profibrotic factor. In some embodiments, the antibody/fragment is capable of inhibiting gene or protein expression in fibroblasts, or fibroblast-derived cells (e.g. myofibroblasts), of one or more extracellular matrix components, e.g. following stimulation with a profibrotic factor.

In the experimental examples herein, myofibroblast generation from fibroblasts is analysed by measuring αSMA protein expression levels using Operetta High-Content Imaging System following stimulation of the fibroblasts with TGFβ1.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting myofibroblast generation from fibroblasts to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of myofibroblast generation from fibroblasts in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing myofibroblast generation from fibroblasts to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of myofibroblast generation from fibroblasts in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting gene or protein expression in fibroblasts of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2, e.g. following stimulation with a profibrotic factor (e.g. TGFβ1). In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting gene or protein expression to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of gene or protein expression in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing gene or protein expression to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of gene or protein expression in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting extracellular matrix production by fibroblasts, e.g. following stimulation with a profibrotic factor (e.g. TGFβ1). Extracellular matrix production can be evaluated, for example, by measuring the level of an extracellular matrix component. Extracellular matrix components according to the present invention include e.g. proteoglycan, heparan sulphate, chondroitin sulphate, keratan sulphate, hyaluronic acid, collagen, periostin, fibronectin, vitronectin, elastin, fibronectin, laminin, nidogen, gelatin and aggrecan.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting extracellular matrix production by fibroblasts to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of extracellular matrix production by fibroblasts in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing extracellular matrix production by fibroblasts to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of extracellular matrix production in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting proliferation and/or survival of cells of a cancer. The skilled person is able to determine whether an antibody/fragment is capable of inhibiting proliferation and/or survival of cells of a cancer for example by analysing the effect of the antibody/fragment on cells of the cancer. For example, proliferation of cells can be measured as described herein, e.g. by ^{3}H thymidine incorporation or CFSE dilution assays. Cell survival can be analysed by measuring cells for markers of cell viability/cell death following treatment with the antibody/fragment.

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting proliferation and/or survival of cells of a cancer to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of proliferation and/or survival of cells of a cancer in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing proliferation and/or survival of cells of a cancer to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of proliferation and/or survival of cells of a cancer in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention is capable of inhibiting tumour growth to less than 100%, e.g. one of 99% or less, 95% or less, 90% or less, 85% or less, 75% or less, 70% or less, 65% or less, 60% or less, 55% or less, 50% or less, 45% or less, 40% or less, 35% or less, 30% or less, 25% or less, 20% or less, 15% or less, 10% or less, 5% or less, or 1% or less of the level of tumour growth in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment). In some embodiments, the antibody/fragment is capable of reducing tumour growth to less than 1 times, e.g. one of ≤0.99 times, ≤0.95 times, ≤0.9 times, ≤0.85 times, ≤0.8 times, ≤0.85 times, ≤0.75 times, ≤0.7 times, ≤0.65 times, ≤0.6 times, ≤0.55 times, ≤0.5 times, ≤0.45 times, ≤0.4 times, ≤0.35 times, ≤0.3 times, ≤0.25 times, ≤0.2 times, ≤0.15 times, ≤0.1 times the level of tumour growth in the absence of the antibody/fragment (or in the presence of an appropriate control antibody/fragment).

In some embodiments, the antibody/fragment according to the present invention has one or more improved properties as compared to a prior art anti-IL-11 antibody/fragment. In some embodiments the prior art anti-IL-11 antibody/ antigen binding fragment may be, or may comprise the CDRs and/or VL and VH sequences of, monoclonal mouse anti-human IL-11 antibody clone #22626; Catalog No. MAB218 (R&D Systems, MN, USA).

In some embodiments, the antibody/fragment of the present invention displays one or more of the following properties as compared to a prior art antibody/antigen binding fragment (e.g. monoclonal mouse antibody clone #22626; Catalog No. MAB218):

(i) binds to IL-11 with greater specificity relative to one or more of IL-6, LIF, OSM, CT-1, CNTF, and CLC (i.e. reduced cross-reactivity for proteins of the IL-6 cytokine family other than IL-11);
(ii) binds to IL-11 (e.g. human IL-11) with greater affinity (e.g. has lower EC50 as determined by ELISA);
(iii) inhibits interaction between IL-11 and IL-11Rα to a greater extent;
(iv) inhibits interaction between IL-11 and gp130 to a greater extent;
(v) inhibits interaction between IL-11 and IL-11Rα:gp130 receptor complex to a greater extent;
(vi) inhibits interaction between IL-11:IL-11Rα complex and gp130 to a greater extent;
(vii) inhibits signalling mediated by IL-11 to a greater extent;
(viii) inhibits signalling mediated by binding of IL-11 to IL-11Rα:gp130 receptor complex to a greater extent;
(ix) inhibits signalling mediated by binding of IL-11:IL-11Rα complex to gp130 (i.e. IL-11 *trans* signalling) to a greater extent;
(x) inhibits fibroblast proliferation to a greater extent;
(xi) inhibits myofibroblast generation from fibroblasts to a greater extent;
(xii) inhibits a pathological process mediated by IL-11 to a greater extent;
(xiii) inhibits fibrosis to a greater extent;
(xiv) inhibits gene or protein expression in fibroblasts of one or more of collagen, fibronectin, periostin, IL-6, IL-11, αSMA, TIMP1, MMP2, e.g. following stimulation with a profibrotic factor to a greater extent;
(xv) inhibits extracellular matrix production by fibroblasts to a greater extent;
(xvi) inhibits proliferation and/or survival of cells of a cancer to a greater extent; or
(xvii) inhibits tumour growth to a greater extent.

In some embodiments, "greater specificity" or "greater affinity" or "inhibition to a greater extent" herein is, respectively, a level of specificity, affinity or inhibition which is greater than 1 times, e.g. ≥1.01 times, ≥1.02 times, ≥1.03 times, ≥1.04 times, ≥1.05 times, ≥1.06 times, ≥1.07 times, ≥1.08 times, ≥1.09 times, ≥1.1 times, ≥1.2 times, ≥1.3 times, ≥1.4 times, ≥1.5 times, ≥1.6 times, ≥1.7 times, ≥1.8 times, ≥1.9 times, ≥2 times, ≥2.1 times, ≥2.2 times, ≥2.3 times, ≥2.4 times, ≥2.5 times, ≥2.6 times, ≥2.7 times, ≥2.8 times, ≥2.9 times, ≥3 times, ≥3.5 times, ≥4 times, ≥4.5 times, ≥5 times, ≥6 times, ≥7 times, ≥8 times, ≥9 times, ≥10 times, ≥15 times, ≥20 times, ≥25 times, ≥30 times, ≥35 times, ≥40 times, ≥45 times, ≥50 times, ≥60 times, ≥70 times, ≥80 times, ≥90 times, ≥100 times, ≥200 times, ≥300 times, ≥400 times, ≥500 times, ≥600 times, ≥700 times, ≥800 times, ≥900 times, ≥1000 times the specificity or affinity or level of inhibition displayed by the prior art antibody/antigen binding fragment in a comparable assay.

Therapeutic applications

Antibodies and antigen binding fragments according to the present invention and compositions comprising such agents may be provided for use in methods of medical treatment or prevent of a disease/disorder, or alleviation of the symptoms of a disease/disorder. The antibodies/fragments of the present invention may be administered to subjects having a disease/condition in need of treatment, and/or to subjects at risk of such developing or contracting the disease/disorder.

Treatment, prevention or alleviation of fibrosis according to the present invention may be of fibrosis that is associated with an upregulation of IL-11 and/or IL-11Rα, e.g. an upregulation of IL-11 and/or IL-11Rα in cells or tissue in which the disease/disorder occurs or may occur, or upregulation of extracellular IL-11 or IL-11Rα. In some embodiments, IL-11 or IL-11R expression is locally or systemically upregulated in the subject.

Treatment or alleviation of a disease/disorder may be effective to prevent progression of the disease/disorder, e.g. to prevent worsening of the condition or to slow the rate of development. In some embodiments treatment or alleviation may lead to an improvement in the disease/disorder, e.g. a reduction in the symptoms of the disease/disorder or reduction in some other correlate of the severity/activity of the disease/disorder.

Prevention of a disease/disorder may refer to prevention of a worsening of the condition or prevention of the development of the disease/disorder, e.g. preventing an early stage disease/disorder developing to a later, chronic, stage.

The antibodies/fragments of the present invention are preferably able to bind to and inhibit the biological activity of IL-11 and IL-11-containing molecules/complexes (e.g. IL-11:IL-11Rα complex). Accordingly, the antibodies/fragments of the present invention find use in the treatment or prevention of diseases and disorders in which IL-11 is implicated in the pathology of the disease/disorder. That is, the antibodies/fragments of the present invention find use in the treatment or prevention of diseases and disorders associated with IL-11/IL-11R signalling.

In some embodiments, the disease/disorder may be associated with increased IL-11, IL-11Rα and/or gp130 gene or protein expression, e.g. as compared to the control (i.e. non-diseased) state. In some embodiments,

the disease/disorder may be associated with an increased level of IL-11-medated signalling as compared to the control state. In some embodiments, the disease/disorder may be associated with an increased level of signalling through ERK and/or STAT3 pathways as compared to the control state. In some embodiments, the increased expression/activity of IL-11, IL-11Rα and/or gp130, and/or the increased level of IL-11-medated signalling, may be observed in effector cells of the disease/disorder (e.g. for a cancer, the cancerous cells). In some embodiments, the increased expression/activity of IL-11, IL-11Rα and/or gp130, and/or the increased level of IL-11-medated signalling, may be observed in cells other than the effector cells.

Signalling through ERK can be measured e.g. using an assay for ERK phosphorylation such as an assay described in Assay Guidance Manual: Phospho-ERK Assays, Kim E. Garbison, Beverly A. Heinz, Mary E. Lajiness, Jeffrey R. Weidner, and G. Sitta Sittampalam, Eli Lilly & Company, Sittampalam GS, Coussens NP, Nelson H, et al., editors Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004. Signalling through STAT3 can be measured e.g. using an assay for phosphorylation of STAT3, such as the Phospho-STAT3 (Tyr705) Cellular Assay Kit (Cisbio Assays).

In some embodiments, the treatment is of a disease/disorder for which a reduction in IL-11 mediated signalling is therapeutic. In some embodiments, the treatment is of a disease/disorder associated with excess ERK and/or STAT3 signalling. In some embodiments, the treatment is of a disease/disorder associated with excess proliferation or hyperactivation of fibroblasts, or associated with an excess of myofibroblasts.

In some embodiments, the treatment may be aimed at preventing or treating a disease/disorder by decreasing the number or proportion of myofibroblasts or αSMA-positive fibroblasts.

In some embodiments, the disease/disorder may be fibrosis, a fibrotic condition, or a disease/disorder characterised by fibrosis. As used herein, “fibrosis” refers to the formation of excess fibrous connective tissue as a result of the excess deposition of extracellular matrix components, for example collagen. Fibrous connective tissue is characterised by having extracellular matrix (ECM) with a high collagen content. The collagen may be provided in strands or fibers, which may be arranged irregularly or aligned. The ECM of fibrous connective tissue may also include glycosaminoglycans.

As used herein, “excess fibrous connective tissue” refers to an amount of connective tissue at a given location (e.g. a given tissue or organ, or part of a given tissue or organ) which is greater than the amount of connective tissue present at that location in the absence of fibrosis, e.g. under normal, non-pathological conditions. As used herein, “excess deposition of extracellular matrix components” refers to a level of deposition of one or more extracellular matrix components which is greater than the level of deposition in the absence of fibrosis, e.g. under normal, non-pathological conditions.

The cellular and molecular mechanisms of fibrosis are described in Wynn, J. Pathol. (2008) 214(2): 199-210, and Wynn and Ramalingam, Nature Medicine (2012) 18:1028-1040, which are hereby incorporated by reference in their entirety. The main cellular effectors of fibrosis are myofibroblasts, which produce a collagen-rich extracellular matrix.

In response to tissue injury, damaged cells and leukocytes produce pro-fibrotic factors such as TGFβ, IL-13 and PDGF, which activate fibroblasts to αSMA-expressing myofibroblasts, and recruit myofibroblasts to the site of injury. Myofibroblasts produce a large amount of extracellular matrix, and are important mediators in aiding contracture and closure of the wound. However, under conditions of persistent infection or during chronic inflammation there can be overactivation and recruitment of myofibroblasts, and thus over-production of extracellular matrix components, resulting in the formation of excess fibrous connective tissue.

In some embodiments fibrosis may be triggered by pathological conditions, e.g. conditions, infections or disease states that lead to production of pro-fibrotic factors such as TGFβ1. In some embodiments, fibrosis may be caused by physical injury/stimuli, chemical injury/stimuli or environmental injury/stimuli. Physical injury/stimuli may occur during surgery, e.g. iatrogenic causes. Chemical injury/stimuli may include drug induced fibrosis, e.g. following chronic administration of drugs such as bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold and nitrofurantoin (Daba et al., Saudi Med J 2004 Jun; 25(6): 700-6). Environmental injury/stimuli may include exposure to asbestos fibres or silica.

Fibrosis can occur in many tissues of the body. For example, fibrosis can occur in the lung, liver (e.g. cirrhosis), kidney, heart, blood vessels, eye, skin, pancreas, spleen, bowel (e.g. large or small intestine), brain, and bone marrow. Fibrosis may also occur in multiple organs at once.

In embodiments herein, fibrosis may involve an organ of the gastrointestinal system, e.g. of the liver, small intestine, large intestine, or pancreas. In some embodiments, fibrosis may involve an organ of the respiratory system, e.g. the lungs. In embodiments, fibrosis may involve an organ of the cardiovascular system, e.g. of the heart or blood vessels. In some embodiments, fibrosis may involve the skin. In some embodiments, fibrosis may involve an organ of the nervous system, e.g. the brain. In some embodiments, fibrosis may involve an organ of the urinary system, e.g. the kidneys. In some embodiments, fibrosis may involve an organ of the musculoskeletal system, e.g. muscle tissue.

In some preferred embodiments, the fibrosis is cardiac or myocardial fibrosis, hepatic fibrosis, or renal fibrosis. In some embodiments cardiac or myocardial fibrosis is associated with dysfunction of the musculature or electrical properties of the heart, or thickening of the walls or valves of the heart. In some embodiments fibrosis is of the atrium and/or ventricles of the heart. Treatment or prevention of atrial or ventricular fibrosis may help reduce risk or onset of atrial fibrillation, ventricular fibrillation, or myocardial infarction.

In some preferred embodiments hepatic fibrosis is associated with chronic liver disease or liver cirrhosis. In some preferred embodiments renal fibrosis is associated with chronic kidney disease.

Diseases/disorders characterised by fibrosis in accordance with the present invention include but are not limited to: respiratory conditions such as pulmonary fibrosis, cystic fibrosis, idiopathic pulmonary fibrosis, progressive massive fibrosis, scleroderma, obliterative bronchiolitis, Hermansky-Pudlak syndrome, asbestosis, silicosis, chronic pulmonary hypertension, AIDS associated pulmonary hypertension,

sarcoidosis, tumor stroma in lung disease, and asthma; chronic liver disease, primary biliary cirrhosis (PBC), schistosomal liver disease, liver cirrhosis; cardiovascular conditions such as hypertrophic cardiomyopathy, dilated cardiomyopathy (DCM), fibrosis of the atrium, atrial fibrillation, fibrosis of the ventricle, ventricular fibrillation, myocardial fibrosis, Brugada syndrome, myocarditis, endomyocardial fibrosis, myocardial infarction, fibrotic vascular disease, hypertensive heart disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), tubulointerstitial and glomerular fibrosis, atherosclerosis, varicose veins, cerebral infarcts; neurological conditions such as gliosis and Alzheimer's disease; muscular dystrophy such as Duchenne muscular dystrophy (DMD) or Becker's muscular dystrophy (BMD);gastrointestinal conditions such as Chron's disease, microscopic colitis and primary sclerosing cholangitis (PSC); skin conditions such as scleroderma, nephrogenic systemic fibrosis and cutis keloid; arthrofibrosis; Dupuytren's contracture; mediastinal fibrosis; retroperitoneal fibrosis; myelofibrosis; Peyronie's disease; adhesive capsulitis; kidney disease (e.g., renal fibrosis, nephritic syndrome, Alport's syndrome, HIV associated nephropathy, polycystic kidney disease, Fabry's disease, diabetic nephropathy, chronic glomerulonephritis, nephritis associated with systemic lupus); progressive systemic sclerosis (PSS); chronic graft versus host disease; diseases/disorders of the eye and associated processes, such as Grave's opthalmopathy, epiretinal fibrosis (e.g. diabetic retinopathy (DR)), glaucoma, subretinal fibrosis (e.g. associated with macular degeneration (e.g. wet age-related macular degeneration (AMD))), macular edema, drusen formation, post-surgical fibrosis (e.g. of the posterior capsule following cataract surgery, or of the bleb following trabeculectomy for glaucoma), conjunctival fibrosis, subconjunctival fibrosis; arthritis; fibrotic pre-neoplastic and fibrotic neoplastic disease; and fibrosis induced by chemical or environmental insult (e.g., cancer chemotherapy, pesticides, radiation/cancer radiotherapy).

It will be appreciated that many of the diseases/conditions listed above are interrelated. For example, fibrosis of the ventricle may occur post myocardial infarction, and is associated with DCM, HCM and myocarditis.

In particular embodiments, the disease/disorder may be one of pulmonary fibrosis, atrial fibrillation, ventricular fibrillation, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), non-alcoholic steatohepatitis (NASH), cirrhosis, chronic kidney disease, scleroderma, systemic sclerosis, keloid, cystic fibrosis, Chron's disease, post-surgical fibrosis or retinal fibrosis, e.g. associated with wet age-related macular degeneration (AMD).

Fibrosis can lead directly or indirectly to, and/or increase susceptibility to development of, diseases/disorders. For example, more than 80% of hepatocellular carcinomas (HCCs) develop in fibrotic or cirrhotic livers (Affo et al. 2016, Annu Rev Pathol.), suggesting an important role for liver fibrosis in the premalignant environment (PME) of the liver.

Accordingly, the antibodies/fragments of the present invention find use in methods for the treatment and prevention of diseases/disorders associated with fibrosis, and/or for which fibrosis is a risk factor. In some embodiments, the disease/disorder associated with fibrosis, or for which fibrosis is a risk factor, is a cancer, e.g. cancer of the liver (e.g. hepatocellular carcinoma).

IL-11 is also implicated in the pathology of other diseases/disorders, and the antibodies and fragments of the present invention accordingly find use in methods to treat, prevent and/or alleviate the symptoms of these diseases/disorders also.

IL-11 has been implicated in the development and progression of various cancers. Studies suggest that IL-11 is important for promoting chronic gastric inflammation and associated gastric, colonic, hepatocellular and breast cancer tumorogenesis through excessive activation of STAT3 (Ernst M, et al. J Clin Invest. (2008);118:1727–1738), that IL-11 may promote tumorigenesis by triggering the JAK-STAT intracellular signalling pathway, and may also promote metastasis via signalling through the PI3K-AKT-mTORC1 pathway (Xu et al., Cancer Letters (2016) 373(2): 156-163). Through STAT3, IL-11 promotes survival, proliferation, invasion angiogenesis and metastasis, the IL-11/GP130/JAK/STAT3 signalling axis may be rate-limiting for the progression of gastrointestinal tumors, and elevated IL-11 expression is associated with poor prognosis of breast cancer patients (Johnstone et al., Cytokine & Growth Reviews (2015) 26(5): 489-498). IL-11 has also been shown to influence breast cancer stem cell dynamics and tumor heterogeneity (Johnstone et al., Cytokine & Growth Reviews (2015) 26(5): 489-498). Recently, IL-11 signalling has been implicated in chemoresistance of lung adenocarcinoma; cancer associated fibroblasts were found to upregulate IL-11, and confer chemoresistance to lung cancer cells through activation of the IL-11/IL-11R/STAT3 anti-apoptotic signalling pathway (Tao et al. 2016, Sci Rep. 6;6:38408). IL-11 signalling may promote the fibroblast-to-myofibroblast transition and extracellular matrix production by fibroblasts in the pre-malignant environment (PME) and tumour micro-environment (TME).

In some embodiments, the antibodies/fragments of the present invention are provided for use in methods to treat/prevent a cancer. In some embodiments, the cancer may be a cancer which leads directly or indirectly to inflammation and/or fibrosis.

A cancer may be any unwanted cell proliferation (or any disease manifesting itself by unwanted cell proliferation), neoplasm or tumor or increased risk of or predisposition to the unwanted cell proliferation, neoplasm or tumor. The cancer may be benign or malignant and may be primary or secondary (metastatic). A neoplasm or tumor may be any abnormal growth or proliferation of cells and may be located in any tissue.

In some embodiments, the antibodies/fragments of the present invention are provided for use in methods to treat/prevent a cancer, e.g. an epithelial cell cancer, breast cancer, gastrointestinal cancer (e.g. esophageal cancer, stomach cancer, pancreatic cancer, liver cancer (e.g. HCC), gallbladder cancer, colorectal cancer, anal cancer, gastrointestinal carcinoid tumor), and lung cancer (e.g. non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC))). In some embodiments, the cancer is a cancer for which acute and/or chronic inflammation is a risk factor. In some embodiments, the cancer is a cancer for which a disease/disorder characterised by fibrosis (e.g. as described herein) is a risk factor.

In some embodiments, the cancer may be associated with increased IL-11, IL-11Rα and/or gp130 gene or protein expression. For example, cells of the cancer may have increased expression of IL-11, IL-11Rα and/or gp130 as compared to comparable, non-cancerous cells, or may be associated with increased expression of IL-11, IL-11Rα and/or gp130 by other cells (e.g. non-cancerous cells) as compared to the level of expression

by comparable cells in the absence of a cancer (e.g. in a healthy control subject). In some embodiments, cells of the cancer may be determined to have an increased level of signalling through ERK and/or STAT3 pathways as compared to comparable non-cancerous cells.

In some embodiments, the cancer may be associated with a mutation in IL-11, IL-11Rα and/or gp130. In some embodiments, such mutation may be associated with increased level of gene or protein expression, or may be associated with an increased level of IL-11/IL-11R signalling relative to the level of expression/signalling observed in the absence of the mutation.

IL-11 has also been implicated in diseases/disorders characterised by inflammation. Intra-articular injection of IL-11 has been shown to cause joint inflammation (Wong et al., Cytokine (2005) 29:72-76), and IL-11 has been shown to be proinflammatory at sites of IL-13-mediated tissue inflammation (Chen et al., J Immunol (2005) 174:2305-2313). IL-11 expression has also been observed to be significantly increased in chronic skin lesions in atopic dermatitis, and is known to be involved in bronchial inflammation (Toda et al., J Allergy Clin Immunol (2003) 111:875-881). IL-11-mediated signalling is implicated in inflammatory bowel disease (IBD) and asthma (Putoczki and Ernst, J Leuko Biol (2010) 88(6)1109-1117). IL-11 has also been identified as a risk factor for multiple sclerosis; IL-11 is elevated in the cerebrospinal fluid of patients with clinically isolated syndrome (CIS) as compared to control subjects, and serum levels of IL-11 are higher during relapses for patients with relapsing-remitting multiple sclerosis, and IL-11 may promote differentiation of CD4+ T cells to a T_H17 phenotype – T_H17 cells are important cells in the pathogenesis of multiple sclerosis (Zhang et al., Oncotarget (2015) 6(32): 32297-32298).

In some embodiments, the antibodies/fragments of the present invention are provided for use in methods to treat/prevent a disease/disorder characterised by inflammation. In some embodiments, a disease or disorder characterised by inflammation may be a disease/disorder which leads directly or indirectly to a cancer and/or fibrosis. Diseases characterised by inflammation include e.g. allergic inflammation such as allergic asthma and bronchial inflammation, atopic dermatitis, allergic rhinitis and ocular allergic diseases, and autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, chronic active hepatitis, type 1 diabetes mellitus, celiac disease, Grave's disease, uveitis, pemphigus, psoriasis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, anaemia and autoimmune thyroiditis.

In some embodiments, the antibodies/fragments of the present invention are provided for use in methods to treat/prevent a disease/disorder associated with infection, in particular where infection leads directly or indirectly to fibrosis, cancer or inflammation. A disease associated with infection may be a disease which is caused or exacerbated by infection with the relevant infectious agent, or may be a disease for which infection with the relevant infectious agent is a risk factor.

An infection may be any infection or infectious disease, e.g. bacterial, viral, fungal, or parasitic infection. In particular embodiments, the disease/disorder may be associated with a viral infection. In some embodiments it may be particularly desirable to treat chronic/persistent infections, e.g. where such infections are associated with inflammation, cancer and/or fibrosis.

The infection may be chronic, persistent, latent or slow, and may be the result of bacterial, viral, fungal or parasitic infection. As such, treatment may be provided to patients having a bacterial, viral or fungal infection. Examples of bacterial infections include infection with *Helicobacter pylori* and *Mycobacterium tuberculosis* infection of the lung. Examples of viral infections include infection with EBV, HPV, HIV, hepatitis B or hepatitis C.

The treatment may involve ameliorating, treating, or preventing the disease/disorder by inhibiting the biological activity of IL-11 or an IL-11-containing complex. Such methods may include the administration of the antibodies/fragments/compositions according to the present invention to bind to and inhibit the biological activity of IL-11 or an IL-11-containing complex. Herein, inhibiting the biological activity of IL-11 or an IL-11-containing complex may be referred to as 'neutralising'.

Methods of treatment may optionally include the co-administration of biological adjuvants (e.g., interleukins, cytokines, Bacillus Comette-Guerin, monophosphoryl lipid A, etc.) in combination with conventional therapies for treating cancer such as treatment with an agent for treating cancer (e.g. chemotherapy), radiation, or surgery. Methods of medical treatment may also involve *in vivo*, *ex vivo*, and adoptive immunotherapies, including those using autologous and/or heterologous cells or immortalized cell lines.

The treatment may be aimed at prevention of a disease/disorder associated with overactive/elevated IL-11 mediated signalling. As such, the antibodies, antigen binding fragments and polypeptides may be used to formulate pharmaceutical compositions or medicaments and subjects may be prophylactically treated against development of a disease state. This may take place before the onset of symptoms of the disease state, and/or may be given to subjects considered to be at greater risk of the disease or disorder.

Administration of an antibody, antigen binding fragment or polypeptide is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins.

Formulating pharmaceutically useful compositions and medicaments

Antibodies and antigen binding fragments according to the present invention may be formulated as pharmaceutical compositions or medicaments for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

The composition may be formulated for topical, parenteral, systemic, intracavitary, intravenous, intra-arterial, intramuscular, intrathecal, intraocular, intraconjunctival, intratumoral, subcutaneous, oral or transdermal routes of administration which may include injection or infusion. Suitable formulations may comprise the antibody/fragment in a sterile or isotonic medium. Medicaments and pharmaceutical compositions may be

formulated in fluid, including gel, form. Fluid formulations may be formulated for administration by injection or via catheter to a selected region of the human or animal body.

In accordance with the present invention methods are also provided for the production of pharmaceutically useful compositions, such methods of production may comprise one or more steps selected from: isolating an antibody or antigen binding fragment as described herein; and/or mixing an isolated antibody or antigen binding fragment as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

For example, a further aspect of the present invention relates to a method of formulating or producing a medicament or pharmaceutical composition for use in a method of medical treatment, the method comprising formulating a pharmaceutical composition or medicament by mixing an antibody or antigen binding fragment as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Methods of detection

Antibodies, or antigen binding fragments, described herein may be used in methods that involve the binding of the antibody or antigen binding fragment to IL-11. Such methods may involve detection of the bound complex of antibody, or antigen binding fragment, and IL-11. As such, in one embodiment a method is provided, the method comprising contacting a sample containing, or suspected to contain, IL-11 with an antibody or antigen binding fragment as described herein and detecting the formation of a complex of antibody, or antigen binding fragment, and IL-11.

Suitable method formats are well known in the art, including immunoassays such as sandwich assays, e.g. ELISA. The method may involve labelling the antibody/antigen binding fragment or IL-11, or both, with a detectable label, e.g. fluorescent, luminescent or radio-label. IL-11 expression may be measured by immunohistochemistry (IHC), for example of a tissue sample obtained by biopsy. In some embodiments, the label may be selected from: a radio-nucleotide, positron-emitting radionuclide (e.g. for positron emission tomography (PET)), MRI contrast agent or fluorescent label.

Analysis *in vitro* or *in vivo* of processes mediated by IL-11 may involve analysis by positron emission tomography (PET), magnetic resonance imaging (MRI), or fluorescence imaging, e.g. by detection of appropriately labelled species.

Methods of this kind may provide the basis of a method of diagnosis of a disease or condition requiring detection and or quantitation of IL-11 or an IL-11-containing complex. Such methods may be performed *in vitro* on a subject sample, or following processing of a subject sample. Once the sample is collected, the subject is not required to be present for the *in vitro* method of diagnosis to be performed and therefore the method may be one which is not practised on the human or animal body.

Such methods may involve determining the amount of IL-11 or IL-11-containing complex present in a subject sample. The method may further comprise comparing the determined amount against a standard or reference value as part of the process of reaching a diagnosis. Other diagnostic tests may be used in

conjunction with those described here to enhance the accuracy of the diagnosis or prognosis or to confirm a result obtained by using the tests described here.

The level of IL-11 or IL-11-containing complex present in a subject sample may be indicative that a subject may respond to treatment with an anti-IL-11 antibody/fragment, e.g. an anti-IL-11 antibody/fragment or composition according to the present invention. The presence of a high level of IL-11 or IL-11-containing complex in a sample may be used to select a subject for treatment with an anti-IL-11 antibody/fragment or composition described herein. The antibodies of the present invention may therefore be used to select a subject for treatment with anti-IL-11 therapy.

Detection in a sample of IL-11 or IL-11-containing complex may be used for the purpose of diagnosis of an infectious disease, autoimmune disorder or a cancerous condition in the subject, diagnosis of a predisposition to an infectious disease, autoimmune disorder or a cancerous condition or for providing a prognosis (prognosticating) of an infectious disease, autoimmune disorder or a cancerous condition. The diagnosis or prognosis may relate to an existing (previously diagnosed) infectious, inflammatory or autoimmune disease/disorder or cancerous condition.

A sample may be taken from any tissue or bodily fluid. The sample may comprise or may be derived from: a quantity of blood; a quantity of serum derived from the individual's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a tissue sample or biopsy; pleural fluid; cerebrospinal fluid (CSF); or cells isolated from said individual. In some embodiments, the sample may be obtained or derived from a tissue or tissues which are affected by the disease/disorder (e.g. tissue or tissues in which symptoms of the disease manifest, or which are involved in the pathogenesis of the disease/disorder).

Methods according to the present invention may preferably be performed *in vitro*. The term "*in vitro*" is intended to encompass experiments with cells in culture whereas the term "*in vivo*" is intended to encompass experiments with and/or treatment of intact multi-cellular organisms.

Combination therapies

Antibodies, antigen binding fragments and compositions according to the present invention may be administered alone or in combination with other treatments. Administration of such combination may be simultaneous or sequential, depending on the disease/disorder to be treated. The other treatment with which the antibody/fragment or composition is administered may be aimed at treating or preventing the disease/disorder. In some embodiments, the other treatment with which the antibody/fragment or composition is administered may be aimed at treating or preventing e.g. infection, inflammation and/or cancer.

Simultaneous administration refers to administration of the antibody, antigen binding fragment or polypeptide and therapeutic agent together, for example as a pharmaceutical composition containing both agents

(combined preparation), or immediately after each other and optionally via the same route of administration, e.g. to the same artery, vein or other blood vessel.

Sequential administration refers to administration of one of the antibody, antigen binding fragment or polypeptide or therapeutic agent followed after a given time interval by separate administration of the other agent. It is not required that the two agents are administered by the same route, although this is the case in some embodiments. The time interval may be any time interval.

In some embodiments, treatment with an antibody, antigen binding fragment or composition of the present invention may be accompanied by an agent for treating or preventing infection (e.g. an antibiotic, anti-viral, anti-fungal or anti-parasitic agent). In some embodiments, treatment with an antibody, antigen binding fragment or composition of the present invention may be accompanied by an agent for treating or preventing inflammation (e.g. a non-steroidal anti-inflammatory drug (NSAID). In some embodiments, treatment with an antibody, antigen binding fragment or composition of the present invention may be accompanied by radiotherapy (i.e. treatment with ionising radiation, e.g. X-rays or γ-rays) and/or an agent for treating or preventing cancer (e.g. a chemotherapeutic agent). In some embodiments, the antibody, antigen binding fragment or composition of the present invention may be administered as part of a combination treatment with an immunotherapy.

A treatment may involve administration of more than one drug. A drug may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

Routes of administration

Antibodies, antigen binding fragments, medicaments and pharmaceutical compositions according to aspects of the present invention may be formulated for administration by a number of routes, including but not limited to, parenteral, intravenous, intra-arterial, intraocular, intraconjunctival, intramuscular, subcutaneous, intradermal, intratumoral injection or infusion, and oral administration. Antibodies, antigen binding fragments, polypeptides and other therapeutic agents, may be formulated in fluid or solid form. Fluid formulations may be formulated for administration by injection or infusion to a selected region of the human or animal body.

Kits

In some aspects of the present invention a kit of parts is provided. In some embodiments the kit may have at least one container having a predetermined quantity of the antibody, fragment, or composition. The kit may provide the antibody/fragment in the form of a medicament or pharmaceutical composition, and may be provided together with instructions for administration to a subject in order to treat a specified disease/disorder. The antibody, fragment or composition may be formulated so as to be suitable for injection or infusion to a tumor or to the blood.

In some embodiments the kit may further comprise at least one container having a predetermined quantity of another therapeutic agent (e.g. anti-infective agent or chemotherapy agent). In such embodiments, the kit may also comprise a second medicament or pharmaceutical composition such that the two medicaments or

pharmaceutical compositions may be administered simultaneously or separately such that they provide a combined treatment for the specific disease or condition. The therapeutic agent may also be formulated so as to be suitable for injection or infusion to a tumor or to the blood.

Subjects

The subject to be treated may be any animal or human. The subject is preferably mammalian, more preferably human. The subject may be a non-human mammal, but is more preferably human. The subject may be male or female. The subject may be a patient. A subject may have been diagnosed with a disease or condition requiring treatment, or be suspected of having such a disease or condition.

In some embodiments the subject may be at risk of developing/contracting a disease or disorder.

Protein Expression

Molecular biology techniques suitable for producing the proteins (e.g. the antibodies/fragments) according to the invention in cells are well known in the art, such as those set out in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989

The polypeptide may be expressed from a nucleotide sequence. The nucleotide sequence may be contained in a vector present in a cell, or may be incorporated into the genome of the cell.

A “vector” as used herein is an oligonucleotide molecule (DNA or RNA) used as a vehicle to transfer exogenous genetic material into a cell. The vector may be an expression vector for expression of the genetic material in the cell. Such vectors may include a promoter sequence operably linked to the nucleotide sequence encoding the gene sequence to be expressed. A vector may also include a termination codon and expression enhancers. Any suitable vectors, promoters, enhancers and termination codons known in the art may be used to express polypeptides from a vector according to the invention. Suitable vectors include plasmids, binary vectors, viral vectors and artificial chromosomes (e.g. yeast artificial chromosomes).

In this specification the term “operably linked” may include the situation where a selected nucleotide sequence and regulatory nucleotide sequence (e.g. promoter and/or enhancer) are covalently linked in such a way as to place the expression of the nucleotide sequence under the influence or control of the regulatory sequence (thereby forming an expression cassette). Thus a regulatory sequence is operably linked to the selected nucleotide sequence if the regulatory sequence is capable of effecting transcription of the nucleotide sequence. Where appropriate, the resulting transcript may then be translated into a desired protein or polypeptide.

Any cell suitable for the expression of polypeptides may be used for producing polypeptides according to the invention. The cell may be a prokaryote or eukaryote. Suitable prokaryotic cells include *E.coli*. Examples of eukaryotic cells include a yeast cell, a plant cell, insect cell or a mammalian cell (e.g. Chinese Hamster Ovary (CHO) cells). In some cases the cell is not a prokaryotic cell because some prokaryotic cells do not allow for the same post-translational modifications as eukaryotes. In addition, very high expression levels are

possible in eukaryotes and proteins can be easier to purify from eukaryotes using appropriate tags. Specific plasmids may also be utilised which enhance secretion of the protein into the media.

Methods of producing a polypeptide of interest may involve culture or fermentation of a cell modified to express the polypeptide. The culture or fermentation may be performed in a bioreactor provided with an appropriate supply of nutrients, air/oxygen and/or growth factors. Secreted proteins can be collected by partitioning culture media/fermentation broth from the cells, extracting the protein content, and separating individual proteins to isolate secreted polypeptide. Culture, fermentation and separation techniques are well known to those of skill in the art.

Bioreactors include one or more vessels in which cells may be cultured. Culture in the bioreactor may occur continuously, with a continuous flow of reactants into, and a continuous flow of cultured cells from, the reactor. Alternatively, the culture may occur in batches. The bioreactor monitors and controls environmental conditions such as pH, oxygen, flow rates into and out of, and agitation within the vessel such that optimum conditions are provided for the cells being cultured.

Following culture of cells that express the polypeptide of interest, that polypeptide is preferably isolated. Any suitable method for separating polypeptides from cell culture known in the art may be used. In order to isolate a polypeptide of interest from a culture, it may be necessary to first separate the cultured cells from media containing the polypeptide of interest. If the polypeptide of interest is secreted from the cells, the cells may be separated from the culture media that contains the secreted polypeptide by centrifugation. If the polypeptide of interest collects within the cell, it will be necessary to disrupt the cells prior to centrifugation, for example using sonification, rapid freeze-thaw or osmotic lysis. Centrifugation will produce a pellet containing the cultured cells, or cell debris of the cultured cells, and a supernatant containing culture medium and the polypeptide of interest.

It may then be desirable to isolate the polypeptide of interest from the supernatant or culture medium, which may contain other protein and non-protein components. A common approach to separating polypeptide components from a supernatant or culture medium is by precipitation. Polypeptides/proteins of different solubility are precipitated at different concentrations of precipitating agent such as ammonium sulfate. For example, at low concentrations of precipitating agent, water soluble proteins are extracted. Thus, by adding increasing concentrations of precipitating agent, proteins of different solubility may be distinguished. Dialysis may be subsequently used to remove ammonium sulfate from the separated proteins.

Other methods for distinguishing different polypeptides/proteins are known in the art, for example ion exchange chromatography and size chromatography. These may be used as an alternative to precipitation, or may be performed subsequently to precipitation.

Once the polypeptide of interest has been isolated from culture it may be necessary to concentrate the protein. A number of methods for concentrating a protein of interest are known in the art, such as ultrafiltration or lyophilisation.

Sequence Identity

Alignment for purposes of determining percent amino acid or nucleotide sequence identity can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalW 1.82. T-coffee or Megalign (DNASTAR) software. When using such software, the default parameters, e.g. for gap penalty and extension penalty, are preferably used. The default parameters of ClustalW 1.82 are: Protein Gap Open Penalty = 10.0, Protein Gap Extension Penalty = 0.2, Protein matrix = Gonnet, Protein/DNA ENDGAP = -1, Protein/DNA GAPDIST = 4.

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The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Aspects and embodiments of the present invention will now be illustrated, by way of example, with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise,” and variations such as “comprises” and “comprising,” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment.

Brief Description of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures, in which:

Figure 1. Graph showing read depth for whole transcriptome sequencing of human atrial fibroblasts from 160 individuals with and without stimulation with TGFβ1.

Figure 2. Graphs showing expression of endothelial, cardiomyocyte and fibroblast marker genes as determined by RNA-seq of the tissue of origin (human atrial tissues samples, n=8) and primary, unstimulated fibroblast cultures. (**A**) PECAM1, (**B**) MYH6 (**C**) TNNT2, (**D**) COL1A2, and (**E**) ACTA2.

Figure 3. Graphs showing upregulation of IL-11 expression in fibroblasts in response to stimulation with TGFβ1. (**A** and **B**) Graphs showing fold change in gene expression in fibrosis; IL-11 is the most upregulated gene in response to TGFβ1 treatment. (**C**) IL-11 secretion by fibroblasts in response to stimulation with TGFβ1. (**D**) Comparison of IL-11 gene expression in tissues of healthy individuals and in atrial fibroblasts, with or without TGFβ1 stimulation. (**E**) Correspondence of fold change in IL-11 expression as determined by RNA-seq vs. qPCR.

Figure 4. Graphs showing induction of IL-11 secretion in primary fibroblasts by various profibrotic cytokines, as determined by ELISA. (**A**) TGFβ1, ET-1, AngII, PDGF, OSM and IL-13 induce IL-11 secretion, and IL-11 also induces IL-11 expression in a positive feedback loop. (**B**) Graph showing that the ELISA only detects native IL-11 secreted from cells, and does not detect recombinant IL-11 used for the IL-11 stimulation condition. (**C**) and (**D**) Cells were stimulated with recombinant IL-11, IL-11 RNA was measured and the native IL-11 protein level was measured in the cell culture supernatant by ELISA at the indicated time points.

Figure 5. Graphs and images showing myofibroblast generation from, and production of ECM and cytokine expression by, atrial fibroblasts in response to stimulation with TGFβ1 or IL-11. (**A**) myofibroblast generation and ECM production by primary atrial fibroblasts following stimulation with TGFβ1 or IL-11, as measured by fluorescence microscopy following staining for a α-SMA, collagen or periostin. (**B**) Collagen content of cell culture supernatant as determined by Sirius Red staining. Secretion of the fibrosis markers (**C**) IL-6, (**D**) TIMP1 and (**E**) MMP2 as measured by ELISA. (**F**) Activation of murine fibroblasts by stimulation with human or mouse recombinant IL-11. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ [Mean ± SD, Dunnett].

Figure 6. Graphs showing the profibrotic effect of IL-11. (**A**) Mouse fibroblasts from different tissues of origin can be activated by IL-11 and display increased ECM production. [Mean ± SD, Dunnett]. Injection of mice with recombinant IL-11 or AngII results in (**B**) an increase in organ weight [Mean ± SEM], and (**C**) an increase in collagen content (as determined by HPA assay). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ [Mean ± SD, Dunnett].

Figure 7. Graphs and images showing that IL-11 is required the pro-fibrotic effects of TGFβ1 on fibroblasts. (**A**) myofibroblast generation and ECM production by primary atrial fibroblasts, with or without stimulation with TGFβ1, and in the presence/absence of neutralising anti-IL-11 antibody or isotype control IgG, as measured by fluorescence microscopy following staining for (**A**) α-SMA, (**B**) EdU or (**C**) Periostin. (**D** to **F**) Secretion of the fibrosis markers (**D**) IL-6, (**E**) TIMP1, and (**F**) MMP2 was analysed by ELISA. Fluorescence was normalized to the control group without stimulation. [Mean ± SD, Dunnett] * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ or **** $P < 0.0001$.

Figure 8. Graphs and images showing the effect of neutralisation of IL-11 on collagen production triggered by TGFβ1. Collagen production by cardiac fibroblasts with or without stimulation with TGFβ1, and in the presence/absence of neutralising anti-IL-11 antibody or isotype control IgG, as determined by (**A**) Operetta assay or (**B**) Sirius Red staining. [Mean ± SD, Dunnett] * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ or **** $P < 0.0001$.

Figure 9. Graphs showing the ability of various IL-11 and IL-11Rα antagonists to inhibit fibrosis. Human atrial fibroblasts were treated with neutralizing antibody against IL-11, neutralizing antibody against IL-11Rα, decoy IL-11 receptor molecule that binds to IL-11, siRNA that downregulates IL-11 expression or siRNA that downregulates IL-11RA expression and the effect on the TGFβ1-driven pro-fibrotic response in fibroblasts *in vitro* was analysed. [Mean ± SD, Dunnett] * P < 0.05, ** P < 0.01, *** P < 0.001 or **** P < 0.0001.

Figure 10. Bar charts showing the response of fibroblasts from IL-11-RA knockout mice to pro-fibrotic treatment. Fibroblasts derived from IL-11RA WT (+/+), Heterozygous (+/-) and Homozygous null (-/-) mice were incubated for 24h with TGFβ1, IL-11 or AngII (5 ng/ml). (**A**) Percentage of myofibroblasts as determined by analysis αSMA content, (**B**) Percentage proliferating cells as determined by staining for EdU, (**C**) Collagen content and (**D**) ECM production as measured by detection of periostin [Mean ± SD].

Figure 11. Graphs showing the effect of IL-11 neutralisation on fibrosis in response to various pro-fibrotic stimuli. Fibroblasts were cultured *in vitro* in the presence/absence of various different pro-fibrotic factors, and in the presence/absence of neutralising anti-IL-11 antibody or pan anti-TGFβ antibody (**A**) Collagen production and (**B**) myofibroblast generation as determined by analysis of αSMA expression. [Mean ± SD, Dunnett] * P < 0.05, ** P < 0.01, *** P < 0.001 or **** P < 0.0001.

Figure 12. Bar charts showing expression of markers of fibrosis in the atrium and heart of WT and IL-11RA (-/-) animals following treatment with AngII treatment. (**A**) Collagen content, as measured by hydroxyproline assay. (**B**) Collagen (Col1A2) expression. (**C**) αSMA (ACTA2) expression. (**D**) Fibronectin (Fn1) expression.

Figure 13. Schematics of the experimental procedures for analysing fibrosis in (**A**) lung, (**B**) skin and (**C**) eye for IL-11RA -/- mice as compared to IL-11RA +/+ mice.

Figure 14. Scatterplots showing fold change in gene expression. (**A**) Fold changes in gene expression in fibroblasts following stimulation with TGFβ1, IL-11 or TGFβ1 and IL-11. (**B**) Fold changes in gene expression in fibroblasts obtained from IL-11RA+/+ and IL-11RA-/- mice following stimulation with TGFβ1.

Figure 15. Light chain variable domain sequences for human anti-IL-11 antibody clones. CDRs are underlined and shown separately.

Figure 16. Heavy chain variable domain sequences for human anti-IL-11 antibody clones. CDRs are underlined and shown separately.

Figure 17. Table showing light chain CDR sequences for human anti-IL-11 antibody clones.

Figure 18. Table showing heavy chain CDR sequences for human anti-IL-11 antibody clones.

Figure 19. Tables showing light chain CDR sequences for human anti-IL-11 antibody clones and consensus sequences, for (**A**) LC-CDR1, (**B**) LC-CDR2 and (**C**) LC-CDR3.

Figure 20. Tables showing heavy chain CDR sequences for human anti-IL-11 antibody clones and consensus sequences, for (**A**) HC-CDR1, (**B**) HC-CDR2 and (**C**) HC-CDR3.

Figure 21. Table summarising panning strategies used to identify human anti-human IL-11 antibodies capable of binding to both human IL-11 and mouse IL-11.

Figure 22. Scatterplot showing strength of binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for 86 human anti-IL-11 antibody candidates.

Figure 23. Table summarising the 56 human anti-human IL-11 antibody clones.

Figure 24. Bar charts showing inhibition by the human anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of αSMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGFβ1, in the presence of the human anti-IL-11 antibodies. (**A**) Bar chart showing fold change in proportion of αSMA-positive cells relative to unstimulated cells (=1). (**B**) Bar chart showing the percentage of αSMA-positive cells (activated fibroblasts).

Figure 25. Bar chart showing inhibition by the human anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in (**A**) mouse atrial fibroblasts and (**B**) mouse dermal fibroblasts, as determined by fold change in the percentage of αSMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGFβ1, in the presence of the human anti-IL-11 antibodies.

Figure 26. Bar chart showing inhibition by the human anti-IL-11 antibodies of IL-11 *trans* signalling mediated by hyper IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of αSMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with hyper IL-11, in the presence of the human anti-IL-11 antibodies.

Figure 27. Table summarising the fold-change data of Figures 24 to 26 for the 56 human anti-IL-11 antibodies. Antibody candidates numbered 1 to 56 correspond to clone designations as indicated in Figure 23. Industry standard is monoclonal mouse anti-IL-11 IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA.

Figure 28. Graphs showing binding of human anti-IL-11 antibodies to human IL-11 as determined by ELISA analysis. (**A**) ELISA for clones YU45-A3, YU45-A10, YU45-D11, YU45-E11, YU45-D12 and YU33-A2(IgG). (**B**) ELISA for clones YU45-G1, YU45-B2, YU45-A5, YU45-E3, YU45-F8 and YU33-H3(IgG). (**C**) ELISA for clones YU45-G8, YU45-F9, YU45-H10, YU45-F2, YU45-H3 and YU33-E3(IgG). (**D**) ELISA for clones YU45-A8, YU45-B5, YU45-D9, YU45-G7, YU45-B6 and YU45-F9. (**E**) ELISA for clones YU45-F5, YU46-B5, YU45-C1, YU46-A8, YU46-B6 and YU45-F9. (**F**) ELISA for clones YU46-E3, YU46-G8, YU46-D3, YU45-B6, YU45-C1 and YU45-F9.

Figure 29. Table summarising EC_{50} values determined for binding of human anti-IL-11 antibodies to IL-11 as determined by ELISA analysis.

Figure 30. Schematic representation of the process of antibody light chain shuffling.

Figure 31. Table summarising the 16 mouse anti-human IL-11 antibody clones.

Figure 32. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the percentage of αSMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGFβ1, in the presence of the mouse anti-IL-11 antibodies.

Figure 33. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of signalling mediated by IL-11 *in vitro* in mouse atrial fibroblasts, as determined by fold change in the percentage of αSMA positive cells as compared to control (unstimulated) fibroblasts, following stimulation with TGFβ1, in the presence of the mouse anti-IL-11 antibodies.

Figure 34. Bar chart showing inhibition by the mouse anti-IL-11 antibodies of IL-11 *trans* signalling mediated by hyper IL-11 *in vitro* in human atrial fibroblasts, as determined by fold change in the amount of MMP2 in the cell culture supernatant as compared to control (unstimulated) fibroblasts, following stimulation with hyper IL-11, in the presence of the mouse anti-IL-11 antibodies.

Figure 35. Table summarising the fold-change data of Figures 32 to 34 for the 16 mouse anti-IL-11 antibodies. Antibody candidates numbered 1 to 16 correspond to clone designations as indicated in Figure 31. Industry standard is monoclonal mouse anti-IL-11 IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA.

Figure 36. Table and bar chart showing binding of mouse-anti-IL-11 antibodies to human IL-11, as determined by iQue analysis (**A**) Table summarising the results of the experiments. (**B**) Bar chart showing strength of binding relative to the positive control anti-FLAG antibody (100%); numbers correspond to the clones as indicated in Figure 35.

Figure 37. Graphs showing the effect of IL-11RA knockout on folate-induced kidney fibrosis as measured by collagen content in kidney tissue.

Figure 38. Photographs showing the effect of IL-11RA knockout on wound healing and fibrosis in the eye following trabeculectomy (filtration surgery). (**A**) Eye sections of IL-11RA+/+ (WT) and IL-11RA-/- (KO) animals 7 days after filtration surgery. (**B**) Maturation of collagen fibres as evaluated by picro-sirius red/polarization light technique (Szendröi et al. 1984, Acta Morphol Hung 32, 47–55); more fibrosis is observed in WT mice than KO mice.

Figure 39. Graphs showing that IL-11 is required the pro-fibrotic effects of TGFβ1 in liver fibroblasts. Activation and proliferation of primary human liver fibroblasts, with or without stimulation with TGFβ1, and in the presence/absence of neutralising anti-IL-11 antibody or isotype control IgG, as measured by analysis of the proportion of (**A**) α-SMA positive cells, and (**B**) EdU positive cells, (**C**) Collagen positive cells and (**D**) Periostin positive cells as compared to the unstimulated cells (Baseline). [Mean ± SD, Dunnett] * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ or **** $P < 0.0001$.

Figure 40. Bar chart showing that IL-11 is required for the pro-fibrotic effects of TGFβ1 in skin fibroblasts. Activation of mouse skin fibroblasts, with or without stimulation with TGFβ1, and in the presence/absence of neutralising anti-IL-11 antibody, as measured by analysis of the percentage of α-SMA positive cells (activated fibroblasts).

Figure 41. Bar chart showing lung fibroblast cell migration with and without IL-11 signalling. Migration of lung fibroblasts from IL-11RA+/+ (WT) and IL-11RA-/- (KO) animals was analysed in an *in vitro* scratch assay without stimulus, or in the presence of TGFβ1 or IL-11.

Figure 42. Graphs showing fibroblast activation in response to hyper IL-11. Cells were stimulated with the indicated amount (in ng/ml) of hyper IL-11 or recombinant IL-11, and fibroblast activation was measured by analysis of the percentage of α-SMA positive cells. (**A**) and (**B**) present the results of two different experiments.

Figure 43. Graph showing induction of IL-11 secretion in primary fibroblasts by hyper IL-11. Cells were stimulated with hyper IL-11, and IL-11 RNA and native IL-11 protein levels were measured in the cell culture supernatant by ELISA at the indicated time points.

Figure 44. Light chain variable domain sequences for human anti-IL-11 antibody clones after light chain shuffling. CDRs are underlined and shown separately.

Figure 45. Heavy chain variable domain sequences for human anti-IL-11 antibody clones after light chain shuffling. CDRs are underlined and shown separately.

Figure 46. Table showing light chain CDR sequences for human anti-IL-11 antibody clones after light chain shuffling.

Figure 47. Table showing heavy chain CDR sequences for human anti-IL-11 antibody clones after light chain shuffling.

Figure 48. Tables showing light chain CDR sequences for human anti-IL-11 antibody clones after light chain shuffling, and consensus sequences, for (**48A**) LC-CDR1, (**48B**) LC-CDR2 and (**48C**) LC-CDR3.

Figure 49. Tables showing heavy chain CDR sequences for human anti-IL-11 antibody clones after light chain shuffling, and consensus sequences, for (**49A**) HC-CDR1, (**49B**) HC-CDR2 and (**49C**) HC-CDR3.

Figure 50. Single-chain variable antibody fragment (ScFv) amino acid sequences for human anti-IL-11 antibody clones after light chain shuffling.

Figure 51. Nucleotide sequences encoding scFv for human anti-IL-11 antibody clones after light chain shuffling.

Figure 52. Table summarising panning strategies used to identify human anti-human IL-11 antibodies capable of binding to both human IL-11 and mouse IL-11, after light chain shuffling.

Figure 53. Scatterplot showing binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for light chain-shuffled human anti-IL-11 antibodies. 66 antibodies displaying cross-reactive binding to human IL-11 and mouse IL-11 were identified (black circles). Antibodies displaying binding to mouse IL-11 only are indicated by grey circles.

Figure 54. Bar chart (Figure 54A) and Table (Figure 54B) showing binding signal to human IL-11 and mouse IL-11 as determined by ELISA assay for the 64 unique light chain-shuffled human anti-IL-11 antibodies.

Figure 55. Bar chart showing EC50 values in ng/ml for binding of the indicated light-chain shuffled anti-IL-11 antibodies to human IL-11, as determined by ELISA.

Figure 56. Bar chart showing the effect of anti-IL-11 antibodies on MMP2 secretion by human cardiac atrial fibroblasts in response to TGFβ1. Figures 56A and 56B show the results of two separate experiments. Cells were cultured in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence of the indicated light chain shuffled anti-IL-11 antibodies, or in the presence of human IgG1 isotype control. Basal MMP2 secretion by the cells in culture was measured by culture in the absence of TGFβ1, in the presence of human IgG1 isotype control. Horizontal lines show basal MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of human IgG1 isotype control antibody in the absence of TGFβ1 (NEG); and MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of 5 ng/ml TGFβ and the human IgG1 isotype control antibody (POS).

Figure 57. Table summarising the results of Figures 55 and 56 relating to functional characterisation of the indicated light-chain shuffled anti-IL-11 antibody clones. N.D. = not determined.

Figures 58A and 58B. Images and graph showing the results of histological analysis of kidney sections from mice subjected to different treatments in a mouse model of kidney fibrosis. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180 mg/kg) in vehicle (0.3M $NaHCO_3$) mice; control mice were administered vehicle alone. Mice were administered isotype control IgG2 (20mg/kg, 3 x per week, intraperitoneal), anti-IL-11 antibody (20mg/kg, 3 x per week, intraperitoneally) from day 1 post folic acid injury and for the duration of the experiment. Animals were sacrificed 28 days after folic acid-induced kidney damage and analysed for fibrosis histologically using Masson's Trichrome stain. (**58A**) Images of Masson's

Trichrome stained kidney sections. Fibrotic areas containing collagen appear darker as compared to healthy areas that appear lighter. (**58B**) Graphs showing semi-quantitative analysis of collagen area expressed as a percentage (%) of the total kidney area (graph). ***, P< 0.001 compared to FA+IgG, ANOVA.

Figure 59. Graph showing the urinary albumin/creatine ratio in mice subjected to different treatments in a mouse model of kidney fibrosis. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180mg/kg) in vehicle (0.3M $NaHCO_3$) mice; control mice were administered vehicle alone. FA treated mice were administered isotype control IgG2 (20mg/kg, 3 x per week, intraperitoneal) or anti-IL11 antibody (20mg/kg, 3 x per week, intraperitoneal) from day 1 post folic acid injury and for the duration of the experiment. Mice were placed in metabolic cages and urinary creatinine and albumin measured using commercial assays (Abcam) according to the manufacturer's instructions. ***, P< 0.001 compared to FA+IgG, ANOVA.

Figure 60. Graph showing total collagen in kidney tissue in mice subjected to different treatments in a mouse model of kidney fibrosis. Kidney fibrosis was induced by intraperitoneal (IP) injection of folic acid (FA, 180mg/kg) in vehicle (0.3M $NaHCO_3$) mice; control mice were administered vehicle alone. From day one of the experiment, mice in the treatment groups were given isotype control IgG2 (20mg/kg, 3 x per week) or neutralizing anti-IL11 antibody at varying doses: 20mg/kg x 3/week; 10mg/kg x 3/week; 10mg/kg x 2/week; 5mg/kg x 3/week; 5mg/kg x 2/week; 1mg/kg x 2/week), all intraperitoneal. Animals were sacrificed 28 days post-injection and kidney analysed for fibrosis (micrograms/g (µg/g)) by hydroxyproline assay using Quickzyme Total Collagen assay kit (Quickzyme Biosciences) according to the manufacturer's protocol. **, P<0.01; ***, P< 0.001 compared to FA+IgG, ANOVA.

Figures 61A and 61B. Images and graph showing the results of histological analysis of kidney sections from mice subjected to different treatments in a mouse model of acute renal injury. (**61A**) Mice were treated by sham operation or ureteric obstruction of one ureter. Mice received IgG, anti-IL-11 antibody (20mg/kg on surgical days -1, 1, 3, 5) and injured kidneys (UUO IgG, IL-11) or contralateral (Con) uninjured kidneys (Con IgG, IL-11) were harvested on day 7 post surgery. (**61B**) Semi-quantitative assessment of tubular injury was determined by histological analysis of casts, tubular atrophy or tubular expansion blinded to experimental conditions (Tubular injury score: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe). *, P<0.05 compared to UUO IgG, ANOVA.

Figure 62. Image showing the results of ELISA western blot for IL-11 of human liver samples. Liver samples obtained from patients undergoing liver surgery were used for western blot analysis. Blotting of GAPDH was used as a loading control. Samples from normal human liver (NHL) had low levels of IL-11 protein, whereas samples from patients with fibrotic liver diseases including alcoholic liver disease (ALD), primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC) or non-alcoholic steatohepatitis (NASH) had higher levels of IL-11.

Figure 63. Bar chart showing the results of ELISA analysis of secretion of IL-11 by human PCLS subjected to different treatments.

Figures 64A and 64B. Images and graph showing the results of analysis of liver tissue from mice subjected to different treatments in a mouse model of nonalcoholic steatohepatitis. Diabetic mice (db/db; deficient for the leptin receptor) were maintained for 8 weeks on a normal chow diet (left, round symbols) or on a NASH-inducing (methionine/choline deficient (MCD)) diet. In a subset of animals neutralizing anti-IL11 antibody was administered (20mg/kg, 3x/week, intraperitoneal) for the final 3 weeks of the 8 week NASH diet. Liver samples were photographed (**64A**) and assessed for collagen content per mg of liver tissue (**64B**); each symbol represents an individual animal. P values shown on graph, ANOVA.

Figures 65A and 65B. Bar chart and images showing the results of analysis of eye fibrosis from mice subjected to different treatments in a mouse model of retinal fibrosis. Mice (10 per group) were subjected to laser-induced retinal damage (4 burns per retina) and administered intraocularly with 0.5 µg of anti-IL-11 antibody or IgG control antibody on days 1, 7, 14 and 21. Eyes were harvested for histological analyses on day 28. The area of fibrosis at burn sites were measured by Masson's Trichrome staining. (**65A**) Bar cahrt showing quantification of the fibrosis areas in control (IgG) or anti-IL11 (IL11) treated mice. (**65B**) representative images showing staining of fibrotic areas in control antibody treated eyes (IGG, top panel) or anti-IL11 treated eyes (IL11, bottom panel).

Figures 66A to 66C. Schematic, images and bar chart relating to analysis of skin fibrosis in mice subjected to different treatments in a mouse model of skin fibrosis. (**66A**) Schematic representation of experimental procedures for different treatment groups. Groups 1 and 2 were treated with bleomycin (BLM), and either anti-IL-11 antibody (Group 1) or IgG control antibody (Group 2). Group 3 were injected with vehicle (PBS) only and do not develop fibrosis. (**66B**) Images showing Masson's trichrome staining of skin section at equal distances from the injection site. Dermal thickness is indicated by the black bar. (**66C**) Bar chart showing the results of analysis of dermal thickness (blinded for treatment groups). Average dermal thickness was determined from the bottom of epithelial layer to top of dermal white adipose tissue layer across 40 fields of view per sample. Each point indicates an animal. P value was calculated using an unpaired two-tailed t-test.

Figure 67. Images showing the results of histological analysis of heart fibrosis in mice subjected to different treatments in a mouse model of cardiac fibrosis. Mice (C57Bl6, male, 8-12 weeks old) were subjected to fibrosis-inducing transverse aortic constriction (TAC) or sham operations. TAC-treated animals received either control antibody (20mg/kg, 3x/week, intraperitoneal) or neutralizing anti-IL-11 antibody (20mg/kg, 3x/week, intraperitoneal). After two weeks hearts were harvested and assessed for fibrosis extent using Masson's Trichrome stain.

Figure 68. Heavy chain variable domain sequences for mouse anti-IL-11 antibody clones. CDRs are underlined and shown separately.

Figure 69. Light chain variable domain sequences for mouse anti-IL-11 antibody clones. CDRs are underlined and shown separately.

Figure 70. Table showing heavy chain CDR sequences for mouse anti-IL-11 antibody clones.

Figure 71. Table showing light chain CDR sequences for mouse anti-IL-11 antibody clones.

Figure 72. Tables showing heavy chain CDR sequences for mouse anti-IL-11 antibody clones, and consensus sequences, for (**72A**) HC-CDR1, (**72B**) HC-CDR2 and (**72C**) HC-CDR3.

Figure 73. Tables showing light chain CDR sequences for mouse anti-IL-11 antibody clones, and consensus sequences, for (**73A**) LC-CDR1, (**73B**) LC-CDR2 and (**73C**) LC-CDR3.

Figure 74. Nucleotide sequences encoding mouse anti-IL-11 antibody clone heavy chains and light chains.

Examples

In the following Examples, the inventors identify a role for IL-11/IL-11R signalling in fibrosis in a variety of tissues, and described the generation of anti-human IL-11 antibodies, and *in vitro* and *in vivo* functional characterisation of the antibodies.

Example 1: A role for IL-11 in fibrosis

1.1 IL-11 is upregulated in fibrosis

To understand the molecular processes underlying the transition of fibroblasts to activated myofibroblasts, atrial tissue was obtained from more than 200 patients that underwent cardiac bypass surgery at the National Heart Centre Singapore. Cells were cultured *in vitro* at low passage (passage <4), and either not stimulated or stimulated with TGFβ1 for 24h. We subsequently performed high-throughput RNA sequencing (RNA-seq) analysis of unstimulated fibroblasts and cells stimulated with the prototypic pro-fibrotic stimulus TGFβ1 across 160 individuals; average read depth was ~70M reads per sample (paired-end 100bp; Figure 1).

To ensure the purity of the atrial fibroblast cell cultures, we analysed expression of endothelial cell, cardiomyocyte and fibroblast cell type marker genes from the atrium (Hsu et al., 2012 Circulation Cardiovasc Genetics 5, 327–335) in the RNA-seq dataset.

The results are shown in Figures 2A to 2E, and confirm the purity of the atrial fibroblast cultures.

Gene expression was assessed by RNA-seq of the tissue of origin (human atrial tissues samples, n=8) and primary, unstimulated fibroblast cultures. No/very low expression of the endothelial cell marker PECAM1 (Figure 2A), and the cardiomyocyte markers MYH6 (Figure 2B) and TNNT2 (Figure 2C) was detected in the fibroblast cell culture samples. Markers for fibroblasts COL1A2 (Figure 2D) and ACTA2 (Figure 2E) were highly expressed compared to the tissue of origin.

Next, the RNA-seq data was analysed to identify genes whose expression was increased or decreased upon stimulation with TGFβ1, and this information was integrated with the large RNA-seq dataset across 35+ human tissues provided by the GTEx project (The GTEx Consortium, 2015 Science 348, 648–660). This enabled the identification of gene expression signatures that were specific to the fibroblast-myofibroblast transition.

The results are shown in Figures 3A to 3E. Across the 10000+ genes expressed in the fibroblasts, IL-11 was the most strongly upregulated gene in response to stimulation with TGFβ1, and on average across the 160 individuals was upregulated more than 10-fold (Figure 3B).

Upregulation of IL-11 expression was confirmed by ELISA analysis of the cell culture supernatant of TGFβ1 stimulated fibroblasts (Figure 3C). As compared to the level of expression level of IL-11 in other tissues of healthy individuals, this response was observed to be highly specific to activated fibroblasts (Figure 3D). Various fold changes of IL-11 RNA expression were also confirmed by qPCR analysis (Figure 3E).

Next, fibroblasts were cultured *in vitro* and stimulated with several other known pro-fibrotic factors: ET-1, ANGII, PDGF, OSM and IL-13, and also with human recombinant IL-11. For analysing upregulation of IL-11 produced in response to stimulation with IL-11, it was confirmed that the ELISA was only able to detect native IL-11 secreted from cells and does not detect recombinant IL-11 used for the stimulations (Figure 4B).

The results are shown in Figure 4A. Each factor was found to significantly induce IL-11 secretion from fibroblasts. IL-11 is shown to act in an autocrine loop in fibroblasts, which can result in an upregulation of IL-11 protein as much as 100-fold after 72 hours (Figure 4D).

Interestingly, this autocrine loop for IL-11 is similar to the autocrine production of IL-6. IL-6 is from the same cytokine family and also signals via the gp130 receptor (Garbers and Scheller, 2013 Biol Chem 394, 1145–1161), which is proposed to ensure the continued survival and growth of lung and breast cancer cells (Grivennikov and Karin, 2008 Cancer Cell 13, 7–9).

No increase in IL-11 RNA level was detected in response to stimulation with IL-11 (Figure 4D). Unlike TGFβ1, which increases IL-11 expression at both the RNA and protein level, therefore IL-11 seems to upregulate IL-11 expression only at the post-transcriptional level.

1.2 IL-11 has a profibrotic role in fibrosis of heart tissue

To explore whether the autocrine production of IL-11 is pro- or anti-fibrotic, fibroblasts were cultured *in vitro* with recombinant IL-11, and the fraction of myofibroblasts (αSMA-positive cells) and extracellular matrix production was analysed.

The expression of αSMA, collagen and periostin was monitored with the Operetta High-Content Imaging System in an automated, high-throughput fashion. In parallel, secretion of fibrosis marker proteins such as MMP2, TIMP1 and IL-6 was analysed by ELISA assays, and the levels of collagen were confirmed by calorimetric Sirius Red analysis of the cell culture supernatant.

Briefly, atrial fibroblasts derived from 3 individuals were incubated in 2 wells each for 24h without stimulation, with TGFβ1 (5 ng/ml), or with IL-11 (5 ng/ml). Following incubation, cells were stained to analyse α-SMA content to estimate the fraction of myofibroblasts, and for collagen and periostin to estimate ECM production. Fluorescence was measured in 7 fields per well. The supernatant of 2 wells per individual was also assessed

for collagen content by Sirius Red staining. The signal was normalized to the control group without stimulation. Secretion of the fibrosis markers IL-6, TIMP1 and MMP2 was analysed via ELISA.

The results are shown in Figures 5A to 5F. TGFβ1 activated fibroblasts and increased ECM production (Figure 5A). Unexpectedly, and in contrast with the anti-fibrotic role described for IL-11 in heart tissue in the scientific literature, recombinant IL-11 caused an increase in the fraction of myofibroblasts in fibroblast cultures, and also promoted the production of extracellular matrix proteins collagen and periostin to the same extent as TGFβ1 (Figure 5A). Both of IL-11 and TGFβ1 cytokines also significantly increased the secretion of pro-fibrotic markers IL-6, TIMP1 and MMP2 (Figures 5B to 5E), and to a similar level.

The inventors hypothesized that the contradiction between the present finding that IL-11 is profibrotic in heart tissue and the antifibrotic role described in the literature might be related to the use of human IL-11 in rodents in those previous studies (Obana et al., 2010, 2012; Stangou et al., 2011; Trepicchio and Dorner, 1998).

To investigate this hypothesis, serial dilutions of both human and mouse IL-11 were performed, and the activation of human atrial fibroblasts was monitored (Figure 5F). No activation of fibroblasts was observed at low concentrations of human IL-11 on mouse cells, suggesting that previous insights into IL-11 function may in part be due to IL-11-non-specific observations.

1.3 IL-11 has a profibrotic role in fibrosis of a variety of tissues

To test whether the profibrotic action of IL-11 was specific to atrial fibroblasts, human fibroblasts derived from several different tissues (heart, lung, skin, kidney and liver) were cultured *in vitro*, stimulated with human IL-11, and fibroblast activation and ECM production was analysed as described above. Increased fibroblast activation and production of ECM was observed as compared to non-stimulated cultures in fibroblasts derived from each of the tissues analysed.

1.3.1 Liver fibrosis

To test whether IL-11 signalling is important in liver fibrosis, human primary liver fibroblasts (Cell Biologics, Cat#: H-6019) were cultured at low passage in wells of 96-well plates and either not stimulated, stimulated with TGFβ1 (5ng/ml, 24h), IL-11 (5 ng/ml, 24h) or incubated with both TGFβ1 (5 ng/ml) and a neutralising IL-11 antibody (2 µg/ml), or TGFβ1 (5 ng/ml) and an Isotype control antibody. Fibroblast activation (αSMA positive cells), cell proliferation (EdU positive cells) and ECM production (Periostin and Collagen) was analysed using the Operetta platform.

The results of the experiments with primary human liver fibroblasts are shown in Figures 39A to 39D. IL-11 was found to activate liver fibroblasts, and IL-11 signalling was found to be necessary for the profibrotic action of TGFβ1 in liver fibroblasts. Both activation and proliferation of fibroblasts was inhibited by neutralising anti-IL-11 antibody.

1.3.2 Skin fibrosis

To test whether IL-11 signalling is important in skin fibrosis, primary mouse skin fibroblasts were cultured at low passage in wells of 96-well plates and either not stimulated, stimulated with TGFβ1 (5ng/ml, 24h) or incubated for 24h with both TGFβ1 (5 ng/ml) and a neutralising IL-11 antibody (2 µg/ml). Fibroblast activation (αSMA positive cells) was then analysed using the Operetta platform.

The results are shown in Figure 40. TGFβ1-mediated activation of skin fibroblasts was inhibited by neutralising anti-IL-11 antibody.

1.3.3 Fibrosis in multiple organs

Next, mouse recombinant IL-11 was injected (100µg/kg, 3 days/week, 28 days) into mice to test whether IL-11 can drive global tissue fibrosis *in vivo*.

The results are shown in Figure 6. Compared to injection of AngII (a cytokine that causes an elevation in blood pressure and hypertrophy of the heart), IL-11 also increased the heart weight but also kidney, lung and liver weight indexed to body weight (Figure 6B). Assessing collagen content in these issues by hydroxyproline assay revealed an upregulation of collagen production in these tissues, indicating fibrosis as the likely cause for the increase in organ weight (Figure 6C). Expression of fibrosis marker genes ACTA2 (= αSMA), Col1a1, Col3a1, Fn1, Mmp2 and Timp1 was also detected by qPCR analysis of RNA isolated from heart, kidney, lung and liver tissues of these animals

Example 2: Therapeutic potential of IL-11/IL-11R antagonism

2.1 Inhibition of the fibrotic response using neutralising antagonists of IL-11/IL-11R

Next it was investigated whether the autocrine loop of IL-11 secretion was required for the pro-fibrotic effect of TGFβ1 on fibroblasts.

IL-11 was inhibited using a commercially available neutralizing antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA). Fibroblasts were treated with TGFβ1 in the presence or absence of the antibody, and fibroblast activation, the proportion of proliferating cells and ECM production and markers of the fibrotic response were measured.

Briefly, atrial fibroblasts derived from 3 individuals were incubated for 24h with TGFβ1 (5 ng/ml) or TGFβ1 in the presence of neutralising anti-IL-11 antibody or isotype control antibody. Following incubation, cells were stained for αSMA to determine the fraction of myofibroblasts, the proportion of proliferating cells was determined by analysing the cells for EdU incorporation, and periostin was measured to determine ECM production. Fluorescence was measured with the Operetta platform for 14 fields across 2 wells for each individual. Secretion of the fibrosis markers IL-6, TIMP1 and MMP2 was also analysed by ELISA. Fluorescence was normalized to the control group without stimulation.

The results are shown in Figures 7A to 7F. IL-11 inhibition was found to ameliorate TGFβ1-induced fibrosis, and it was shown that IL-11 is essential for the pro-fibrotic effect of TGFβ1. Inhibition of IL-11 was found to 'rescue' the TGFβ1 phenotype at the protein level.

Collagen production was also analysed. Cardiac fibroblasts derived from 3 individuals were incubated for 24h with TGFβ1 (5 ng/ml) or TGFβ1 and a neutralizing IL-11 antibody. Following incubation the cells were stained for collagen using the Operetta assay and florescence was quantified as described above. Secreted collagen levels in the cell culture supernatant were assessed by Sirius Red staining.

The results are shown in Figures 8A and 8B, and confirm the anti-fibrotic effect of inhibition of IL-11 using a neutralising antibody.

Next, the ability of several other IL-11/IL-11R antagonists to inhibit fibrosis was analysed *in vitro* using the atrial fibroblast, TGFβ1-induced myofibroblast transition assay described herein above.

Briefly, human atrial fibroblasts cells were cultured *in vitro*, stimulated for 24h with TGFβ1 (5 ng/ml) or left unstimulated, in the presence/absence of: (i) neutralising anti-IL-11 antibody, (ii) a IL-11RA-gp130 fusion protein (iii) neutralising anti-IL-11RA antibody, (iv) treatment with siRNA directed against IL-11 or (v) treatment with siRNA directed against IL-11RA. The proportion of activated fibroblasts (myofibroblasts) was analysed by evaluating αSMA content as described above.

The results are shown in Figure 9. Each of the antagonists of IL-11/IL-11R signalling was found to be able to abrogate TGFβ1-mediated profibrotic response.

Example 3: *In vivo* confirmation of a profibrotic role for IL-11/IL-11R signalling

3.1 *In vitro* studies using cells derived from IL-11RA gene knock-out mice

All mice were bred and housed in the same room and provided food and water ad libitum. Mice lacking functional alleles for IL-11Rα (IL-11RA1 KO mice) were on C57Bl/6 genetic background. Mice were of 9-11 weeks of age and the weight of animals did not differ significantly.

To further confirm the anti-fibrotic effect of inhibition of IL-11 signalling, primary fibroblasts were generated from IL-11RA gene knock-out mice and incubated with primary fibroblast cells harvested from IL-11RA+/+ (i.e. wildtype), IL-11RA+/- (i.e. heterozygous knockout) and IL-11RA-/- (i.e. homozygous knockout) animals with TGFβ1, IL-11 or AngII. Activation and proliferation of fibroblasts and ECM production was analysed.

Fibroblasts derived from IL-11RA+/+, IL-11RA+/- and IL-11RA-/- mice were incubated for 24 hours with TGFβ1, IL-11 or AngII (5 ng/ml). Following incubation, cells were stained for αSMA content to estimate the fraction of myofibroblasts, for EdU to identify the fraction of proliferating cells, and for collagen and periostin to estimate ECM production. Fluorescence was measured using the Operetta platform.

The results are shown in Figures 10A to 10D. IL-11RA-/- mice were found not to respond to pro-fibrotic stimuli. These results suggested that IL-11 signalling is also required for AngII-induced fibrosis.

Next, it was investigated whether this was also true for other pro-fibrotic cytokines.

Briefly, fibroblasts were cultured *in vitro* in the presence/absence of various different pro-fibrotic factors (ANG2, ET-1 or PDGF), and in the presence/absence of neutralising anti-IL-11 antibody or pan anti-TGFβ antibody. After 24 hours, collagen production by the cells was determined by analysis using the Operetta system as described above, and myofibroblast generation was determined by analysis of αSMA expression as described above.

The results are shown in Figures 11A and 11B. IL-11 was found to be required for fibrosis downstream of various profibrotic stimuli, and was thus identified as a central mediator of fibrosis induced by a variety of different profibrotic factors.

In a further experiment, the role of IL-11 signalling was investigated in lung fibrosis, using an *in vitro* scratch assay of migration of lung fibroblasts. In response to pro-fibrotic stimuli, fibroblasts are activated and migrate within the fibrotic niche in the body. The migration rate of cells is a measure of cell-cell and cell-matrix interactions and a model for wound healing *in vivo* (Liang et al., 2007; Nat Protoc. 2(2):329-33).

Fibroblasts derived from lung tissue from both wild type (WT) and also homozygous IL-11RA (-/-) knockout mice were grown at low passage on a plastic surface until they formed a uniform cell monolayer. A scratch was then created in the cell layer, and cell migration close to the scratch was monitored, either in the absence of stimulation, or in the presence of TGFβ1 or IL-11. Images captured at images at the two time points of immediately after creating the scratch and at 24h were used to determine the area covered by cells, and the rate of migration was compared between WT and KO fibroblasts. Cell migration (area in the scratch covered by cells after 24h) was normalized to the migration rate of WT cells without stimulus.

The results are shown in Figure 41. Lung fibroblasts derived from WT mice were shown to migrate faster in the presence of TGFβ1 and IL-11, indicating a pro-fibrotic effect of both cytokines in lung fibroblasts. Cells lacking IL-11 signalling derived from KO mice migrated more slowly as compared to WT cells. They also did not migrate faster in the presence of TGFβ1. The scratch assay revealed that lung fibroblasts lacking IL-11 signalling have a decrease cell migration rate both in the presence of TGFβ1 or IL-11, and at baseline. Thus, inhibition of IL-11 signalling is anti-fibrotic in the lung.

3.2 Heart fibrosis

The efficacy of IL-11 inhibition to treat fibrotic disorders was investigated *in vivo*. A mouse model for cardiac fibrosis, in which fibrosis is induced by treatment with AngII, was used to investigate whether IL-11RA -/- mice were protected from cardiac fibrosis.

Briefly, a pump was implanted, and wildtype (WT) IL-11RA(+/+) and knockout (KO) IL-11RA(-/-) mice were treated with AngII (2mg/kg/day) for 28 days. At the end of the experiment, collagen content was assessed in the atria of the mice using a calorimetric hydroxyproline-based assay kit, and the level of RNA expression of the markers or fibrosis Col1A2, αSMA (ACTA2) and fibronectin (Fn1) were analysed by qPCR.

The results are shown in Figures 12A to 12D. The IL-11RA-/- mice were found to be protected from the profibrotic effects of AngII.

3.3 Kidney fibrosis

A mouse model for kidney fibrosis was established in wildtype (WT) IL-11RA(+/+) and knockout (KO) IL-11RA(-/-) mice by intraperitoneal injection of folic acid (180mg/kg) in vehicle (0.3M $NaHCO_3$); control mice were administered vehicle alone.

Kidneys were removed 28 days post-injection, weighed and either fixed in 10% neutral-buffered formalin for Masson's trichrome and Sirius staining or snap-frozen for collagen assay, RNA, and protein studies.

Total RNA was extracted from the snap-frozen kidney using Trizol reagent (Invitrogen) and Qiagen TissueLyzer method followed by RNeasy column (Qiagen) purification. The cDNA was prepared using iScriptTM cDNA synthesis kit, in which each reaction contained 1µg of total RNA, as per the manufacturer's instructions. Quantitative RT-PCR gene expression analysis was performed on triplicate samples with either TaqMan (Applied Biosystems) or fast SYBR green (Qiagen) technology using StepOnePlusTM (Applied Biosystem) over 40 cycles. Expression data were normalized to GAPDH mRNA expression level and we used the 2-ΔΔCt method to calculate the fold-change. The snap-frozen kidneys were subjected to acid hydrolysis by heating in 6M HCl at a concentration of 50 mg/ml (95°C, 20 hours). The amount of total collagen in the hydrolysate was quantified based on the colorimetric detection of hydroxyproline using Quickzyme Total Collagen assay kit (Quickzyme Biosciences) as per the manufacturer's instructions.

The results of the analysis are shown in Figure 37. Folate-induced kidney fibrosis is shown to be dependent on IL-11 mediated signalling. A significant increase in collagen content in kidney tissue was observed in IL-11RA+/+ mice, indicative of kidney fibrosis. No significant increase in collagen content was observed in IL-11RA -/- mice. Animals deficient for IL-11 signalling had significantly less collagen deposition in kidneys after toxic injury as compared to wild type animals.

3.4 Lung fibrosis

IL-11 is confirmed as a key mediator of fibrosis in the lung, skin and eye in further *in vivo* models using the IL-11RA -/- knockout mice. Schematics of the experiments are shown in Figures 13A to 13C.

To analyse pulmonary fibrosis, IL-11RA -/- mice and IL-11RA +/+ mice are treated by intratracheal administration of bleomycin on day 0 to establish a fibrotic response in the lung (pulmonary fibrosis). Fibrosis of the lung develops by 21 days, at which point animals are sacrificed and analysed for differences in fibrosis markers between animals with and without IL-11 signalling. IL-11RA -/- mice have a reduced fibrotic response in lung tissue as compared to IL-11RA +/+ mice, as evidenced by reduced expression of markers of fibrosis.

3.5 Skin fibrosis

To analyse fibrosis of the skin, IL-11RA -/- mice and IL-11RA +/+ mice are treated by subcutaneous administration of bleomycin on day 0 to establish a fibrotic response in the skin. Fibrosis of the skin develops by 28 days, at which point animals are sacrificed and analysed for differences in fibrosis markers between

animals with and without IL-11 signalling. IL-11RA -/- mice have a reduced fibrotic response in skin tissue as compared to IL-11RA +/+ mice, as evidenced by reduced expression of markers of fibrosis.

3.6 Eye fibrosis

To analyse fibrosis in the eye, IL-11RA -/- mice and IL-11RA +/+ mice underwent trabeculectomy (filtration surgery) on day 0 to initiate a wound healing response in the eye. This mouse model of glaucoma filtration surgery has been shown to be an efficient model to evaluate the wound healing response in the eye (Khaw et al. 2001, Curr Opin Ophthalmol 12, 143–148; Seet et al. 2011, Mol. Med. 17, 557–567) and has successfully shown the beneficial effect of fibrotic modulators *in vivo* (Mead et al. 2003, Invest. Ophthalmol. Vis. Sci. 44, 3394–3401; Wong et al. 2003 Invest. Ophthalmol. Vis. Sci. 44, 1097–1103; Wong et al. 2005, Invest. Ophthalmol. Vis. Sci. 46, 2018–2022).

Briefly, the conjunctiva was dissected to expose the underlying sclera, after which an incision was made through the sclera into the anterior chamber of the eye using a 30-gauge needle. The created fistula allowed aqueous humor to exit into and underneath the conjunctiva. The dissected conjunctiva was then secured and closed at the limbus by a 10-0 (0.2 metric) Ethilon black monofilament nylon scleral suture. Fucithalmic ointment was instilled at the end of the procedure. The surgery was performed under anaesthesia by intraperitoneal injection of a 0.1 ml ketamine/xylazine mixture, as well as topical application of one drop per eye of 1% xylocaine. Fucithalmic ointment was instilled post-surgery to prevent infection. Surgery was performed with 70% propyl alcohol sterilized surgical scissors and forceps and sterile needles.

The accumulated fluid underneath the sutured conjunctiva was observed as a conjunctival bleb. Mice were euthanized on day 7 post-surgery for analyses. For qualitative immune-histological analyses, eyes from mice will be harvested by enucleation and then sectioned. Maturation of collagen fibres was evaluated with using the picro-sirius red/polarization light technique (Szendröi et al. 1984, Acta Morphol Hung 32, 47–55); orange-red indicated mature collagen, and yellow/green indicated newly formed immature collagen.

The results of the experiment are shown in Figures 38A and 38B. IL-11RA -/- mice were found to have a reduced fibrotic response in eye tissue as compared to IL-11RA +/+ mice.

3.7 Other tissues

The effect of IL-11RA knockout on fibrosis is also analysed in mouse models of fibrosis for other tissues, such as the liver, bowel, and is also analysed in a model relevant to multiorgan (i.e. systemic) fibrosis. The fibrotic response is measured and compared between the IL-11RA -/- mice and IL-11RA +/+ mice. IL-11RA -/- mice have a reduced fibrotic response as compared to IL-11RA +/+ mice, as evidenced by reduced expression of markers of fibrosis.

Example 4: Analysis of the molecular mechanisms underlying IL-11-mediated induction of fibrosis

The canonical mode of action of IL-11 is thought to be regulation of RNA expression via STAT3-mediated transcription (Zhu et al., 2015 PLoS ONE 10, e0126296), and also through activation of ERK.

STAT3 activation is observed following stimulation with IL-11. However, when fibroblasts are incubated with TGFβ1, only activation of the canonical SMAD pathway and ERK pathways is seen, and activation of STAT3 is not observed, even in spite of the fact that IL-11 is secreted in response to TGFβ1. Only ERK activation is common to both TGFβ1 and IL-11 signal transduction.

Cross-talk between TGFβ1 and IL-6 signalling has previously been described, wherein TGFβ1 blocks the activation of STAT3 by IL-6 (Walia et al., 2003 FASEB J. 17, 2130–2132). Given the close relationship between IL-6 and IL-11, similar cross-talk may be observed for IL-11 mediated signalling.

The inventors investigated by RNA-seq analysis whether regulation of RNA abundance was the underlying mechanism for the increased expression of fibrosis marker proteins in response to IL-11, which would suggest STAT3 as the underlying signalling pathway for IL-11 mediated profibrotic processes. Fibroblasts were incubated for 24 hours either without stimulus, or in the presence of TGFβ1, IL-11 or TGFβ1 and IL-11.

The results are shown in Figure 14A. TGFβ1 induced the expression of collagen, ACTA2 (αSMA) and other fibrosis marker at the RNA level. However, IL-11 did not regulate the expression of these genes, but a different set of genes.

Gene ontology analysis suggests that a pro-fibrotic effect in fibroblasts is driven by IL-11-regulated RNA expression. Both TGFβ1 and IL-11 regulate an almost completely different set of genes on the RNA level.

Whilst TGFβ1 increases IL-11 secretion, the target genes of IL-11 are not regulated when both TGFβ1 and IL-11 are present. This suggests that TGFβ1 upregulates IL-11 and simultaneously blocks the canonical IL-11-driven regulation of RNA expression via STAT3, similar to what is known about the interaction of TGFβ1 and IL-6 pathways (Walia et al., 2003 FASEB J. 17, 2130–2132).

We also analysed whether RNA expression differences induced by TGFβ1 are dependent on IL-11 signalling, by analysing changes in RNA expression in fibroblasts obtained from IL-11RA -/- mice as compared to IL-11RA +/+ mice. RNA expression regulated by TGFβ1 is still observed when IL-11RA knockout cells were stimulated with TGFβ1, and RNA levels of αSMA, collagen etc. were still upregulated in the absence of IL-11 signalling (in IL-11RA -/- fibroblasts). When the pro-fibrotic effect of IL-11 and the anti-fibrotic effect of IL-11 inhibition was investigated *in vitro*, reduced expression of markers of fibrosis was only observed at the protein level, not at the transcriptional level as determined by qPCR.

The activation of non-canonical pathways (e.g. ERK signal transduction) is known to be crucial for the pro-fibrotic action of TGFβ1 (Guo and Wang, 2008 Cell Res 19, 71–88). It is likely that non-canonical pathways are likely to be important for signalling for all known pro-fibrotic cytokines, and that IL-11 is a post-transcriptional regulator which is essential for fibrosis.

Example 5: Human anti-human IL-11 antibodies

Fully human anti-human IL-11 antibodies were developed via phage display.

Recombinant human IL-11 (Cat. No. Z03108-1) and recombinant murine IL-11 (Cat. No. Z03052-1) were obtained from GenScript (NJ, USA). Recombinant human IL-11 was expressed in CHO cells, both as an Fc-tagged version and a tag-free version. Tag-free murine IL-11 was expressed in HEK293 cells.

IL-11 bioactivity of recombinant human IL-11 and mouse IL-11 was confirmed by *in vitro* analysis using primary fibroblast cell cultures.

Recombinant, biotinylated human IL-11 and murine IL-11 were also prepared by biotinylation of the recombinant human IL-11 and murine IL-11 molecules, according to standard methods.

Antibodies capable of binding to both human IL-11 and murine IL-11 (i.e. cross-reactive antibodies) were identified by phage display using a human naïve library by panning using biotinylated and non-biotinylated recombinant human and murine IL-11, based on 16 different panning strategies as summarised in Figure 21.

The phage display identified 175 scFv binders, as 'first hits'. Sequence analysis of the CDR sequences from these 175 scFv identified 86 unique scFv.

The soluble scFv were produced by recombinant expression in E. coli, and analysed for their ability to bind to human IL-11 and murine IL-11 by ELISA. Briefly, the respective antigen was coated to wells of an ELISA plate, the cell culture supernatant containing the respective scFv was added at a 1:2 dilution, and binding was detected.

The results of the ELISA analysis of binding to human IL-11 and murine IL-11 are shown in Figure 22. The analysis revealed:

- 8 scFV capable of binding only to human IL-11;
- 6 scFv capable of binding to murine IL-11 only;
- 32 scFv displaying only weak binding to human/murine IL-11, with a high signal to noise ratio, and;
- 40 scFv having cross-reactivity for both human IL-11 and murine IL-11.

From these 86 scFV, 56 candidates were selected for further functional characterisation. For further analyses, the scFV were cloned into scFV-Fc format in E. coli.

The antibody clone designations are shown in Figure 23.

The amino acid sequence information for the antibodies is shown in Figures 15 to 20.

The VH and VL sequences of the antibodies were cloned into expression vectors for the generation of scFv-Fc (human IgG1) antibodies. The vectors were transiently expressed in mammalian cells cultured in serum-free media, and isolated by protein A purification.

Example 6: Functional characterisation of human anti-human IL-11 antibodies

The antibodies described in Example 5 were analysed in *in vitro* assays for their ability to (i) inhibit human IL-11-mediated signalling, (ii) inhibit mouse IL-11-mediated signalling, and (iii) inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA. The affinity of the antibodies for human IL-11 was also analysed by ELISA.

6.1 Ability to inhibit human IL-11 mediated signalling

To investigate ability to neutralise human IL-11-mediated signalling, cardiac atrial human fibroblasts were cultured in wells of 96-well plates in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence or absence of the anti-IL-11 antibodies. TGFβ1 promotes the expression of IL-11, which in turn drives the transistion of quiescent fibroblasts to activated, αSMA-positive fibroblasts. It has previously been shown that neutralising IL-11 prevents TGFβ1-induced transition to activated, αSMA-positive fibroblasts.

Expression of αSMA was analysed with the Operetta High-Content Imaging System in an automated high-throughput fashion.

In non-stimulated cultures, ~29.7% (= 1) of the fibroblasts were αSMA-positive, activated fibroblasts at the end of the 24 hour culture period, whilst ~52% (= 1.81) of fibroblasts were αSMA-positive in cultures that were stimulated with TGFβ1 in the absence of anti-IL-11 antibodies.

Anti-IL-11 antibodies (2 µg/ml) were added to fibroblast cultures that were stimulated with TGFβ1, and at the end of the 24 hour culture period, the percentage of αSMA-positive fibroblasts was determined. The percentages were normalised based on the percentage of αSMA-positive fibroblasts observed in cultures of fibroblasts which had not been stimulated with TGFβ1.

The results of the experiments are shown in Figures 24A, 24B and 27. 28 of the antibodies were demonstrated to be capable of neutralising signalling mediated by human IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 28.3% (=0.99).

Several of the clones neutralised signalling by human IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU45-C11/A10 (#6), YU45-G1 (#11), YU45-E3 (#16), YU45-F8 (#18), YU45-F9 (#21), YU45-H10 (#22), YU45-F2 (#24), YU45-H3 (#25), YU45-G7 (#33), YU45-B6 (#36), YU45-C1 (#42), YU46-B6 (#47), YU46-E3 (#50), YU46-G8 (#54) and YU46-D3 (#56).

6.2 Ability to inhibit mouse IL-11 mediated signalling

The ability of the human antibodies to inhibit mouse IL-11-mediated signalling was also investigated, following the same procedure as described in section 6.1 above, but using mouse atrial fibroblasts instead of human atrial fibroblasts.

After 24 hours in culture, about 31.8% (=1) of non-stimulated cells in culture were activated fibroblasts. Stimulation with TGFβ1 resulted in a ~2-fold increase in the percentage of activated fibroblasts (68.8% = 2.16) as compared to non-stimulated cultures.

The results of the experiments are shown in Figures 25 and 27. The antibodies were demonstrated to be capable of neutralising signalling mediated by mouse IL-11. Monoclonal Mouse IgG2A clone #22626, catalog No. MAB218 anti-IL-11 antibody was also analysed for ability to inhibit signalling by mouse IL-11. This antibody was found to be able to reduce the percentage of activated fibroblasts to 39.4% (=1.24).

Several of the clones neutralised signalling by IL-11 in mouse atrial fibroblasts to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU33-B4/YU45-G2/A3 (#3), YU45-H11/D12 (#9), YU45-G1 (#11), YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5 (#14), YU45-B3 (#15), YU45-F8 (#18), YU45-H10 (#22), YU46-A10 (#23), YU45-A8/C6 (#27), YU45-D9/D3 (#31), YU45-B6 (#36), YU45-C1 (#42), YU46-A8 (#45), YU46-C1 (#48), YU46-H8 (#52), YU46-G8 (#54) and YU46-D3 (#56).

The ability of the human antibodies to inhibit mouse IL-11-mediated signalling was also investigated using mouse skin fibroblasts.

The results of the experiments are shown in Figure 27. The antibodies were demonstrated to be capable of neutralising signalling mediated by mouse IL-11.

Several of the clones neutralised signalling by IL-11 in mouse skin fibroblasts to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): YU45-B6 (#36), YU45-C1 (#42), and YU46-H8 (#52).

6.3 Ability to inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA

Trans signalling is recognised as a major aspect of IL-6 signalling, where a complex of IL-6 and soluble IL-6Rα can activate cells that express gp130, but lack the IL-6 receptor (Hunter and Jones, 2015 Nature Immunology 16, 448–457).

It has recently been suggested that *trans* signalling by a complex of IL-11 and soluble IL-11RA is also important for IL-11 biology (Lokau et al., Cell Reports (2016) 14, 1761–1773). Using a recombinant fusion protein of IL-11 and IL-11Rα (as described in Pflanz et al., Febs Lett (1999) 450: 117-122), anti-IL-11 antibodies were screened for the ability to inhibit *trans* signalling mediated by IL-11:IL-11Rα complex.

Importantly, antibodies which are capable of inhibiting both classical IL-11 mediated signalling and IL-11 *trans* signalling by IL-11:IL-11Rα complex are able to inhibit all known modes of IL-11/IL-11R signalling.

The IL-11:IL-11Rα fusion protein (hereafter referred to as hyper IL-11) consists of the extracellular domain of the IL-11 receptor alpha (IL-11Rα) linked to IL-11.

Hyper IL-11 was found to be a more potent activator of human fibroblasts than recombinant IL-11 protein. Briefly, in two separate experiments human fibroblasts were cultured without stimulation (Baseline), in the presence of different amounts of hyper IL-11 (0.008 ng/ml, 0.04 ng/ml, 0.2 ng/ml, 1 ng/ml and 5 ng/ml), or 5 ng/ml recombinant human IL-11 obtained from a commercial source, and fibroblast activation was analysed by determining the percentage of αSMA-positive cells as described herein. The results are shown in (Figures 42A and 42B). Hyper-IL-11 activated fibroblasts in a dose-dependent fashion, and was a more potent activator than IL-11.

The IL-11:IL-11Rα fusion protein was prepared as follows:

- DNA encoding IL-11:IL-11Rα fusion protein (i.e. SEQ ID NO:265) was cloned into pTT5 vector, and transfected into 293-6E cells in culture in serum-free FreeStyle™ 293 Expression Medium (Thermo Fisher Scientific).
- Cells were maintained in Erlenmeyer Flasks (Corning Inc.) at 37°C with 5% CO_2 on an orbital shaker (VWR Scientific).
- Cell culture supernatants were collected on day 6 were used for purification.
- Cell culture supernatant was loaded onto an affinity purification column.
- After washing and elution with appropriate buffer, the eluted fractions were pooled and buffer exchanged to final formulation buffer.
- The purified IL-11:IL-11Rα fusion protein was analyzed by SDS-PAGE, Western blot to confirm molecular weight and purity.

DNA encoding IL-11:IL-11Rα fusion protein (SEQ ID NO:265):

GAATTCCCGCCGCCACCATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACAGCCACCG
GCGTGCACTCTCCACAGGCTTGGGGACCTCCAGGCGTGCAGTATGGCCAGCCTGGCAGATCC
GTGAAGCTGTGCTGTCCTGGCGTGACAGCTGGCGACCCTGTGTCCTGGTTCAGAGATGGCGA
GCCCAAGCTGCTGCAGGGCCCAGATTCTGGACTGGGCCACGAACTGGTGCTGGCCCAGGCCG
ATTCTACCGACGAGGGCACCTACATCTGCCAGACCCTGGATGGCGCCCTGGGCGGAACAGTG
ACACTGCAGCTGGGCTACCCTCCCGCCAGACCTGTGGTGTCTTGTCAGGCCGCCGACTACGA
GAACTTCAGCTGCACATGGTCCCCCAGCCAGATCAGCGGCCTGCCCACCAGATACCTGACCAG
CTACCGGAAGAAAACCGTGCTGGGCGCCGACAGCCAGAGAAGAAGCCCTTCTACAGGCCCCT
GGCCCTGCCCTCAGGATCCTCTGGGAGCTGCCAGATGTGTGGTGCACGGCGCCGAGTTCTGG
TCCCAGTACCGGATCAACGTGACCGAAGTGAACCCCCTGGGCGCCTCCACAAGACTGCTGGAT
GTGTCCCTGCAGAGCATCCTGCGGCCCGATCCTCCACAGGGCCTGAGAGTGGAAAGCGTGCC
CGGCTACCCCAGAAGGCTGAGAGCCAGCTGGACATACCCCGCCTCTTGGCCTTGCCAGCCCC
ACTTCCTGCTGAAGTTTCGGCTGCAGTACCGGCCAGCCCAGCACCCTGCTTGGAGCACAGTGG
AACCTGCCGGCCTGGAAGAAGTGATCACAGACGCCGTGGCCGGACTGCCTCATGCTGTGCGG
GTGTCCGCCAGAGACTTTCTGGATGCCGGCACCTGGTCTACCTGGTCCCCAGAAGCCTGGGG
CACACCTTCTACTGGCGGACCTGCTGGACAGTCTGGCGGAGGCGGAGGAAGTGGCGGAGGAT
CAGGGGGAGGATCTGTGCCTGGACCTCCTCCAGGACCCCCTAGAGTGTCCCCAGATCCTAGG
GCCGAGCTGGACTCTACCGTGCTGCTGACCAGATCCCTGCTGGCCGACACAAGGCAGCTGGC
TGCCCAGCTGAGAGACAAGTTCCCCGCCGACGGCGACCACAACCTGGATAGCCTGCCTACCCT
GGCCATGTCTGCTGGCGCACTGGGGGCTCTGCAGCTGCCTGGGGTGCTGACTAGACTGAGAG

CCGACCTGCTGAGCTACCTGCGGCATGTGCAGTGGCTGAGAAGGGCTGGCGGCAGCAGCCTG
AAAACCCTGGAACCTGAGCTGGGCACACTGCAGGCCAGACTGGACAGACTGCTGCGCAGACT
GCAGCTGCTGATGAGCAGACTGGCTCTGCCCCAGCCTCCTCCTGACCCTCCTGCTCCTCCACT
GGCTCCTCCAAGCTCTGCTTGGGGCGGAATTAGAGCCGCCCACGCCATTCTGGGAGGCCTGC
ACCTGACACTGGATTGGGCAGTGCGGGGCCTGCTGCTGCTGAAAACCAGACTGCACCACCAC
CATCACCACTGATAAGCTT

Amino acid sequence of IL-11:IL-11Rα fusion protein (SEQ ID NO:266):

MGWSCIILFLVATATGVHSPQAWGPPGVQYGQPGRSVKLCCPGVTAGDPVSWFRDGEPKLLQGP
DSGLGHELVLAQADSTDEGTYICQTLDGALGGTVTLQLGYPPARPVVSCQAADYENFSCTWSPSQI
SGLPTRYLTSYRKKTVLGADSQRRSPSTGPWPCPQDPLGAARCVVHGAEFWSQYRINVTEVNPLG
ASTRLLDVSLQSILRPDPPQGLRVESVPGYPRRLRASWTYPASWPCQPHFLLKFRLQYRPAQHPA
WSTVEPAGLEEVITDAVAGLPHAVRVSARDFLDAGTWSTWSPEAWGTPSTGGPAGQSGGGGGSG
GGSGGGSVPGPPPGPPRVSPDPRAELDSTVLLTRSLLADTRQLAAQLRDKFPADGDHNLDSLPTLA
MSAGALGALQLPGVLTRLRADLLSYLRHVQWLRRAGGSSLKTLEPELGTLQARLDRLLRRLQLLMS
RLALPQPPPDPPAPPLAPPSSAWGGIRAAHAILGGLHLTLDWAVRGLLLLKTRLHHHHHH

Fibroblasts cultured *in vitro* and stimulated with hyper IL-11 were shown to upregulate IL-11 protein expression, as determined by ELISA (Figure 43). Interestingly, an increase in IL-11 RNA level was not detected in response to stimulation with hyper IL-11. Unlike TGFβ1, which increases IL-11 expression at both the RNA and the protein level, hyper IL-11 seems to upregulate IL-11 expression only post-transcriptionally, at the protein level.

The ability of the human antibodies to inhibit signalling mediated by hyper IL-11 was investigated.

Human atrial fibroblasts derived from 3 individuals were incubated for 24h with hyper IL-11 (0.2 ng/ml) in the presence of neutralising anti-IL-11 antibody or isotype control antibody. Following incubation, cells were stained for αSMA to determine the fraction of myofibroblasts.

After 24 hours in culture, about 26.5.% (=1) of non-stimulated cells in culture were activated fibroblasts. Stimulation with hyper IL-11 resulted in a ~2-fold increase in the percentage of activated fibroblasts (56.4% = 2.13) as compared to non-stimulated cultures.

The results of the experiments are shown in Figures 26 and 27. The antibodies were demonstrated to be capable of neutralising signalling mediated by hyper IL-11 (i.e. IL-11 *trans* signalling).

Monoclonal Mouse IgG2A clone #22626, catalog No. MAB218 anti-IL-11 antibody was also analysed for ability to inhibit signalling by hyper IL-11. This antibody was found to be able to reduce the percentage of activated fibroblasts to 33.8% (=1.28).

Clone YU33-B4/YU45-G2/A3 (#3) neutralised IL-11 *trans* signalling by hyper IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard).

The results of the experimental procedures described in hereinabove identified antibody clones which possess functional properties which are relevant for their pre-clinical and clinical development of antibodies capable of inhibiting IL-11/IL-11-R signalling.

Clones YU33-B4/YU45-G2/A3 (#3), YU45-E3 (#16), YU45-F2 (#24), YU45-F5 (#39), YU46-A8 (#45) and YU46-G8 (#54) were identified as particularly promising candidates, showing good ability to inhibit signalling by both human and mouse IL-11, and good inhibition of IL-11 *trans* signalling.

6.4 Analysis of antibody affinity for human IL-11

The human anti-human IL-11 antibodies were analysed for their affinity of binding to human IL-11 by ELISA assay.

Recombinant human IL-11 was obtained from Genscript and Horseradish peroxidase (HRP)-conjugated anti-human IgG (Fc-specific) antibody was obtained from Sigma. Corning 96-well ELISA plates were obtained from Sigma. Pierce 3,3´,5,5´-tetramethylbenzidine (TMB) ELISA substrate kit was obtained from Life Technologies (0.4 g/mL TMB solution, 0.02 % hydrogen peroxide in citric acid buffer). Bovine serum albumin and sulphuric acid was obtained from Sigma. Wash buffer comprised 0.05% Tween-20 in phosphate buffered saline (PBS-T). ScFv-Fc antibodies were generated as described in Example 5. Purified mouse and human IgG controls were purchased from Life Technologies. Tecan Infinite 200 PRO NanoQuant was used to measure absorbance.

Criss-cross serial dilution analysis was performed as described by Hornbeck et al., (2015) Curr Protoc Immunol 110, 2.1.1-23) to determine the optimal concentration of coating antigen, primary and secondary antibodies.

An indirect ELISA was performed to assess the binding affinity of primary ScFv-Fc antibodies at 50% of effective concentration (EC_{50}) as previously described (Unverdorben et al., (2016) MAbs 8, 120–128.). ELISA plates were coated with 1 µg/mL of recombinant human IL-11 overnight at 4°C and remaining binding sites were blocked with 2 % BSA in PBS. ScFv-Fc antibodies were diluted in 1% BSA in PBS, titrated to obtain working concentrations of 800, 200, 50, 12.5, 3.125, 0.78, 0.195, and 0.049 ng/mL, and incubated in duplicates for 2 hours at room temperature. Detection of antigen-antibody binding was performed with 15.625 ng/mL of HRP-conjugated anti-human IgG (Fc-specific) antibody. Following 2 hours of incubation with the detection antibody, 100 µl of TMB substrate was added for 15 mins and chromogenic reaction stopped with 100 µl of 2 M H_2SO_4. Absorbance reading was measured at 450 nm with reference wavelength correction at 570 nm. Data were fitted with GraphPad Prism software with log transformation of antibody concentrations followed by non-linear regression analysis with the asymmetrical (five-parameter) logistic dose-response curve to determine individual EC50 values.

The same materials and procedures as described above were performed to determine the affinity of binding for the murine monoclonal anti-IL-11 antibodies, with the exception that HRP-conjugated anti-mouse IgG (H&L) was used instead of HRP-conjugated anti-human IgG.

The same materials and procedures as described above were performed to determine the affinity of binding for the human monoclonal anti-IL-11 antibodies and murine monoclonal anti-IL-11 antibodies to recombinant murine IL-11 obtained from Genscript.

The results of the ELISA assays are shown in Figure 28A to 28F, and were used to determine EC_{50} values for the antibodies which are shown in Figure 29.

6.5 Ability to inhibit human IL-11 mediated signalling in a variety of tissues

Ability of the antibodies to neutralise IL-11-mediated signalling and *trans* signalling in fibroblasts obtained from a variety of different tissues is investigated, essentially as described in sections 6.1 and 6.3 except that instead of cardiac atrial human fibroblasts, human fibroblasts derived from liver, lung, kidney, eye, skin, pancreas, spleen, bowel, brain, and bone marrow are used for the experiments.

Anti-IL-11 antibodies are demonstrated to be capable of neutralising signalling in fibroblasts derived from the various different tissues, as determined by observation of a relative decrease in the proportion of αSMA-positive fibroblasts at the end of the 24 h culture period in the presence of the anti-IL-11 antibodies as compared to culture in the absence of the antibodies.

Example 7: Light chain shuffling of human anti-human IL-11 antibodies

Human IL-11 antibodies are affinity-matured by light chain shuffling to obtain antibodies having improved affinity for IL-11.

Chain shuffling to improve antibody affinity is a well-known technique in the field of antibody technology, and is described in detail in Marks, Antibody Affinity Maturation by Chain Shuffling, Antibody Engineering Methods and Protocols, Humana Press (2004) Vol. 248, pp327-343, incorporated by reference herein. In particular, Light chain shuffling is described in detail at sections 3.1 and 3.2 thereof.

The heavy chain variable regions of the human anti-human IL-11 antibodies are combined with a repertoire of light chain variable region partners to identify new VL/VH combinations having high affinity for IL-11.

A schematic representation of light chain shuffling is shown in Figure 30. Briefly, nucleic acid encoding the VH domain for an antibody is cloned into a phage display vector comprising a repertoire of VL chains, and scFv comprising new VH/VL combinations are analysed for binding to human IL-11 by ELISA.

The scFv having VH/VL combinations displaying the strongest binding affinity for IL-11 are then analysed for cross-reactivity against murine IL-11.

The VH/VL sequences of the scFv are then cloned into expression vectors for the generation of scFv-Fc (human IgG1) antibodies, the vectors are transiently expressed in mammalian cells cultured in serum-free media, and isolated by protein A purification.

Example 8: Mouse monoclonal anti-human IL-11 antibodies

Mouse monoclonal antibodies directed against human IL-11 protein were also generated, as follows.

cDNA encoding the amino acid for human IL-11 was cloned into expression plasmids (Aldevron GmbH, Freiburg, Germany).

Mice were immunised by intradermal application of DNA-coated gold-particles using a hand-held device for particle-bombardment ("gene gun"). Serum samples were collected from mice after a series of immunisations, and tested in flow cytometry on HEK cells which had been transiently transfected with human IL-11 expression plasmids (cell surface expression of human IL-11 by transiently transfected HEK cells was confirmed with anti-tag antibodies recognising a tag added to the N-terminus of the IL-11 protein).

Antibody-producing cells were isolated from the mice and fused with mouse myeloma cells (Ag8) according to standard procedures.

Hybridomas producing antibodies specific for IL-11 were identified by screening for ability to bind to IL-11 expressing HEK cells by flow cytometry.

Cell pellets of positive hybridomas cells were prepared using an RNA protection agent (RNAlater, cat. #AM7020 by ThermoFisher Scientific) and further processed for sequencing of the variable domains of the antibodies.

In total, 16 mouse monoclonal anti-human IL-11 antibodies were prepared (Figure 31).

Example 9: Functional characterisation of mouse monoclonal anti-human IL-11 antibodies

9.1 Ability to inhibit human IL-11 mediated signalling

The ability of the murine monoclonal anti-human IL-11 antibodies to inhibit signalling mediated by human IL-11 was investigated using the same assay as described in Example 6.1 above.

The results of the Experiments are shown in Figures 32 and 35. The antibodies were demonstrated to be capable of neutralising signalling mediated by human IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 0.89 times.

Clone A7 (BSN-3C11) was found to neutralise signalling by human IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard).

9.2 Ability to inhibit mouse IL-11 mediated signalling

The ability of the murine monoclonal anti-human IL-11 antibodies to inhibit signalling mediated by murine IL-11 was investigated using the same assay as described in Example 6.2 above, but using mouse atrial fibroblasts instead of mouse dermal fibroblasts.

The results of the Experiments are shown in Figures 33 and 35. The antibodies were demonstrated to be capable of neutralising signalling mediated by murine IL-11.

A commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA) was also analysed for ability to inhibit signalling by human IL-11 in the experiments. This antibody was found to be able to reduce the percentage of activated fibroblasts to 43.0% (=1.44).

Several of the clones neutralised signalling by murine IL-11 to a greater extent than the commercially available mouse anti-IL-11 antibody (industry standard): A3 (BSN-2E1), A5 (BSN-2G6) and A6 (BSN-3C6).

9.3 Ability of mouse anti-IL-11 antibodies to inhibit IL-11 *trans* signalling, by IL-11 in complex with IL-11RA

The ability of the mouse anti-IL-11 antibodies to inhibit signalling mediated by hyper IL-11 was investigated.

Human atrial fibroblasts were incubated for 24h with hyper IL-11 (0.2 ng/ml) in the presence of anti-IL-11 antibodies (2 µg/ml) or isotype control antibody. Following incubation, cell culture supernatant was analysed for MMP2. Stimulation with hyper IL-11 results in an increase in the secretion of MMP2 as compared to non-stimulated cultures.

The results of the experiments are shown in Figures 34 and 35. The mouse anti-IL-11 antibodies were found to be capable of neutralising signalling mediated by hyper IL-11 (i.e. IL-11 *trans* signalling), and several were found to be capable of inhibiting *trans* signalling to a greater extent than the commercial monoclonal mouse anti-IL-11 antibody (Monoclonal Mouse IgG2A; Clone #22626; Catalog No. MAB218; R&D Systems, MN, USA): BSN-2G6 (A5), BSN-3C6 (A6), BSN-5B8 (A9) and BSN-7D4 (A12).

Clone BSN-3C6 (A6) was identified as a particularly promising candidate for further development (highlighted in Figure 35), showing good ability to inhibit both human IL-11 and mouse IL-11 mediated signalling, and good inhibition of IL-11 *trans* signalling.

9.4 Screening for ability of mouse anti-IL-11 antibodies to bind IL-11

The mouse hybridomas producing anti-human IL-11 antibodies were sub-cloned, and cell culture supernatant from the subcloned hybridomas was analysed by “mix-and-measure” iQue assay for (i) ability to bind to human IL-11, and (ii) cross reactivity for antigen other than IL-11.

Briefly, labelled control cells (not expressing IL-11 at the cell surface) and unlabelled target cells expressing human IL-11 at their surface (following transient transfection with a plasmid encoding a FLAG-tagged human IL-11) were mixed together with the cell culture supernatant (containing mouse-anti-IL-11 antibodies) and secondary detection antibodies (fluorescently-labelled anti-mouse IgG antibody).

The cells were then analysed using the HTFC Screening System (iQue) for the two labels (i.e. the cell label and the label on the secondary antibody). Detection of the secondary antibody on the unlabelled, IL-11 expressing cells indicated ability of the mouse-anti-IL-11 antibodies to bind to IL-11. Detection of the secondary antibody on the labelled, control cells indicated cross-reactivity of the mouse-anti-IL-11 antibodies for target other than IL-11.

As a positive control condition, labelled and unlabelled cells were incubated with a mouse anti-FLAG tag antibody as the primary antibody.

The results are shown in Figures 36A and 36B. The majority of the subcloned hybridomas expressed antibody which was able to bind to human IL-11, and which recognised this target with high specificity.

Clones BSN-2G6, BSN-5B8 and BSN-7F9 displayed some binding to cells not expressing IL-11, and so may have cross-reactivity for target(s) other than IL-11. Antibody produced by subcloned BSN-3C11 was found not to bind to human IL-11.

13 of the 16 antibodies displayed stronger signal for binding to IL-11 than signal for the positive control anti-tag antibody for the tag, indicating that these antibodies bind to IL-11 with high affinity.

Example 10: Chimeric and humanised versions of the mouse anti-human IL-11 antibodies

Mouse/human chimeric and humanised versions of the mouse monoclonal anti-human IL-11 antibodies of Example 8 are prepared according to standard methods.

10.1 Mouse/human chimeric antibodies

Mouse/human chimeric antibodies are prepared from the mouse monoclonal anti-human IL-11 antibodies as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 8 thereof.

Briefly, the DNA sequences encoding the VH and VL of hybridomas producing the mouse anti-human IL-11 antibodies are determined, and combined with DNA sequence encoding human immunoglobulin constant regions to produce a mouse/human chimeric antibody sequence, from which a chimeric mouse/human antibody is expressed in mammalian cells.

10.2 Humanised antibodies

Humanised antibodies are prepared from the mouse monoclonal anti-human IL-11 antibodies as described in Human Monoclonal Antibodies: Methods and Protocols, Michael Steinitz (Editor), Methods in Molecular Biology 1060, Springer Protocols, Humana Press (2014), in Chapter 7 thereof, in particular at section 3.1 of Chapter 7 entitled ‘Antibody Humanization’.

Briefly, the DNA sequences encoding the VH and VL of hybridomas producing the mouse anti-human IL-11 antibodies are determined, and inserted into DNA sequence encoding human antibody variable region

framework regions and immunoglobulin constant regions, to produce a humanised antibody sequence, from which a humanised antibody is expressed in mammalian cells.

Example 11: Further biochemical analysis of anti-IL-11 antibodies

The antibodies described above are subjected to further biochemical analysis.

The antibodies are analysed by BIAcore, Biolayer interferometry (BLI) and MicroScale Thermophoresis (MST) analysis to determine the affinity of binding to human IL-11 and mouse IL-11.

BIAcore determination of antibody affinity by surface plasmon resonance (SPR) analysis is performed as described in Rich et al., Anal Biochem. 2008 Feb 1; 373(1):112-20.

Biolayer interferometry analysis of antibody affinity is performed as described in Concepcion et al., Comb Chem High Throughput Screen. 2009 Sep; 12(8):791-800.

MicroScale Thermophoresis analysis of antibody affinity is performed as described in Jerabek-Willemsen et al., Assay Drug Dev Technol. 2011 Aug; 9(4): 342–353.

Aggregation of the antibodies is analysed by size exclusion chromatography (SEC), as described in Iacob et al., J Pharm Sci. 2013 Dec; 102(12): 4315–4329.

Hydophobicity of the antibodies is analysed by Hydrophobic interaction chromatography (HIC) as described in Haverick et al., MAbs. 2014 Jul-Aug;6(4):852-8.

The melting temperature of the antibodies is analysed by Differential scanning fluorimetry (DSF) as described in Menzen and Friess, J Pharm Sci. 2013 Feb;102(2):415-28.

Example 12: Inhibition of fibrosis *in vivo* using anti-IL-11 antibodies

The therapeutic utility of the anti-human IL-11 antibodies is demonstrated in *in vivo* mouse models of fibrosis for various different tissues. The mice used in the experiments are wildtype (i.e. IL-11RA+/+) mice.

12.1 Heart fibrosis

A pump is implanted, and mice are treated with AngII (2mg/kg/day) for 28 days.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. At the end of the experiment, collagen content is assessed in the atria of the mice using a calorimetric hydroxyproline-based assay kit, and the level of RNA expression of the markers or fibrosis Col1A2, αSMA (ACTA2) and fibronectin (Fn1) were analysed by qPCR.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in heart tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

12.2 Kidney fibrosis

A mouse model for kidney fibrosis is established, in which fibrosis is induced by intraperitoneal injection of folic acid (180mg/kg) in vehicle (0.3M $NaHCO_3$); control mice were administered vehicle alone.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Kidneys are removed at day 28, weighed and either fixed in 10% neutral-buffered formalin for Masson's trichrome and Sirius staining or snap-frozen for collagen assay, RNA, and protein studies.

Total RNA is extracted from the snap-frozen kidney using Trizol reagent (Invitrogen) and Qiagen TissueLyzer method followed by RNeasy column (Qiagen) purification. The cDNA is prepared using iScriptTM cDNA synthesis kit, in which each reaction contained 1µg of total RNA, as per the manufacturer's instructions. Quantitative RT-PCR gene expression analysis is performed on triplicate samples with either TaqMan (Applied Biosystems) or fast SYBR green (Qiagen) technology using StepOnePlusTM (Applied Biosystem) over 40 cycles. Expression data are normalized to GAPDH mRNA expression level and the $2^{-\Delta\Delta Ct}$ method is used to calculate the fold-change. The snap-frozen kidneys are subjected to acid hydrolysis by heating in 6M HCl at a concentration of 50 mg/ml (95°C,20 hours). The amount of total collagen in the hydrolysate is quantified based on the colorimetric detection of hydroxyproline using Quickzyme Total Collagen assay kit (Quickzyme Biosciences) as per the manufacturer's instructions.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in kidney tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

12.3 Lung fibrosis

Mice are treated by intratracheal administration of bleomycin on day 0 to establish a fibrotic response in the lung (pulmonary fibrosis).

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Mice are sacrificed at day 21, and analysed for differences in fibrosis markers.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in lung tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

12.4 Skin fibrosis

Mice are treated by subcutaneous administration of bleomycin on day 0 to establish a fibrotic response in the skin.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection. Mice are sacrificed at day 21, and analysed for differences in fibrosis markers.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in skin tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

12.5 Eye fibrosis

Mice undergo trabeculectomy procedure as described in Example 3.6 above to initiate a wound healing response in the eye.

Neutralising anti-IL-11 antibodies, or control antibodies, are administered to different groups of mice by intravenous injection, and fibrosis is monitored in the eye tissue.

Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response in eye tissue as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

12.6 Other tissues

The effect of treatment with neutralising anti-IL-11 antibodies on fibrosis is also analysed in mouse models of fibrosis for other tissues, such as the liver, kidney, bowel, and is also analysed in a model relevant to multiorgan (i.e. systemic) fibrosis.

The fibrotic response is measured and compared between mice treated with neutralising anti-IL-11 antibodies and mice treated with control antibodies. . Mice treated with neutralising anti-IL-11 antibodies have a reduced fibrotic response as compared to mice treated with control antibodies, as evidenced by reduced expression of markers of fibrosis.

Example 13: Treatment of cancer *in vivo* using anti-IL-11 antibodies

The effect of treatment with neutralising anti-IL-11 antibodies on cancer is analysed in mouse models of cancer.

Models of breast, lung, and gastrointestinal cancers are established in mice, the mice are treated by administration of neutralising anti-IL-11 antibodies, or control antibodies, and the development/progression of cancer is monitored.

An anti-cancer effect is observed for the neutralising anti-IL-11 antibodies, as evidenced by reduced symptoms of cancer and/or increased survival as compared to mice treated with control antibodies.

Example 14: Treatment of AMD using anti-IL-11 antibodies

The effect of treatment with neutralising anti-IL-11 antibodies is investigated in wet age-related macular degeneration (AMD).

Neutralising anti-IL-11 antibody is administered to subjects having wet AMD. In some treatment conditions, subjects are administered with VEGF antagonist therapy (e.g. ranibizumab, bevacizumab, pegaptanib, brolucizumab or aflibercept), PDGF antagonist therapy (e.g. pegpleranib), or are treated by laser coagulation therapy in addition to treatment with anti-IL-11 antibody.

A reduction in wet AMD pathology and/or improvement in the symptoms of wet AMD is observed in subjects treated with anti-IL-11 antibody as compared to subjects not treated with anti-IL-11 antibody.

Example 15: Light Chain Shuffled Antibodies

Light chain shuffling was performed as represented schematically in Figure 30.

The heavy chains of the following IL-11-binding antibody clones were used for light chain shuffling: YU45-E03, YU45-F02, YU45-F05, YU45-G02, YU46-A08, YU46-G08.

Variable regions of the heavy chains were amplified by PCR, and the resulting amplicons were pooled and cloned into phagemid vectors (phagemids) each containing a specific VL chain, and representing naïve lambda and kappa light chain library repertoires. The VH and VL containing phagemids were used to produce a new library of antibody-phages, which was used to select clones displaying binding to IL-11 under stringent conditions (i.e. antigen limitation, large number washing steps).

Antibodies capable of binding to both human IL-11 and murine IL-11 (i.e. cross-reactive antibodies) were identified by phage display by panning using biotinylated and non-biotinylated recombinant human and murine IL-11, based on the panning strategy shown in Figure 52.

The analysis identified 66 cross-reactive antibodies (Figure 53). Sequence analysis identified 64 unique antibody clones, the amino acid sequences of which are shown in Figure 50, and the nucleotide sequences of which are shown in Figure 51.

The 64 antibody clones were analysed for binding signal to human IL-11 and murine IL-11 in an ELISA assay. The results are shown in Figures 54A and 54B.

Example 16: Functional Characterisation of the Light Chain Shuffled Antibodies

54 of the light chain shuffled antibodies were analysed for their ability to bind IL-11 and inhibit IL-11 mediated signalling.

16.1 Binding to human IL-11

The light chain shuffled anti-IL-11 antibodies were analysed to determine the EC50 for binding to human IL-11 by ELISA according to standard methods. Briefly, wells of microtiter plates were coated with recombinant human IL-11 (100 ng/well), scFv-Fc comprising the VH and VL domains of the clones were added in a dilution series and antibody binding was detected using a polyclonal antibody detection system.

The results of the ELISA assays were used to calculate EC50 values (ng/ml) for the light chain shuffled antibody clones, and these are shown in Figure 55.

16.2 Ability to inhibit human IL-11 mediated signalling

To investigate the ability of light chain shuffled antibody clones to neutralise human IL-11-mediated signalling, cardiac atrial human fibroblasts were cultured in wells of 96-well plates in the presence of TGFβ1 (5 ng/ml) for 24 hours, in the presence of anti-IL-11 antibodies in scFv-human IgG1-Fc format, or in the presence of human IgG1 isotype control antibody, at a final concentration of 2 mg/ml. Levels of the pro-fibrotic marker MMP2 in the cell culture supernatant were then measured by ELISA. Basal MMP2 secretion by the cells in culture was measured by culture in the absence of TGFβ1, in the presence of human IgG1 isotype control (2 mg/ml).

The results of two separate experiments are shown in Figures 56A and 56B. Horizontal lines in the bar charts represent the basal MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of human IgG1 isotype control antibody in the absence of TGFβ1 stimulation ('NEG' in Figures 56A and 56B), and MMP2 secretion by cardiac atrial human fibroblasts cultured for 24 hours in the presence of 5 ng/ml TGFβ and the human IgG1 isotype control antibody ('POS' in Figures 56A and 56B).

The light chain shuffled anti-IL-11 antibodies were shown to be able to bind to human IL-11, and to inhibit IL-11 mediated signalling.

Example 17: Inhibition of kidney fibrosis using anti-IL-11 antibodies

10–12 week old littermate mice of similar weight had kidney fibrosis induced by intraperitoneal (i.p.) injection of folic acid (180 mg kg^{-1}) in vehicle (0.3 M $NaHCO_3$); control mice were administered vehicle alone.

Anti-IL11 antibody clone BSN-3C6 was administered one day after folic acid treatment and then 3 times per week at a dose of 20 mg/kg. Mice were euthanized 28 days post-injection.

The mouse plasma levels of urea and creatinine were quantified using urea assay kit (ab83362, Abcam) and creatinine assay kit (ab65340, Abcam), respectively according to the manufacturer's instructions. The amount of total collagen in the kidney was quantified on the basis of colourimetric detection of hydroxyproline using a Quickzyme Total Collagen assay kit (Quickzyme Biosciences). All colourimetric assays were performed according to the manufacturer's instructions.

Tissues were paraffin-embedded, and kidneys were sectioned at 3 µm. For paraffin sections, tissues were fixed for 24 h, at room temperature in 10% neutral-buffered formalin (Sigma-Aldrich), dehydrated and embedded in paraffin. For cryosections, freshly dissected organs were embedded with Tissue-Tek Optimal Cutting Temperature compound (VWR International). Cryomoulds were then frozen in a metal beaker with isopentane cooled in liquid nitrogen and sections were stored in −80 °C. Total collagen was stained with Masson's trichrome stain kit (HT15, Sigma-Aldrich) according to the manufacturer's instructions. Images of the sections were captured and blue-stained fibrotic areas were semi-quantitatively determined with ImageJ software (version 1.49). For immunohistochemistry, the tissue sections were incubated with anti-ACTA2 antibody (ab5694, Abcam). Primary antibody staining was visualized using an ImmPRESS HRP Anti-Rabbit IgG Polymer Detection kit (Vector Laboratories) with ImmPACT DAB Peroxidase Substrate (Vector Laboratories) as the chromogen. The sections were then counterstained with Mayer's haematoxylin (Merck).

Figures 58A and 58B show that mice treated with anti-IL11 antibody were found to have significantly reduced staining for collagen, indicating that anti-IL-11 antibody treatment had inhibited kidney fibrosis.

Figure 59 shows that the urinary albumin/creatine ratio was significantly reduced by treatment with anti-IL11 antibody, indicating a reduced level of kidney damage in mice treated with anti-IL-11 antibody.

Figure 60 shows that treatment with the anti-IL-11 antibody inhibited folic acid-induced kidney fibrosis in a dose-dependent fashion.

In another experiment a mouse model of acute renal injury was induced by unilateral ureteric obstruction (UUO). Briefly, mice were treated by sham operation or ureteric obstruction of one ureter. Mice received IgG, anti-IL-11 antibody clone BSN-3C6 (20mg/kg; on surgical days -1, 1, 3, 5) and injured kidneys ('UUO') or contralateral uninjured kidneys (Con) were harvested on day 7 post surgery.

Semi-quantitative assessment of tubular injury was performed by histological analysis of casts, tubular atrophy or tubular expansion blinded to experimental conditions (Tubular injury score: 0, none; 1, minimal; 2, mild; 3, moderate; 4, severe).

Figures 61A and 61B show that treatment with anti-IL-11 antibody reduced tubular damage in a mouse model of acute renal injury.

Example 18: IL-11 and liver fibrosis

Protein expression of IL-11 in healthy and diseased livers was confirmed by western blots in matched samples of human livers. Matched frozen liver samples were prepared for western blotting and levels of IL11 determined using Human IL-11 Antibody Monoclonal Mouse IgG2A Clone # 22626, catalog number MAB218 from R&D Systems. Film images were generated.

The results are shown in Figure 62. Increased expression of IL-11 was detected in most diseased tissue as compared to normal healthy livers.

To determine whether IL-11 expression changed with disease, an ELISA was performed on media from Precision Cut Liver Slices (PCLS) was performed using Human IL-11 DuoSet 15 plate kit, catalog number DY218 from R&D Systems.

Human PCLS were cut and incubated with media treatments after a 24 h rest period for acclimatisation to media plates. Samples were treated with media only (control), media with LPS, a combination of profibrogenic stimuli inducing TGFβ1, or a combination of profibrogenic stimuli inducing TGFβ1 and the TGFβ1 inhibitor ALK5.

The results are shown in Figure 63. The profibrogenic stimuli induced upregulation of IL-11 protein expression, and ALK5 inhibitor was found to inhibit TGFβ1 receptor signalling, which reduced the expression of IL-11 protein down to control levels.

18.1 Inhibition of liver fibrosis using anti-IL-11 antibodies in a preclinical model of NASH

Diabetic mice (db/db; deficient for the leptin receptor) were maintained for 8 weeks on a normal chow diet or on a NASH-inducing (methionine/choline deficient (MCD)) diet. To test the efficacy of neutralizing anti-IL11 antibodies, we administered anti-IL-11 antibody clone BSN-3C6 (20mg/kg, 3x/week, intraperitoneally) for the final 3 weeks of the 8 week NASH diet (Figure 64A, bottom panels). Gross liver histology was assessed at time of euthanasia, and collagen content of the liver was analysed by hydroxyproline assay.

The results are shown in Figures 64A and 64B. Inhibition of IL-11 mediated signalling by anti-IL-11 antibody treatment improved liver histology in a mouse model of nonalcoholic steatohepatitis (Figure 64A) as evidenced by partial restoration of liver morphology and texture in anti-IL-11 antibody-treated animals on NASH diet as compared to untreated animals on NASH diet. Livers from mice treated with anti-IL-11 antibody on NASH diet were also found to have reduced collagen content as compared to untreated animals on NASH diet (Figure 64B).

Example 19: Inhibition of eye fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was assessed in a mouse model of retinal fibrosis in which Bruch's membrane is disrupted, as described in Caballero et al., Exp Eye Res. (2009) Mar;88(3):367-77.

Briefly, mice were subjected to laser-induced retinal damage (4 burns per retina) and were then treated by intraocular administration of antibodies (0.5 µg of either IgG control or anti-IL11 antibody clone BSN-3C6) on days 1, 7, 14 and 21. Eyes were harvested for histological analyses on day 28. The area of fibrosis at burn sites was measured using Masson's Trichrome staining, blinded to treatment.

The results are shown in Figures 65A and 65B. The area of fibrosis was significantly greater in control IgG-treated mice as compared to anti-IL11 antibody treated mice.

Example 20: Inhibition of skin fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was analysed in a mouse model of skin fibrosis stablished by subcutaneous injection of bleomycin (BLM, Sigma B2434, 50 µg/day).

Briefly, the fur on the middle of the back of the mice (~9 cm^2) was trimmed using a scissors, and hair removal cream was applied to remove fur completely. Subcutaneous injections of 100 µL of bleomycin dissolved in PBS at a concentration of 0.5 mg/ml were performed on the top half of the injection site. Subcutaneous injections of 60 µL of anti-IL11 antibody clone BSN-3C6 or control IgG antibody were subsequently performed on the bottom half of the injection site (dosage = 15mg/kg/day). Injections were

performed daily for 21 days and animals were sacrificed one day after the final injection and analysed histologically for dermal thickness and collagen content (by Masson's trichrome staining).

Figures 66B and 66C show that dermal thickness was significantly reduced in mice treated with neutralising anti-IL-11 antibody as compared to control IgG-treated mice. Increased collagen staining can also be seen for the control IgG-treated group (Figure 66B, middle panel).

Example 21: Inhibition of heart fibrosis using anti-IL-11 antibodies

The anti-fibrotic effect of anti-IL-11 antibody treatment was analysed in a mouse model of cardiac fibrosis.

Briefly, transverse aortic constriction (TAC) was performed in male mice as described previously (Tarnavski, O. et al. Mouse cardiac surgery: comprehensive techniques for the generation of mouse models of human diseases and their application for genomic studies. Physiol. Genomics 16, 349–360 (2004)). Age-matched mice underwent a sham operative procedure without TAC. Trans-thoracic two-dimensional Doppler echocardiography was used to confirm increased pressure gradients (>40 mm Hg), indicative of successful TAC.

Mice were euthanized at 2 weeks post-TAC for histological and molecular assessment. Anti-IL-11 antibody clone BSN-3C6 or control IgG antibody were administered intraperitoneally 3 times per week at a dose of 20 mg/kg. After two weeks hearts were harvested and assessed for fibrosis extent using Masson's Trichrome stain kit (HT15, Sigma-Aldrich), in accordance with the manufacturer's instructions.

The results of the analysis is shown in Figure 67. Mice treated with neutralising anti-IL-11 antibody were found to have reduced levels of fibrosis in the epicardium, endocardium and in perivascular regions as compared to mice treated with IgG control antibody.

Claims:

1. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, wherein the antibody or antigen binding fragment is a fully human antibody or antigen binding fragment and is capable of inhibiting IL-11 *trans* signalling.

2. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: $X_1X_2DX_3GX_4YX_5Y$ (SEQ ID NO:239);
$X_6SNX_7GX_8X_9X_{10}$ (SEQ ID NO:240);
$QX_{11}X_{12}SSX_{13}$ (SEQ ID NO:241);
$X_{14}GX_{15}IASNX_{16}$ (SEQ ID NO:242);
QDVGRY (SEQ ID NO:101); or
SLRGYY (SEQ ID NO:161);

ii) LC-CDR2: DVX_{17} (SEQ ID NO:243);
$X_{18}NX_{19}$ (SEQ ID NO:244);
$X_{20}AS$ (SEQ ID NO:245);
$X_{21}DX_{22}$ (SEQ ID NO:246);
EVX_{23} (SEQ ID NO:247); or
$DX_{24}X_{25}$ (SEQ ID NO:248);

iii) LC-CDR3: $X_{26}SYTX_{27}X_{28}X_{29}X_{30}X_{31}VX_{32}$ (SEQ ID NO:249);
$X_{33}SYAX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO:250);
$X_{50}X_{51}WDX_{52}X_{53}LX_{54}X_{55}X_{56}V$ (SEQ ID NO:251);
$QQX_{57}X_{58}X_{59}PX_{60}X_{61}X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}$ (SEQ ID NO:252);
$QSYX_{73}X_{74}SX_{75}X_{76}X_{77}X_{78}$ (SEQ ID NO:253);
$X_{79}SYX_{80}SSX_{81}X_{82}X_{83}VX_{84}$ (SEQ ID NO:254);
NSYVTGNNWA (SEQ ID NO:169); or
DSRGRSGDHWL (SEQ ID NO:163);

iv) HC-CDR1: $GFTFSSYX_{85}$ (SEQ ID NO:255);
$GX_{86}X_{87}X_{88}X_{89}SYG$ (SEQ ID NO:256);
$X_{90}X_{91}X_{92}X_{93}X_{94}SYA$ (SEQ ID NO:257);
WIFLKSYA (SEQ ID NO:204);
VSSNSAAWN (SEQ ID NO:180);
GGSISSSNW (SEQ ID NO:220); or
GFTFSGAY (SEQ ID NO:183);

v) HC-CDR2: $ISYDGSX_{95}K$ (SEQ ID NO:258);
IIPIFGTA (SEQ ID NO:210);
YRSKWYN (SEQ ID NO:181);
ISAYNGNT (SEQ ID NO:229); or

IYHSGST (SEQ ID NO:221);

vi) HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

$AKX_{96}X_{97}X_{98}GX_{99}X_{100}X_{101}X_{102}DY$ (SEQ ID NO:259);

$ARDX_{103}GYSSGWYFDY$ (SEQ ID NO:260);

$ARLX_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}X_{120}AFDI$ (SEQ ID NO:261);

ARIMGYDYGDYDVVDY (SEQ ID NO:199);

$ARIX_{121}X_{122}X_{123}X_{124}X_{125}X_{126}DX_{127}X_{128}X_{129}X_{130}$ (SEQ ID NO:262);

ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

$X_{131}X_{132}X_{133}X_{134}RGYX_{135}DY$ (SEQ ID NO:263);

ARITHDYGDFSDAFDI (SEQ ID NO:194);

$ARX_{136}GVLX_{137}DY$ (SEQ ID NO:264);

AKGSYYFDY (SEQ ID NO:235);

ARLYSGYPSRYYYGMDV (SEQ ID NO:206);

ARVQSGEPESDY (SEQ ID NO:216);

AKIGATDPLDY (SEQ ID NO:187);

ARDLYAFDI (SEQ ID NO:185);

ARPDDDY (SEQ ID NO:203);

AKGGKSYYGFDY (SEQ ID NO:207);

ARADSSAGGGPYYYGMDV (SEQ ID NO:231);

ARVYYDSSGTQGDSFDY (SEQ ID NO:233);

ARVVAAARSYYYYMDV (SEQ ID NO:230);

ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

ARMVNLYYGDAFDI (SEQ ID NO:218);

ARGLITGTTP (SEQ ID NO:211);

ARGQNVDL (SEQ ID NO:198);

ARVQNLGGGSYYVGAFDY (SEQ ID NO:222); or

ARLVGATADDY (SEQ ID NO:219);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X_1 = S or I, X_2 = S or R, X_3 = V or I, X_4 = G, A or N, X_5 = N, E, K or D, X_6 = S or Y, X_7 = I or V, X_8 = S, N or Y, X_9 = N, Y or D, X_{10} = L, Y, T or A, X_{11} = G, S or I, X_{12} = S, I or V, X_{13} = Y or N, X_{14} = S or T, X_{15} = S or N, X_{16} = Y or R, X_{17} = S, T or G, X_{18} = R, I or G, X_{19} = N or D, X_{20} = A or G, X_{21} = E, D or N, X_{22} = N or D, X_{23} = S, F or N, X_{24} = N or V, X_{25} = H or T, X_{26} = S, N or G, X_{27} = S or T, X_{28} = S or G, X_{29} = S, N, G or I, X_{30} = T or S, X_{31} = W, L, V or Q, X_{32} = absent or V, X_{33} = C or S, X_{34} = G or D, X_{35} = S, Y, N or T, X_{36} = Y or N, X_{37} = T or N, X_{38} = W or F, X_{39} = V, G or L, X_{40} = absent or V, X_{41} = absent or R, X_{42} = absent or R, X_{43} = absent or R, X_{44} = absent or D, X_{45} = absent or R, X_{46} = absent or A, X_{47} = absent or D, X_{48} = absent or R, X_{49} = absent or P, X_{50} = A or G , X_{51} = A or T, X_{52} = D, G or S, X_{53} = S or G, X_{54} = S, K or N , X_{55} = G or A, X_{56} = W, G or H, X_{57} = S or Y, X_{58} = Y, R or N, X_{59} = S or N, X_{60} = T, A or W, X_{61} = L or T, X_{62} = Y, A, W or T, X_{63} = T, absent or F, X_{64} = absent or G, X_{65} = absent or G, X_{66} = absent or G, X_{67} = absent or T, X_{68} = absent or K, X_{69} = absent or V, X_{70} = absent or E, X_{71} = absent or F, X_{72} = absent or K, X_{73} = D or N, X_{74} = S or Y, X_{75} = K, S or N, X_{76} = V or L, X_{77} = I, V or W, X_{78} = absent or V, X_{79} = T or N, X_{80} = T or S, X_{81} = T or S, X_{82} = P or T,

X_{83} = Y or L, X_{84} = absent or A, X_{85} = A or G, X_{86} = F or Y, X_{87} = S or T, X_{88} = L or F, X_{89} = G, R, T, S or N, X_{90} = G or I, X_{91} = G, F or L, X_{92} = T, S or P, X_{93} = F or S, X_{94} = S or D, X_{95} = N or D, X_{96} = L, F or D, X_{97} = Y, A or L, X_{98} = S or R, X_{99} = S, V or L, X_{100} = S, Y or P, X_{101} = N, L or I, X_{102} = F or I, X_{103} = S or V, X_{104} = H or A, X_{105} = S, Q or F, X_{106} = S or G, X_{107} = absent or Y, X_{108} = absent or S, X_{109} = absent, R or S, X_{110} = Q, N or S, X_{111} = W or Y, X_{112} = absent, Y or F, X_{113} = absent or E, X_{114} = absent or W, X_{115} = absent or E, X_{116} = absent or P, X_{117} = absent, G or S, X_{118} = absent, R or T, X_{119} = G, E or I, X_{120} = D or H, X_{121} = A or G, X_{122} = A or G, X_{123} = A or Y, X_{124} = D or absent, X_{125} = G or D, X_{126} = F, M or R, X_{127} = V, Y or A, X_{128} = absent or F, X_{129} = absent or D, X_{130} = absent or I, X_{131} = absent or A, X_{132} = absent or R, X_{133} = A or G, X_{134} = R or T, X_{135} = F or G, X_{136} = absent or S, X_{137} = absent or F.

3. The antibody or antigen binding fragment according to claim 2, wherein HC-CDR1 is one of VSSNSAAWN (SEQ ID NO:180), GFTFSGAY (SEQ ID NO:183), GFTFSSYG (SEQ ID NO:186), GFTFSSYA (SEQ ID NO:190), GFSFRSYG (SEQ ID NO:193), GFTFRSYG (SEQ ID NO:196), GFSFSSYA (SEQ ID NO:212), WIFLKSYA (SEQ ID NO:204), GFSLNSYG (SEQ ID NO:217), GGTFSSYA (SEQ ID NO:209), GGSISSSNW (SEQ ID NO:220), GFSLSSYG (SEQ ID NO:201), GGTFSSYA (SEQ ID NO:209), ILPSDSYA (SEQ ID NO:226), GYTFTSYG (SEQ ID NO:228), GFTFGSYG (SEQ ID NO:234) or GFSLGSYG (SEQ ID NO:238).

4. The antibody or antigen binding fragment according to claim 2 or claim 3, wherein HC-CDR2 is one of YRSKWYN (SEQ ID NO:181), ISYDGSNK (SEQ ID NO:184), ISYDGSDK (SEQ ID NO:188), IIPIFGTA (SEQ ID NO:210), IYHSGST (SEQ ID NO:221), or ISAYNGNT (SEQ ID NO:229).

5. The antibody or antigen binding fragment according to any one of claims 2 to 4, wherein HC-CDR3 is one of ARGTRGYFDY (SEQ ID NO:182), ARDLYAFDI (SEQ ID NO:185), AKIGATDPLDY (SEQ ID NO:187), AKDLSGLPIIDY (SEQ ID NO:189),
ARRGYFDY (SEQ ID NO:191), ARIAAADGMDV (SEQ ID NO:192), ARITHDYGDFSDAFDI (SEQ ID NO:194), AKLYSGSSNFDY (SEQ ID NO:195), AKLSGPNGVDY (SEQ ID NO:197), ARGQNVDL (SEQ ID NO:198), ARIMGYDYGDYDVVDY (SEQ ID NO:199), ARRGYGDY (SEQ ID NO:213), ARVGFSSWYPDLYYFDY (SEQ ID NO:205), AKFARGVYLFDY (SEQ ID NO:215), ARVQSGEPESDY (SEQ ID NO:216), ARMVNLYYGDAFDI (SEQ ID NO:218), ARLVGATADDY (SEQ ID NO:219), AKLSGPNGVDY (SEQ ID NO:197), ARGLITGTTP (SEQ ID NO:211), ARVQNLGGGSYYVGAFDY (SEQ ID NO:222), ARLHFSQYFSTIDAFDI (SEQ ID NO:223), ARDVGYSSGWYFDY (SEQ ID NO:200), ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202), ARPDDDY (SEQ ID NO:203) AKLSGPNGVDY (SEQ ID NO:197), ARLYSGYPSRYYYGMDV (SEQ ID NO:206), AKGGKSYYGFDY (SEQ ID NO:207), ARLHSGRNWGDAFDI (SEQ ID NO:208), ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224), ARDSGYSSGWYFDY (SEQ ID NO:225), ARIAAAGRDAFDI (SEQ ID NO:227), ARVVAAARSYYYYMDV (SEQ ID NO:230), ARADSSAGGGPYYYGMDV (SEQ ID NO:231), ARIGGYDDFDY (SEQ ID NO:232), ARVYYDSSGTQGDSFDY (SEQ ID NO:233), AKGSYYFDY (SEQ ID NO:235), ARGVLFDY (SEQ ID NO:236) or ARSGVLDY (SEQ ID NO:237).

6. The antibody or antigen binding fragment according to any one of claims 2 to 5, wherein LC-CDR1 is one of QDVGRY (SEQ ID NO:101), TGNIASNR (SEQ ID NO:104), SSDVGGYNY (SEQ ID NO:107), SSDVGAYNY (SEQ ID NO:110), SSDIGAYNY (SEQ ID NO:114), SSNIGSNY (SEQ ID NO:116),

ISDVGGYNY (SEQ ID NO:122), SSNIGNNL (SEQ ID NO:126), SSDVGGYDY (SEQ ID NO:128), QSVSSN (SEQ ID NO:137), SSNIGNNY (SEQ ID NO:140), YSNVGSNL (SEQ ID NO:144), SSNIGSNT (SEQ ID NO:147), SRDVGGYNY (SEQ ID NO:150), SGSIASNY (SEQ ID NO:152), QIISSY (SEQ ID NO:155), SSDVGGYEY (SEQ ID NO:159), SLRGYY (SEQ ID NO:161), SSNIGSYY (SEQ ID NO:164), SSDVGAYNY (SEQ ID NO:167), SSNIGYDA (SEQ ID NO:170),
QGSSSY (SEQ ID NO:173), SSDVGGYKY (SEQ ID NO:175) or SSDVGNYKY (SEQ ID NO:178).

7. The antibody or antigen binding fragment according to any one of claims 2 to 6, wherein LC-CDR2 is one of AAS (SEQ ID NO:102), DNH (SEQ ID NO:105), DVS (SEQ ID NO:108), EVS (SEQ ID NO:111), RNN (SEQ ID NO:117), DVT (SEQ ID NO:123), DVH (SEQ ID NO:129), DVG (SEQ ID NO:133), EVN (SEQ ID NO:135), DVT (SEQ ID NO:123), GAS (SEQ ID NO:138), DNT (SEQ ID NO:141), EDD (SEQ ID NO:145), INN (SEQ ID NO:148), DDN (SEQ ID NO:153), EDN (SEQ ID NO:157), GNN (SEQ ID NO:162), RND (SEQ ID NO:165), EVF (SEQ ID NO:168) or NDN (SEQ ID NO:171).

8. The antibody or antigen binding fragment according to any one of claims 2 to 7, wherein LC-CDR3 is one of QQYRSAPLA (SEQ ID NO:103), QSYDYSSVI (SEQ ID NO:106), SSYTSSSSWV (SEQ ID NO:109), SSYTSSNTLV (SEQ ID NO:112), SSYTSSSTVV (SEQ ID NO:113), SSYTTSSTVV (SEQ ID NO:115), AAWDGSLSGWV (SEQ ID NO:118), SSYTSSSTWV (SEQ ID NO:119), CSYAGSYTFV (SEQ ID NO:120), NSYTSSTPYV (SEQ ID NO:121), SSYAGSYTWV (SEQ ID NO:124), GSYTSSNTQV (SEQ ID NO:125), AAWDDSLSAGV (SEQ ID NO:127), SSYTSSITWV (SEQ ID NO:130), CSYAGSYTWV (SEQ ID NO:131), GSYTSSSTWV (SEQ ID NO:132), SSYTSGSTWV (SEQ ID NO:134), SSYAGTNNFVV (SEQ ID NO:136), QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139), GTWDSSLSGGV (SEQ ID NO:142), SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143), AAWDDSLKGHV (SEQ ID NO:146), AAWDDSLNGWV (SEQ ID NO:149), CSYADYYTWV (SEQ ID NO:151), QSYDSSNLWV (SEQ ID NO:154), QQSYSTPTWT (SEQ ID NO:156), QSYNSSKVV (SEQ ID NO:158), NSYTSSGTLVV (SEQ ID NO:160), DSRGRSGDHWL (SEQ ID NO:163), ATWDDGLSGWV (SEQ ID NO:166), NSYVTGNNWA (SEQ ID NO:169), AAWDDSLSGWV (SEQ ID NO:172), QQSYSTPLYT (SEQ ID NO:174), CSYAGNYTWL (SEQ ID NO:176), TSYSSSSTLVA (SEQ ID NO:177) or SSYTSSSTLVV (SEQ ID NO:179).

9. The antibody or antigen binding fragment according to any one of claims 2 to 8, having at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: VSSNSAAWN (SEQ ID NO:180)
HC-CDR2: YRSKWYN (SEQ ID NO:181)
HC-CDR3: ARGTRGYFDY (SEQ ID NO:182);

or

HC-CDR1: GFTFSGAY (SEQ ID NO:183)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDLYAFDI (SEQ ID NO:185);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSDK (SEQ ID NO:188)
HC-CDR3: AKDLSGLPIIDY (SEQ ID NO:189);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYFDY (SEQ ID NO:191);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAADGMDV (SEQ ID NO:192);

or

HC-CDR1: GFSFRSYG (SEQ ID NO:193)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFRSYG (SEQ ID NO:196)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGQNVDL (SEQ ID NO:198);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFSFSSYA (SEQ ID NO:212)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYGDY (SEQ ID NO:213);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVQSGEPESDY (SEQ ID NO:216);

or

HC-CDR1: GFSLNSYG (SEQ ID NO:217)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARMVNLYYGDAFDI (SEQ ID NO:218);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLVGATADDY (SEQ ID NO:219);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGLITGTTP (SEQ ID NO:211);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGSISSSNW (SEQ ID NO:220)
HC-CDR2: IYHSGST (SEQ ID NO:221)
HC-CDR3: ARVQNLGGGSYYVGAFDY (SEQ ID NO:222);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHFSQYFSTIDAFDI (SEQ ID NO:223);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDVGYSSGWYFDY (SEQ ID NO:200);

or

HC-CDR1: GFSLSSYG (SEQ ID NO:201)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARPDDDY (SEQ ID NO:203);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLYSGYPSRYYYGMDV (SEQ ID NO:206);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHSGRNWGDAFDI (SEQ ID NO:208);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: ILPSDSYA (SEQ ID NO:226)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAAGRDAFDI (SEQ ID NO:227);

or

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: ISAYNGNT (SEQ ID NO:229)
HC-CDR3: ARVVAAARSYYYYMDV (SEQ ID NO:230);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARADSSAGGGPYYYGMDV (SEQ ID NO:231);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIGGYDDFDY (SEQ ID NO:232);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVYYDSSGTQGDSFDY (SEQ ID NO:233);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFSLGSYG (SEQ ID NO:238)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGVLFDY (SEQ ID NO:236);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARSGVLDY (SEQ ID NO:237).

10. The antibody or antigen binding fragment according to any one of claims 2 to 9, having at least one light chain variable region incorporating the following CDRs:

LC-CDR1: QDVGRY (SEQ ID NO:101)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQYRSAPLA (SEQ ID NO:103);

or

LC-CDR1: TGNIASNR (SEQ ID NO:104)
LC-CDR2: DNH (SEQ ID NO:105)
LC-CDR3: QSYDYSSVI (SEQ ID NO:106);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVS (SEQ ID NO:111)
LC-CDR3: SSYTSSNTLV (SEQ ID NO:112);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113);

or

LC-CDR1: SSDIGAYNY (SEQ ID NO:114)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTTSSTVV (SEQ ID NO:115);

or

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTFV (SEQ ID NO:120);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSTPYV (SEQ ID NO:121);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSNTQV (SEQ ID NO:125);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)

LC-CDR2: DVH (SEQ ID NO:129)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSSTWV (SEQ ID NO:132);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: SSYTSGSTWV (SEQ ID NO:134);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: EVN (SEQ ID NO:135)
LC-CDR3: SSYAGTNNFVV (SEQ ID NO:136);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: QSVSSN (SEQ ID NO:137)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139);

or

LC-CDR1: SSNIGNNY (SEQ ID NO:140)
LC-CDR2: DNT (SEQ ID NO:141)
LC-CDR3: GTWDSSLSGGV (SEQ ID NO:142);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143);

or

LC-CDR1: YSNVGSNL (SEQ ID NO:144)
LC-CDR2: EDD (SEQ ID NO:145)
LC-CDR3: AAWDDSLKGHV (SEQ ID NO:146);

or

LC-CDR1: SSNIGSNT (SEQ ID NO:147)
LC-CDR2: INN (SEQ ID NO:148)
LC-CDR3: AAWDDSLNGWV (SEQ ID NO:149);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYADYYTWV (SEQ ID NO:151);

or

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127);

or

LC-CDR1: SGSIASNY (SEQ ID NO:152)
LC-CDR2: DDN (SEQ ID NO:153)
LC-CDR3: QSYDSSNLWV (SEQ ID NO:154);

or

LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SGSIASNY (SEQ ID NO:152)

LC-CDR2: EDN (SEQ ID NO:157)
LC-CDR3: QSYNSSKVV (SEQ ID NO:158);

or

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160);

or

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SLRGYY (SEQ ID NO:161)
LC-CDR2: GNN (SEQ ID NO:162)
LC-CDR3: DSRGRSGDHWL (SEQ ID NO:163);

or

LC-CDR1: SSNIGSYY (SEQ ID NO:164)
LC-CDR2: RND (SEQ ID NO:165)
LC-CDR3: ATWDDGLSGWV (SEQ ID NO:166);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVF (SEQ ID NO:168)
LC-CDR3: NSYVTGNNWA (SEQ ID NO:169);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119);

or

LC-CDR1: SSNIGYDA (SEQ ID NO:170)
LC-CDR2: NDN (SEQ ID NO:171)
LC-CDR3: AAWDDSLSGWV (SEQ ID NO:172);

or

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174);

or

LC-CDR1: SSDVGGYKY (SEQ ID NO:175)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGNYTWL (SEQ ID NO:176);

or

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS(SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: TSYSSSSTLVA (SEQ ID NO:177);

or

LC-CDR1: SSDVGNYKY (SEQ ID NO:178)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTLVV (SEQ ID NO:179).

11. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, having at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: VSSNSAAWN (SEQ ID NO:180)
HC-CDR2: YRSKWYN (SEQ ID NO:181)
HC-CDR3: ARGTRGYFDY (SEQ ID NO:182);

or

HC-CDR1: GFTFSGAY (SEQ ID NO:183)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDLYAFDI (SEQ ID NO:185);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSDK (SEQ ID NO:188)
HC-CDR3: AKDLSGLPIIDY (SEQ ID NO:189);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYFDY (SEQ ID NO:191);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAADGMDV (SEQ ID NO:192);

or

HC-CDR1: GFSFRSYG (SEQ ID NO:193)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFRSYG (SEQ ID NO:196)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGQNVDL (SEQ ID NO:198);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFSFSSYA (SEQ ID NO:212)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYGDY (SEQ ID NO:213);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVQSGEPESDY (SEQ ID NO:216);

or

HC-CDR1: GFSLNSYG (SEQ ID NO:217)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARMVNLYYGDAFDI (SEQ ID NO:218);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLVGATADDY (SEQ ID NO:219);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGLITGTTP (SEQ ID NO:211);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GGSISSSNW (SEQ ID NO:220)
HC-CDR2: IYHSGST (SEQ ID NO:221)
HC-CDR3: ARVQNLGGGSYYVGAFDY (SEQ ID NO:222);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHFSQYFSTIDAFDI (SEQ ID NO:223);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDVGYSSGWYFDY (SEQ ID NO:200);

or

HC-CDR1: GFSLSSYG (SEQ ID NO:201)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARPDDDY (SEQ ID NO:203);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLYSGYPSRYYYGMDV (SEQ ID NO:206);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHSGRNWGDAFDI (SEQ ID NO:208);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225);

or

HC-CDR1: ILPSDSYA (SEQ ID NO:226)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAAGRDAFDI (SEQ ID NO:227);

or

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: ISAYNGNT (SEQ ID NO:229)
HC-CDR3: ARVVAAARSYYYYMDV (SEQ ID NO:230);

or

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARADSSAGGGPYYYGMDV (SEQ ID NO:231);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIGGYDDFDY (SEQ ID NO:232);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVYYDSSGTQGDSFDY (SEQ ID NO:233);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197);

or

HC-CDR1: GFSLGSYG (SEQ ID NO:238)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGVLFDY (SEQ ID NO:236);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)

HC-CDR2: ISYDGSNK (SEQ ID NO:184)

HC-CDR3: ARSGVLDY (SEQ ID NO:237); and

having at least one light chain variable region arrived at following light chain shuffling.

12. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of $X_1X_2DX_3GX_4YX_5Y$ (SEQ ID NO:239), $X_6SNX_7GX_8X_9X_{10}$ (SEQ ID NO:240), $QX_{11}X_{12}SSX_{13}$ (SEQ ID NO:241), $X_{14}GX_{15}IASNX_{16}$ (SEQ ID NO:242), QDVGRY (SEQ ID NO:101), or SLRGYY (SEQ ID NO:161); LC-CDR2: one of DVX_{17} (SEQ ID NO:243), $X_{18}NX_{19}$ (SEQ ID NO:244), $X_{20}AS$ (SEQ ID NO:245), $X_{21}DX_{22}$ (SEQ ID NO:246), EVX_{23} (SEQ ID NO:247), or $DX_{24}X_{25}$ (SEQ ID NO:248); LC-CDR3: one of $X_{26}SYTX_{27}X_{28}X_{29}X_{30}X_{31}VX_{32}$ (SEQ ID NO:249), $X_{33}SYAX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO:250), $X_{50}X_{51}WDX_{52}X_{53}LX_{54}X_{55}X_{56}V$ (SEQ ID NO:251), $QQX_{57}X_{58}X_{59}PX_{60}X_{61}X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}$ (SEQ ID NO:252), $QSYX_{73}X_{74}SX_{75}X_{76}X_{77}X_{78}$ (SEQ ID NO:253), $X_{79}SYX_{80}SSX_{81}X_{82}X_{83}VX_{84}$ (SEQ ID NO:254), NSYVTGNNWA (SEQ ID NO:169), or DSRGRSGDHWL (SEQ ID NO:163); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: one of $GFTFSSYX_{85}$ (SEQ ID NO:255), $GX_{86}X_{87}X_{88}X_{89}SYG$ (SEQ ID NO:256), $X_{90}X_{91}X_{92}X_{93}X_{94}SYA$ (SEQ ID NO:257), WIFLKSYA (SEQ ID NO:204), VSSNSAAWN (SEQ ID NO:180), GGSISSSNW (SEQ ID NO:220), or GFTFSGAY (SEQ ID NO:183); HC-CDR2: one of $ISYDGSX_{95}K$ (SEQ ID NO:258), IIPIFGTA (SEQ ID NO:210), YRSKWYN (SEQ ID NO:181), ISAYNGNT (SEQ ID NO:229), or IYHSGST (SEQ ID NO:221); HC-CDR3: one of AKLSGPNGVDY (SEQ ID NO:197), $AKX_{96}X_{97}X_{98}GX_{99}X_{100}X_{101}X_{102}DY$ (SEQ ID NO:259), $ARDX_{103}GYSSGWYFDY$ (SEQ ID NO:260), $ARLX_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}X_{120}AFDI$ (SEQ ID NO:261), ARIMGYDYGDYDVVDY (SEQ ID NO:199), $ARIX_{121}X_{122}X_{123}X_{124}X_{125}X_{126}DX_{127}X_{128}X_{129}X_{130}$ (SEQ ID NO:262), ARVGFSSWYPDLYYFDY (SEQ ID NO:205), $X_{131}X_{132}X_{133}X_{134}RGYX_{135}DY$ (SEQ ID NO:263), ARITHDYGDFSDAFDI (SEQ ID NO:194), $ARX_{136}GVLX_{137}DY$ (SEQ ID NO:264), AKGSYYFDY (SEQ ID NO:235), ARLYSGYPSRYYYGMDV (SEQ ID NO:206), ARVQSGEPESDY (SEQ ID NO:216), AKIGATDPLDY (SEQ ID NO:187), ARDLYAFDI (SEQ ID NO:185), ARPDDDY (SEQ ID NO:203), AKGGKSYYGFDY (SEQ ID NO:207), ARADSSAGGGPYYYGMDV (SEQ ID NO:231), ARVYYDSSGTQGDSFDY (SEQ ID NO:233), ARVVAAARSYYYYMDV (SEQ ID NO:230), ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224), ARMVNLYYGDAFDI (SEQ ID NO:218), ARGLITGTTP (SEQ ID NO:211), ARGQNVDL (SEQ ID NO:198), ARVQNLGGGSYYVGAFDY (SEQ ID NO:222), or ARLVGATADDY (SEQ ID NO:219);

wherein X_1 = S or I, X_2 = S or R, X_3 = V or I, X_4 = G, A or N, X_5 = N, E, K or D, X_6 = S or Y, X_7 = I or V, X_8 = S, N or Y, X_9 = N, Y or D, X_{10} = L, Y, T or A, X_{11} = G, S or I, X_{12} = S, I or V, X_{13} = Y or N, X_{14} = S or T, X_{15} = S or N, X_{16} = Y or R, X_{17} = S, T or G, X_{18} = R, I or G, X_{19} = N or D, X_{20} = A or G, X_{21} = E, D or N, X_{22} = N or D, X_{23} = S, F or N, X_{24} = N or V, X_{25} = H or T, X_{26} = S, N or G, X_{27} = S or T, X_{28} = S or G, X_{29} = S, N, G or I, X_{30} = T or S, X_{31} = W, L, V or Q, X_{32} = absent or V, X_{33} = C or S , X_{34} = G or D, X_{35} = S, Y, N or T, X_{36} = Y or N, X_{37} = T or N, X_{38} = W or F, X_{39} = V, G or L, X_{40} = absent or V, X_{41} = absent or R, X_{42} = absent or R, X_{43} =

absent or R, X_{44} = absent or D, X_{45} = absent or R, X_{46} = absent or A, X_{47} = absent or D, X_{48} = absent or R, X_{49} = absent or P, X_{50} = A or G , X_{51} = A or T, X_{52} = D, G or S, X_{53} = S or G, X_{54} = S, K or N , X_{55} = G or A, X_{56} = W, G or H, X_{57} = S or Y, X_{58} = Y, R or N, X_{59} = S or N, X_{60} = T, A or W, X_{61} = L or T, X_{62} = Y, A, W or T, X_{63} = T, absent or F, X_{64} = absent or G, X_{65} = absent or G, X_{66} = absent or G, X_{67} = absent or T, X_{68} = absent or K, X_{69} = absent or V, X_{70} = absent or E, X_{71} = absent or F, X_{72} = absent or K, X_{73} = D or N, X_{74} = S or Y, X_{75} = K, S or N, X_{76} = V or L, X_{77} = I, V or W, X_{78} = absent or V, X_{79} = T or N, X_{80} = T or S, X_{81} = T or S, X_{82} = P or T, X_{83} = Y or L, X_{84} = absent or A, X_{85} = A or G, X_{86} = F or Y, X_{87} = S or T, X_{88} = L or F, X_{89} = G, R, T, S or N, X_{90} = G or I, X_{91} = G, F or L, X_{92} = T, S or P, X_{93} = F or S, X_{94} = S or D, X_{95} = N or D, X_{96} = L, F or D, X_{97} = Y, A or L, X_{98} = S or R, X_{99} = S, V or L, X_{100} = S, Y or P, X_{101} = N, L or I, X_{102} = F or I, X_{103} = S or V, X_{104} = H or A, X_{105} = S, Q or F, X_{106} = S or G, X_{107} = absent or Y, X_{108} = absent or S, X_{109} = absent, R or S, X_{110} = Q, N or S, X_{111} = W or Y, X_{112} = absent, Y or F, X_{113} = absent or E, X_{114} = absent or W, X_{115} = absent or E, X_{116} = absent or P, X_{117} = absent, G or S, X_{118} = absent, R or T, X_{119} = G, E or I, X_{120} = D or H, X_{121} = A or G, X_{122} = A or G, X_{123} = A or Y, X_{124} = D or absent, X_{125} = G or D, X_{126} = F, M or R, X_{127} = V, Y or A, X_{128} = absent or F, X_{129} = absent or D, X_{130} = absent or I, X_{131} = absent or A, X_{132} = absent or R, X_{133} = A or G, X_{134} = R or T, X_{135} = F or G, X_{136} = absent or S, X_{137} = absent or F.

13. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs:1 to 50, and;

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs:51 to 100.

14. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, which is capable of inhibiting IL-11 *trans* signalling, optionally wherein the antibody or antigen binding fragment is an antibody or antigen binding fragment according to any one of claims 2 to 13.

15. The antibody or antigen binding fragment according to any one of claims 1 to 14, conjugated to a drug moiety or a detectable moiety.

16. An *in vitro* complex, optionally isolated, comprising an antibody or antigen binding fragment according to any one of claims 1 to 15 bound to IL-11.

17. A composition comprising the antibody or antigen binding fragment according to any one of claims 1 to 15, and at least one pharmaceutically-acceptable carrier.

18. An isolated nucleic acid encoding the antibody or antigen binding fragment according to any one of claims 1 to 15.

19. A vector comprising the nucleic acid of claim 18.

20. A host cell comprising the vector of claim 19.

21. A method for making an antibody or antigen binding fragment according to any one of claims 1 to 15, comprising culturing the host cell of claim 20 under conditions suitable for the expression of the antibody or antigen binding fragment, and recovering the antibody or antigen binding fragment.

22. An antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 for use in therapy, or in a method of medical treatment.

23. An antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 for use in the treatment or prevention of fibrosis, or a disease/disorder characterised by fibrosis.

24. An antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 for use in the treatment of a cancer.

25. Use of an antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 in the manufacture of a medicament for use in the treatment or prevention of fibrosis or a disease/disorder characterised by fibrosis.

26. Use of an antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 in the manufacture of a medicament for use in the treatment or prevention of a cancer.

27. A method of treating fibrosis comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 to a subject suffering from fibrosis or a disease/disorder characterised by fibrosis.

28. A method of treating cancer comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 1 to 15 or 17 to a subject suffering from a cancer.

29. An antibody or antigen binding fragment for use in a method of treating a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

30. Use of an antibody or antigen binding fragment in the manufacture of a medicament for use in the treatment of a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

31. A method of treating a disease in which IL-11 mediated signalling is implicated in the pathology of the disease, comprising administering an antibody or antigen binding fragment to a subject suffering from the disease, wherein the antibody or antigen binding fragment is capable of inhibiting IL-11 *trans* signalling.

32. A method comprising contacting a sample containing, or suspected to contain, IL-11 with an antibody or antigen binding fragment according to any one of claims 1 to 15 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

33. A method of diagnosing a disease or condition in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding fragment according to any one of claims 1 to 15 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

34. A method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with the antibody or antigen binding fragment according to any one of claims 1 to 15 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

35. Use of an antibody or antigen binding fragment according to any one of claims 1 to 15 for the detection of IL-11 *in vitro* or *in vivo*.

36. Use of an antibody or antigen binding fragment according to any one of claims 1 to 15 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

37. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: $X_{138}X_{139}$DVGGYX$_{140}X_{141}$ (SEQ ID NO:393), SSDVX$_{142}X_{143}$YX$_{144}$Y (SEQ ID NO:394), X$_{145}X_{146}$DX$_{147}$GAYNY (SEQ ID NO:395), SSDIGX$_{148}$YNY (SEQ ID NO:396), X$_{149}$SDVGAYDY (SEQ ID NO:397), SGDVGTYX$_{150}$Y (SEQ ID NO:398), QX$_{151}$IX$_{152}$SY (SEQ ID NO:399), QSX$_{153}$SSSY (SEQ ID NO:400), RX$_{154}$DX$_{155}$GGYDX$_{156}$ (SEQ ID NO:401), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:349) or QSVNSAY (SEQ ID NO:359);

ii) LC-CDR2: DVX$_{157}$ (SEQ ID NO:402) or X$_{158}$AS (SEQ ID NO:403);

iii) LC-CDR3: X$_{159}$SYAGX$_{160}X_{161}X_{162}$WX$_{163}$ (SEQ ID NO:404), SSYTX$_{164}X_{165}X_{166}X_{167}$WV (SEQ ID NO:405), QQSYSX$_{168}$PX$_{169}$WT (SEQ ID NO:406), SSFX$_{170}X_{171}$SX$_{172}X_{173}$WV (SEQ ID NO:407), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357), or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282);

iv) HC-CDR1: GFTFX$_{174}$SYX$_{175}$ (SEQ ID NO:409);

v) HC-CDR2: ISYDGSNX$_{176}$ (SEQ ID NO:410);

vi) HC-CDR3: AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKLSGPNGVDY (SEQ ID NO:197) or AKGX$_{177}X_{178}$SYYX$_{179}$FDY (SEQ ID NO:411);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X_{138} = S, N or I, X_{139} = S or R, X_{140} = N, E or D, X_{141} = Y or F, X_{142} = G or A, X_{143} = D, G or T, X_{144} = N or D, X_{145} = S or N, X_{146} = N, T or S, X_{147} = V or I, X_{148} = V or G, X_{149} = S or G, X_{150} = N or D, X_{151} = A or I, X_{152} = N or S, X_{153} = F or V, X_{154} = S or R, X_{155} = I or V, X_{156} = Y or F, X_{157} = S, T, N, G, V or D, X_{158} = A or G,

X_{159} = C, S, A or N, X_{160} = S, R, N, G, T or F, X_{161} = Y or H, X_{162} = T, N, I, S or V, X_{163} = V, M or I, X_{164} = S or N, X_{165} = S or N, X_{166} = T, I, S or R, X_{167} = T or S, X_{168} = T or D, X_{169} = S, R or T, X_{170} = T or A, X_{171} = T or S, X_{172} = I or T, X_{173} = A or T, X_{174} = S or G, X_{175} = G or A, X_{176} = K or R, X_{177} = absent or G, X_{178} = absent or K, and X_{179} = absent or G.

38. The antibody or antigen binding fragment according to claim 37, wherein HC-CDR1 is one of GFTFSSYG (SEQ ID NO:186), GFTFSSYA (SEQ ID NO:190) or GFTFGSYG (SEQ ID NO:234).

39. The antibody or antigen binding fragment according to claim 37 or claim 38, wherein HC-CDR2 is one of ISYDGSNK (SEQ ID NO:184) or ISYDGSNR (SEQ ID NO:381).

40. The antibody or antigen binding fragment according to any one of claims 37 to 39, wherein HC-CDR3 is one of AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKGGKSYYGFDY (SEQ ID NO:207), AKGSYYFDY (SEQ ID NO:235) or AKLSGPNGVDY (SEQ ID NO:197).

41. The antibody or antigen binding fragment according to any one of claims 37 to 40, wherein LC-CDR1 is one of SSDVGGYNF (SEQ ID NO:294), SSDVGGYEY (SEQ ID NO:159), SRDVGGYNY (SEQ ID NO:150), NSDVGGYNY (SEQ ID NO:300), SSDVGGYDY (SEQ ID NO:128), SSDVGGYNY (SEQ ID NO:107), ISDVGGYNY (SEQ ID NO:122), SSDVGDYDY (SEQ ID NO:317), SSDVAGYNY (SEQ ID NO:330), SSDVGTYNY (SEQ ID NO:344), NTDVGAYNY (SEQ ID NO:272), SNDIGAYNY (SEQ ID NO:306), SSDVGAYNY (SEQ ID NO:110), SSDIGVYNY (SEQ ID NO:347), SSDIGGYNY (SEQ ID NO:326), SSDVGAYDY (SEQ ID NO:333), GSDVGAYDY (SEQ ID NO:322), SGDVGTYNY (SEQ ID NO:298), SGDVGTYDY (SEQ ID NO:302), QAINSY (SEQ ID NO:352), QIISSY (SEQ ID NO:155), QSFSSSY (SEQ ID NO:356), QSVSSSY (SEQ ID NO:367), RSDIGGYDY (SEQ ID NO:290), RRDVGGYDF (SEQ ID NO:339), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:349) or QSVNSAY (SEQ ID NO:359).

42. The antibody or antigen binding fragment according to any one of claims 37 to 41, wherein LC-CDR2 is one of DVS (SEQ ID NO:108), DVV (SEQ ID NO:275), DVT (SEQ ID NO:123), DVD (SEQ ID NO:295), DVN (SEQ ID NO:291), DVG (SEQ ID NO:133), AAS (SEQ ID NO:102) or GAS (SEQ ID NO:138).

43. The antibody or antigen binding fragment according to any one of claims 37 to 42, wherein LC-CDR3 is one of CSYAGSYTWV (SEQ ID NO:131), SSYAGSYTWV (SEQ ID NO:124), CSYAGSYSWV (SEQ ID NO:273), CSYAGGYTWV (SEQ ID NO:276), NSYAGSYTWV (SEQ ID NO:278), CSYAGSYVWV (SEQ ID NO:285), CSYAGRYTWI (SEQ ID NO:296), CSYAGRYTWM (SEQ ID NO:336), CSYAGTYTWV (SEQ ID NO:340), CSYAGFYTWV (SEQ ID NO:345), CSYAGSHIWV (SEQ ID NO:308), CSYAGRYTWV (SEQ ID NO:313), CSYAGNYTWM (SEQ ID NO:315), CSYAGSYTWI (SEQ ID NO:324), ASYAGNYNWV (SEQ ID NO:304), SSYAGGYTWV (SEQ ID NO:364), SSYTNSRTWV (SEQ ID NO:292), SSYTSNTTWV (SEQ ID NO:311), SSYTSSTTWV (SEQ ID NO:320), SSYTSSSSWV (SEQ ID NO:109), SSYTSSISWV (SEQ ID NO:288), SSYTSSITWV (SEQ ID NO:130), QQSYSTPSWT (SEQ ID NO:354), QQSYSDPRWT (SEQ ID NO:360), QQSYSTPTWT (SEQ ID NO:156), SSFTTSIAWV (SEQ ID NO:268), SSFTSSTTWV (SEQ ID NO:281), SSFATSISWV (SEQ ID NO: 408), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357) or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282).

44. The antibody or antigen binding fragment according to any one of claims 37 to 43, having at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNR (SEQ ID NO:381)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207);

or

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235);

or

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197).

45. The antibody or antigen binding fragment according to any one of claims 37 to 44, having at least one light chain variable region incorporating the following CDRs:

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTTSIAWV (SEQ ID NO:268);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)

LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);
or
LC-CDR1: NTDVGAYNY (SEQ ID NO:272)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVV (SEQ ID NO:275)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);
or
LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTSSTTWV (SEQ ID NO:281);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282);
or
LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYVWV (SEQ ID NO:285);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSISWV (SEQ ID NO:288);

or

LC-CDR1: RSDIGGYDY (SEQ ID NO:290)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTNSRTWV (SEQ ID NO:292);

or

LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVD (SEQ ID NO:295)
LC-CDR3: CSYAGRYTWI (SEQ ID NO:296);

or

LC-CDR1: SGDVGTYNY (SEQ ID NO:298)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);

or

LC-CDR1: NSDVGGYNY (SEQ ID NO:300)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SGDVGTYDY (SEQ ID NO:302)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278);

or

LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: ASYAGNYNWV (SEQ ID NO:304);

or

LC-CDR1: SNDIGAYNY (SEQ ID NO:306)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSHIWV (SEQ ID NO:308);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273);

or

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)

LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYTSNTTWV (SEQ ID NO:311);
or
LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGRYTWV (SEQ ID NO:313);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGNYTWM (SEQ ID NO:315);
or
LC-CDR1: SSDVGDYDY (SEQ ID NO:317)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSTTWV (SEQ ID NO:320);
or
LC-CDR1: GSDVGAYDY (SEQ ID NO:322)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSFATSISWV (SEQ ID NO:408);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWI (SEQ ID NO:324);
or
LC-CDR1: SSDIGGYNY (SEQ ID NO:326)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);
or
LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);
or
LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);
or
LC-CDR1: SSDVAGYNY (SEQ ID NO:330)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGAYDY (SEQ ID NO:333)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: ASYTRSSVWV (SEQ ID NO:334);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGRYTWM (SEQ ID NO:336);

or

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);

or

LC-CDR1: RRDVGGYDF (SEQ ID NO:339)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276);

or

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: SSDVGTYNY (SEQ ID NO:344)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGFYTWV (SEQ ID NO:345);

or

LC-CDR1: SSDIGVYNY (SEQ ID NO:347)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131);

or

LC-CDR1: GSNVGGYNY (SEQ ID NO:349)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340);

or

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)

LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109);
or
LC-CDR1: QAINSY (SEQ ID NO:352)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPSWT (SEQ ID NO:354);
or
LC-CDR1: QSFSSSY (SEQ ID NO:356)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSSTSPTWA (SEQ ID NO:357);
or
LC-CDR1: QSVNSAY (SEQ ID NO:359)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSYSDPRWT (SEQ ID NO:360);
or
LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156);
or
LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291
LC-CDR3: NSYTSGSTWV (SEQ ID NO:362);
or
LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGGYTWV (SEQ ID NO:364);
or
LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102);
or
LC-CDR1: QSVSSSY (SEQ ID NO:367)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156).

46. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of $X_{138}X_{139}$DVGGY$X_{140}X_{141}$ (SEQ ID NO:393), SSDV$X_{142}X_{143}$YX_{144}Y (SEQ ID

NO:394), $X_{145}X_{146}DX_{147}GAYNY$ (SEQ ID NO:395), $SSDIGX_{148}YNY$ (SEQ ID NO:396), $X_{149}SDVGAYDY$ (SEQ ID NO:397), $SGDVGTYX_{150}Y$ (SEQ ID NO:398), $QX_{151}IX_{152}SY$ (SEQ ID NO:399), $QSX_{153}SSSY$ (SEQ ID NO:400), $RX_{154}DX_{155}GGYDX_{156}$ (SEQ ID NO:401), SSNVGGYNY (SEQ ID NO:284), GSNVGGYNY (SEQ ID NO:349) or QSVNSAY (SEQ ID NO:359); LC-CDR2: one of DVX_{157} (SEQ ID NO:402) or $X_{158}AS$ (SEQ ID NO:403); LC-CDR3: one of $X_{159}SYAGX_{160}X_{161}X_{162}WX_{163}$ (SEQ ID NO:404), $SSYTX_{164}X_{165}X_{166}X_{167}WV$ (SEQ ID NO:405), $QQSYSX_{168}PX_{169}WT$ (SEQ ID NO:406), $SSFX_{170}X_{171}SX_{172}X_{173}WV$ (SEQ ID NO:407), NSYTSGSTWV (SEQ ID NO:362), ASYTRSSVWV (SEQ ID NO:334), QQSSTSPTWA (SEQ ID NO:357), or SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: $GFTFX_{174}SYX_{175}$ (SEQ ID NO:409); HC-CDR2: $ISYDGSNX_{176}$ (SEQ ID NO:410); HC-CDR3: AKIGATDPLDY (SEQ ID NO:187), ARIMGYDYGDYDVVDY (SEQ ID NO:199), AKLSGPNGVDY (SEQ ID NO:197) or $AKGX_{177}X_{178}SYYX_{179}FDY$ (SEQ ID NO:411);

wherein X_{138} = S, N or I, X_{139} = S or R, X_{140} = N, E or D, X_{141} = Y or F, X_{142} = G or A, X_{143} = D, G or T, X_{144} = N or D, X_{145} = S or N, X_{146} = N, T or S, X_{147} = V or I, X_{148} = V or G, X_{149} = S or G, X_{150} = N or D, X_{151} = A or I, X_{152} = N or S, X_{153} = F or V, X_{154} = S or R, X_{155} = I or V, X_{156} = Y or F, X_{157} = S, T, N, G, V or D, X_{158} = A or G, X_{159} = C, S, A or N, X_{160} = S, R, N, G, T or F, X_{161} = Y or H, X_{162} = T, N, I, S or V, X_{163} = V, M or I, X_{164} = S or N, X_{165} = S or N, X_{166} = T, I, S or R, X_{167} = T or S, X_{168} = T or D, X_{169} = S, R or T, X_{170} = T or A, X_{171} = T or S, X_{172} = I or T, X_{173} = A or T, X_{174} = S or G, X_{175} = G or A, X_{176} = K or R, X_{177} = absent or G, X_{178} = absent or K, and X_{179} = absent or G.

47. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs: 267, 269, 270, 271, 274, 277, 279, 280, 540, 283, 286, 287, 289, 353, 293, 297, 299, 301, 303, 305, 307, 309, 310, 312, 314, 316, 318, 319, 321, 323, 325, 327, 328, 329, 331, 332, 335, 337, 338, 341, 342, 343, 346, 348, 214, 350, 13, 3, 351, 355, 358, 35, 361, 363, 365, 366, or 20; and

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs: 53, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 85, 390, 73, 391, or 392.

48. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising an amino acid sequence having at least 85% sequence identity to the sequence of one of SEQ ID NOs: 412 to 475.

49. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, which is capable of inhibiting IL-11 *trans* signalling, optionally wherein the antibody or antigen binding fragment is an antibody or antigen binding fragment according to any one of claims 37 to 48.

50. The antibody or antigen binding fragment according to any one of claims 37 to 49, conjugated to a drug moiety or a detectable moiety.

51. An *in vitro* complex, optionally isolated, comprising an antibody or antigen binding fragment according to any one of claims 37 to 50 bound to IL-11.

52. A composition comprising the antibody or antigen binding fragment according to any one of claims 37 to 50, and at least one pharmaceutically-acceptable carrier.

53. An isolated nucleic acid encoding the antibody or antigen binding fragment according to any one of claims 37 to 50.

54. A vector comprising the nucleic acid of claim 53.

55. A host cell comprising the vector of claim 54.

56. A method for making an antibody or antigen binding fragment according to any one of claims 37 to 50, comprising culturing the host cell of claim 55 under conditions suitable for the expression of the antibody or antigen binding fragment, and recovering the antibody or antigen binding fragment.

57. An antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 for use in therapy, or in a method of medical treatment.

58. An antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 for use in the treatment or prevention of fibrosis, or a disease/disorder characterised by fibrosis.

59. An antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 for use in the treatment of a cancer.

60. Use of an antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 in the manufacture of a medicament for use in the treatment or prevention of fibrosis or a disease/disorder characterised by fibrosis.

61. Use of an antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 in the manufacture of a medicament for use in the treatment or prevention of a cancer.

62. A method of treating fibrosis comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 to a subject suffering from fibrosis or a disease/disorder characterised by fibrosis.

63. A method of treating cancer comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 37 to 50 or 52 to a subject suffering from a cancer.

64. A method comprising contacting a sample containing, or suspected to contain, IL-11 with an antibody or antigen binding fragment according to any one of claims 37 to 50 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

65. A method of diagnosing a disease or condition in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding fragment according to any one of claims 37 to 50 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

66. A method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with the antibody or antigen binding fragment according to any one of claims 37 to 50 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

67. Use of an antibody or antigen binding fragment according to any one of claims 37 to 50 for the detection of IL-11 *in vitro* or *in vivo*.

68. Use of an antibody or antigen binding fragment according to any one of claims 37 to 50 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

69. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising the amino acid sequences i) to vi):

i) LC-CDR1: ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565);
ii) LC-CDR2: X_{184}AS (SEQ ID NO:569);
iii) LC-CDR3: X_{185}Q$X_{186}X_{187}$S$X_{188}X_{189}X_{190}$T (SEQ ID NO:570);
iv) HC-CDR1: GYTFTX_{180}YX_{181} (SEQ ID NO:567);
v) HC-CDR2: INPX_{182}NGGX_{183} (SEQ ID NO:568) or IYPRSSNT (SEQ ID NO:552);
vi) HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553);

or a variant thereof in which one or two or three amino acids in one or more of the sequences i) to vi) are replaced with another amino acid;

wherein X_{180} = D or S, X_{181} =N or G, X_{182} = H, D or N, X_{183} = P, T or I, X_{184} = G, Y or W, X_{185} = Q or G X_{186} = Y, G or S, X_{187} = Y, N or S, X_{188} = Y or W, X_{189} = P or absent, and X_{190} = L, Y or R.

70. The antibody or antigen binding fragment according to claim 69, wherein HC-CDR1 is one of GYTFTDYN (SEQ ID NO:542) or GYTFTSYG (SEQ ID NO:228).

71. The antibody or antigen binding fragment according to claim 69 or claim 70, wherein HC-CDR2 is one of INPHNGGP (SEQ ID NO:543), INPDNGGT (SEQ ID NO:546), INPNNGGI (SEQ ID NO:549) or IYPRSSNT (SEQ ID NO:552).

72. The antibody or antigen binding fragment according to one of claims 69 to 71, wherein HC-CDR3 is one of ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553).

73. The antibody or antigen binding fragment according to one of claims 69 to 72, wherein LC-CDR1 is one of ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565).

74. The antibody or antigen binding fragment according to one of claims 69 to 73, wherein LC-CDR2 is one of GAS (SEQ ID NO:138), YAS (SEQ ID NO:559) or WAS (SEQ ID NO:563).

75. The antibody or antigen binding fragment according to one of claims 69 to 74, wherein LC-CDR3 is one of GQGYSYPYT (SEQ ID NO:556), QQSNSWPLT (SEQ ID NO:560), QQYYSYPLT (SEQ ID NO:563) or QQYSSYRT (SEQ ID NO:566).

76. The antibody or antigen binding fragment according to any one of claims 69 to 75, having at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPHNGGP (SEQ ID NO:543)
HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544);
or
HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPDNGGT (SEQ ID NO:546)
HC-CDR3: AREGPYGYTWFAY (SEQ ID NO:547);
or
HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPNNGGI (SEQ ID NO:549)
HC-CDR3: ARNPSLYDGYLDC (SEQ ID NO:550);
or
HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: IYPRSSNT (SEQ ID NO:552)
HC-CDR3: ARANWVGYFDV (SEQ ID NO:553).

77. The antibody or antigen binding fragment according to any one of claims 69 to 76, having at least one heavy chain variable region incorporating the following CDRs:

LC-CDR1: ENVVTY (SEQ ID NO:555)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: GQGYSYPYT (SEQ ID NO:556);
or
LC-CDR1: QSIGTS (SEQ ID NO:558)
LC-CDR2: YAS (SEQ ID NO:559)
LC-CDR3: QQSNSWPLT (SEQ ID NO:560);
or
LC-CDR1: QSLLYNSSQKNY (SEQ ID NO:562)
LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYYSYPLT (SEQ ID NO:581);
or
LC-CDR1: QDVGTA (SEQ ID NO:565)

LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYSSYRT (SEQ ID NO:566).

78. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of ENVVTY (SEQ ID NO:555), QSIGTS (SEQ ID NO:558), QSLLYNSSQKNY (SEQ ID NO:562) or QDVGTA (SEQ ID NO:565); LC-CDR2: X_{184}AS (SEQ ID NO:569); LC-CDR3: $X_{185}QX_{186}X_{187}SX_{188}X_{189}X_{190}T$ (SEQ ID NO:570); and

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: GYTFT$X_{180}YX_{181}$ (SEQ ID NO:567); HC-CDR2: one of INPX_{182}NGGX_{183} (SEQ ID NO:568) or IYPRSSNT (SEQ ID NO:552); HC-CDR3: one of ARGELGHWYFDV (SEQ ID NO:544), AREGPYGYTWFAY (SEQ ID NO:547), ARNPSLYDGYLDC (SEQ ID NO:550) or ARANWVGYFDV (SEQ ID NO:553);

wherein X_{180} = D or S, X_{181} =N or G, X_{182} = H, D or N, X_{183} = P, T or I, X_{184} = G, Y or W, X_{185} = Q or G X_{186} = Y, G or S, X_{187} = Y, N or S, X_{188} = Y or W, X_{189} = P or absent, and X_{190} = L, Y or R.

79. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, comprising a light chain and a heavy chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of one of SEQ ID NOs:554, 557, 561 or 564; and

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of one of SEQ ID NOs:541, 545, 548 or 551.

80. An antibody or antigen binding fragment, optionally isolated, which is capable of binding to IL-11, which is capable of inhibiting IL-11 *trans* signalling, optionally wherein the antibody or antigen binding fragment is an antibody or antigen binding fragment according to any one of claims 69 to 79.

81. The antibody or antigen binding fragment according to any one of claims 69 to 79, conjugated to a drug moiety or a detectable moiety.

82. An *in vitro* complex, optionally isolated, comprising an antibody or antigen binding fragment according to any one of claims 69 to 81 bound to IL-11.

83. A composition comprising the antibody or antigen binding fragment according to any one of claims 69 to 81, and at least one pharmaceutically-acceptable carrier.

84. An isolated nucleic acid encoding the antibody or antigen binding fragment according to any one of claims 69 to 81.

85. A vector comprising the nucleic acid of claim 84.

86. A host cell comprising the vector of claim 85.

87. A method for making an antibody or antigen binding fragment according to any one of claims 69 to 81, comprising culturing the host cell of claim 86 under conditions suitable for the expression of the antibody or antigen binding fragment, and recovering the antibody or antigen binding fragment.

88. An antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 for use in therapy, or in a method of medical treatment.

89. An antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 for use in the treatment or prevention of fibrosis, or a disease/disorder characterised by fibrosis.

90. An antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 for use in the treatment of a cancer.

91. Use of an antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 in the manufacture of a medicament for use in the treatment or prevention of fibrosis or a disease/disorder characterised by fibrosis.

92. Use of an antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 in the manufacture of a medicament for use in the treatment or prevention of a cancer.

93. A method of treating fibrosis comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 to a subject suffering from fibrosis or a disease/disorder characterised by fibrosis.

94. A method of treating cancer comprising administering an antibody, antigen binding fragment, or composition according to any one of claims 69 to 81 or 83 to a subject suffering from a cancer.

95. A method comprising contacting a sample containing, or suspected to contain, IL-11 with an antibody or antigen binding fragment according to any one of claims 69 to 81 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

96. A method of diagnosing a disease or condition in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding fragment according to any one of claims 69 to 81 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

97. A method of selecting or stratifying a subject for treatment with an IL-11-targeted agent, the method comprising contacting, *in vitro*, a sample from the subject with the antibody or antigen binding fragment according to any one of claims 69 to 81 and detecting the formation of a complex of the antibody or antigen binding fragment with IL-11.

98. Use of an antibody or antigen binding fragment according to any one of claims 69 to 81 for the detection of IL-11 *in vitro* or *in vivo*.

99. Use of an antibody or antigen binding fragment according to any one of claims 69 to 81 as an *in vitro* or *in vivo* diagnostic or prognostic agent.

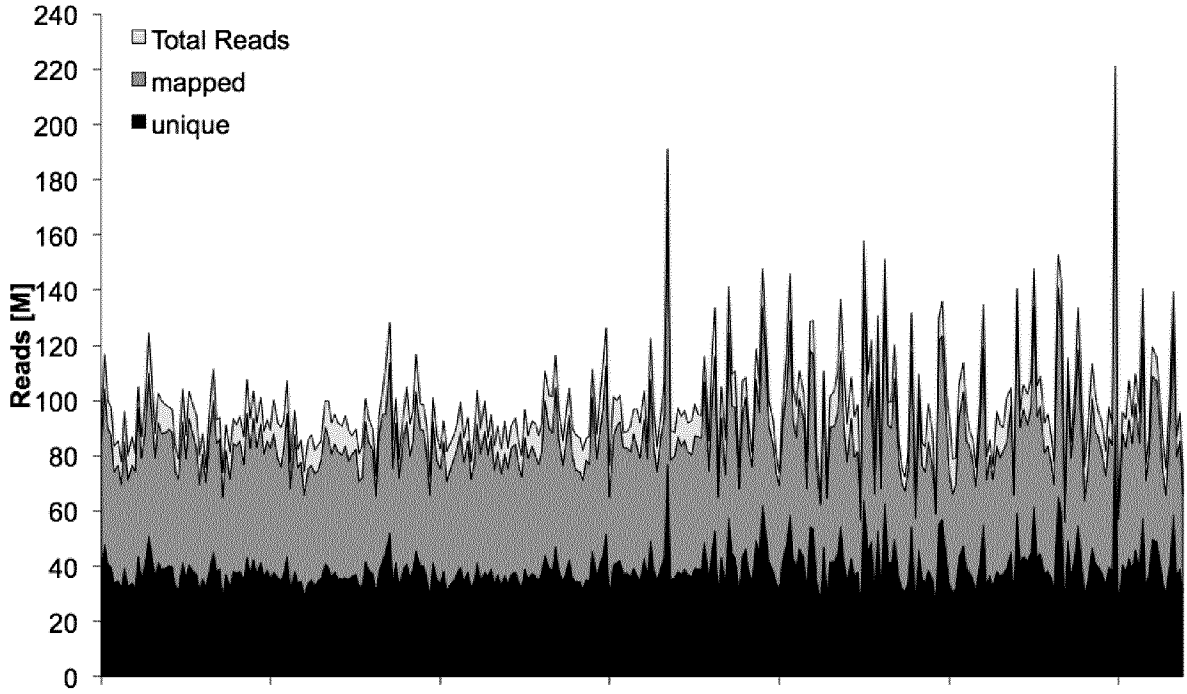


Figure 1

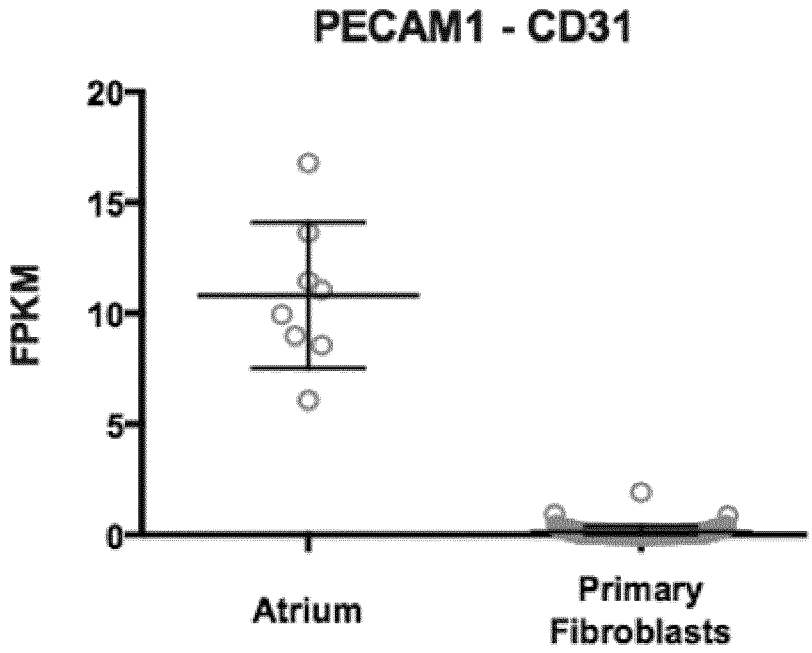


Figure 2A

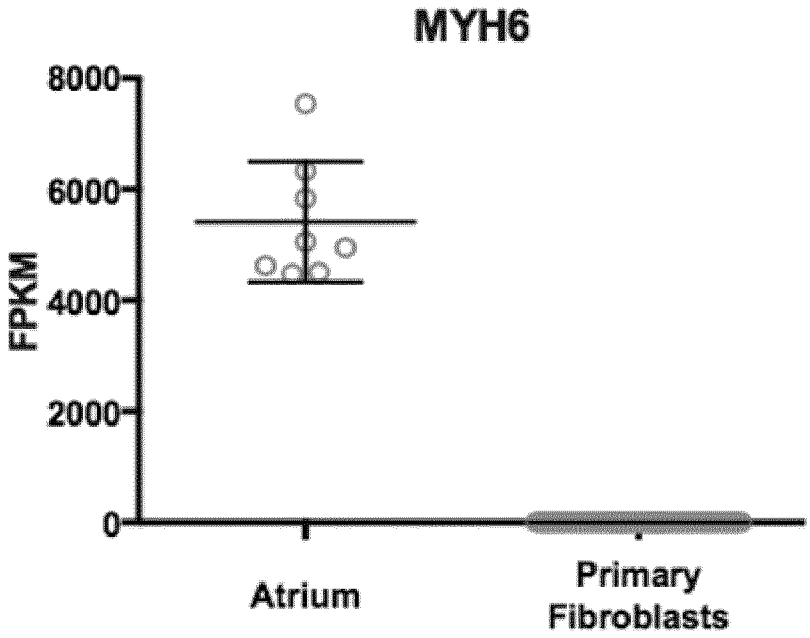


Figure 2B

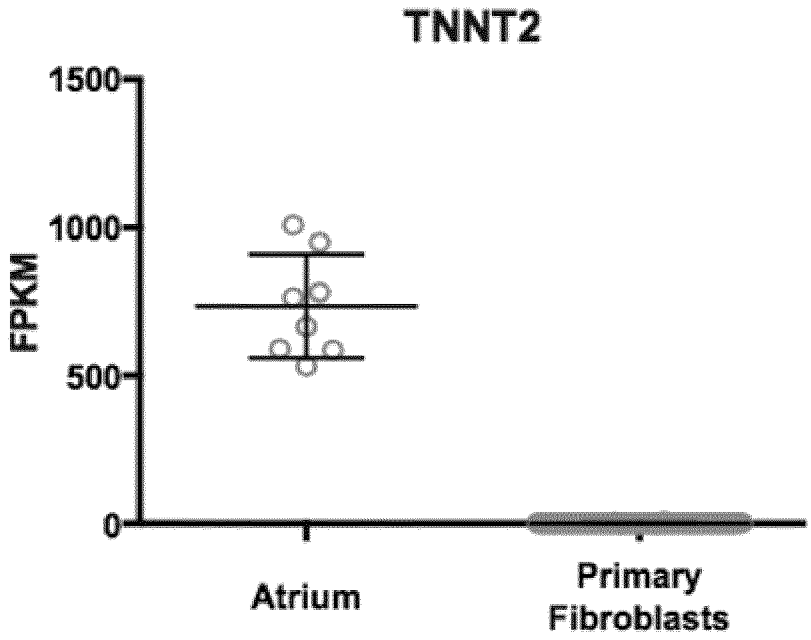


Figure 2C

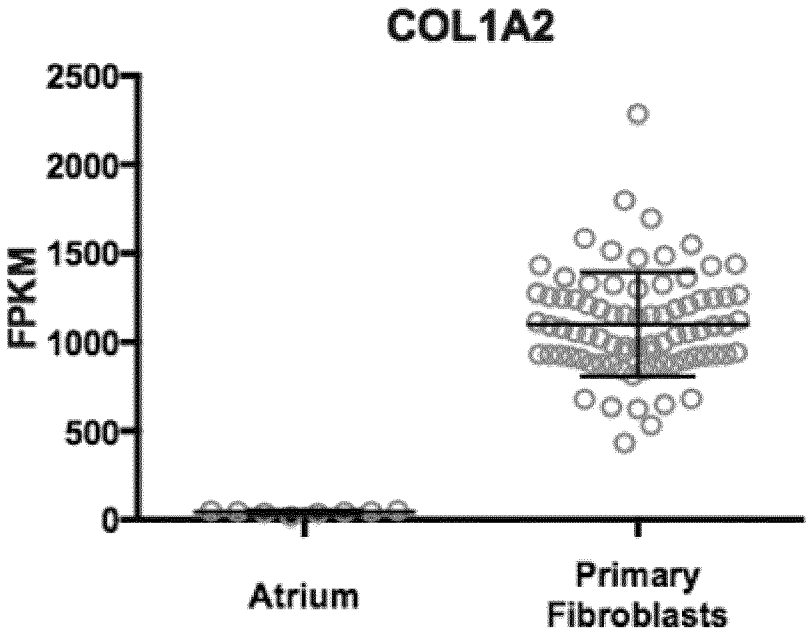


Figure 2D

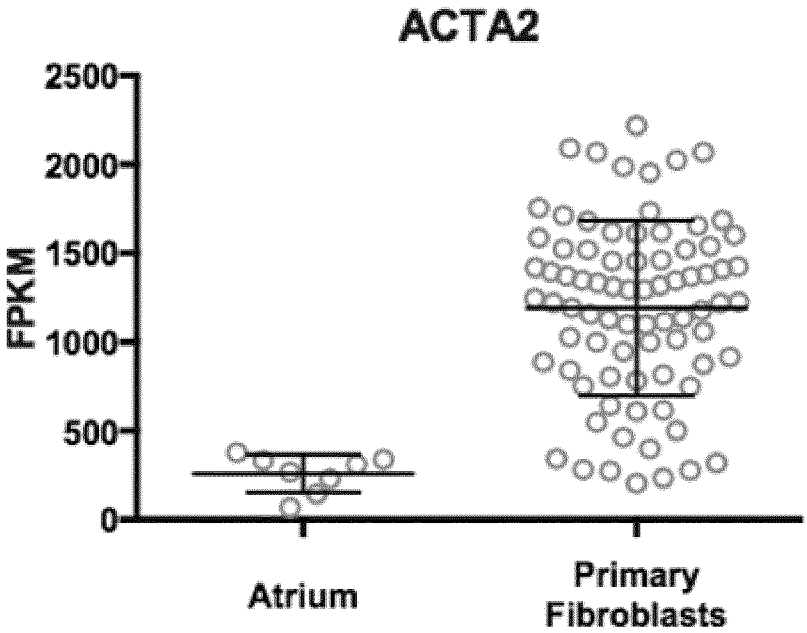


Figure 2E

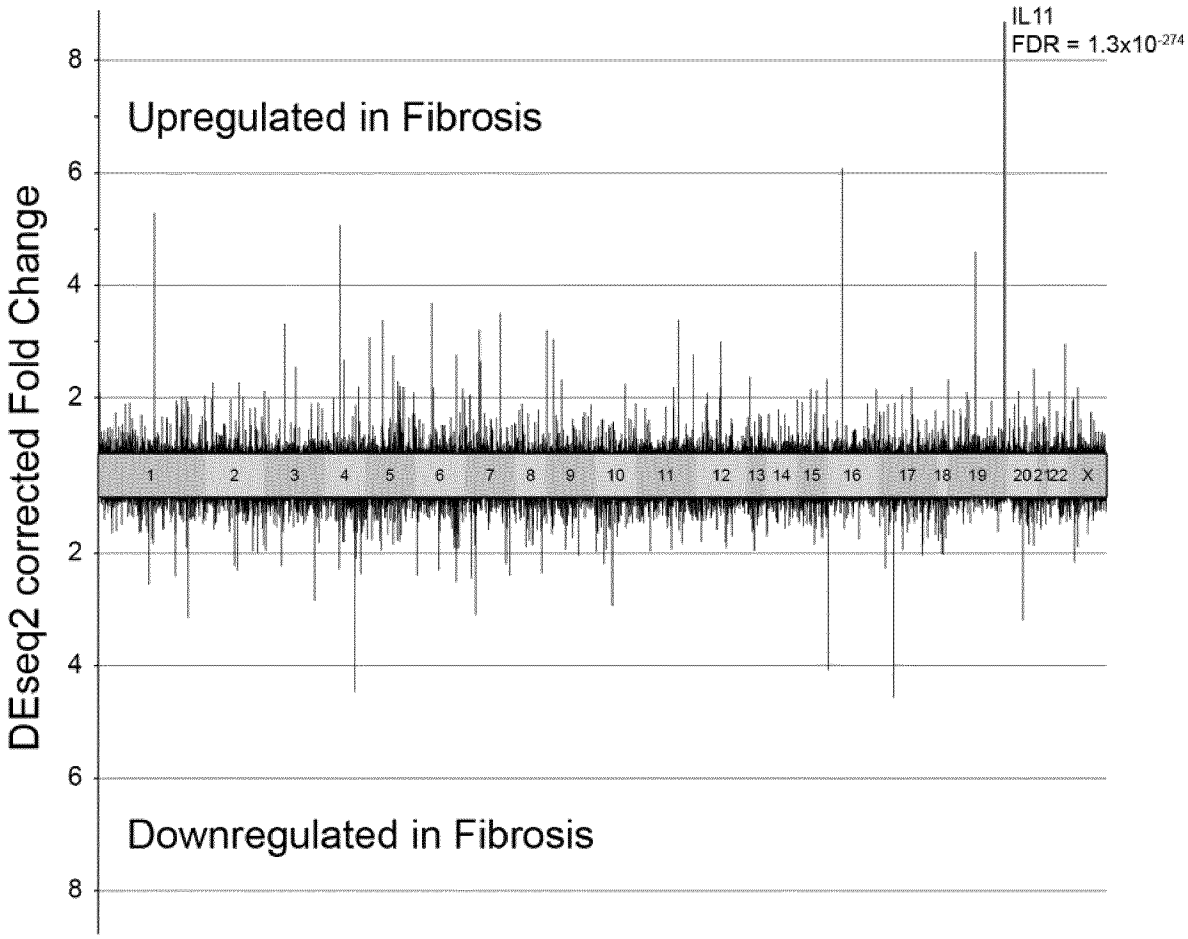


Figure 3A

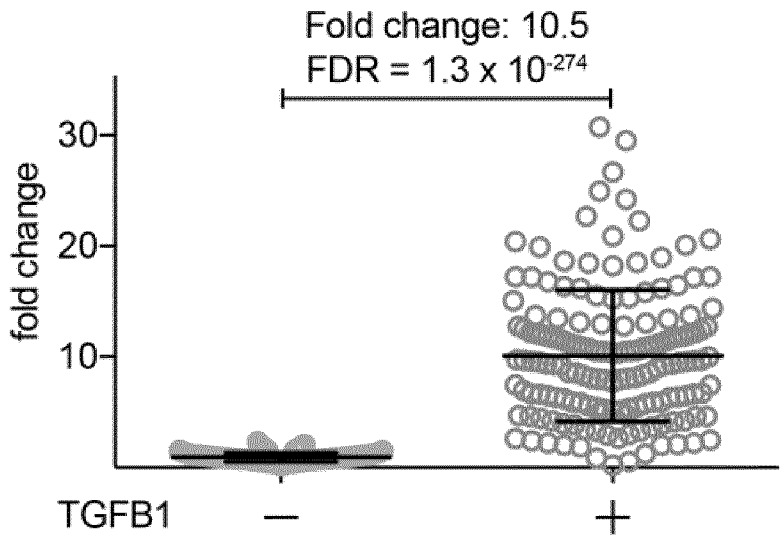


Figure 3B

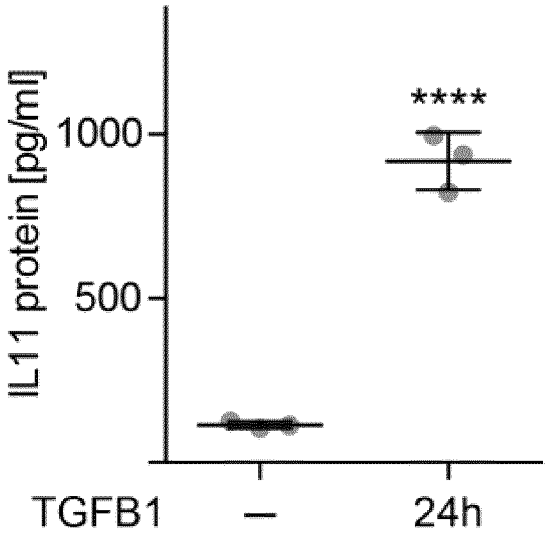


Figure 3C

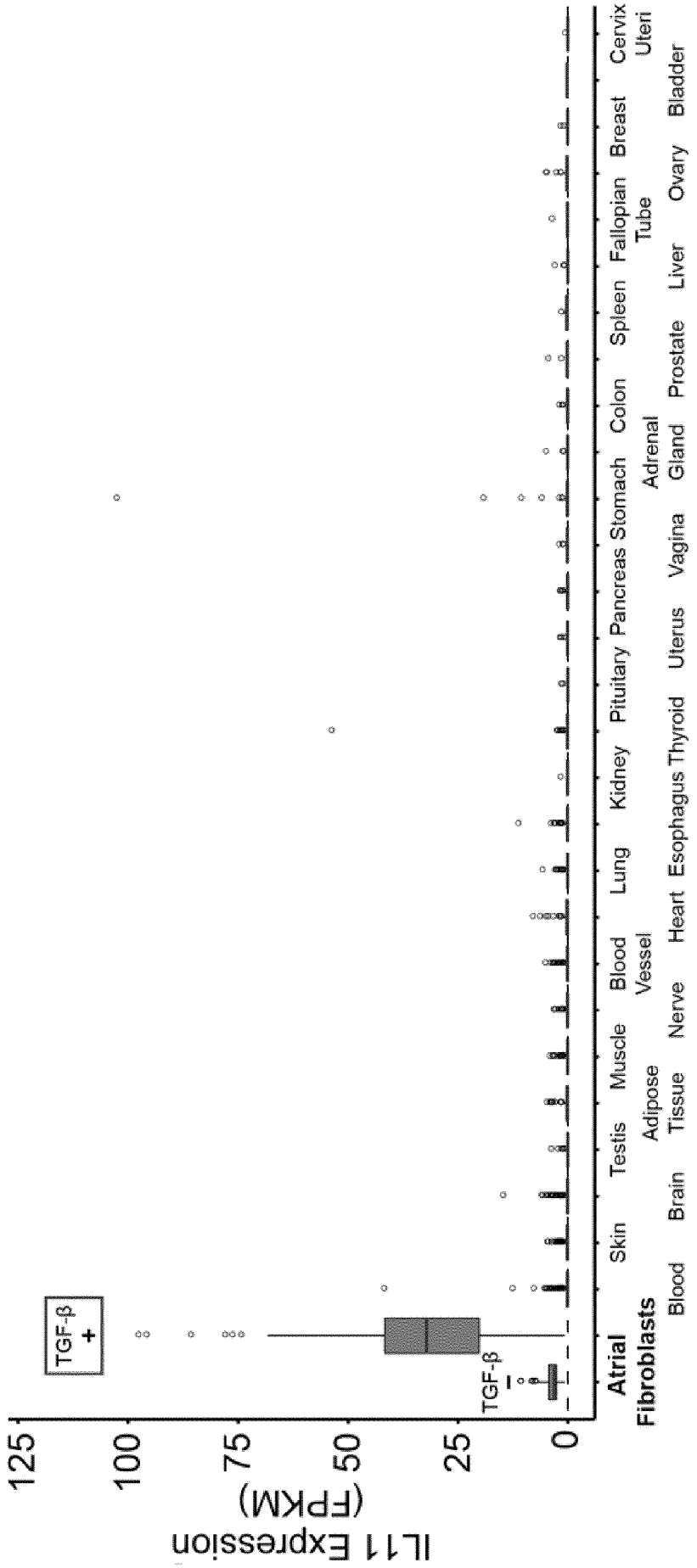

IL11 Expression (FPKM)
125
100
75
50
25
0
TGF-β +
TGF-β -
Atrial Fibroblasts
Blood
Brain
Skin
Tissue
Testis
Adipose
Muscle
Nerve
Blood Vessel
Heart
Lung
Esophagus
Kidney
Thyroid
Pituitary
Uterus
Pancreas
Vagina
Stomach
Adrenal Gland
Colon
Prostate
Spleen
Liver
Fallopian Tube
Ovary
Breast
Bladder
Cervix Uteri

Figure 3D

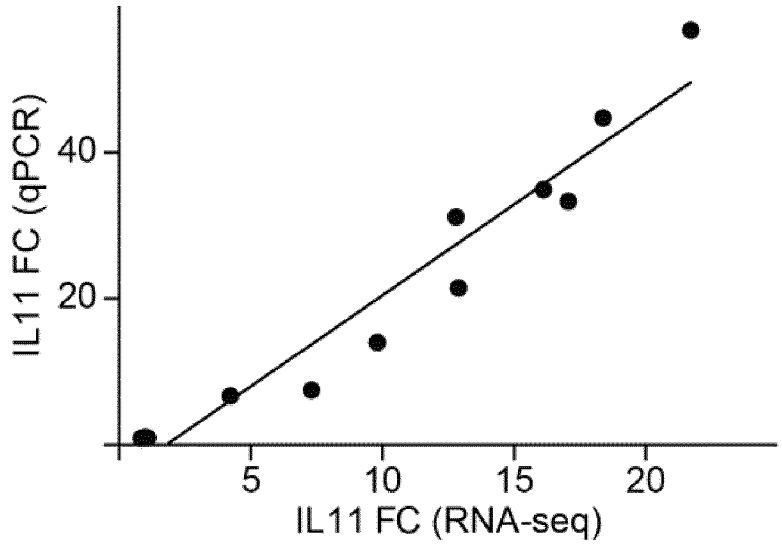


Figure 3E

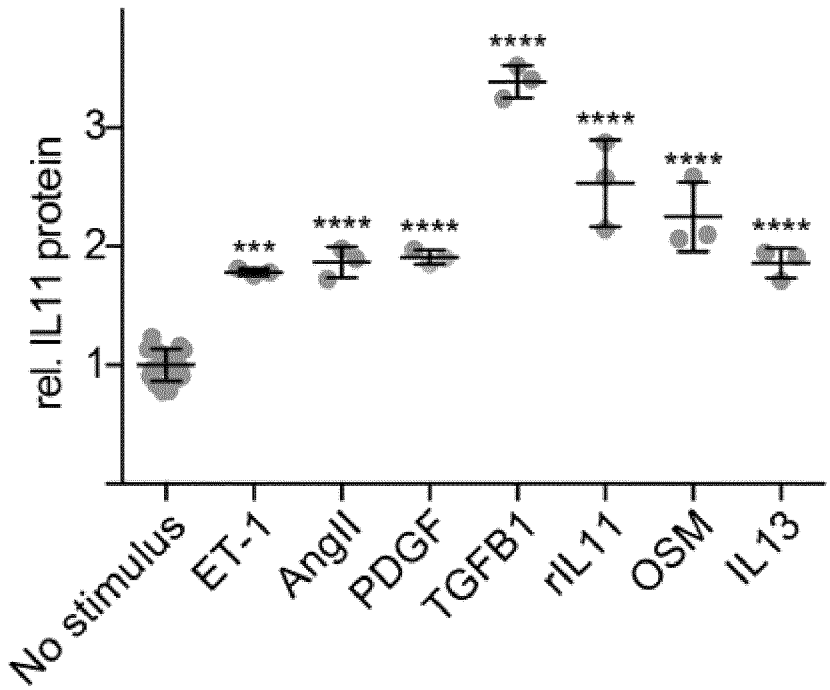


Figure 4A

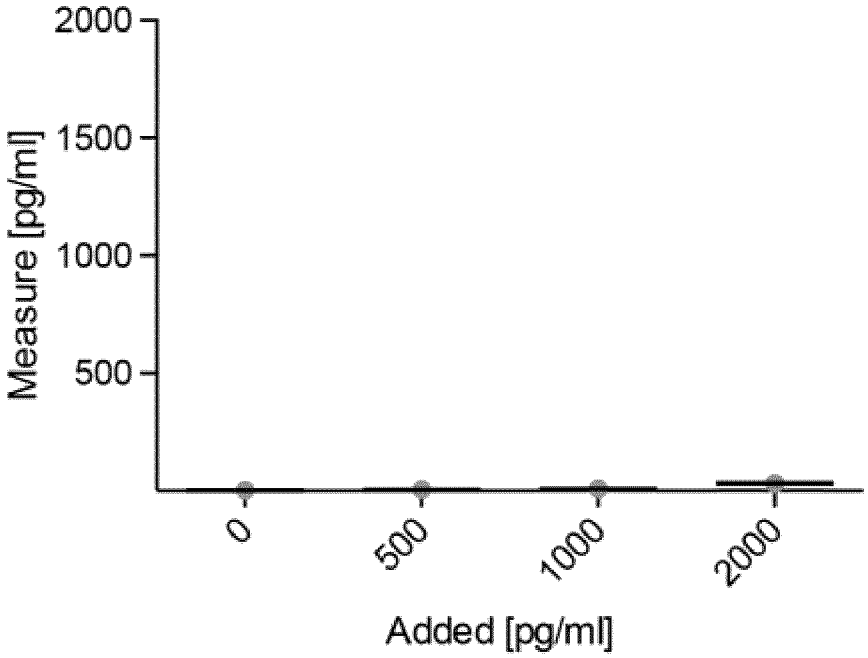


Figure 4B

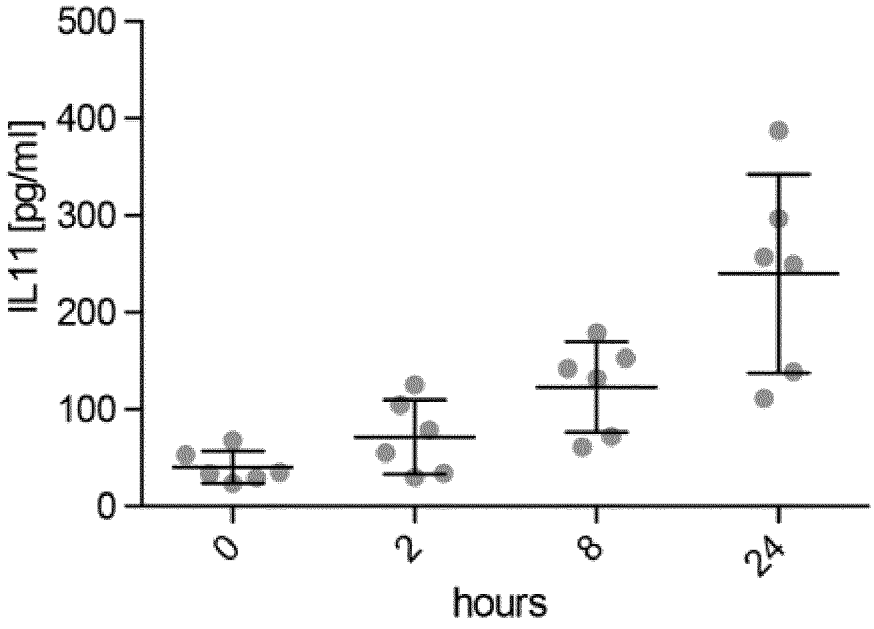


Figure 4C

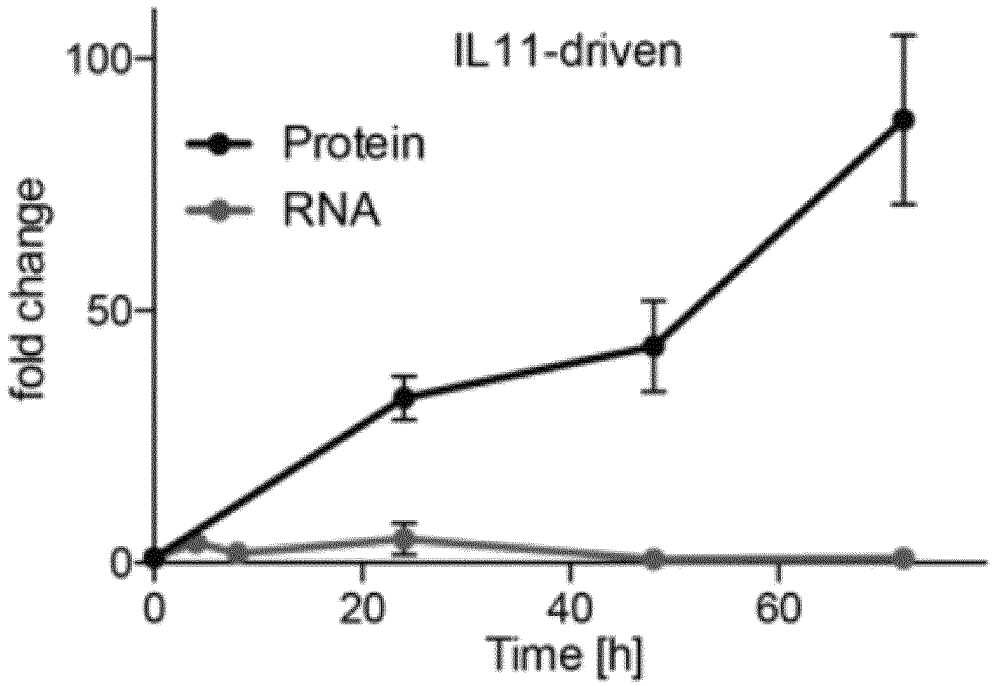


Figure 4D

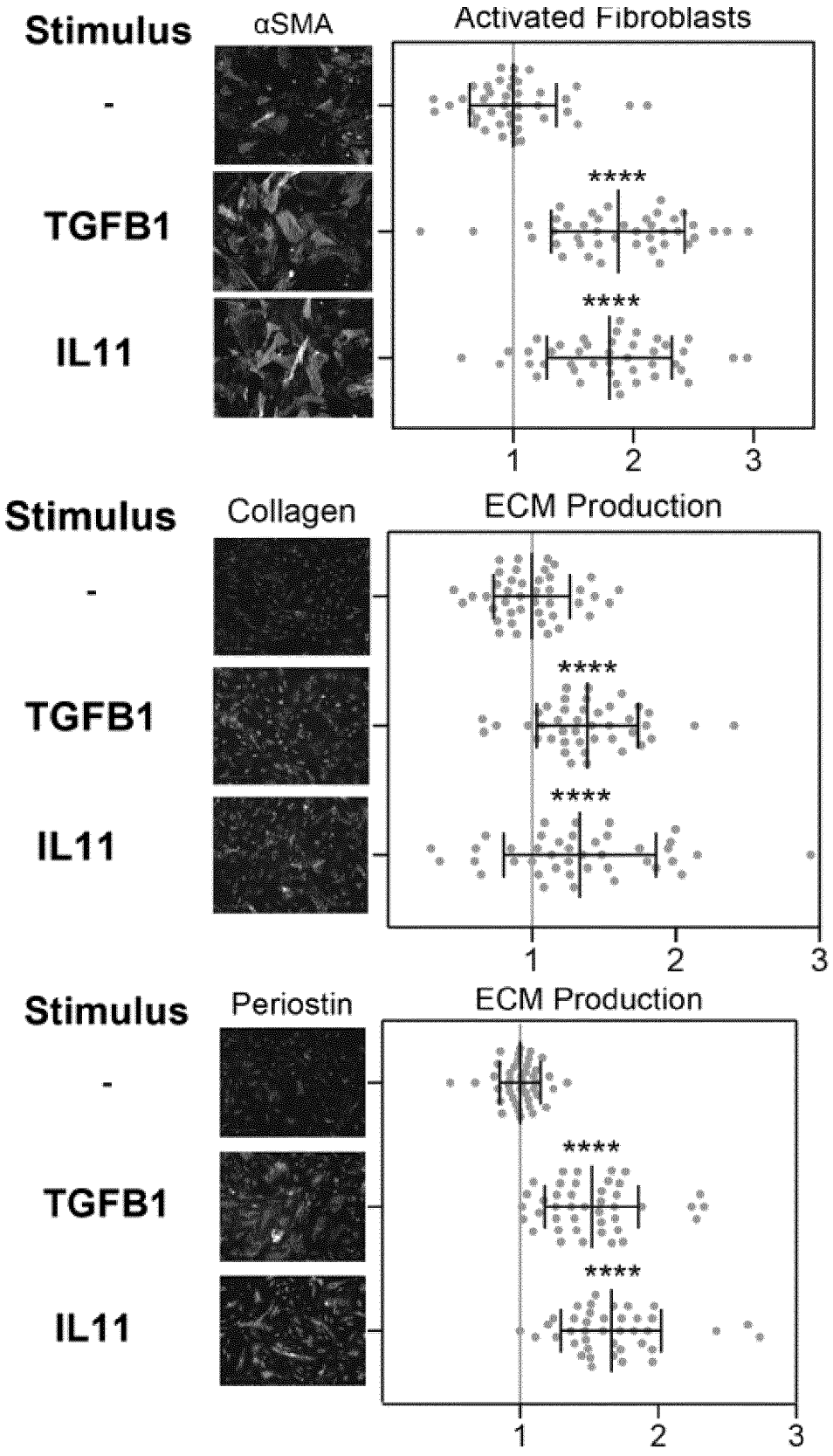

Stimulus
αSMA
Activated Fibroblasts
-
TGFB1
IL11
****
****
1
2
3
Stimulus
Collagen
ECM Production
-
TGFB1
IL11
****
****
1
2
3
Stimulus
Periostin
ECM Production
-
TGFB1
IL11
****
****
1
2
3

Figure 5A

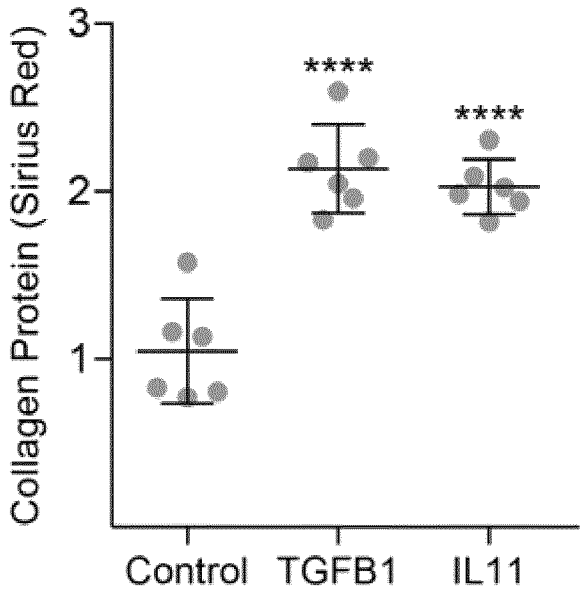


Figure 5B

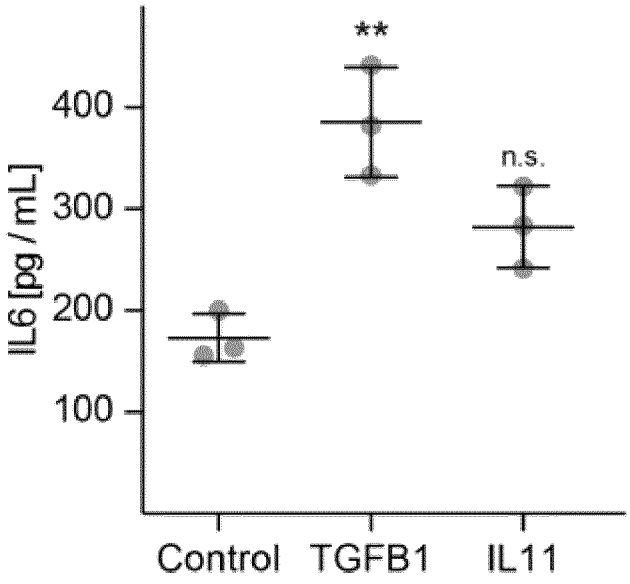


Figure 5C

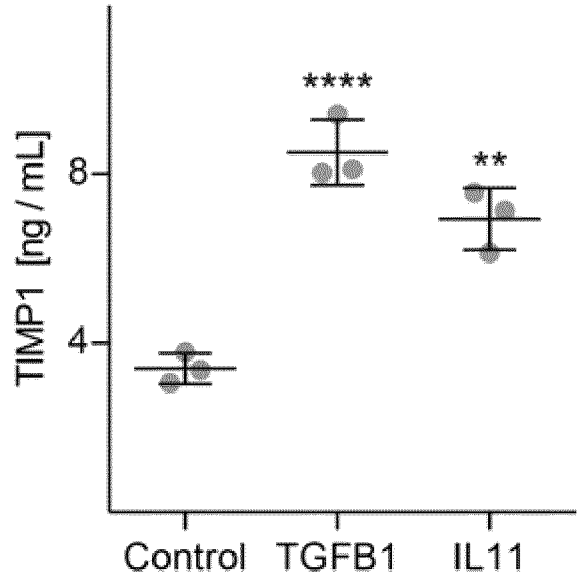


Figure 5D

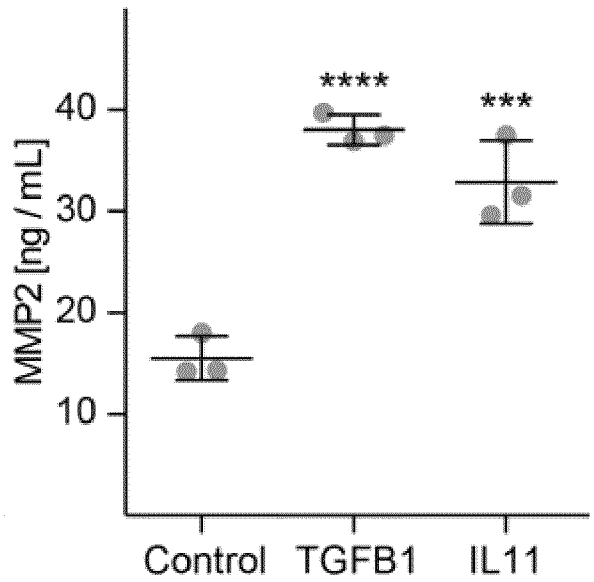


Figure 5E

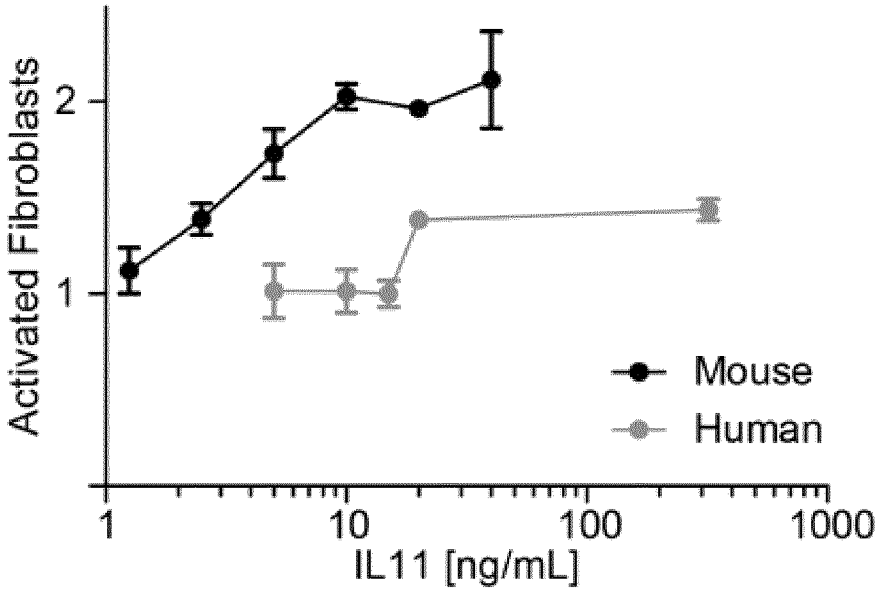

Activated Fibroblasts
2
1
Mouse
Human
1
10
100
1000
IL11 [ng/mL]

Figure 5F

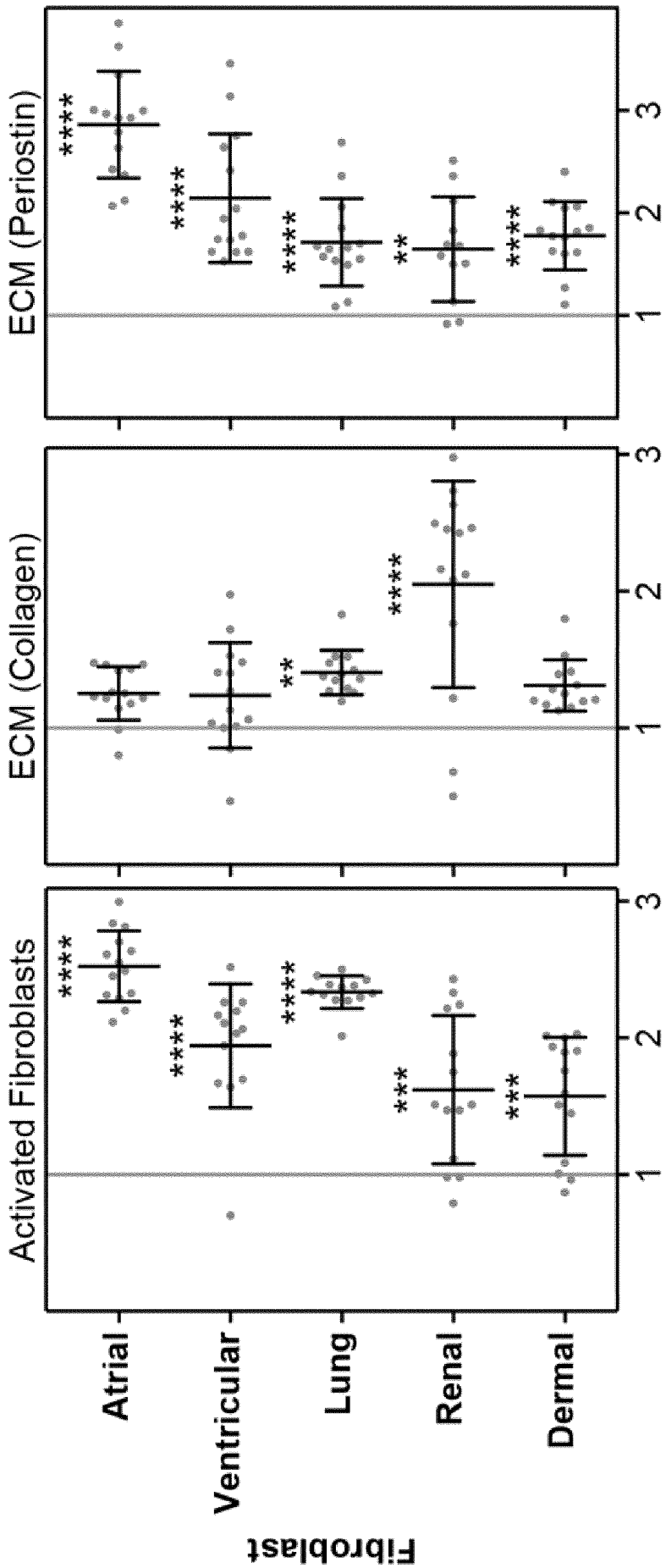

Activated Fibroblasts
ECM (Collagen)
ECM (Periostin)
****
****
****
***
***
**
****
****
****
**
****
1
2
3
Atrial
Ventricular
Lung
Renal
Dermal
Fibroblast

Figure 6A

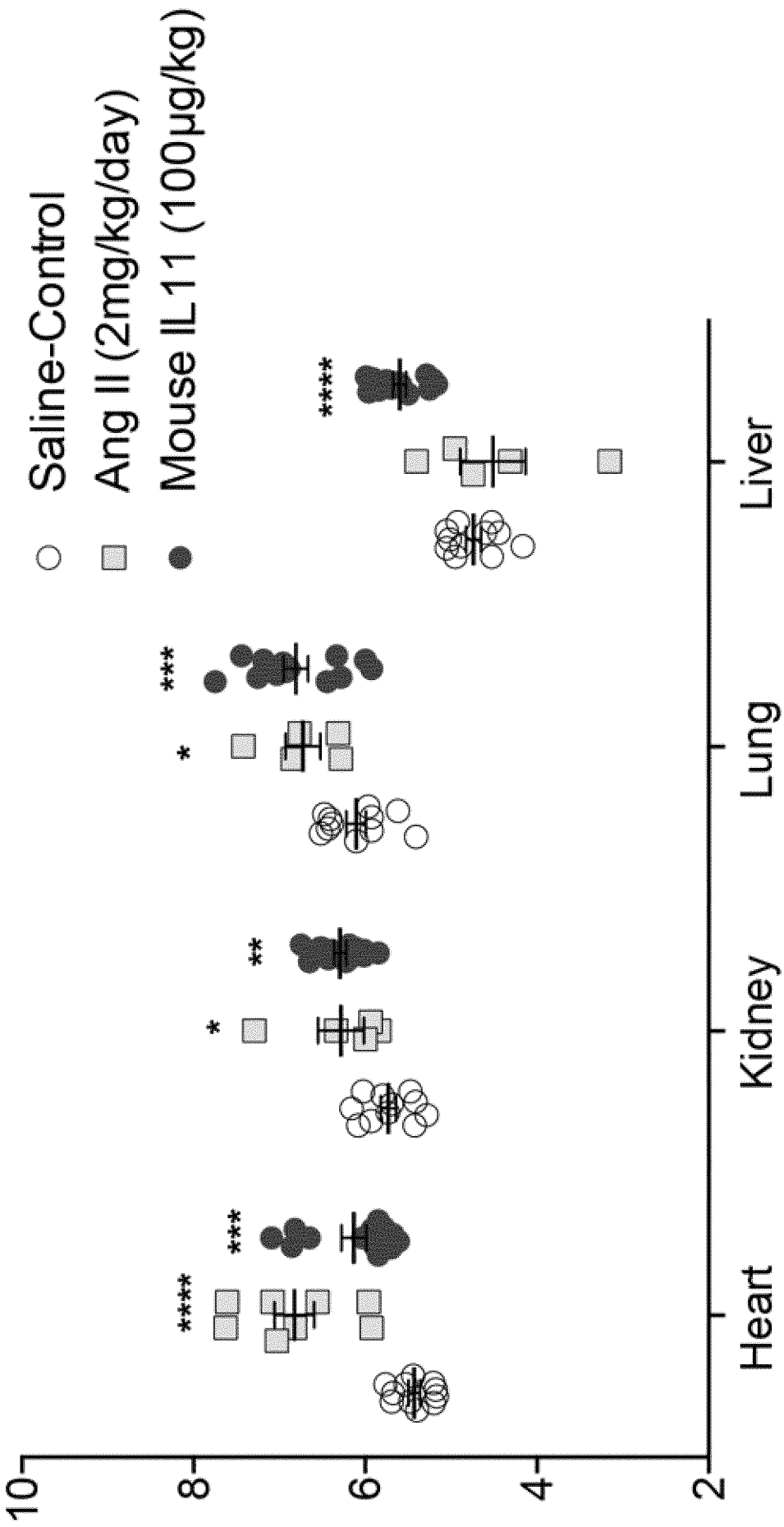

Saline-Control
Ang II (2mg/kg/day)
Mouse IL11 (100µg/kg)
10
8
6
4
2
Heart
Kidney
Lung
Liver
****
***
**
*
*
***
*
****

Figure 6B

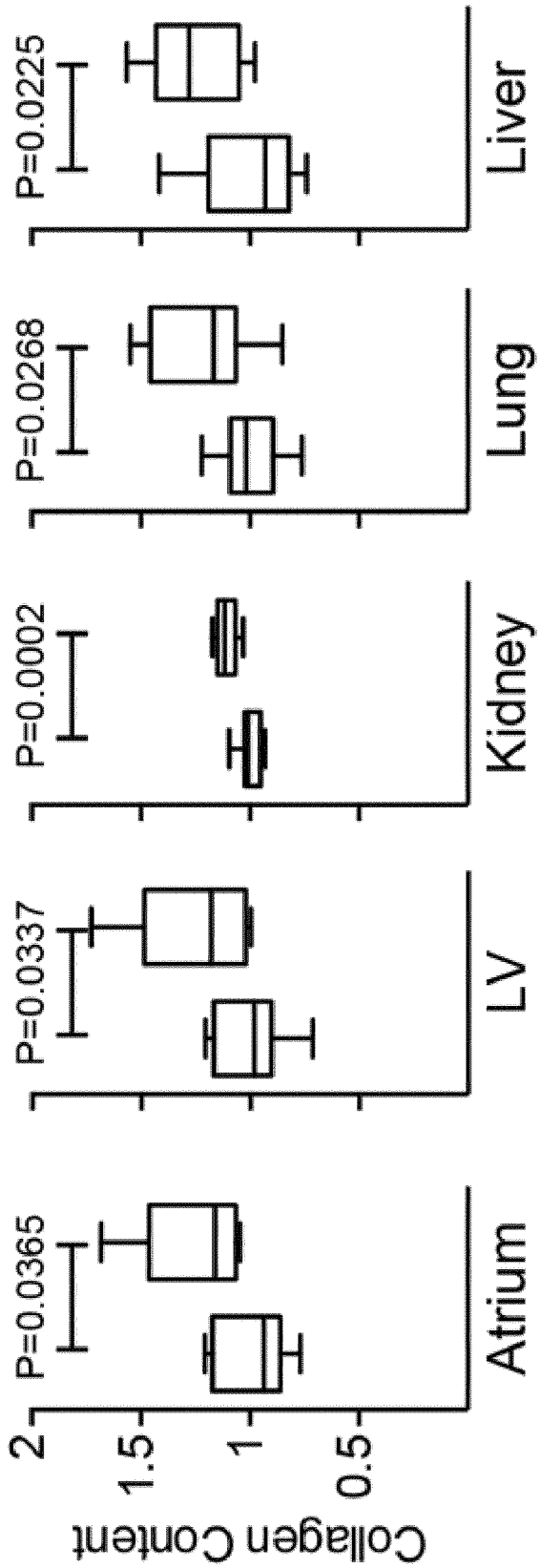

Collagen Content
2
1.5
1
0.5
P=0.0365
Atrium
P=0.0337
LV
P=0.0002
Kidney
P=0.0268
Lung
P=0.0225
Liver

Figure 6C

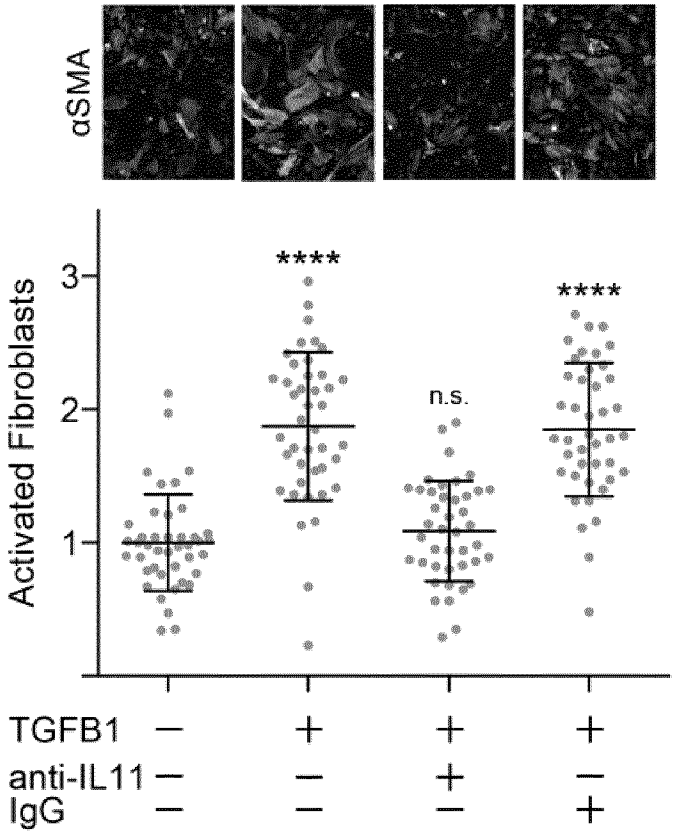


Figure 7A

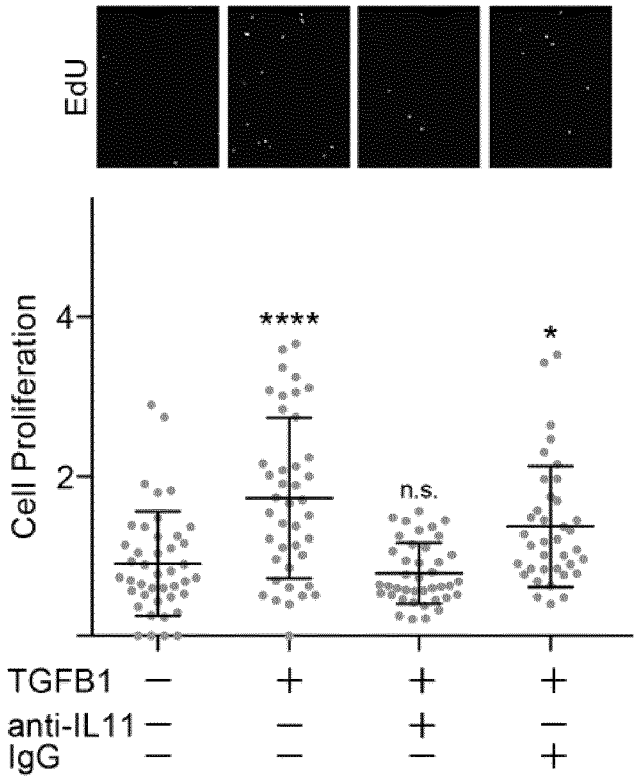


Figure 7B

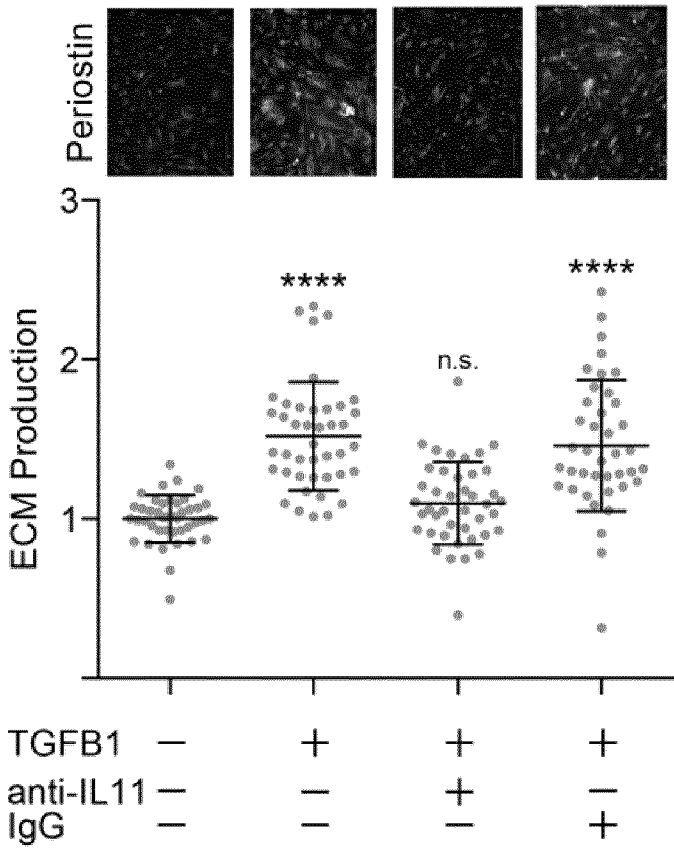


Figure 7C

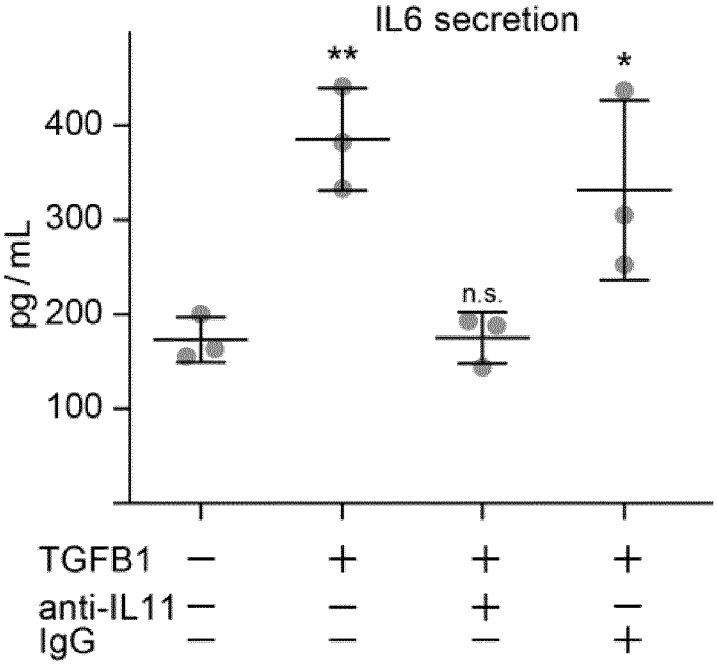


Figure 7D

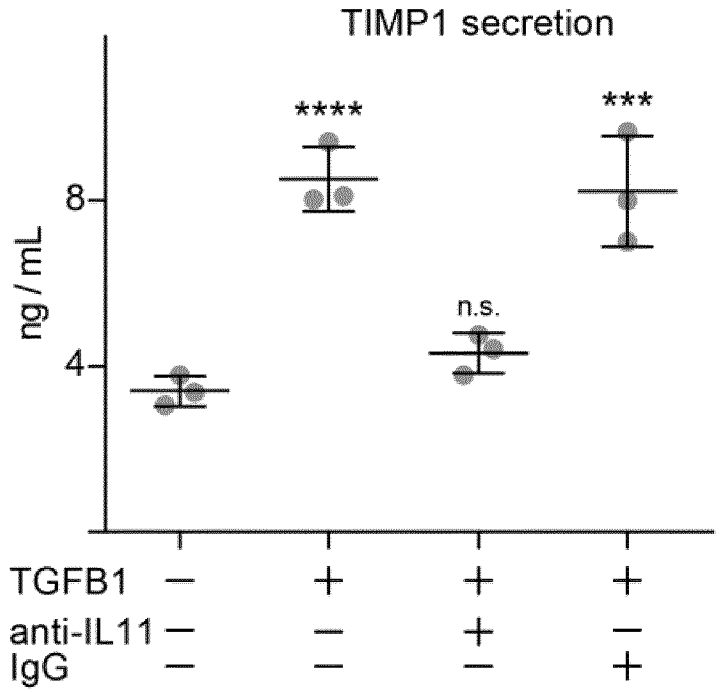


Figure 7E

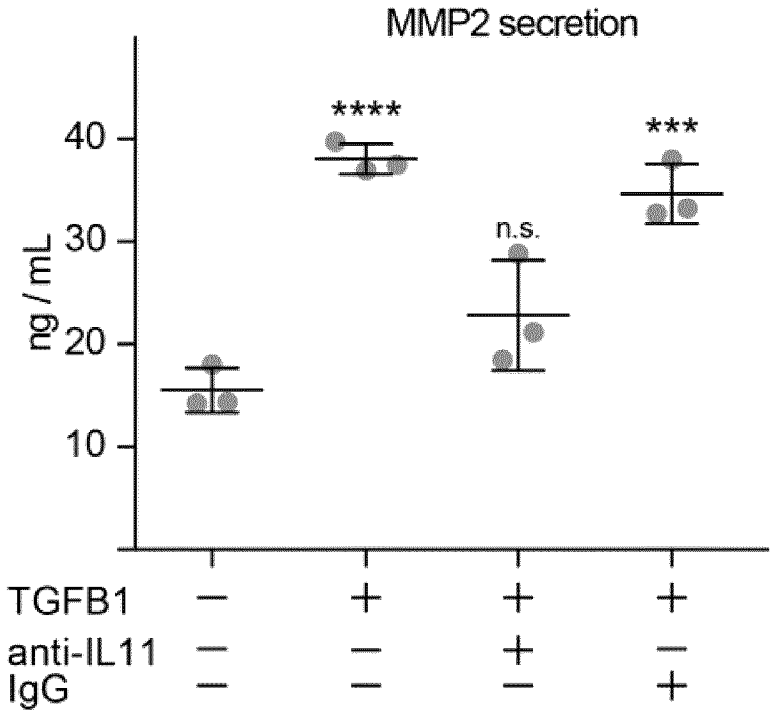


Figure 7F

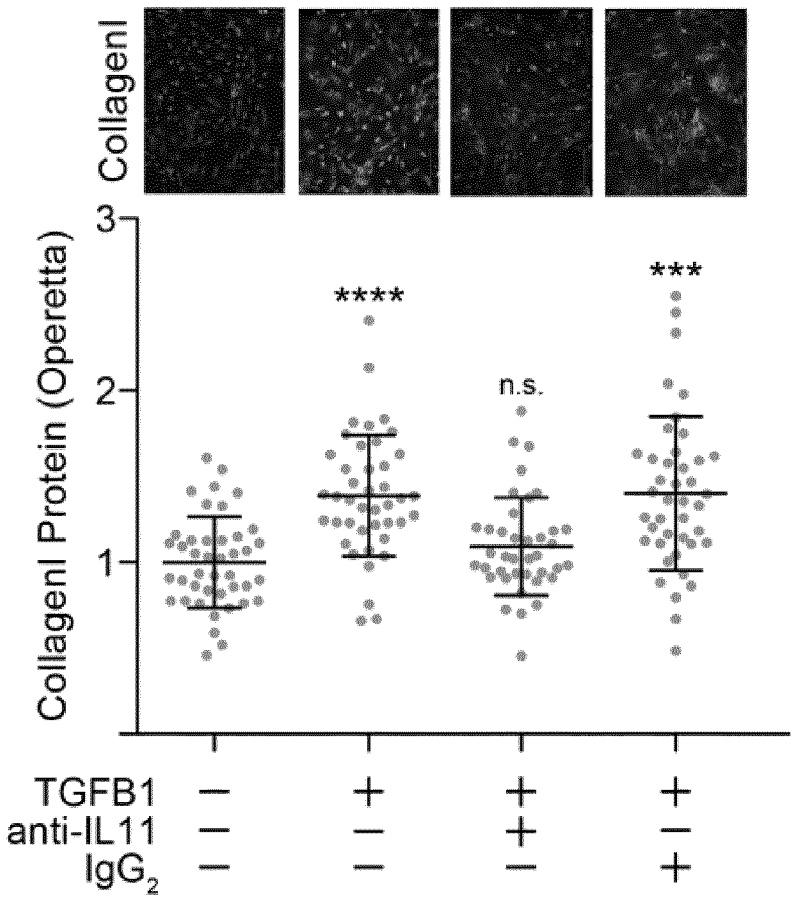


Figure 8A

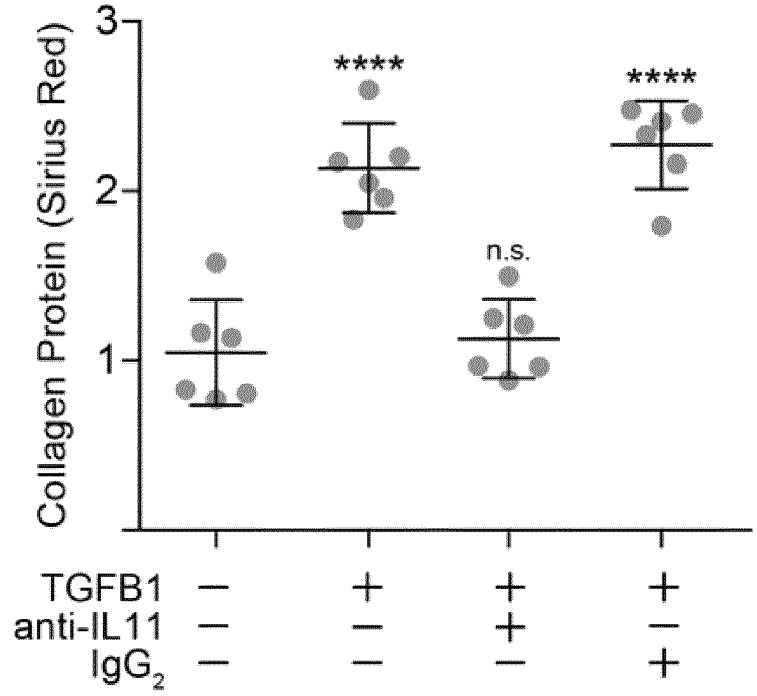


Figure 8B

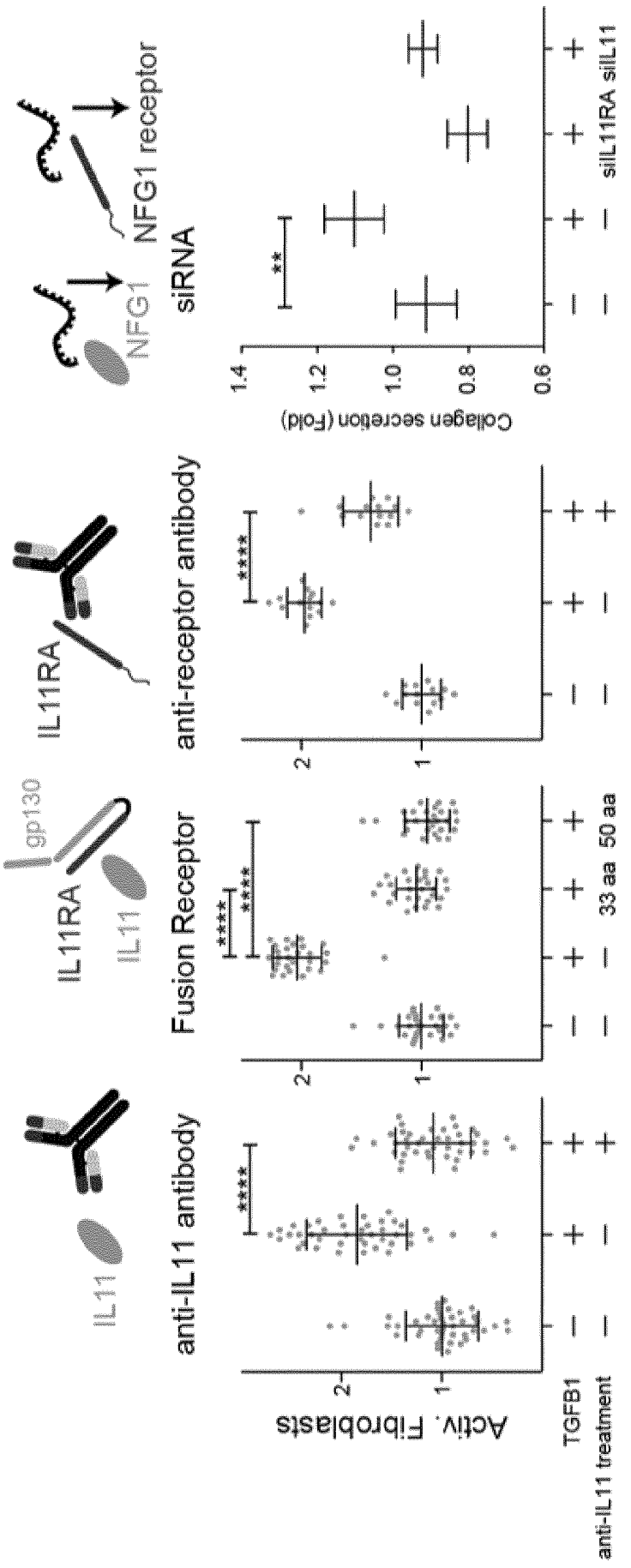

IL11
anti-IL11 antibody
IL11RA
gp130
IL11
Fusion Receptor
IL11RA
anti-receptor antibody
NFG1
NFG1 receptor
siRNA
Activ. Fibroblasts
Collagen secretion (Fold)
TGFB1
anti-IL11 treatment
33 aa
50 aa
linker between
gp130 & IL11RA
siIL11RA
siIL11

Figure 9

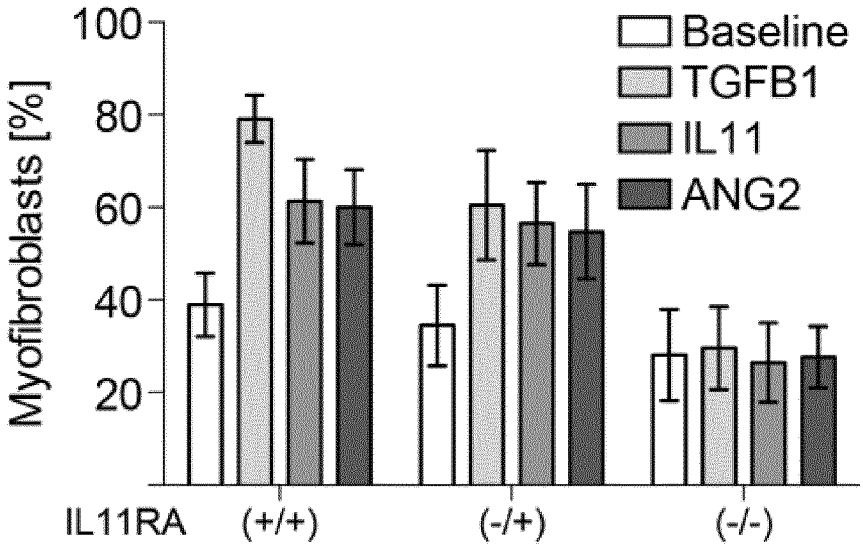


Figure 10A

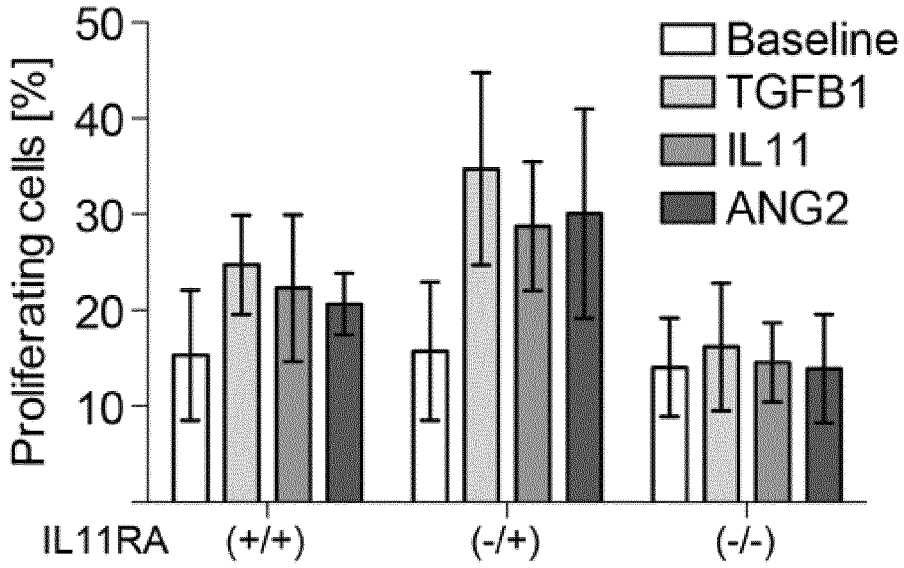


Figure 10B

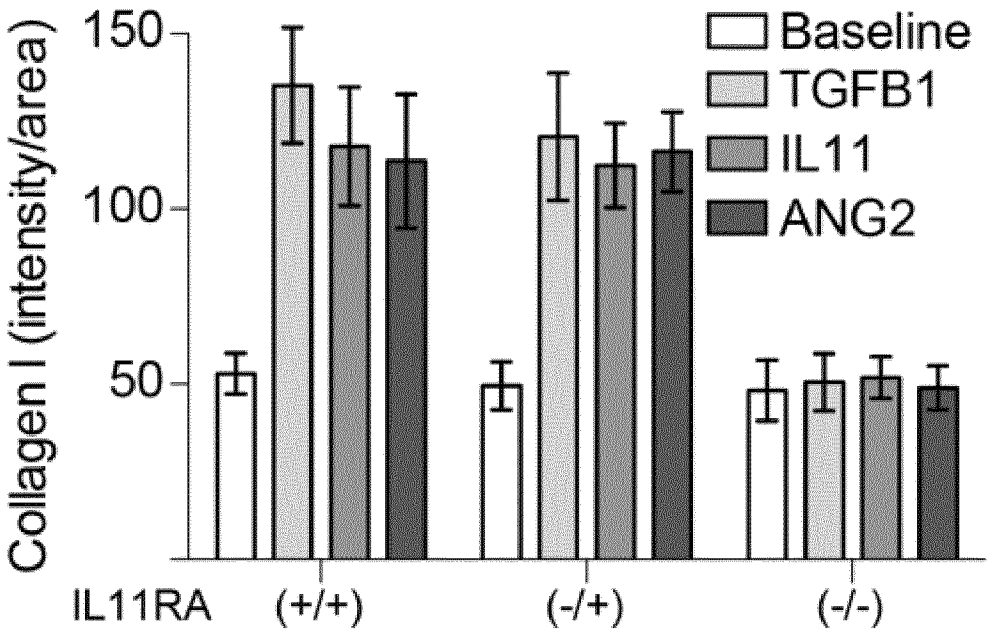


Figure 10C

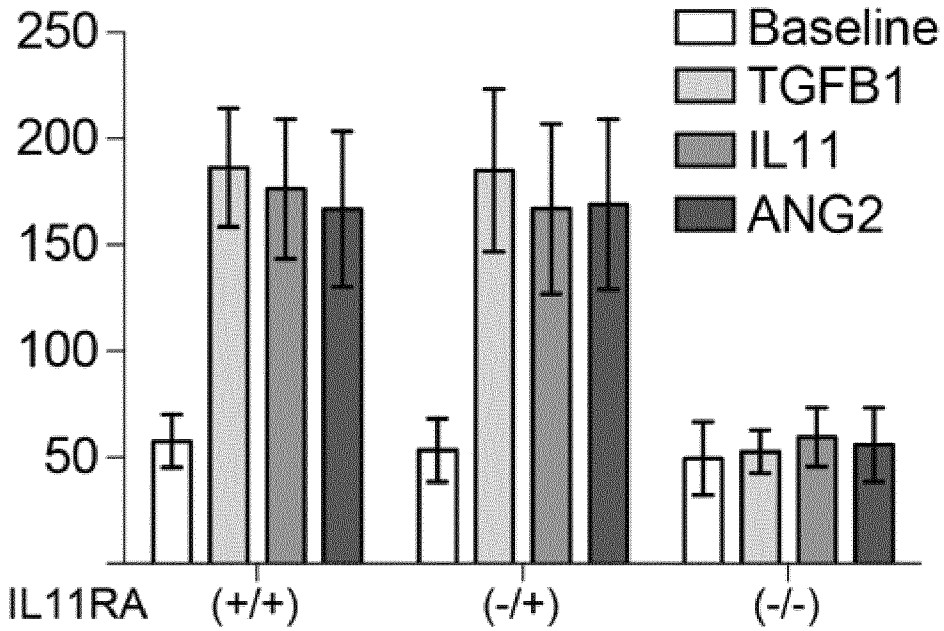


Figure 10D

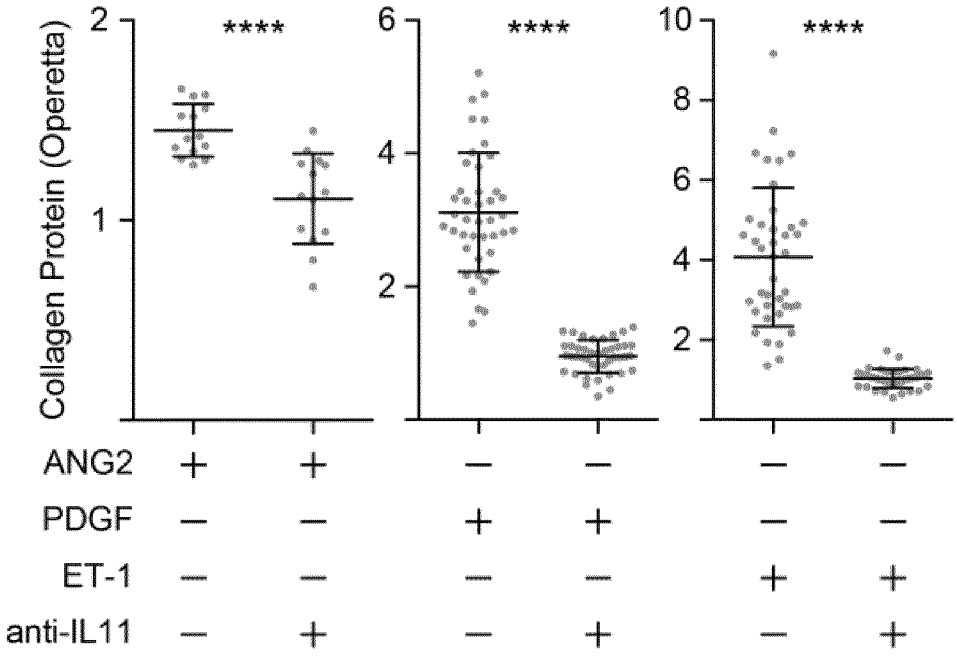


Figure 11A

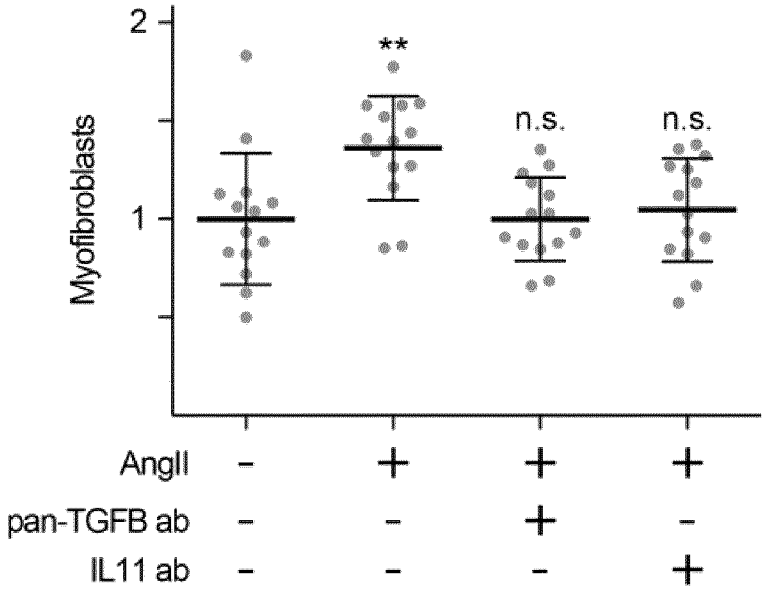


Figure 11B

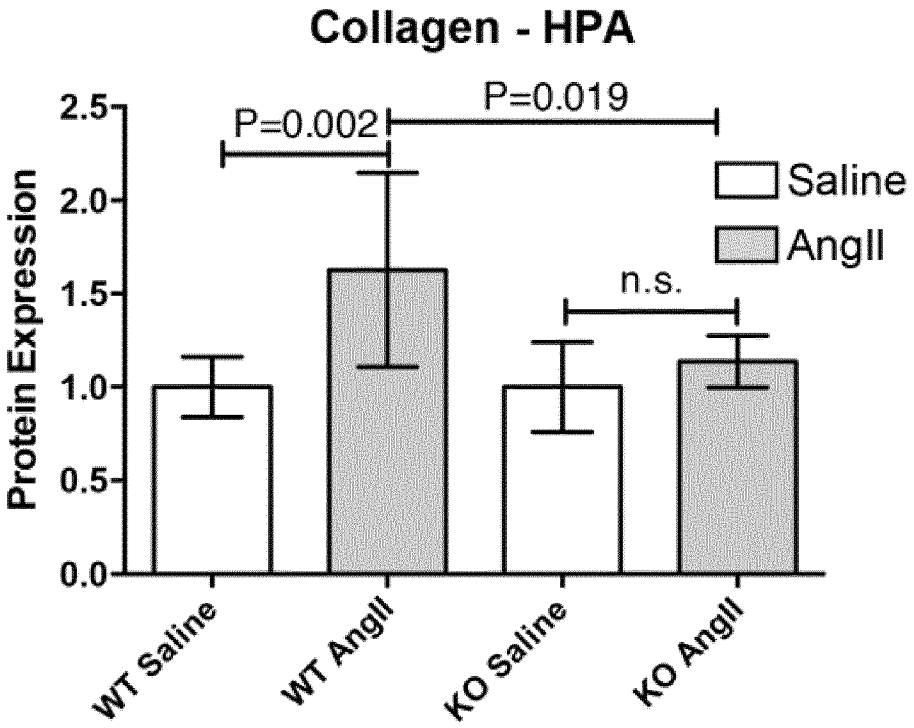


Figure 12A

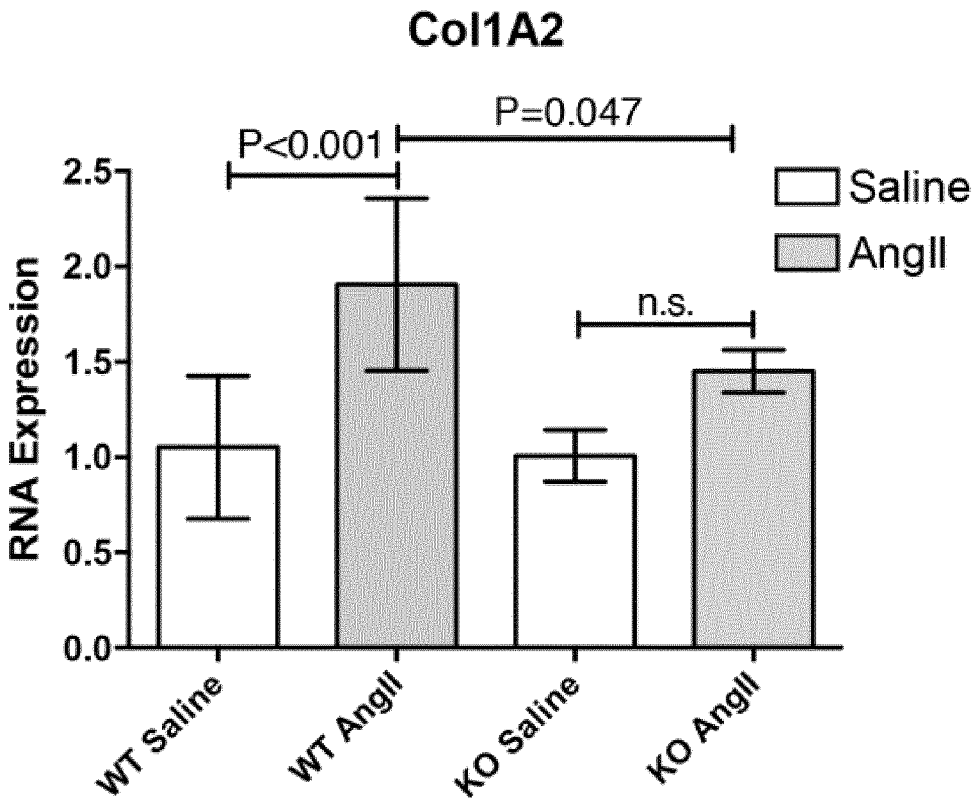


Figure 12B

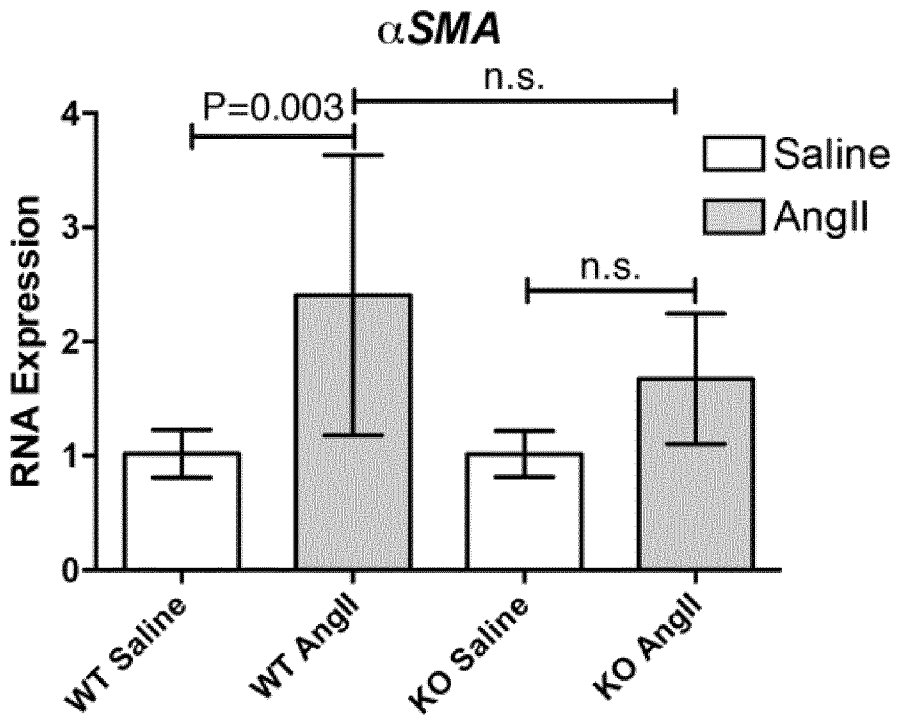


Figure 12C

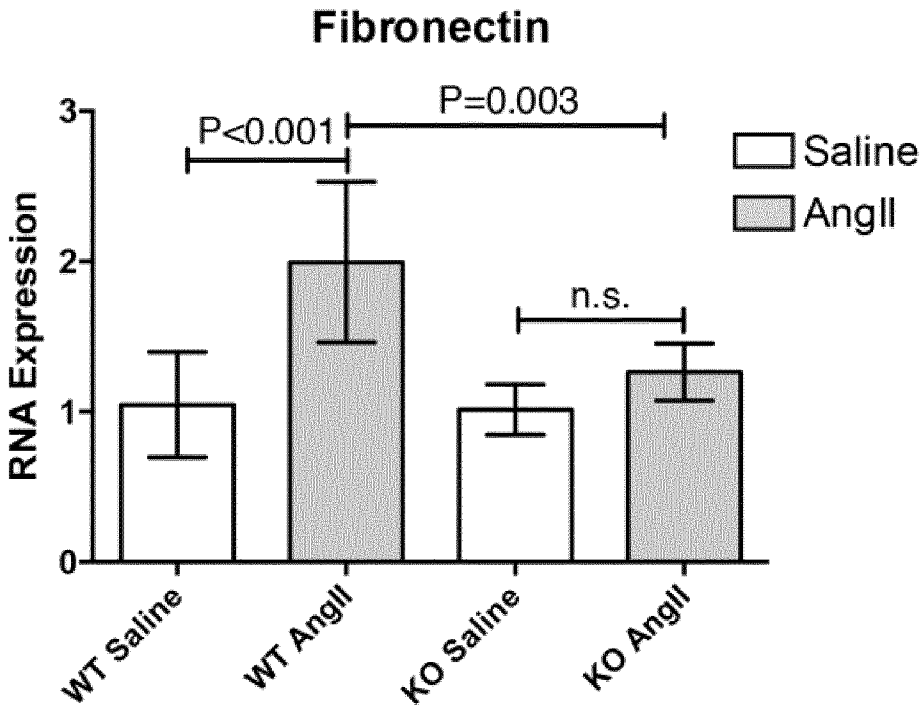


Figure 12D

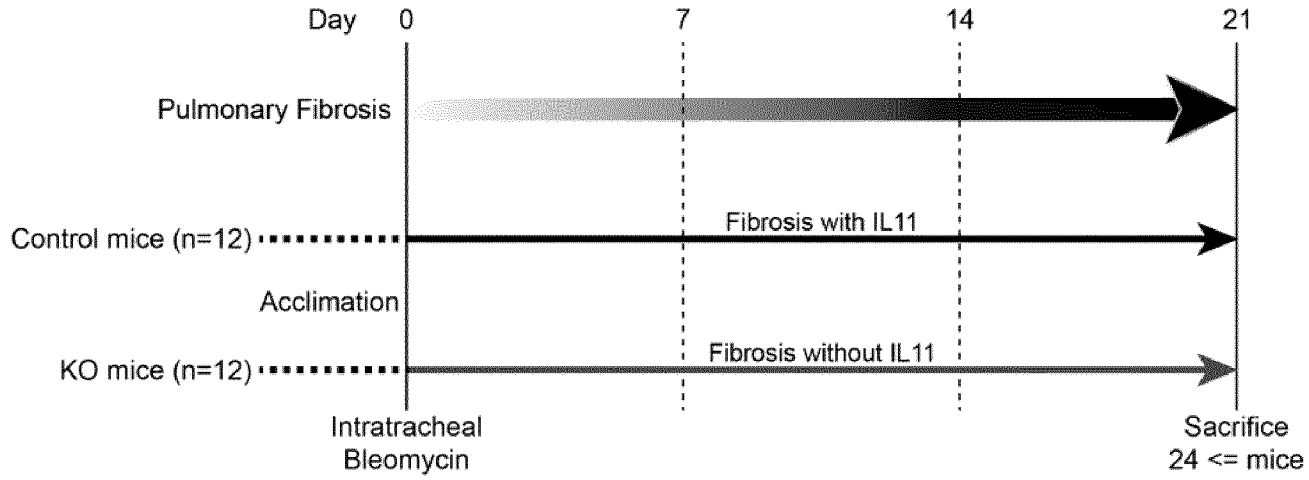


Figure 13A

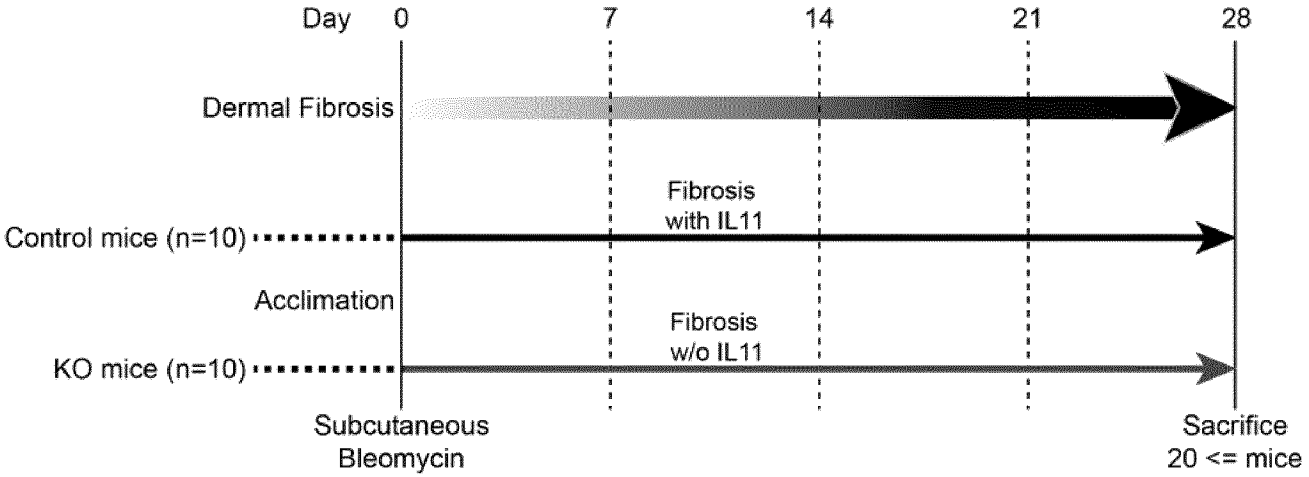


Figure 13B

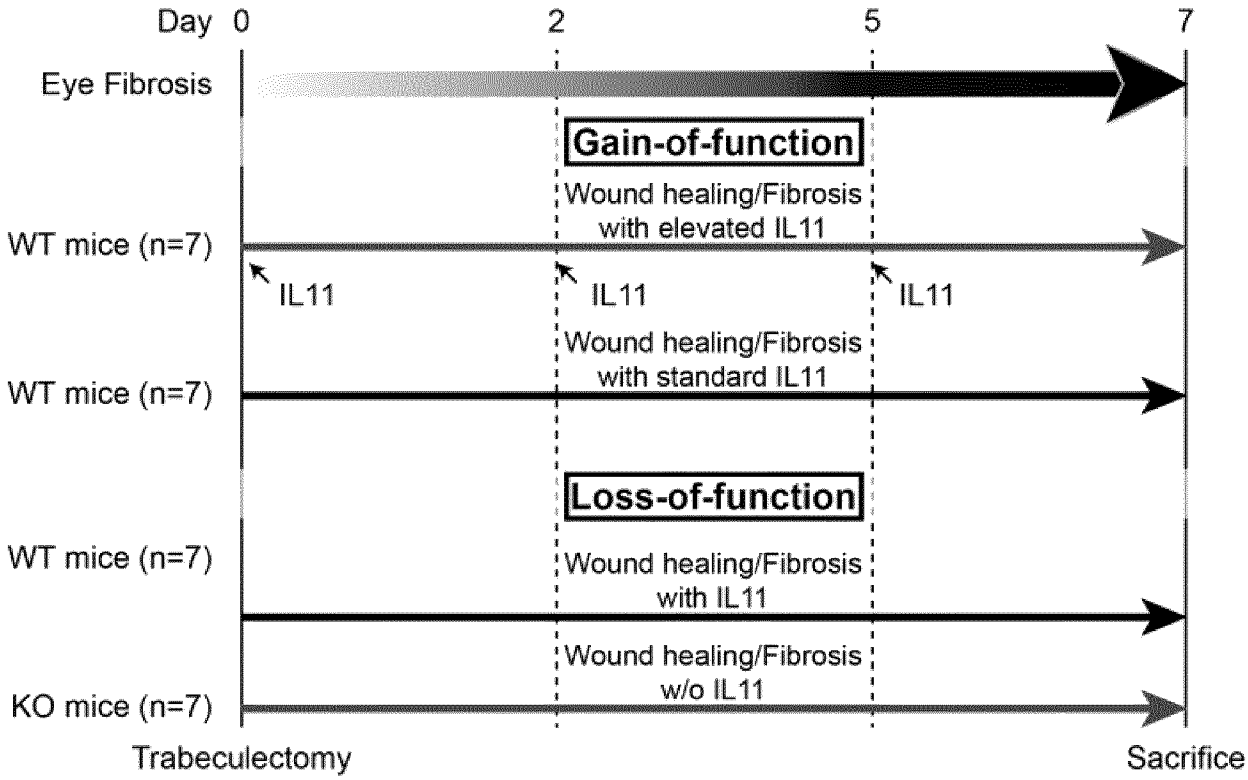

Day 0
2
5
7
Eye Fibrosis
Gain-of-function
Wound healing/Fibrosis with elevated IL11
WT mice (n=7)
IL11
IL11
IL11
Wound healing/Fibrosis with standard IL11
WT mice (n=7)
Loss-of-function
WT mice (n=7)
Wound healing/Fibrosis with IL11
Wound healing/Fibrosis w/o IL11
KO mice (n=7)
Trabeculectomy
Sacrifice

Figure 13C

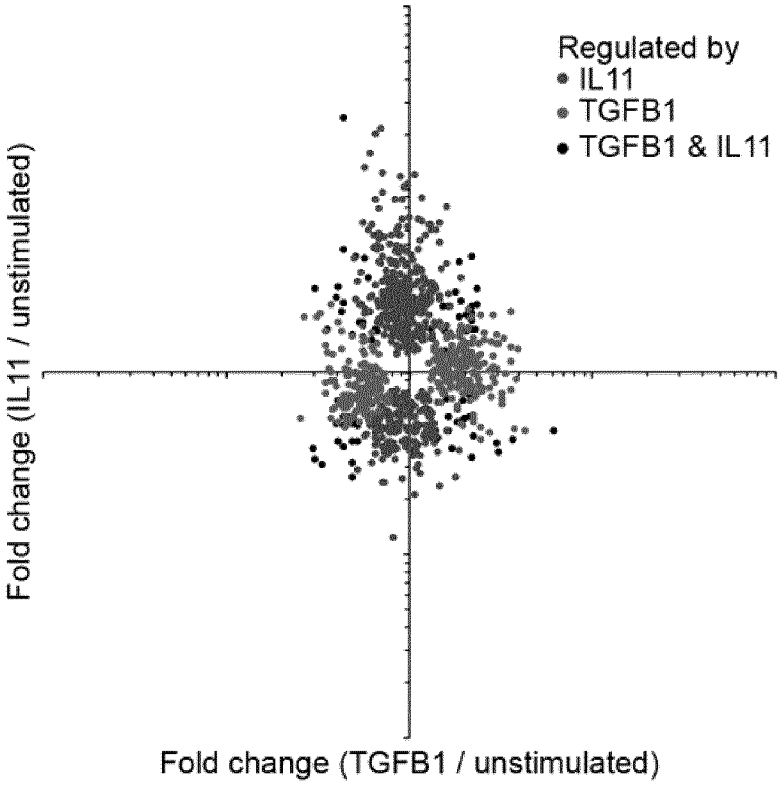


Figure 14A

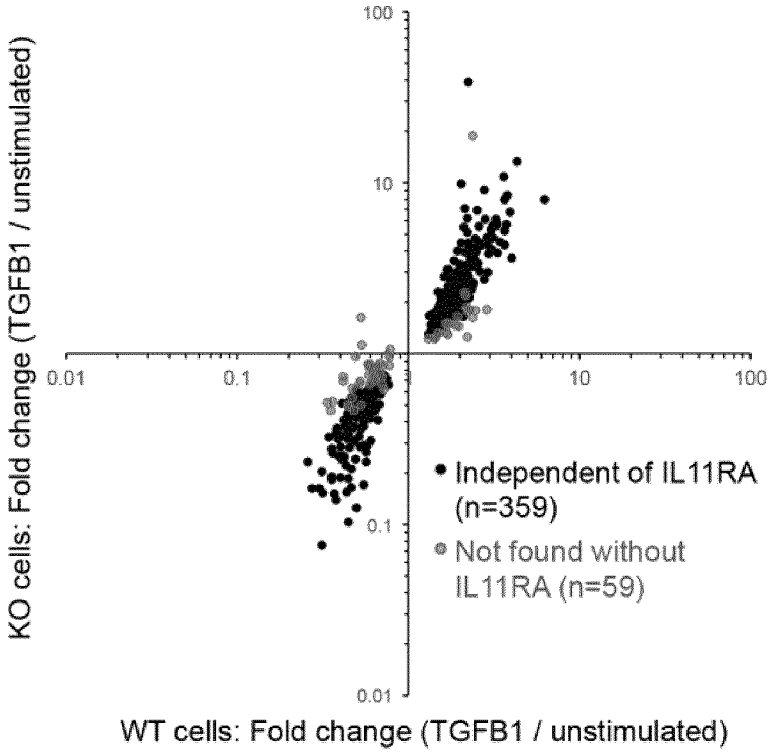


Figure 14B

YU33-A2

DVVMTQSPSSLSASVGDRVTITCRASQDVGRYVAWYQQKVGKVPRLLIYAASALQSGVPS
RFSGTASETSFTLTISSLQPEDVASYYCQQYRSAPLAFGGGTGVEIK (SEQ ID NO:1)

LC-CDR1: QDVGRY (SEQ ID NO:101)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQYRSAPLA (SEQ ID NO:103)

YU33-B3/H3

LPVLTQPHSVSESPGRTVTISCTRNTGNIASNRVQWYQQRPASAPTVVIYDNHQRPSGVPD
RFSGSIDTSPNSAYLTISGLKTEDEADYYCQSYDYSSVIFGGGTQLTVL (SEQ ID NO:2)

LC-CDR1: TGNIASNR (SEQ ID NO:104)
LC-CDR2: DNH (SEQ ID NO:105)
LC-CDR3: QSYDYSSVI (SEQ ID NO:106)

YU33-B4/YU45-G2/A3

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTIFGLQAEDEADYYCSSYTSSSSWVFGGGTKLTVL (SEQ ID NO:3)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109)

YU33-E6

QSALTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHPGKAPKLMIYEVSHRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSNTLVFGGGTKLTVL (SEQ ID NO:4)

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVS (SEQ ID NO:111)
LC-CDR3: SSYTSSNTLV (SEQ ID NO:112)

Figure 15

YU45-C11/A10

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTVVFGGGTKLTVL (SEQ ID NO:5)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113)

YU45-D11/F11

QSALTQPASVSGSPGQSITISCTGTSSDIGAYNYVSWYQQHPGKAPKLMIYDVSHRPSGVS
NRFSGSKSGNAASLTISGVQAEDGADYYCSSYTTSSTVVFGGGTQLTVL (SEQ ID NO:6)

LC-CDR1: SSDIGAYNY (SEQ ID NO:114)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTTSSTVV (SEQ ID NO:115)

YU45-E11/E12

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPD
RFSGSKSGTSASLAISGLRSEDEADYYCAAWDGSLSGWVFGGGTKLTVL (SEQ ID NO:7)

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118)

YU45-H11/D12

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL (SEQ ID NO:8)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119)

Figure 15 (Cont.)

YU45-A12/G10

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPD RFSGSKSGTSASLAISGLRSEDEADYYCAAWDGSLSGWVFGGGTKLTVL (SEQ ID NO:9)

LC-CDR1: SSNIGSNY (SEQ ID NO:116)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDGSLSGWV (SEQ ID NO:118)

YU45-G1

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTVSGLQAEDEADYYCCSYAGSYTFVFGGGTKLTVL (SEQ ID NO:10)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTFV (SEQ ID NO:120)

YU45-C2/A7/B10

QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSRSGNTASLTISGLQAEDEADYYCNSYTSSTPYVFGTGTKVTVL (SEQ ID NO:11)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSTPYV (SEQ ID NO:121)

YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:12)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

Figure 15 (Cont.)

YU45-E3

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:13)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU45-C8/E8

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMVYDVSNRPSGV SDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSNTQVFGGGTKLTVL (SEQ ID NO:14)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSNTQV (SEQ ID NO:125)

YU45-F8

QPVLTQPPSVSAAPGQKVTISCSGSSSNIGNNLVYWYQQLPGTAPKLLIYRNNQRPSGVPD RFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSAGVFGGGTKLTAL (SEQ ID NO:15)

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127)

YU45-G8/H6

QSALTQPASVSGSPGQSITISCTGTSSDVGGYDYVSWYQQHPGTAPKLMISDVHNRPLGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSITWVFGGGTKLTVL (SEQ ID NO:16)

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVH (SEQ ID NO:129)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130)

Figure 15 (Cont.)

YU45-F9

QSALTQPRSVSRSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:17)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU45-H10

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL (SEQ ID NO:18)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119)

YU46-A10

QPVLTQPPSVSAAPGQKVTISCSGSSSNIGNNLVYWYQQLPGTAPKLLIYRNNQRPSGVPD RFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSAGVFGGGTKLTAL (SEQ ID NO:19)

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127)

YU45-F2

QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKVMIYDVSKRPSG VPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:20)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 15 (Cont.)

YU45-H3

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTVVFGGGTKLTVL (SEQ ID NO:21)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTVV (SEQ ID NO:113)

YU45-A1

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTWVFGGGTKLTVL (SEQ ID NO:22)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: GSYTSSSTWV (SEQ ID NO:132)

YU45-A8/C6

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVGNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSGSTWVFGGGTKLTVL (SEQ ID NO:23)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: SSYTSGSTWV (SEQ ID NO:134)

YU45-B5/A4

QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVNKRPSGV PDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGTNNFVVFGGGTKLTVL (SEQ ID NO:24)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: EVN (SEQ ID NO:135)
LC-CDR3: SSYAGTNNFVV (SEQ ID NO:136)

Figure 15 (Cont.)

YU45-C3/A6

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:25)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU45-D1

ETTLTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASSRATGIPAR FSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEFK (SEQ ID NO:26)

LC-CDR1: QSVSSN (SEQ ID NO:137)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139)

YU45-D9/D3

QSVLTQPPSVSAAPGQEVTISCSGSSSNIGNNYVSWYQHLPGTAPKLLIYDNTERPSGIPDR FSGSRSGTSVTLGITGLQTGDEADYYCGTWDSSLSGGVFGGGTKLTVL (SEQ ID NO:27)

LC-CDR1: SSNIGNNY (SEQ ID NO:140)
LC-CDR2: DNT (SEQ ID NO:141)
LC-CDR3: GTWDSSLSGGV (SEQ ID NO:142)

YU45-E5

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWGVRRRDRADRP (SEQ ID NO:28)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143)

Figure 15 (Cont.)

YU45-G7

QSVLTQPPSVSAAPGRTVTISCSGSYSNVGSNLVSWYQQLPGTAPKLVIYEDDKRLSGIPD RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLKGHVFGGGTQLTVL (SEQ ID NO:29)

LC-CDR1: YSNVGSNL (SEQ ID NO:144)
LC-CDR2: EDD (SEQ ID NO:145)
LC-CDR3: AAWDDSLKGHV (SEQ ID NO:146)

YU45-B4

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYINNQRPSGVPD RFSGSKSGTSASLAISGLQSEDETDYYCAAWDDSLNGWVFGGGTKLTVL (SEQ ID NO:30)

LC-CDR1: SSNIGSNT (SEQ ID NO:147)
LC-CDR2: INN (SEQ ID NO:148)
LC-CDR3: AAWDDSLNGWV (SEQ ID NO:149)

YU45-H4

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTAL (SEQ ID NO:31)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU45-B6

QSALTQPRSVSGSPGQSVTISCTGTSRDVGGYNYVSWYQQHPGEAPKLMIFDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYADYYTWVFGGGTKVTVL (SEQ ID NO:32)

LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYADYYTWV (SEQ ID NO:151)

Figure 15 (Cont.)

YU45-D6

QPVLTQPPSVSAAPGQKVTISCSGSSSNIGNNLVYWYQQLPGTAPKLLIYRNNQRPSGVPD
RFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSAGVFGGGTKLTAL (SEQ ID NO:33)

LC-CDR1: SSNIGNNL (SEQ ID NO:126)
LC-CDR2: RNN (SEQ ID NO:117)
LC-CDR3: AAWDDSLSAGV (SEQ ID NO:127)

YU45-E7

LPVLTQPHSVSESPGKTVTISCTGSSGSIASNYVQWYQQRPGSAPTTVIYDDNQRPSGVPD
RFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSNLWVFGGGTKLTVL (SEQ ID NO:34)

LC-CDR1: SGSIASNY (SEQ ID NO:152)
LC-CDR2: DDN (SEQ ID NO:153)
LC-CDR3: QSYDSSNLWV (SEQ ID NO:154)

YU45-F5

DIQMTQSPSFLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTWTFGQGTKVEIK (SEQ ID NO:35)

LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156)

YU45-H7/46-B5

QSALTQPPSASGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL (SEQ ID NO:36)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119)

Figure 15 (Cont.)

YU46-G1

LPVLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPTTVIYEDNQRPSGVPD RFSGSIDSSSNSASLTISGLRTEDEADYYCQSYNSSKVVFGGGTKLTVL (SEQ ID NO:37)

LC-CDR1: SGSIASNY (SEQ ID NO:152)
LC-CDR2: EDN (SEQ ID NO:157)
LC-CDR3: QSYNSSKVV (SEQ ID NO:158)

YU46-A2

QSALTQPRSVSGSPGQSITISCTGTSSDVGGYEYVSWYQQHPGKAPRLLIYDVSNRPSGVS NRFSGSKSGNTASLTVSGLQAEDEADYYCNSYTSSGTLVVFGGGTKLTVL (SEQ ID NO:38)

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160)

YU46-A8

QSALTQPRSVSGSPGQSITISCTGTSSDVGGYEYVSWYQQHPGKAPRLLIYDVSNRPSGVS NRFSGSKSGNTASLTVSGLQAEDEADYYCNSYTSSGTLVVFGGGTKLTVL (SEQ ID NO:39)

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYTSSGTLVV (SEQ ID NO:160)

YU46-B2

QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:40)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 15 (Cont.)

YU46-B6

SSELTQDPAVSVALGQTVRITCQGDSLRGYYATWYQQKPGQAPVVVMYGNNNRPSGIPD
RFSGSSSGNTASLTITGAQAEDEADYYCDSRGRSGDHWLFGGGTKLTVL (SEQ ID NO:41)

LC-CDR1: SLRGYY (SEQ ID NO:161)
LC-CDR2: GNN (SEQ ID NO:162)
LC-CDR3: DSRGRSGDHWL (SEQ ID NO:163)

YU46-C1

QAVLTQPPSASGTPGQRVSISCSGSSSNIGSYYVYWYQQVPGTAPKILIYRNDERPSGVPD
RFSGSKSGTSASLAISGLRSEDEAHYYCATWDDGLSGWVFGGGTKLTVL (SEQ ID NO:42)

LC-CDR1: SSNIGSYY (SEQ ID NO:164)
LC-CDR2: RND (SEQ ID NO:165)
LC-CDR3: ATWDDGLSGWV (SEQ ID NO:166)

YU46-D7

QSVLTQPPSASGSPGQSVTISCAGTSSDVGAYNYVAWYQQHPGKAPKLIISEVFRRPSGVP
DRFSGSKSGTTAFLTVSGLQADDEAVYFCNSYVTGNNWAFGGGTKLTVL (SEQ ID NO:43)

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: EVF (SEQ ID NO:168)
LC-CDR3: NSYVTGNNWA (SEQ ID NO:169)

YU46-E3

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV
SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL (SEQ ID NO:44)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTWV (SEQ ID NO:119)

Figure 15 (Cont.)

YU46-E7

QSVLTQPPSASGTPGQRVTISCSGSSSNIGYDAVNWYQQLPGTAPKLVISNDNRRPSGVPA
RFSGSKSGTSASLAISGLQSEDEAYYYCAAWDDSLSGWVFGGGTKLTVL (SEQ ID NO:45)

LC-CDR1: SSNIGYDA (SEQ ID NO:170)
LC-CDR2: NDN (SEQ ID NO:171)
LC-CDR3: AAWDDSLSGWV (SEQ ID NO:172)

YU46-H8

DIQMTQSPSSLSASVGDRVTITCRASQGSSSYLAWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLYTFGQGTKLEIK (SEQ ID NO:46)

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174)

YU46-G9

QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYKYVSWYQQHPGKAPELIIYDVSKRPSGVP
DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGNYTWLFGGGTKVTVL (SEQ ID NO:47)

LC-CDR1: SSDVGGYKY (SEQ ID NO:175)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGNYTWL (SEQ ID NO:176)

YU46-G8

DIQMTQSPSSLSASVGDRVTITCRASQGSSSYLAWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLYTFGQGTKLEIK (SEQ ID NO:48)

LC-CDR1: QGSSSY (SEQ ID NO:173)
LC-CDR2: AAS(SEQ ID NO:102)
LC-CDR3: QQSYSTPLYT (SEQ ID NO:174)

Figure 15 (Cont.)

YU46-B7

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCTSYSSSSTLVAFGGGTKLTVL (SEQ ID NO:49)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: TSYSSSSTLVA (SEQ ID NO:177)

YU46-D3

QSALTQPASVSGSPGQSITISCTGTSSDVGNYKYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVVFGGGTKLTVL (SEQ ID NO:50)

LC-CDR1: SSDVGNYKY (SEQ ID NO:178)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSTLVV (SEQ ID NO:179)

Figure 15 (Cont.)

YU33-A2

QLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYN DYAVSVKSRITINPDTSKNQFTLQLNSVTPDDTAVYYCARGTRGYFDYWGQGTLVTVSS (SEQ ID NO:51)

HC-CDR1: VSSNSAAWN (SEQ ID NO:180)
HC-CDR2: YRSKWYN (SEQ ID NO:181)
HC-CDR3: ARGTRGYFDY (SEQ ID NO:182)

YU33-B3/H3

EVQLVESGGGFVKPGGSLSISCAASGFTFSGAYMNWVRQAPGKGLEWVAVISYDGSNKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLYAFDIWGQGTMVTVSS (SEQ ID NO:52)

HC-CDR1: GFTFSGAY (SEQ ID NO:183)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDLYAFDI (SEQ ID NO:185)

YU33-B4/YU45-G2/A3

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:53)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU33-E6

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSDK YYADSVKGRFTISRDNSKNTVYLQMNSLRAEDTAVYYCAKDLSGLPIIDYWGQGTLVTVSS (SEQ ID NO:54)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSDK (SEQ ID NO:188)
HC-CDR3: AKDLSGLPIIDY (SEQ ID NO:189)

Figure 16

YU45-C11/A10

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGEGLEWVAVISYDGSNKY YADSVKGRFTISRDNAKDSLYLQMNSLRDEDTAVYYCARRGYFDYWGQGTLVTVSS (SEQ ID NO:55)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYFDY (SEQ ID NO:191)

YU45-D11/F11

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIAAADGMDVWGQGTTVTVSS (SEQ ID NO:56)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAADGMDV (SEQ ID NO:192)

YU45-E11/E12

QVQLVQSGGGVVLPGRSLRLSCAASGFSFRSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRTGDTAVYYCARITHDYGDFSDAFDIWGQGTMVA VSS (SEQ ID NO:57)

HC-CDR1: GFSFRSYG (SEQ ID NO:193)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194)

YU45-H11/D12

EVQLLESGGGVVQPGRSRRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLYSGSSNFDYWGQGTLVTVSS (SEQ ID NO:58)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195)

Figure 16 (Cont.)

YU45-A12/G10

QVQLVQSGGGVVLPGRSLRLSCAASGFTFRSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRTGDTAVYYCARITHDYGDFSDAFDIWGQGTMVA VSS (SEQ ID NO:59)

HC-CDR1: GFTFRSYG (SEQ ID NO:196)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARITHDYGDFSDAFDI (SEQ ID NO:194)

YU45-G1

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS (SEQ ID NO:60)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

YU45-C2/A7/B10

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGQNVDLWGQGTLVTVSS (SEQ ID NO:61)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGQNVDL (SEQ ID NO:198)

YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:62)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 16 (Cont.)

YU45-E3

EVQLVESGGGVVQPGRSLRLSCAASGFSFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:63)

HC-CDR1: GFSFSSYA (SEQ ID NO:212)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU45-C8/E8

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARRGYGDYWGQGTLVTVSS (SEQ ID NO:64)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARRGYGDY (SEQ ID NO:213)

YU45-F8

RSAAGGVWGRRGPAWEVPETLLCSLWIFLKSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMTSLRAEDTAVYYCARVGFSSWYPDLYYFDYWGQGTL VTVSS (SEQ ID NO:65)

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205)

YU45-G8/H6

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFARGVYLFDYWGQGTLVTVSS (SEQ ID NO:66)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215)

Figure 16 (Cont.)

YU45-F9

EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVQSGEPESDYWGQGTLVTVSS (SEQ ID NO:67)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVQSGEPESDY (SEQ ID NO:216)

YU45-H10

EVQLLESGGGVVQPGRSRRLSCAASGFSLNSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLYSGSSNFDYWGQGTLVTVSS (SEQ ID NO:68)

HC-CDR1: GFSLNSYG (SEQ ID NO:217)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLYSGSSNFDY (SEQ ID NO:195)

YU46-A10

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMTSLRAEDTAVYYCARVGFSSWYPDLYYFDYWGQGTL VTVSS (SEQ ID NO:69)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205)

YU45-F2

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS (SEQ ID NO:70)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

Figure 16 (Cont.)

YU45-H3

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRLTISRDNSKNTLYLQMNSLRAEDTAVYYCARMVNLYYGDAFDIWGQGTMVTV SS (SEQ ID NO:71)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARMVNLYYGDAFDI (SEQ ID NO:218)

YU45-A1

QLQLQESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLVGATADDYWGQGTLVTVSS (SEQ ID NO:72)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLVGATADDY (SEQ ID NO:219)

YU45-A8/C6

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS (SEQ ID NO:73)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

YU45-B5/A4

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY AQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGLITGTTPWGQGTLVTVSS (SEQ ID NO:74)

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGLITGTTP (SEQ ID NO:211)

Figure 16 (Cont.)

YU45-C3/A6

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS
(SEQ ID NO:75)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

YU45-D1

AQVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQPPGKGLEWIGEIYHSGSTN
YNPSLKSRVTISVDKSKNQFSLKLSSVTAADTAVYYCARVQNLGGGSYYVGAFDYWGQGT
LVTVSS (SEQ ID NO:76)

HC-CDR1: GGSISSSNW (SEQ ID NO:220)
HC-CDR2: IYHSGST (SEQ ID NO:221)
HC-CDR3: ARVQNLGGGSYYVGAFDY (SEQ ID NO:222)

YU45-D9/D3

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLHFSQYFSTIDAFDIWGQGTMV
TISS (SEQ ID NO:77)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHFSQYFSTIDAFDI (SEQ ID NO:223)

YU45-E5

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:78)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 16 (Cont.)

YU45-G7

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDVGYSSGWYFDYWGQGTLVTV SS (SEQ ID NO:79)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDVGYSSGWYFDY (SEQ ID NO:200)

YU45-B4

EVQLVESGGGVVQPGRSLRLSCAASGFSLSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLAQSYSSSWYEWEPGREHAFD IWGQGTMVTVSS (SEQ ID NO:80)

HC-CDR1: GFSLSSYG (SEQ ID NO:201)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202)

YU45-H4

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPDDDYWGQGTLVTVSS (SEQ ID NO:81)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARPDDDY (SEQ ID NO:203)

YU45-B6

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS (SEQ ID NO:82)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

Figure 16 (Cont.)

YU45-D6

RSAAGGVWGRRGPAWEVPETLLCSLWIFLKSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMTSLRAEDTAVYYCARVGFSSWYPDLYYFDYWGQGTL VTVSS (SEQ ID NO:83)

HC-CDR1: WIFLKSYA (SEQ ID NO:204)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVGFSSWYPDLYYFDY (SEQ ID NO:205)

YU45-E7

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARLYSGYPSRYYYGMDVWGQGTT VTVSS (SEQ ID NO:84)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLYSGYPSRYYYGMDV (SEQ ID NO:206)

YU45-F5

*VTLKESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSS (SEQ ID NO:85)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207)

YU45-H7/46-B5

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARLHSGRNWGDAFDIWGQGTMVT VSS (SEQ ID NO:86)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARLHSGRNWGDAFDI (SEQ ID NO:208)

Figure 16 (Cont.)

YU46-G1

QV*LVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYA QKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARGGGPYYDFWSGYYTEFDYWGQG TLVTVSS (SEQ ID NO:87)

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224)

YU46-A2

EVQLLESGGGVVQPGRSLKLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYSSGWYFDYWGQGTLVTV SS (SEQ ID NO:88)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225)

YU46-A8

EVQLLESGGGVVQPGRSLKLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDSGYSSGWYFDYWGQGTLVTV SS (SEQ ID NO:89)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARDSGYSSGWYFDY (SEQ ID NO:225)

YU46-B2

GAAGGVWGRRGPAWEVPETLLCSLWILPSDSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIAAAGRDAFDIWGQGTMVTVSS (SEQ ID NO:90)

HC-CDR1: ILPSDSYA (SEQ ID NO:226)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIAAAGRDAFDI (SEQ ID NO:227)

Figure 16 (Cont.)

YU46-B6

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTN YAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARVVAAARSYYYYMDVWGKGTT VTVSS (SEQ ID NO:91)

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: ISAYNGNT (SEQ ID NO:229)
HC-CDR3: ARVVAAARSYYYYMDV (SEQ ID NO:230)

YU46-C1

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANY AQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARADSSAGGGPYYYGMDVWGQGT TVTVSS (SEQ ID NO:92)

HC-CDR1: GGTFSSYA (SEQ ID NO:209)
HC-CDR2: IIPIFGTA (SEQ ID NO:210)
HC-CDR3: ARADSSAGGGPYYYGMDV (SEQ ID NO:231)

YU46-D7

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLGAEDTAVYYCAKFARGVYLFDYWGQGTLVTVSS (SEQ ID NO:93)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKFARGVYLFDY (SEQ ID NO:215)

YU46-E3

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIGGYDDFDYWGQGTLVTVSS (SEQ ID NO:94)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIGGYDDFDY (SEQ ID NO:232)

Figure 16 (Cont.)

YU46-E7

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVYYDSSGTQGDSFDYWGQGTL VTVSS (SEQ ID NO:95)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARVYYDSSGTQGDSFDY (SEQ ID NO:233)

YU46-H8

EVQLVESGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSS (SEQ ID NO:96)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235)

YU46-G9

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS (SEQ ID NO:97)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

YU46-G8

EVQLVESGGGVVQPGRSLRLSCAASGFSLGSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSS (SEQ ID NO:98)

HC-CDR1: GFSLGSYG (SEQ ID NO:238)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235)

Figure 16 (Cont.)

YU46-B7

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGVLFDYWGQGTLVTVSS (SEQ ID NO:99)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARGVLFDY (SEQ ID NO:236)

YU46-D3

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTSSRDNSKNTLYLQMNSLRAEDTAVYYCARSGVLDYWGQGTLVTVSS (SEQ ID NO:100)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARSGVLDY (SEQ ID NO:237)

Figure 16 (Cont.)

Clone	CDR 1	CDR 2	CDR 3
Light Chain			
YU33-A2	QDVGRY (SEQ ID NO:101)	AAS (SEQ ID NO:102)	QQYRSAPLA (SEQ ID NO:103)
YU33-B3/H3	TGNIASNR (SEQ ID NO:104)	DNH (SEQ ID NO:105)	QSYDYSSVI (SEQ ID NO:106)
YU33-B4/YU45-G2/A3	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSSWV (SEQ ID NO:109)
YU33-E6	SSDVGAYNY (SEQ ID NO:110)	EVS (SEQ ID NO:111)	SSYTSSNTLV (SEQ ID NO:112)
YU45-C11/A10	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTVV (SEQ ID NO:113)
YU45-D11/F11	SSDIGAYNY (SEQ ID NO:114)	DVS (SEQ ID NO:108)	SSYTTSSTVV (SEQ ID NO:115)
YU45-E11/E12	SSNIGSNY (SEQ ID NO:116)	RNN (SEQ ID NO:117)	AAWDGSLSGWV (SEQ ID NO:118)
YU45-H11/D12	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTWV (SEQ ID NO:119)
YU45-A12/G10	SSNIGSNY (SEQ ID NO:116)	RNN (SEQ ID NO:117)	AAWDGSLSGWV (SEQ ID NO:118)
YU45-G1	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTFV (SEQ ID NO:120)
YU45-C2/A7/B10	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	NSYTSSTPYV (SEQ ID NO:121)
YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5	ISDVGGYNY (SEQ ID NO:122)	DVT (SEQ ID NO:123)	SSYAGSYTWV (SEQ ID NO:124)
YU45-E3	ISDVGGYNY (SEQ ID NO:122)	DVT (SEQ ID NO:123)	SSYAGSYTWV (SEQ ID NO:124)
YU45-C8/E8	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	GSYTSSNTQV (SEQ ID NO:125)
YU45-F8	SSNIGNNL (SEQ ID NO:126)	RNN (SEQ ID NO:117)	AAWDDSLSAGV (SEQ ID NO:127)
YU45-G8/H6	SSDVGGYDY (SEQ ID NO:128)	DVH (SEQ ID NO:129)	SSYTSSITWV (SEQ ID NO:130)
YU45-F9	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU45-H10	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTWV (SEQ ID NO:119)
YU46-A10	SSNIGNNL (SEQ ID NO:126)	RNN (SEQ ID NO:117)	AAWDDSLSAGV (SEQ ID NO:127)
YU45-F2	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU45-H3	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTVV (SEQ ID NO:113)
YU45-A1	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	GSYTSSSTWV (SEQ ID NO:132)
YU45-A8/C6	SSDVGGYNY (SEQ ID NO:107)	DVG (SEQ ID NO:133)	SSYTSGSTWV (SEQ ID NO:134)
YU45-B5/A4	SSDVGGYNY (SEQ ID NO:107)	EVN (SEQ ID NO:135)	SSYAGTNNFVV (SEQ ID NO:136)

Figure 17

Clone	CDR 1	CDR 2	CDR 3
YU45-C3/A6	SSDVGGYNY (SEQ ID NO:107)	DVT (SEQ ID NO:123)	CSYAGSYTWV (SEQ ID NO:131)
YU45-D1	QSVSSN (SEQ ID NO:137)	GAS (SEQ ID NO:138)	QQYNNWPLTFGGGTKVEFK (SEQ ID NO:139)
YU45-D9/D3	SSNIGNNY (SEQ ID NO:140)	DNT (SEQ ID NO:141)	GTWDSSLSGGV (SEQ ID NO:142)
YU45-E5	ISDVGGYNY (SEQ ID NO:122)	DVT (SEQ ID NO:123)	SSYAGSYTWGVRRRDRADRP (SEQ ID NO:143)
YU45-G7	YSNVGSNL (SEQ ID NO:144)	EDD (SEQ ID NO:145)	AAWDDSLKGHV (SEQ ID NO:146)
YU45-B4	SSNIGSNT (SEQ ID NO:147)	INN (SEQ ID NO:148)	AAWDDSLNGWV (SEQ ID NO:149)
YU45-H4	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU45-B6	SRDVGGYNY (SEQ ID NO:150)	DVS (SEQ ID NO:108)	CSYADYYTWV (SEQ ID NO:151)
YU45-D6	SSNIGNNL (SEQ ID NO:126)	RNN (SEQ ID NO:117)	AAWDDSLSAGV (SEQ ID NO:127)
YU45-E7	SGSIASNY (SEQ ID NO:152)	DDN (SEQ ID NO:153)	QSYDSSNLWV (SEQ ID NO:154)
YU45-F5	QIISSY (SEQ ID NO:155)	AAS (SEQ ID NO:102)	QQSYSTPTWT (SEQ ID NO:156)
YU45-H7/B5	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTWV (SEQ ID NO:119)
YU46-G1	SGSIASNY (SEQ ID NO:152)	EDN (SEQ ID NO:157)	QSYNSSKVV (SEQ ID NO:158)
YU46-A2	SSDVGGYEY (SEQ ID NO:159)	DVS (SEQ ID NO:108)	NSYTSSGTLVV (SEQ ID NO:160)
YU46-A8	SSDVGGYEY (SEQ ID NO:159)	DVS (SEQ ID NO:108)	NSYTSSGTLVV (SEQ ID NO:160)
YU46-B2	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU46-B6	SLRGYY (SEQ ID NO:161)	GNN (SEQ ID NO:162)	DSRGRSGDHWL (SEQ ID NO:163)
YU46-C1	SSNIGSYY (SEQ ID NO:164)	RND (SEQ ID NO:165)	ATWDDGLSGWV (SEQ ID NO:166)
YU46-D7	SSDVGAYNY (SEQ ID NO:167)	EVF (SEQ ID NO:168)	NSYVTGNNWA (SEQ ID NO:169)
YU46-E3	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSTWV (SEQ ID NO:119)
YU46-E7	SSNIGYDA (SEQ ID NO:170)	NDN (SEQ ID NO:171)	AAWDDSLSGWV (SEQ ID NO:172)
YU46-H8	QGSSSY (SEQ ID NO:173)	AAS (SEQ ID NO:102)	QQSYSTPLYT (SEQ ID NO:174)
YU46-G9	SSDVGGYKY (SEQ ID NO:175)	DVS (SEQ ID NO:108)	CSYAGNYTWL (SEQ ID NO:176)
YU46-G8	QGSSSY (SEQ ID NO:173)	AAS (SEQ ID NO:102)	QQSYSTPLYT (SEQ ID NO:174)
YU46-B7	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	TSYSSSSTLVA (SEQ ID NO:177)
YU46-D3	SSDVGNYKY (SEQ ID NO:178)	DVS (SEQ ID NO:108)	SSYTSSSTLVV (SEQ ID NO:179)

Figure 17 (Cont.)

Clone	CDR 1	CDR 2	CDR 3
Heavy Chain			
YU33-A2	VSSNSAAWN (SEQ ID NO:180)	YRSKWYN (SEQ ID NO:181)	ARGTRGYFDY (SEQ ID NO:182)
YU33-B3/H3	GFTFSGAY (SEQ ID NO:183)	ISYDGSNK (SEQ ID NO:184)	ARDLYAFDI (SEQ ID NO:185)
YU33-B4/YU45-G2/A3	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKIGATDPLDY (SEQ ID NO:187)
YU33-E6	GFTFSSYG (SEQ ID NO:186)	ISYDGSDK (SEQ ID NO:188)	AKDLSGLPIIDY (SEQ ID NO:189)
YU45-C11/A10	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARRGYFDY (SEQ ID NO:191)
YU45-D11/F11	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	ARIAAADGMDV (SEQ ID NO:192)
YU45-E11/E12	GFSFRSYG (SEQ ID NO:193)	ISYDGSNK (SEQ ID NO:184)	ARITHDYGDFSDAFDI (SEQ ID NO:194)
YU45-H11/D12	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLYSGSSNFDY (SEQ ID NO:195)
YU45-A12/G10	GFTFRSYG (SEQ ID NO:196)	ISYDGSNK (SEQ ID NO:184)	ARITHDYGDFSDAFDI (SEQ ID NO:194)
YU45-G1	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)
YU45-C2/A7/B10	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARGQNVDL (SEQ ID NO:198)
YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU45-E3	GFSFSSYA (SEQ ID NO:212)	ISYDGSNK (SEQ ID NO:184)	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU45-C8/E8	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	ARRGYGDY (SEQ ID NO:213)
YU45-F8	WIFLKSYA (SEQ ID NO:204)	ISYDGSNK (SEQ ID NO:184)	ARVGFSSWYPDLYYFDY (SEQ ID NO:205)
YU45-G8/H6	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKFARGVYLFDY (SEQ ID NO:215)
YU45-F9	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARVQSGEPESDY (SEQ ID NO:216)
YU45-H10	GFSLNSYG (SEQ ID NO:217)	ISYDGSNK (SEQ ID NO:184)	AKLYSGSSNFDY (SEQ ID NO:195)
YU46-A10	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARVGFSSWYPDLYYFDY (SEQ ID NO:205)
YU45-F2	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)
YU45-H3	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARMVNLYYGDAFDI (SEQ ID NO:218)
YU45-A1	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARLVGATADDY (SEQ ID NO:219)
YU45-A8/C6	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)

Figure 18

Clone	CDR 1	CDR 2	CDR 3
YU45-B5/A4	GGTFSSYA (SEQ ID NO:209)	IIPIFGTA (SEQ ID NO:210)	ARGLITGTTP (SEQ ID NO:211)
YU45-C3/A6	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)
YU45-D1	GGSISSSNW (SEQ ID NO:220)	IYHSGST (SEQ ID NO:221)	ARVQNLGGGSYYVGAFDY (SEQ ID NO:222)
YU45-D9/D3	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	ARLHFSQYFSTIDAFDI (SEQ ID NO:223)
YU45-E5	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU45-G7	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARDVGYSSGWYFDY (SEQ ID NO:200)
YU45-B4	GFSLSSYG (SEQ ID NO:201)	ISYDGSNK (SEQ ID NO:184)	ARLAQSYSSSWYEWEPGREHAFDI (SEQ ID NO:202)
YU45-H4	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARPDDDY (SEQ ID NO:203)
YU45-B6	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)
YU45-D6	WIFLKSYA (SEQ ID NO:204)	ISYDGSNK (SEQ ID NO:184)	ARVGFSSWYPDLYYFDY (SEQ ID NO:205)
YU45-E7	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARLYSGYPSRYYYGMDV (SEQ ID NO:206)
YU45-F5	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKGGKSYYGFDY (SEQ ID NO:207)
YU45-H7/B5	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARLHSGRNWGDAFDI (SEQ ID NO:208)
YU46-G1	GGTFSSYA (SEQ ID NO:209)	IIPIFGTA (SEQ ID NO:210)	ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224)
YU46-A2	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARDSGYSSGWYFDY (SEQ ID NO:225)
YU46-A8	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARDSGYSSGWYFDY (SEQ ID NO:225)
YU46-B2	ILPSDSYA (SEQ ID NO:226)	ISYDGSNK (SEQ ID NO:184)	ARIAAAGRDAFDI (SEQ ID NO:227)
YU46-B6	GYTFTSYG (SEQ ID NO:228)	ISAYNGNT (SEQ ID NO:229)	ARVVAAARSYYYYMDV (SEQ ID NO:230)
YU46-C1	GGTFSSYA (SEQ ID NO:209)	IIPIFGTA (SEQ ID NO:210)	ARADSSAGGGPYYYGMDV (SEQ ID NO:231)
YU46-D7	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKFARGVYLFDY (SEQ ID NO:215)
YU46-E3	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	ARIGGYDDFDY (SEQ ID NO:232)
YU46-E7	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARVYYDSSGTQGDSFDY (SEQ ID NO:233)
YU46-H8	GFTFGSYG (SEQ ID NO:234)	ISYDGSNK (SEQ ID NO:184)	AKGSYYFDY (SEQ ID NO:235)
YU46-G9	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)
YU46-G8	GFSLGSYG (SEQ ID NO:238)	ISYDGSNK (SEQ ID NO:184)	AKGSYYFDY (SEQ ID NO:235)
YU46-B7	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARGVLFDY (SEQ ID NO:236)
YU46-D3	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARSGVLDY (SEQ ID NO:237)

Figure 18 (Cont.)

Clone(s)	LC-CDR1	Sequence family	Family Consensus
YU46-D3	SSDVGNYKY	LC-CDR1-1	$X_1X_2DX_3GX_4YX_5Y$ (SEQ ID NO:239) X_1 = S or I X_2 = S or R X_3 = V or I X_4 = G, A or N X_5 = N, E, K or D
YU46-G9	SSDVGGYKY		
YU46-A2, YU46-A8	SSDVGGYEY		
YU45-B6	SRDVGGYNY		
YU45-G8/H6	SSDVGGYDY		
YU45-E5, YU45-E3, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5	ISDVGGYNY		
YU45-D11/F11	SSDIGAYNY		
YU33-B4/YU45-G2/A3, YU45-C11/A10, YU45-H11/D12, YU45-G1, YU45-C2/A7/B10, YU45-C8/E8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-B5/A4, YU45-C3/A6, YU45-H4, YU45-H7/46-B5, YU46-B2, YU46-E3, YU46-B7	SSDVGGYNY		
YU33-E6, YU46-D7	SSDVGAYNY		

Figure 19A

Clone(s)	LC-CDR1	Sequence family	Family Consensus
YU46-E7	SSNIGYDA	LC-CDR1-2	$X_6SNX_7GX_8X_9X_{10}$ (SEQ ID NO:240) X_6 = S or Y X_7 = I or V X_8 = S, N or Y X_9 = N, Y or D X_{10} = L, Y, T or A
YU45-G7	YSNVGSNL		
YU46-C1	SSNIGSYY		
YU45-B4	SSNIGSNT		
YU45-D6, YU45-F8, YU45-A10	SSNIGNNL		
YU45-E11/E12, YU45-A12/G10	SSNIGSNY		
YU45-D9/D3	SSNIGNNY		
YU45-F5	QIISSY	LC-CDR1-3	$QX_{11}X_{12}SSX_{13}$ (SEQ ID NO:241) X_{11} = G, S or I X_{12} = S, I or V X_{13} = Y or N
YU46-H8, YU46-G8	QGSSSY		
YU45-D1	QSVSSN		
YU33-B3/H3	TGNIASNR	LC-CDR1-4	$X_{14}GX_{15}IASNX_{16}$ (SEQ ID NO:242) X_{14} = S or T X_{15} = S or N X_{16} = Y or R
YU45-E7, YU46-G1	SGSIASNY		
YU33-A2	QDVGRY	LC-CDR1-5	QDVGRY (SEQ ID NO:101)
YU46-B6	SLRGYY	LC-CDR1-6	SLRGYY (SEQ ID NO:161)

Figure 19A (Cont.)

Clone(s)	LC-CDR2	Sequence family	Family Consensus
YU45-A8/C6	DVG	LC-CDR2-1	DVX_{17} (SEQ ID NO:243) X_{17} = S, T or G
YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-E3, YU45-C3/A6, YU45-E5	DVT		
YU33-B4/YU45-G2/A3, YU45-C11/A10, YU45-D11/F11, YU45-H11/D12, YU45-G1, YU45-C2/A7/B10, YU45-C8/E8, YU45-F9, YU45-H10, YU45-F2, YU45-H3, YU45-A1, YU45-H4, YU45-B6, YU45-H7/46-B5, YU46-A2, YU46-A8, YU46-B2, YU46-E3, YU46-G9, YU46-B7, YU46-D3,	DVS		

Figure 19B

Clone(s)	LC-CDR2	Sequence family	Family Consensus
YU46-C1	RND	LC-CDR2-2	$X_{18}NX_{19}$ (SEQ ID NO:244) X_{18} = R, I or G X_{19} = N or D
YU45-E11/E12, YU45-A12/G10, YU45-F8, YU46-A10, YU45-D6	RNN		
YU45-B4	INN		
YU46-B6	GNN		
YU33-A2, YU45-F5, YU46-H8, YU46-G8	AAS	LC-CDR2-3	X_{20}AS (SEQ ID NO:245) X_{20} = A or G
YU45-D1	GAS		
YU45-G7	EDD	LC-CDR2-4	$X_{21}DX_{22}$ (SEQ ID NO:246) X_{21} = E, D or N X_{22} = N or D
YU45-E7	DDN		
YU46-G1	EDN		
YU46-E7	NDN		
YU33-E6	EVS	LC-CDR2-5	EVX_{23} (SEQ ID NO:247) X_{23} = S, F or N
YU46-D7	EVF		
YU45-B5/A4	EVN		
YU45-D9/D3	DNT	LC-CDR2-6	$DX_{24}X_{25}$ (SEQ ID NO:248) X_{24} = N or V X_{25} = H or T
YU33-B3/H3	DNH		
YU45-G8/H6	DVH		

Figure 19B (Cont.)

Clone(s)	LC-CDR3	Sequence family	Family Consensus
YU45-A8/C6	SSYTSGSTWV	LC-CDR3-1	$X_{26}SYTX_{27}X_{28}X_{29}X_{30}X_{31}VX_{32}$ (SEQ ID NO:249) X_{26} = S, N or G X_{27} = S or T X_{28} = S or G X_{29} = S, N, G or I X_{30} = T or S X_{31} = W, L, V or Q X_{32} = absent or V
YU45-A1	GSYTSSSTWV		
YU45-G8/H6	SSYTSSITWV		
YU33-B4/YU45-G2/A3	SSYTSSSSWV		
YU45-H11/D12, YU45-H10, YU45-H7/46-B5, YU46-E3,	SSYTSSSTWV		
YU45-C8/E8	GSYTSSNTQV		
YU46-A2, YU46-A8	NSYTSSGTLVV		
YU33-E6	SSYTSSNTLV		
YU46-D3	SSYTSSSTLVV		
YU45-C11/A10, YU45-H3	SSYTSSSTVV		
YU45-D11/F11	SSYTTSSTVV		
YU45-B5/A4	SSYAGTNNFVV	LC-CDR3-2	$X_{33}SYAX_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO:250) X_{33} = C or S X_{34} = G or D X_{35} = S, Y, N or T X_{36} = Y or N X_{37} = T or N X_{38} = W or F X_{39} = V, G or L X_{40} = absent or V X_{41} = absent or R X_{42} = absent or R X_{43} = absent or R X_{44} = absent or D X_{45} = absent or R X_{46} = absent or A X_{47} = absent or D X_{48} = absent or R X_{49} = absent or P
YU46-G9	CSYAGNYTWL		
YU45-B6	CSYADYYTWV		
YU45-E5	SSYAGSYTWGVRRRDRADRP		
YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-E3	SSYAGSYTWV		
YU45-G1	CSYAGSYTFV		
YU45-F9, YU45-F2, YU45-C3/A6, YU45-H4, YU46-B2	CSYAGSYTWV		

Figure 19C

Clone(s)	LC-CDR3	Sequence family	Family Consensus
YU45-D9/D3	GTWDSSLSGGV	LC-CDR3-3	$X_{50}X_{51}WDX_{52}X_{53}LX_{54}X_{55}X_{56}V$ (SEQ ID NO:251) X_{50} = A or G X_{51} = A or T X_{52} = D, G or S X_{53} = S or G X_{54} = S, K or N X_{55} = G or A X_{56} = W, G or H
YU46-C1	ATWDDGLSGWV		
YU45-G7	AAWDDSLKGHV		
YU45-F8, YU46-A10, YU45-D6,	AAWDDSLSAGV		
YU45-B4	AAWDDSLNGWV		
YU45-E11/E12, YU45-A12/G10	AAWDGSLSGWV		
YU46-E7	AAWDDSLSGWV		
YU45-F5	QQSYSTPTWT	LC-CDR3-4	$QQX_{57}X_{58}X_{59}PX_{60}X_{61}X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}X_{70}X_{71}X_{72}$ (SEQ ID NO:252) X_{57} = S or Y X_{58} = Y, R or N X_{59} = S or N X_{60} = T, A or W X_{61} = L or T X_{62} = Y, A, W or T X_{63} = T, absent or F X_{64} = absent or G X_{65} = absent or G X_{66} = absent or G X_{67} = absent or T X_{68} = absent or K X_{69} = absent or V X_{70} = absent or E X_{71} = absent or F X_{72} = absent or K
YU46-H8, YU46-G8	QQSYSTPLYT		
YU33-A2	QQYRSAPLA		
YU45-D1	QQYNNWPLTFGGGTKVEFK		

Figure 19C (Cont.)

Clone(s)	LC-CDR3	Sequence family	Family Consensus
YU46-G1	QSYNSSKVV	LC-CDR3-5	$QSYX_{73}X_{74}SX_{75}X_{76}X_{77}X_{78}$ (SEQ ID NO:253) X_{73} = D or N X_{74} = S or Y X_{75} = K, S or N X_{76} = V or L X_{77} = I, V or W X_{78} = absent or V
YU33-B3/H3	QSYDYSSVI		
YU45-E7	QSYDSSNLWV		
YU45-C2/A7/B10	NSYTSSTPYV	LC-CDR3-6	$X_{79}SYX_{80}SSX_{81}X_{82}X_{83}VX_{84}$ (SEQ ID NO:254) X_{79} = T or N X_{80} = T or S X_{81} = T or S X_{82} = P or T X_{83} = Y or L X_{84} = absent or A
YU46-B7	TSYSSSSTLVA		
YU46-D7	NSYVTGNNWA	LC-CDR3-7	NSYVTGNNWA (SEQ ID NO:169)
YU46-B6	DSRGRSGDHWL	LC-CDR3-8	DSRGRSGDHWL (SEQ ID NO:163)

Figure 19C (Cont.)

Clone(s)	HC-CDR1	Sequence family	Family Consensus
YU33-B4/YU45-G2/A3, YU33-E6, YU45-D11/F11, YU45-H11/D12, YU45-G1, YU45-C8/E8, YU45-G8/H6, YU45-F2, YU45-A8/C6, YU45-C3/A6, YU45-D9/D3, YU45-B6, YU45-F5, YU46-D7, YU46-E3, YU46-G9	GFTFSSYG	HC-CDR1-1	GFTFSSYX_{85} (SEQ ID NO:255) X_{85} = A or G
YU45-C11/A10, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-F9, YU46-A10, YU45-H3, YU45-A1, YU45-E5, YU45-G7, YU45-H4, YU45-E7, YU45-H7/46-B5, YU46-A2, YU46-A8, YU46-E7, YU46-B7, YU46-D3	GFTFSSYA		
YU45-H10	GFSLNSYG	HC-CDR1-2	G$X_{86}X_{87}X_{88}X_{89}$SYG (SEQ ID NO:256) X_{86} = F or Y X_{87} = S or T X_{88} = L or F X_{89} = G, R, T, S or N
YU45-B4	GFSLSSYG		
YU46-G8	GFSLGSYG		
YU46-B6	GYTFTSYG		
YU45-E11/E12	GFSFRSYG		
YU45-A12/G10	GFTFRSYG		
YU46-H8	GFTFGSYG		

Figure 20A

Clone(s)	HC-CDR1	Sequence family	Family Consensus
YU45-B5/A4, YU46-G1, YU46-C1	GGTFSSYA	HC-CDR1-3	$X_{90}X_{91}X_{92}X_{93}X_{94}$SYA (SEQ ID NO:257) X_{90} = G or I X_{91} = G, F or L X_{92} = T, S or P X_{93} = F or S X_{94} = S or D
YU45-E3	GFSFSSYA		
YU46-B2	ILPSDSYA		
YU45-F8, YU45-D6	WIFLKSYA	HC-CDR1-4	WIFLKSYA (SEQ ID NO:204)
YU33-A2	VSSNSAAWN	HC-CDR1-5	VSSNSAAWN (SEQ ID NO:180)
YU45-D1	GGSISSSNW	HC-CDR1-6	GGSISSSNW (SEQ ID NO:220)
YU33-B3/H3	GFTFSGAY	HC-CDR1-7	GFTFSGAY (SEQ ID NO:183

Figure 20A (Cont.)

Clone(s)	HC-CDR2	Sequence family	Family Consensus
YU33-B3/H3, YU33-B4/YU45-G2/A3, YU45-C11/A10, YU45-D11/F11, YU45-E11/E12, YU45-H11/D12, YU45-A12/G10, YU45-G1, YU45-C2/A7/B10, YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-E3, YU45-C8/E8, YU45-F8, YU45-G8/H6, YU45-F9, YU45-H10, YU46-A10, YU45-F2, YU45-H3, YU45-A1, YU45-A8/C6, YU45-C3/A6, YU45-D9/D3, YU45-E5, YU45-G7, YU45-B4, YU45-H4, YU45-B6, YU45-D6, YU45-E7, YU45-F5, YU45-H7/B5, YU46-A2, YU46-A8, YU46-B2, YU46-D7, YU46-E3, YU46-E7, YU46-H8, YU46-G9, YU46-G8, YU46-B7, YU46-D3	ISYDGSNK	HC-CDR2-1	ISYDGSX_{95}K (SEQ ID NO:258) X_{95} = N or D
YU33-E6	ISYDGSDK		

Figure 20B

Clone(s)	HC-CDR2	Sequence family	Family Consensus
YU45-B5/A4, YU46-G1, YU46-C1	IIPIFGTA	HC-CDR2-2	IIPIFGTA (SEQ ID NO:210)
YU33-A2	YRSKWYN	HC-CDR2-3	YRSKWYN (SEQ ID NO:181)
YU46-B6	ISAYNGNT	HC-CDR2-4	ISAYNGNT (SEQ ID NO:229)
YU45-D1	IYHSGST	HC-CDR2-4	IYHSGST (SEQ ID NO:221)

Figure 20B (Cont.)

Clone(s)	HC-CDR3	Sequence family	Family Consensus
YU45-G1, YU45-F2, YU45-A8/C6, YU45-C3/A6, YU45-B6, YU46-G9	AKLSGPNGVDY	HC-CDR3-1	AKLSGPNGVDY (SEQ ID NO:197)
YU33-E6	AKDLSGLPIIDY	HC-CDR3-2	$AKX_{96}X_{97}X_{98}GX_{99}X_{100}X_{101}X_{102}$ DY (SEQ ID NO:259) X_{96} = L, F or D X_{97} = Y, A or L X_{98} = S or R X_{99} = S, V or L X_{100} = S, Y or P X_{101} = N, L or I X_{102} = F or I
YU45-H11/D12, YU45-H10	AKLYSGSSNFDY		
YU45-G8/H6, YU46-D7	AKFARGVYLFDY		
YU45-G7	ARDVGYSSGWYFDY	HC-CDR3-3	$ARDX_{103}GYSSGWYFDY$ (SEQ ID NO:260) X_{103} = S or V
YU46-A2, YU46-A8	ARDSGYSSGWYFDY		
YU45-H7/46-B5	ARLHSGRNWGDAFDI	HC-CDR3-4	$ARLX_{104}X_{105}X_{106}X_{107}X_{108}X_{109}X_{110}X_{111}X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}X_{120}$AFDI (SEQ ID NO:261) X_{104} = H or A X_{105} = S, Q or F X_{106} = S or G X_{107} = absent or Y X_{108} = absent or S X_{109} = absent, R or S X_{110} = Q, N or S X_{111} = W or Y X_{112} = absent, Y or F X_{113} = absent or E X_{114} = absent or W X_{115} = absent or E X_{116} = absent or P X_{117} = absent, G or S X_{118} = absent, R or T X_{119} = G, E or I X_{120} = D or H
YU45-B4	ARLAQSYSSSWYEWEPGREHAFDI		
YU45-D9/D3	ARLHFSQYFSTIDAFDI		

Figure 20C

Clone(s)	HC-CDR3	Sequence family	Family Consensus
YU45-D2/H2/C7/F3/C9/E1/E9/C10/G3/H9/C5/A2/A5, YU45-E3, YU45-E5	ARIMGYDYGDYDVVDY	HC-CDR3-5	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU46-E3	ARIGGYDDFDY	HC-CDR3-6	ARI$X_{121}X_{122}X_{123}X_{124}X_{125}X_{126}$D $X_{127}X_{128}X_{129}X_{130}$ (SEQ ID NO:262) X_{121} = A or G X_{122} = A or G X_{123} = A or Y X_{124} = D or absent X_{125} = G or D X_{126} = F, M or R X_{127} = V, Y or A X_{128} = absent or F X_{129} = absent or D X_{130} = absent or I
YU45-D11/F11	ARIAAADGMDV		
YU46-B2	ARIAAAGRDAFDI		
YU45-F8, YU46-A10, YU45-D6	ARVGFSSWYPDLYYFDY	HC-CDR3-7	ARVGFSSWYPDLYYFDY (SEQ ID NO:205)
YU45-C11/A10	ARRGYFDY	HC-CDR3-8	$X_{131}X_{132}X_{133}X_{134}RGYX_{135}$DY (SEQ ID NO:263) X_{131} = absent or A X_{132} = absent or R X_{133} = A or G X_{134} = R or T X_{135} = F or G
YU45-C8/E8	ARRGYGDY		
YU33-A2	ARGTRGYFDY		
YU45-E11/E12, YU45-A12/G10	ARITHDYGDFSDAFDI	HC-CDR3-9	ARITHDYGDFSDAFDI (SEQ ID NO:194)
YU46-D3	ARSGVLDY	HC-CDR3-10	ARX_{136}GVLX_{137}DY (SEQ ID NO:264) X_{136} = absent or S X_{137} = absent or F
YU46-B7	ARGVLFDY		
YU46-H8, YU46-G8	AKGSYYFDY	HC-CDR3-11	AKGSYYFDY (SEQ ID NO:235)

Figure 20C (Cont.)

Clone(s)	HC-CDR3	Sequence family	Family Consensus
YU45-E7	ARLYSGYPSRYYYGMDV	HC-CDR3-12	ARLYSGYPSRYYYGMDV (SEQ ID NO:206)
YU45-F9	ARVQSGEPESDY	HC-CDR3-13	ARVQSGEPESDY (SEQ ID NO:216)
YU33-B4/YU45-G2/A3	AKIGATDPLDY	HC-CDR3-14	AKIGATDPLDY (SEQ ID NO:187)
YU33-B3/H3	ARDLYAFDI	HC-CDR3-15	ARDLYAFDI (SEQ ID NO:185)
YU45-H4	ARPDDDY	HC-CDR3-16	ARPDDDY (SEQ ID NO:203)
YU45-F5	AKGGKSYYGFDY	HC-CDR3-17	AKGGKSYYGFDY (SEQ ID NO:207)
YU46-C1	ARADSSAGGGPYYYGMDV	HC-CDR3-18	ARADSSAGGGPYYYGMDV (SEQ ID NO:231)
YU46-E7	ARVYYDSSGTQGDSFDY	HC-CDR3-19	ARVYYDSSGTQGDSFDY (SEQ ID NO:233)
YU46-B6	ARVVAAARSYYYYMDV	HC-CDR3-20	ARVVAAARSYYYYMDV (SEQ ID NO:230)
YU46-G1	ARGGGPYYDFWSGYYTEFDY	HC-CDR3-21	ARGGGPYYDFWSGYYTEFDY (SEQ ID NO:224)
YU45-H3	ARMVNLYYGDAFDI	HC-CDR3-22	ARMVNLYYGDAFDI (SEQ ID NO:2218)
YU45-B5/A4	ARGLITGTTP	HC-CDR3-23	ARGLITGTTP (SEQ ID NO:211)
YU45-C2/A7/B10	ARGQNVDL	HC-CDR3-24	ARGQNVDL (SEQ ID NO:198)
YU45-D1	ARVQNLGGGSYYVGAFDY	HC-CDR3-25	ARVQNLGGGSYYVGAFDY (SEQ ID NO:222)
YU45-A1	ARLVGATADDY	HC-CDR3-26	ARLVGATADDY (SEQ ID NO:219)

Figure 20C (Cont.)

Strategy No	Round 1	Round 2	Round 3	biotinylated	No first hits
1	h-IL11	m-IL11	h-IL11	Yes	1
2	h-IL11	h-IL11	h-IL11	Yes	-
3	h-IL11	h-IL11	m-IL11	Yes	-
4	m-IL11	m-IL11	m-IL11	Yes	5
5	m-IL11	h-IL11	m-IL11	Yes	-
6	m-IL11	h-IL11	h-IL11	Yes	-
7	h-IL11	h-IL11	h-IL11	No	11
8	h-IL11	m-IL11	h-IL11	No	14
9	h-IL11	m-IL11	h-IL11	Round 2	17
10	h-IL11	h-IL11	m-IL11	No	19
11	h-IL11	h-IL11	m-IL11	Round 3	5
12	m-IL11	h-IL11	m-IL11	Round 3	10
13	m-IL11	m-IL11	h-IL11	Round 1, 2	6
14	m-IL11	m-IL11	m-IL11	No	36
15	m-IL11	h-IL11	m-IL11	No	15
16	m-IL11	m-IL11	h-IL11	No	36

Figure 21

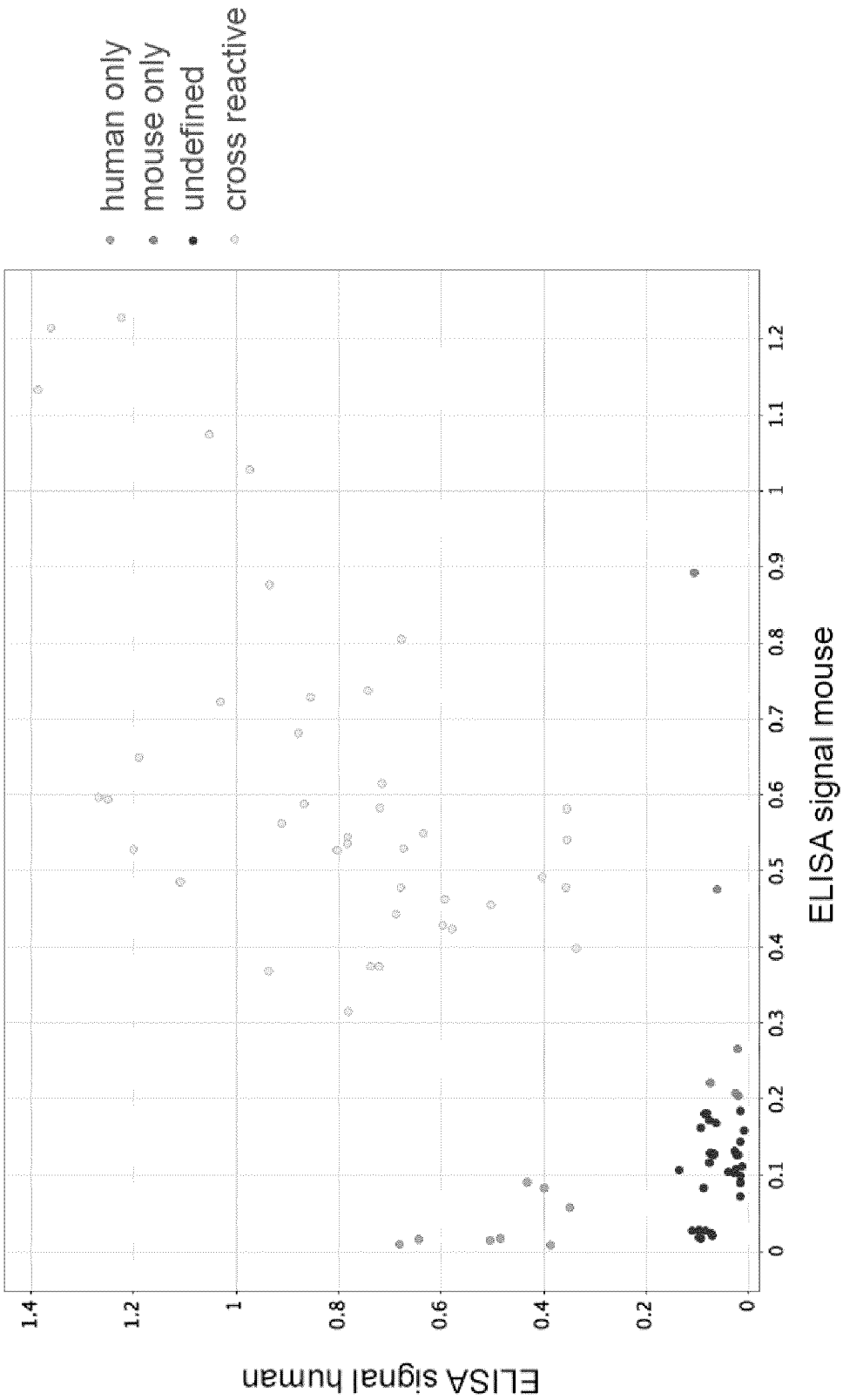

human only
mouse only
undefined
cross reactive
ELISA signal human
ELISA signal mouse
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0.1
0.3
0.5
0.7
0.9
1.1

Figure 22

Identical Sequence	Clone ID	Fc-part
1	YU33-A2	hIgG1-Fc (IgG)
2	YU33-B3	hIgG1-Fc (IgG)
	YU33-H3	hIgG1-Fc (IgG)
3	YU33-B4	hIgG1-Fc (IgG)
	YU45-G2	hIgG1-Fc
	YU45-A3	hIgG1-Fc
4	YU33-E3	hIgG1-Fc (IgG)
5	YU33-E6	hIgG1-Fc (IgG)
6	YU45-C11	hIgG1-Fc
	YU45-A10	hIgG1-Fc
7	YU45-D11	hIgG1-Fc
	YU45-F11	hIgG1-Fc
8	YU45-E11	hIgG1-Fc
	YU45-E12	hIgG1-Fc
9	YU45-H11	hIgG1-Fc
	YU45-D12	hIgG1-Fc
10	YU45-A12	hIgG1-Fc
	YU45-G10	hIgG1-Fc
11	YU45-G1	hIgG1-Fc
12	YU45-B2	hIgG1-Fc
13	YU45-C2	hIgG1-Fc
	YU45-A7	hIgG1-Fc
	YU45-B10	hIgG1-Fc
14	YU45-D2	hIgG1-Fc
	YU45-H2	hIgG1-Fc
	YU45-C7	hIgG1-Fc
	YU45-F3	hIgG1-Fc
	YU45-C9	hIgG1-Fc
	YU45-E1	hIgG1-Fc
	YU45-E9	hIgG1-Fc
	YU45-C10	hIgG1-Fc
	YU45-G3	hIgG1-Fc
	YU45-H9	hIgG1-Fc
	YU45-C5	hIgG1-Fc
	YU45-A2	hIgG1-Fc
	YU45-A5	hIgG1-Fc
15	YU45-B3	hIgG1-Fc
16	YU45-E3	hIgG1-Fc
17	YU45-C8	hIgG1-Fc
	YU45-E8	hIgG1-Fc
18	YU45-F8	hIgG1-Fc
19	YU45-G8	hIgG1-Fc
	YU45-H6	hIgG1-Fc

Identical Sequence	Clone ID	Fc-part
20	YU45-H8	hIgG1-Fc
21	YU45-F9	hIgG1-Fc
22	YU45-H10	hIgG1-Fc
23	YU46-A10	hIgG1-Fc
24	YU45-F2	hIgG1-Fc
25	YU45-H3	hIgG1-Fc
26	YU45-A1	hIgG1-Fc
27	YU45-A8	hIgG1-Fc
	YU45-C6	hIgG1-Fc
28	YU45-B5	hIgG1-Fc
	YU45-A4	hIgG1-Fc
29	YU45-C3	hIgG1-Fc
	YU45-A6	hIgG1-Fc
30	YU45-D1	hIgG1-Fc
31	YU45-D9	hIgG1-Fc
	YU45-D3	hIgG1-Fc
32	YU45-E5	hIgG1-Fc
33	YU45-G7	hIgG1-Fc
34	YU45-B4	hIgG1-Fc
35	YU45-H4	hIgG1-Fc
36	YU45-B6	hIgG1-Fc
37	YU45-D6	hIgG1-Fc
38	YU45-E7	hIgG1-Fc
39	YU45-F5	hIgG1-Fc
40	YU45-H7	hIgG1-Fc
	YU46-B5	hIgG1-Fc
41	YU45-B8	hIgG1-Fc
42	YU45-C1	hIgG1-Fc
43	YU46-G1	hIgG1-Fc
44	YU46-A2	hIgG1-Fc
45	YU46-A8	hIgG1-Fc
46	YU46-B2	hIgG1-Fc
47	YU46-B6	hIgG1-Fc
48	YU46-C1	hIgG1-Fc
49	YU46-D7	hIgG1-Fc
50	YU46-E3	hIgG1-Fc
51	YU46-E7	hIgG1-Fc
52	YU46-H8	hIgG1-Fc
53	YU46-G9	hIgG1-Fc
54	YU46-G8	hIgG1-Fc
55	YU46-B7	hIgG1-Fc
56	YU46-D3	hIgG1-Fc

Figure 23

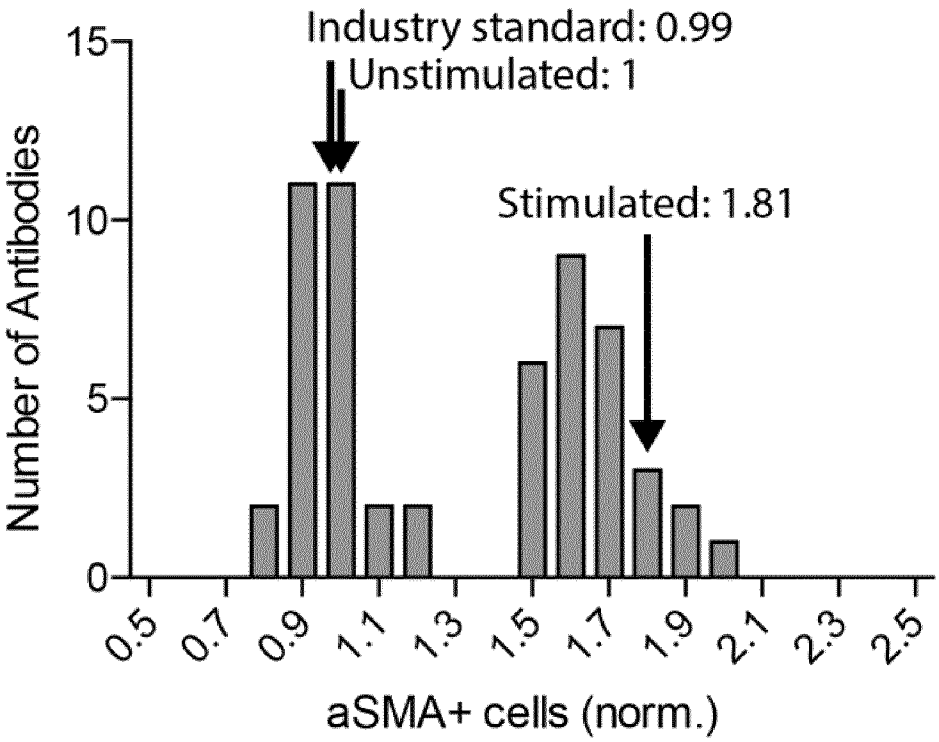


Figure 24A

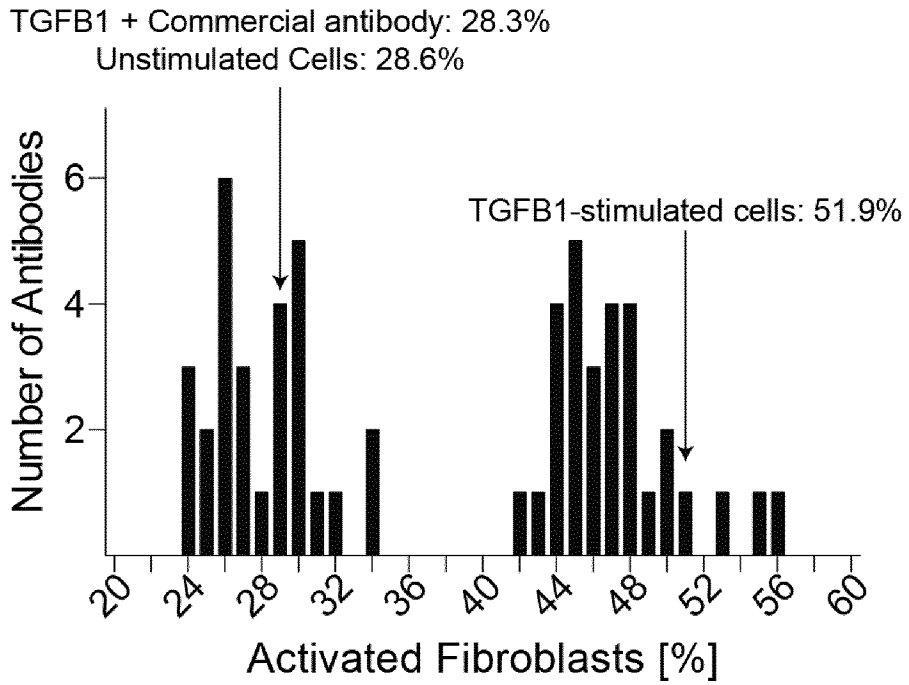


Figure 24B

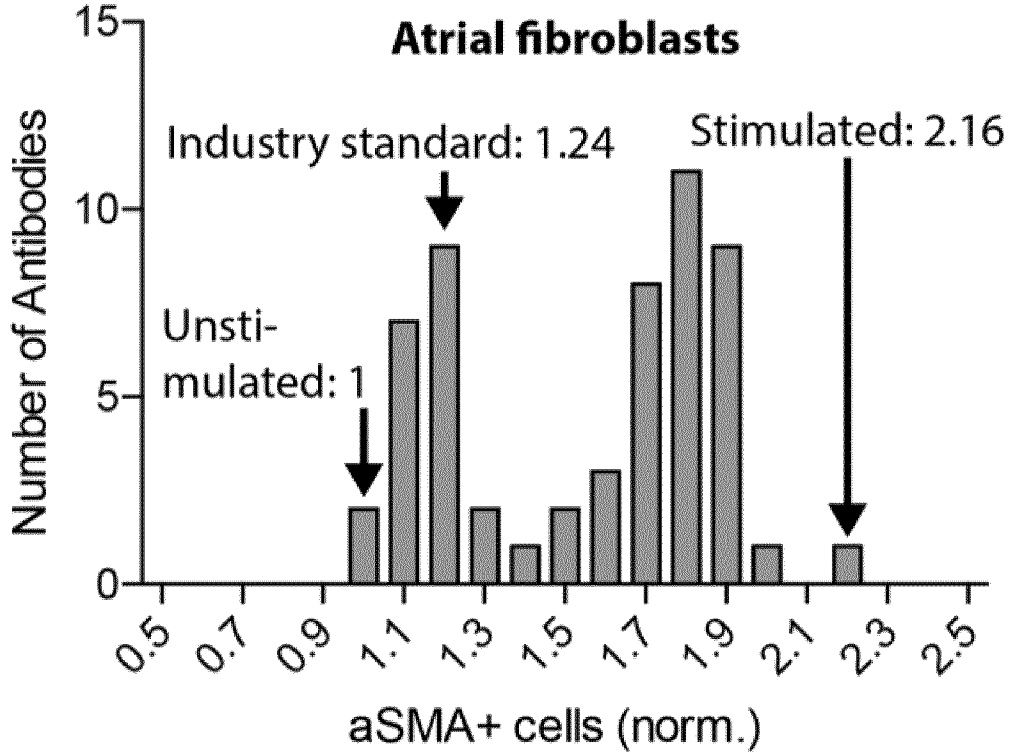


Figure 25A

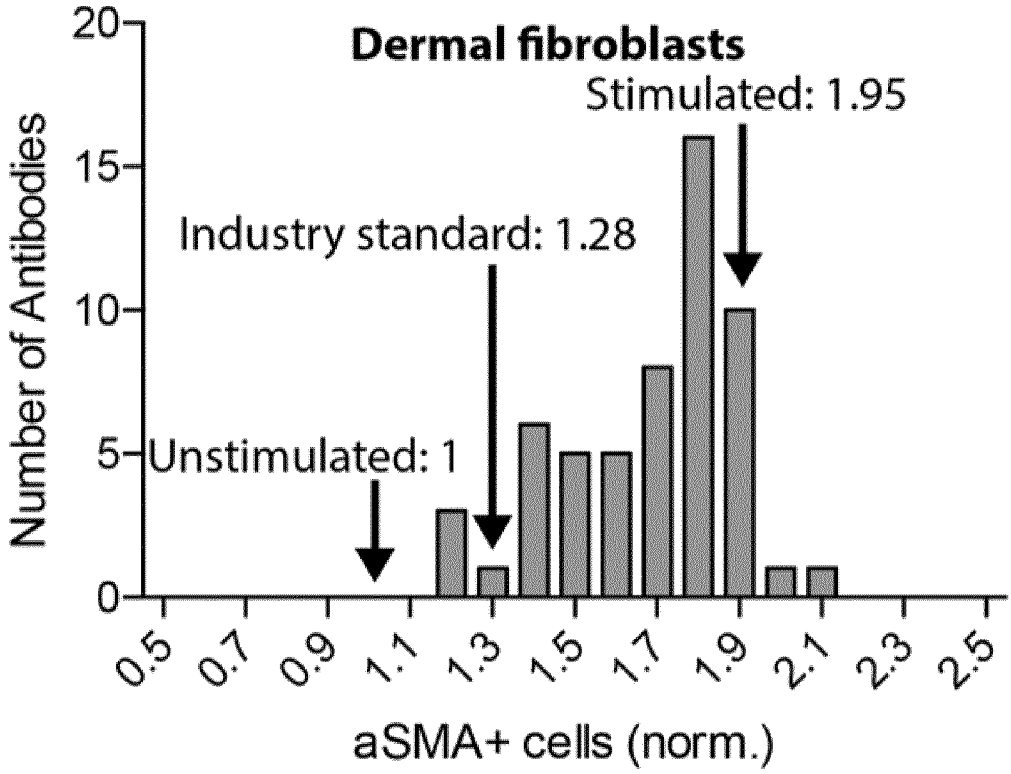


Figure 25B

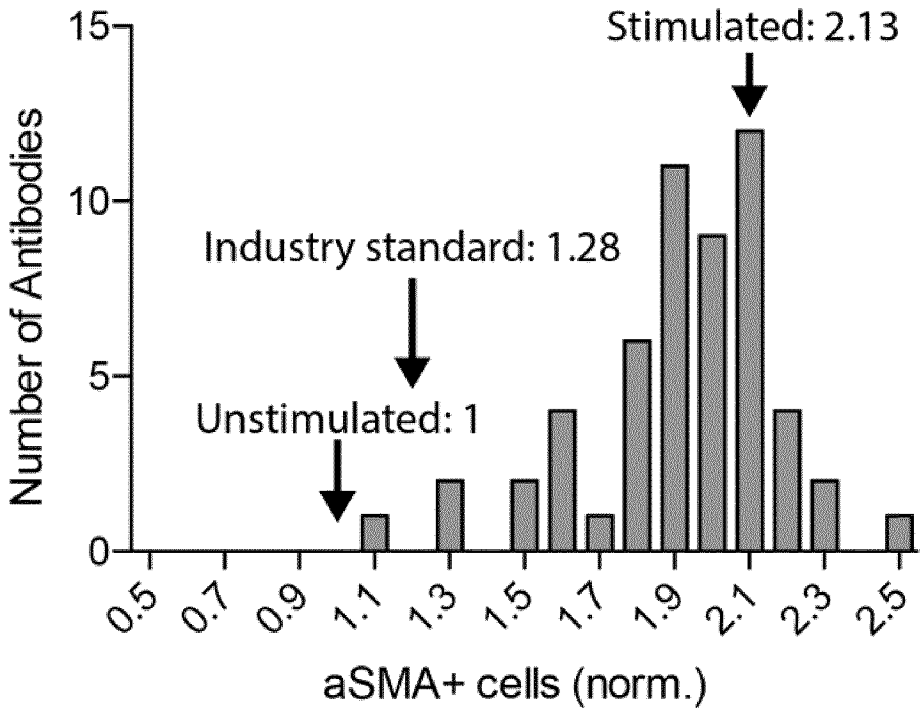

Stimulated: 2.13
Industry standard: 1.28
Unstimulated: 1
Number of Antibodies
15
10
5
0
0.5
0.7
0.9
1.1
1.3
1.5
1.7
1.9
2.1
2.3
2.5
aSMA+ cells (norm.)

Figure 26

Antibody Candidate	Human IL11 Activated fibroblasts (norm.)	Mouse IL11 Activated atrial fibroblasts (norm.)	Trans IL11 Activated fibroblasts (norm.)	Mouse IL11 Activated dermal fibroblasts (norm.)
-	1	1	1	1
-	1.81	2.16	2.13	1.95
Industry Standard	0.99	1.24	1.28	1.28
1	1.91	1.75	2.16	1.98
2	1.95	1.83	2.09	1.91
3	1.11	1.08	1.14	1.59
4	1.85	1.85	2.13	1.83
5	1.78	1.72	2.13	1.62
6	0.91	1.25	2.26	1.40
7	1.03	1.79	2.18	1.93
8	1.01	1.83	2.05	1.85
9	1.17	1.22	1.71	1.54
10	1.67	1.75	1.28	1.86
11	0.94	1.03	2.61	1.49
12	0.99	1.83	1.83	1.94
13	1.76	1.91	1.86	2.09
14	1.04	1.11	2.04	1.46
15	1.57	1.13	1.90	1.39
16	0.88	1.69	1.58	1.76
17	1.55	1.70	1.46	1.76
18	0.82	1.08	1.85	1.40
19	1.01	1.26	1.77	1.53
20	1.65	1.78	1.47	1.78
21	0.89	1.83	2.06	1.83
22	0.92	1.17	2.02	1.56
23	1.69	1.11	2.27	1.72
24	0.96	1.87	1.29	1.89
25	0.94	1.24	2.04	1.43
26	1.68	1.92	2.50	1.94
27	1.05	1.05	2.15	1.44
28	1.09	2.19	2.12	1.79
29	1.65	1.37	2.10	1.61
30	1.63	1.89	1.89	1.88
31	1.04	1.23	1.76	1.28
32	1.68	2.03	2.00	1.89
33	0.95	1.56	1.94	1.79
34	1.59	1.88	1.94	1.83
35	1.76	1.86	2.06	1.73
36	0.84	1.17	1.99	1.20
37	1.61	1.92	1.82	1.75
38	1.54	1.91	1.98	1.81
39	1.02	1.47	1.63	1.82
40	1.18	1.78	1.97	1.85
41	1.57	1.78	1.87	1.69
42	0.85	1.21	2.04	1.19
43	1.54	1.78	2.06	1.72
44	1.57	1.71	2.13	1.61
45	1.03	1.18	1.60	1.79
46	1.67	1.72	2.11	1.77
47	0.89	1.81	1.90	1.76
48	1.50	1.21	1.84	1.41
49	1.60	1.70	1.89	1.70
50	0.86	1.81	1.83	1.82
51	1.55	1.46	2.09	1.66
52	1.62	1.06	2.09	1.23
53	1.47	1.57	1.90	1.68
54	0.90	1.23	1.57	1.82
55	1.56	1.61	2.16	1.80
56	0.91	1.13	1.87	1.47

Figure 27

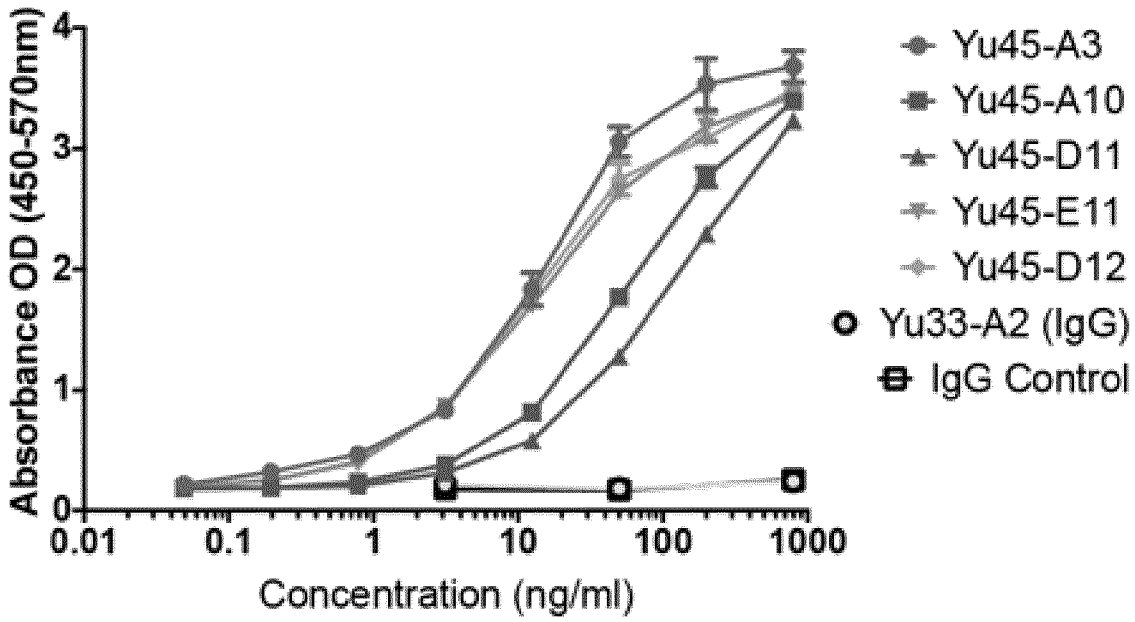


Figure 28A

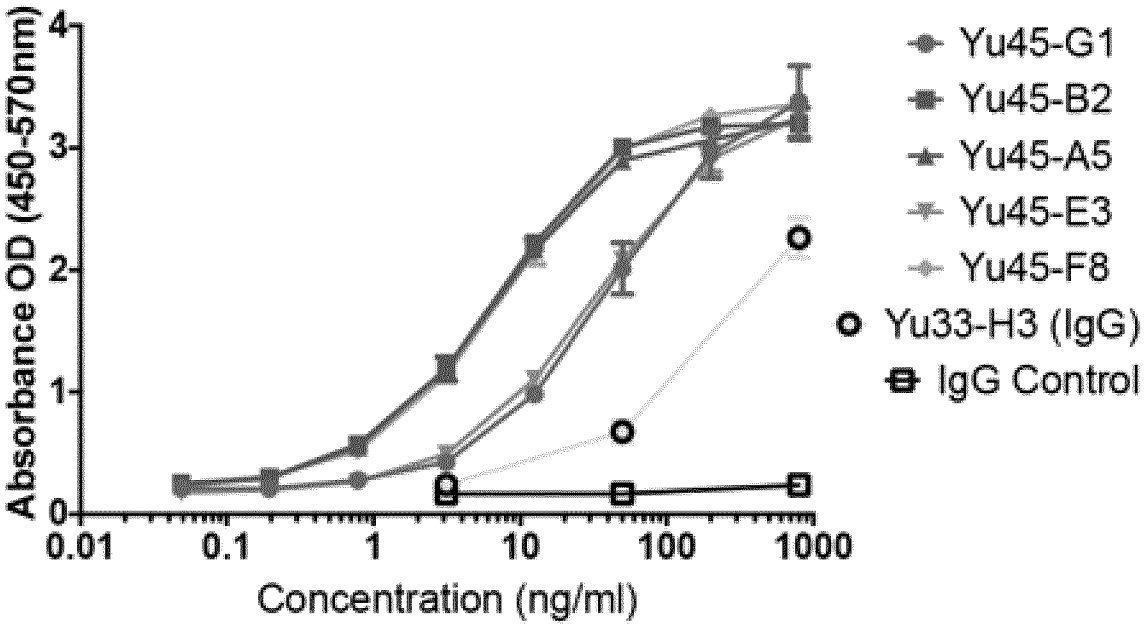


Figure 28B

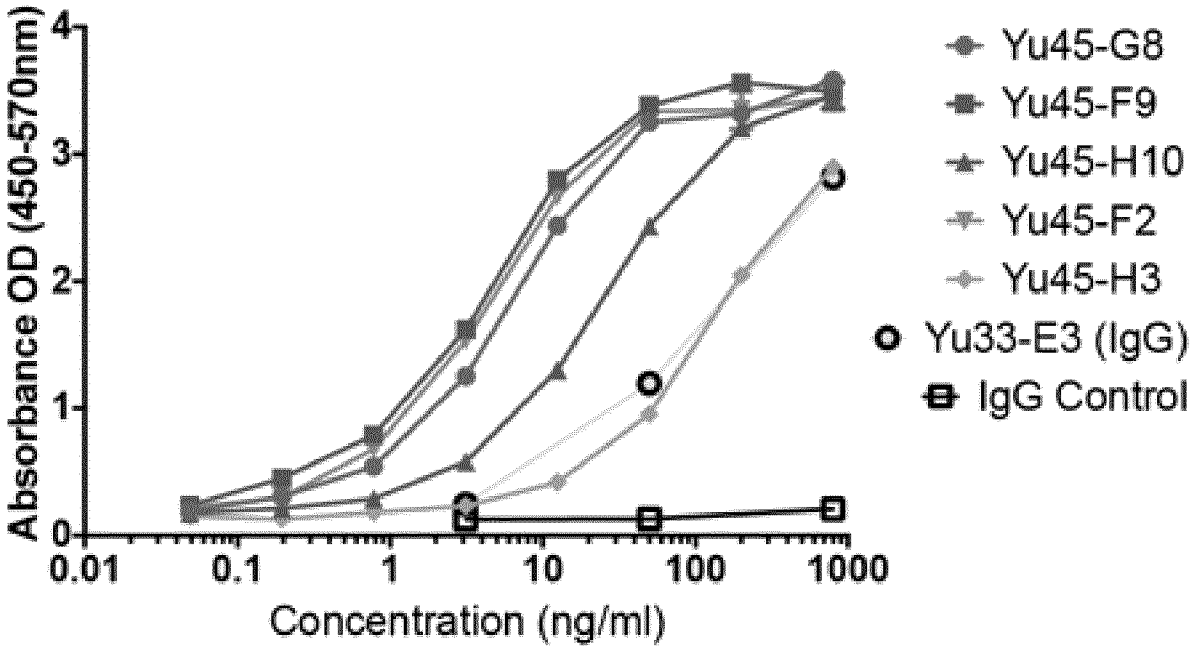


Figure 28C

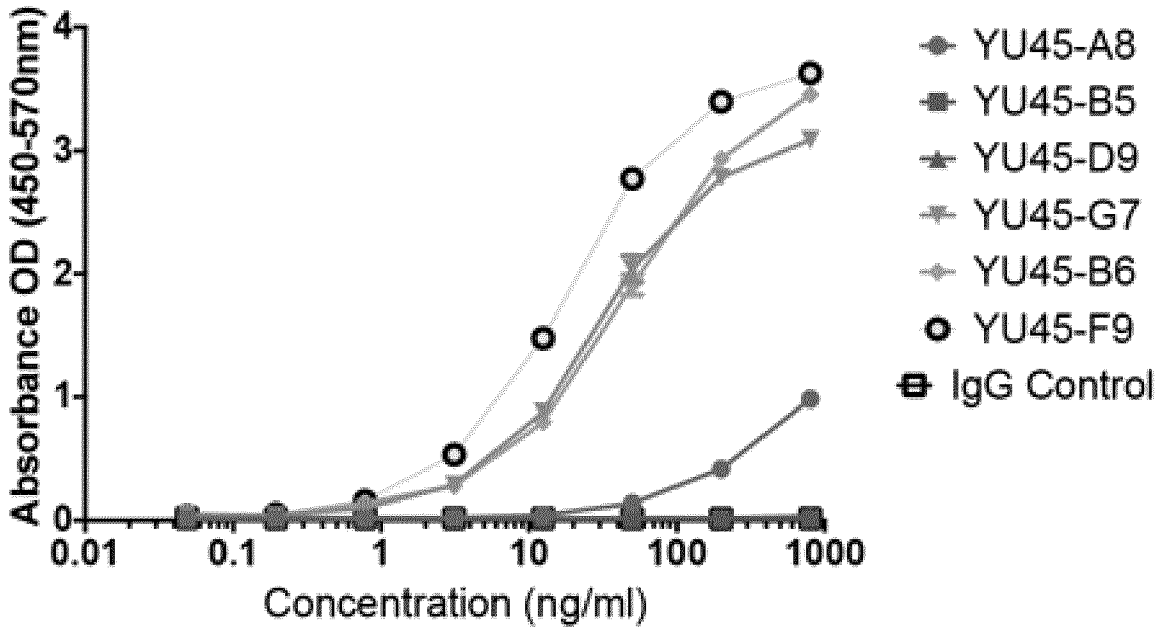


Figure 28D

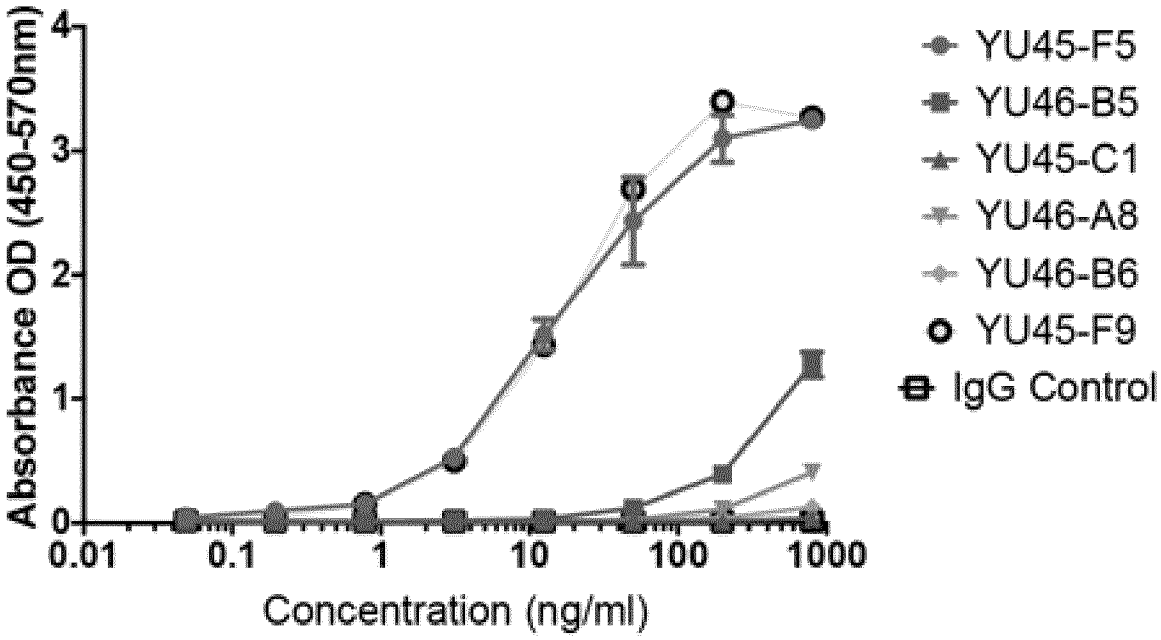


Figure 28E

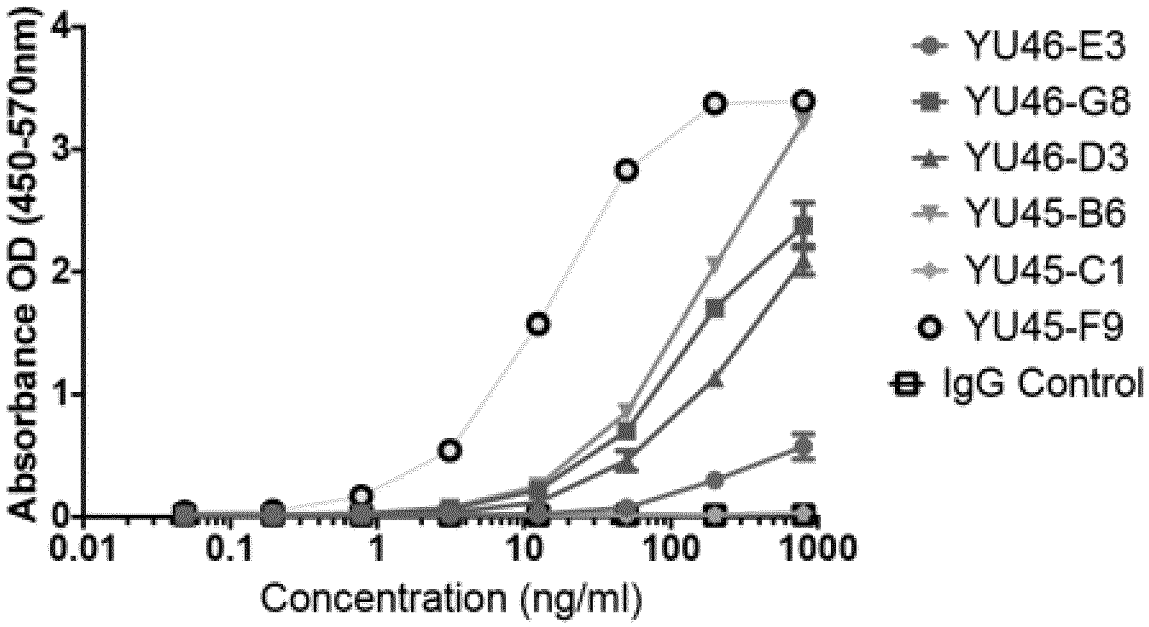


Figure 28F

Sequence Group	Clone	Format	EC50
3	YU45-A3	hIgG-Fc	14.22
6	YU45-A10	hIgG-Fc	67.67
7	YU45-D11	hIgG-Fc	186.5
8	YU45-E11	hIgG-Fc	15.66
9	YU45-D12	hIgG-Fc	14.55
11	YU45-G1	hIgG-Fc	42.75
12	YU45-B2	hIgG-Fc	6.409
14	YU45-A5	hIgG-Fc	6.543
16	YU45-E3	hIgG-Fc	33.19
18	YU45-F8	hIgG-Fc	7.786
19	YU45-G8	hIgG-Fc	6.288
21	YU45-F9	hIgG-Fc	4.016
22	YU45-H10	hIgG-Fc	24.8
24	YU45-F2	hIgG-Fc	4.239
25	YU45-H3	hIgG-Fc	126.1
27	YU45-A8	hIgG-Fc	710
31	YU45-D9	hIgG-Fc	709.8
33	YU45-G7	hIgG-Fc	10.15
36	YU45-B6	hIgG-Fc	4984
39	YU45-F5	hIgG-Fc	10.07
40	YU46-B5	hIgG-Fc	234.1
42	YU45-C1	hIgG-Fc	217
45	YU46-A8	hIgG-Fc	351.2
47	YU46-B6	hIgG-Fc	222.3
50	YU46-E3	hIgG-Fc	706.7
54	YU46-G8	hIgG-Fc	32.27
56	YU46-D3	hIgG-Fc	654.8
3	Yu33-B4	hIgG-Fc	197.6

Figure 29

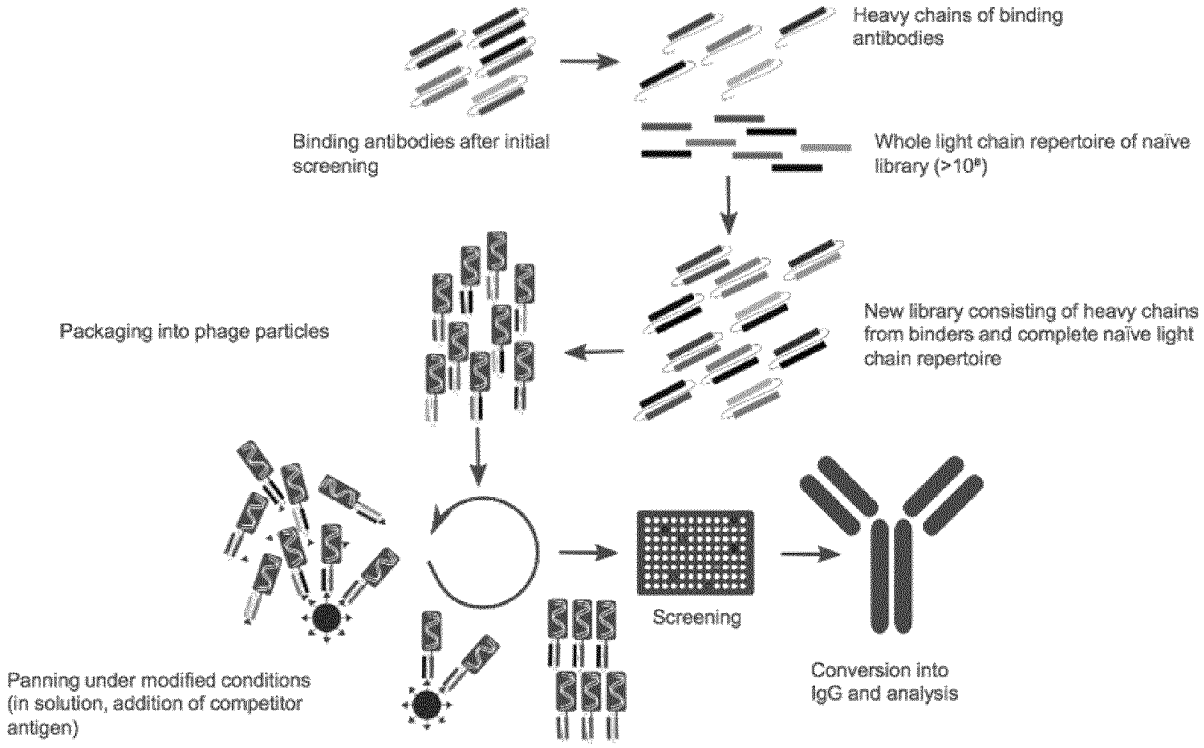


Figure 30

ID	Clone
A1	BSN-1H2
A2	BSN-1H7
A3	BSN-2E1
A4	BSN-2F5
A5	BSN-2G6
A6	BSN-3C6
A7	BSN-3C11
A8	BSN-5A6
A9	BSN-5B8
A10	BSN-5F6
A11	BSN-6F3
A12	BSN-7D4
A13	BSN-7E4
A14	BSN-7F9
A15	BSN-8C4
A16	BSN-8H11

Figure 31

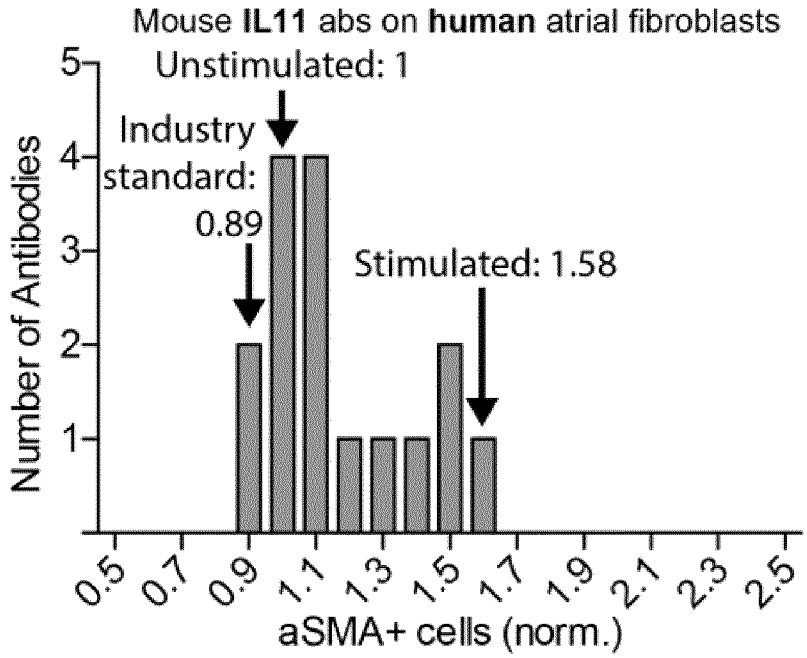


Figure 32

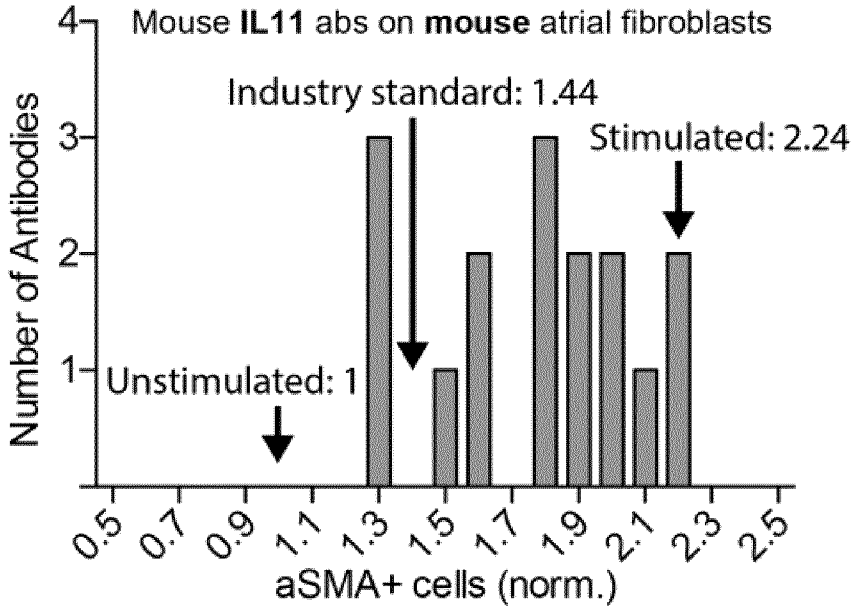


Figure 33

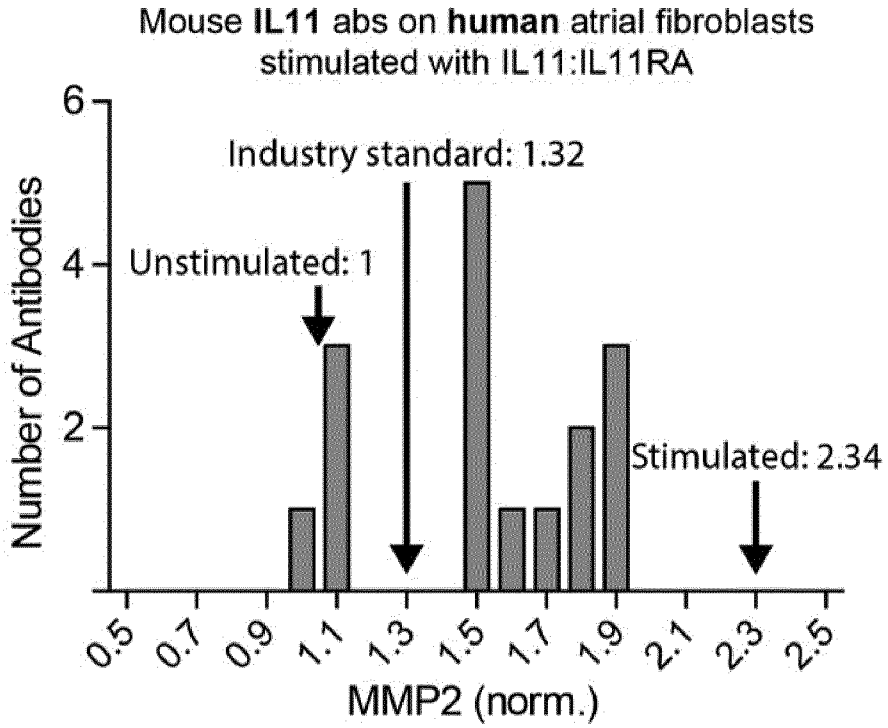


Figure 34

Antibody Candidate	Human IL11 activated fibroblasts (norm.)	Mouse IL11 activated fibroblasts (norm.)	Trans IL11 MMP2 (norm.)
Unstimulated	1	1	1
Stimulated	1.58	2.24	2.34
Industry Standard	0.89	1.44	1.32
A1	1.11	1.63	1.45
A2	1.28	2.17	1.55
A3	1.16	1.30	1.57
A4	1.41	2.14	1.78
A5	0.98	1.28	1.11
A6	0.92	1.31	1.09
A7	0.88	2.24	1.51
A8	1.05	1.49	1.88
A9	1.00	1.91	1.05
A10	1.52	1.80	1.52
A11	1.09	1.99	1.91
A12	1.12	1.82	1.07
A13	1.63	1.99	1.53
A14	1.04	1.89	1.93
A15	1.53	1.64	1.79
A16	1.08	1.82	1.66

Figure 35

		Hybridoma supernatants incubated on cells transfected with pB1-IL11-hum.FL		
		flow cytometry (Attunes)		
		Results of subcloning		
No	**Clone**	GMFI	% positive	**isotype**
1	**BSN-1H2**	197496	157%	**IgG1/kappa**
2	**BSN-1H7**	247434	197%	**IgG2a&IgG2c/kappa**
3	**BSN-2E1**	206192	164%	**IgG1/kappa**
4	**BSN-2F5**	238332	190%	**IgG1/kappa**
5	**BSN-2G6**	28568	23%	**IgG2b/kappa**
6	**BSN-3C6**	221636	176%	**IgG1/kappa**
7	**BSN-3C11**	1687	1%	**n.d. /kappa**
8	**BSN-5A6**	182487	145%	**IgG1/kappa**
9	**BSN-5B8**	236341	188%	**IgG1/kappa**
10	**BSN-5F6**	199029	158%	**IgG1/kappa**
11	**BSN-6F3**	156008	124%	**IgG2a&IgG2c/kappa**
12	**BSN-7D4**	220736	176%	**IgG2a&IgG2c/kappa**
13	**BSN-7E4**	263377	209%	**IgG1/kappa**
14	**BSN-7F9**	12798	10%	**IgG1/kappa**
15	**BSN-8C4**	275552	219%	**IgG1/kappa**
16	**BSN-8H11**	238663	190%	**IgG2b/kappa**
	positive control	125733	100%	
	negative control	1028	1%	

Figure 36A

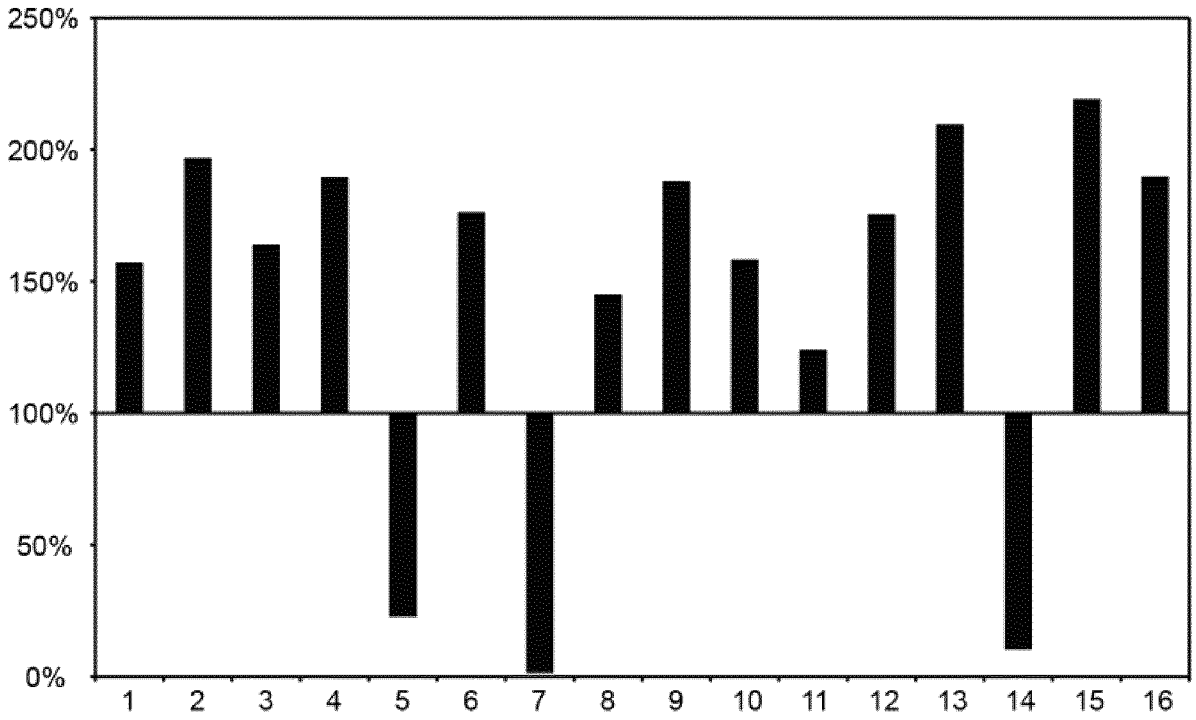


Figure 36B

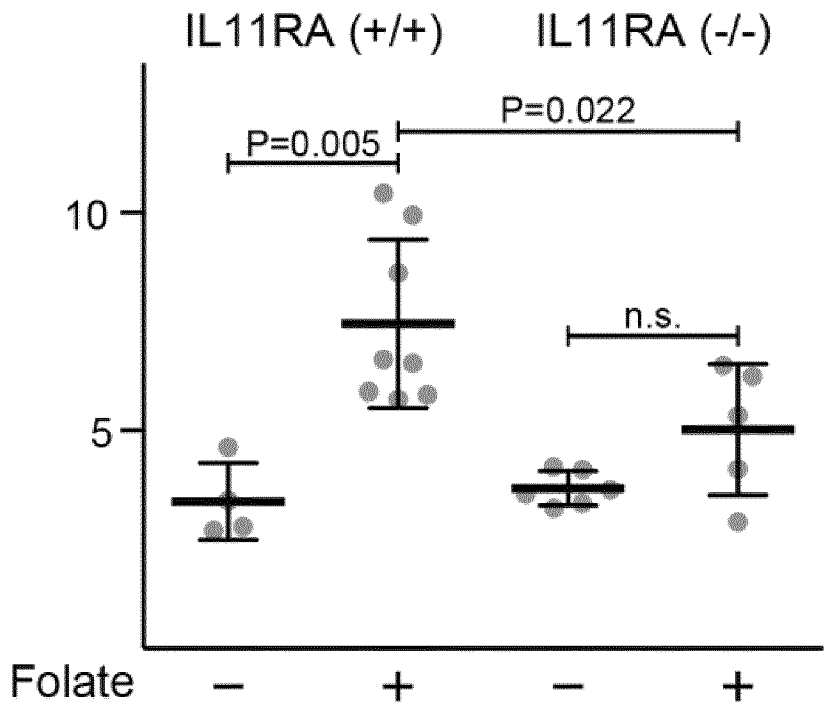


Figure 37

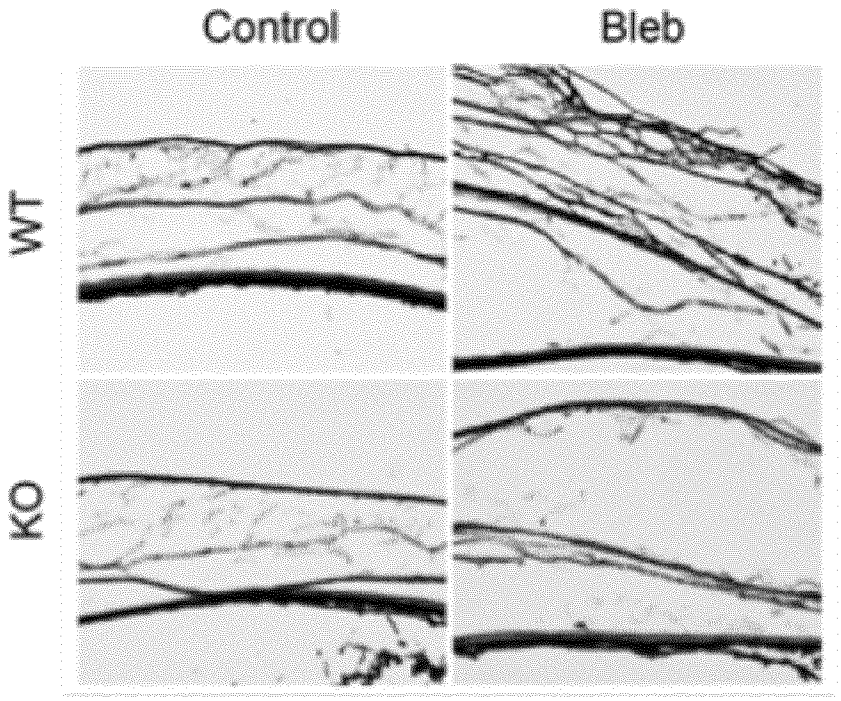


Figure 38A

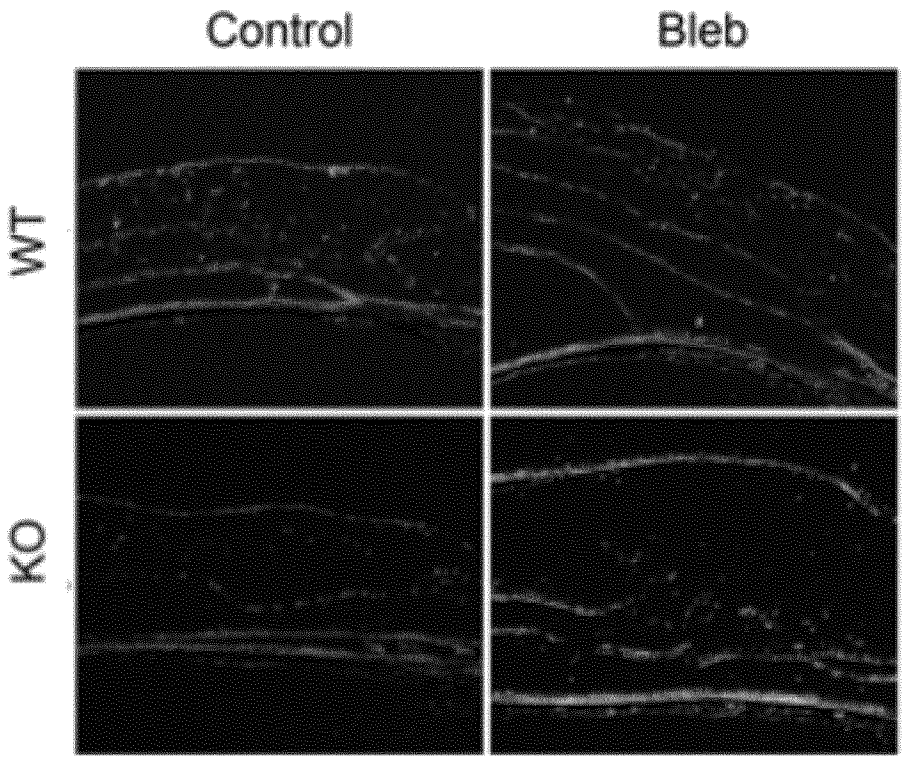


Figure 38B

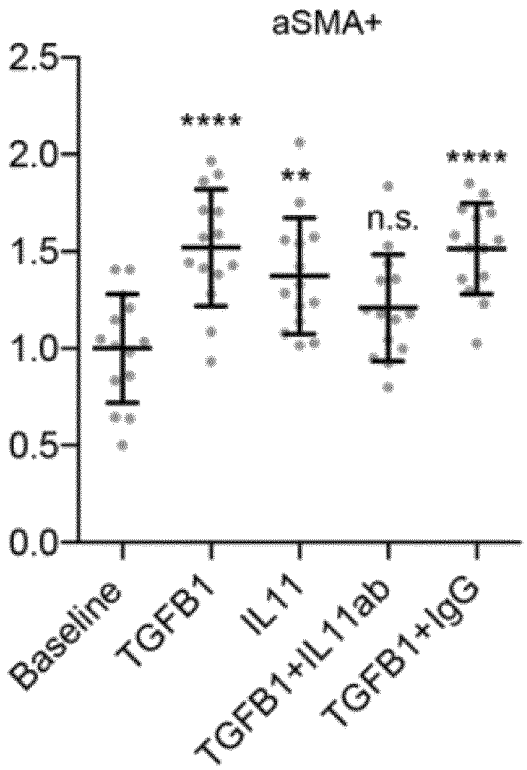


Figure 39A

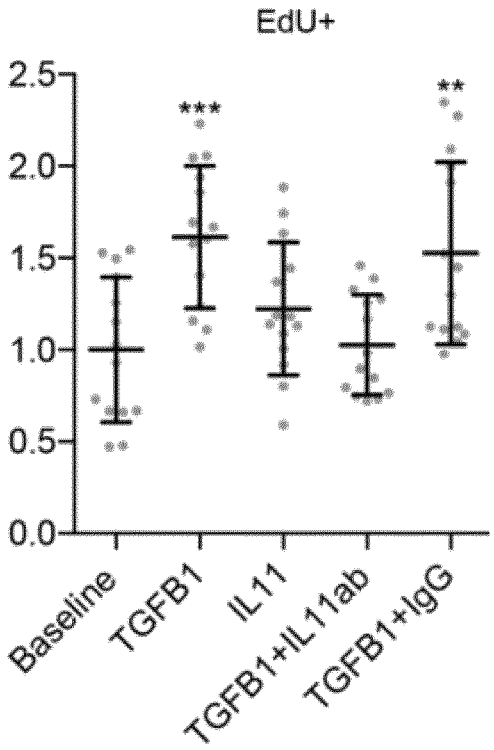


Figure 39B

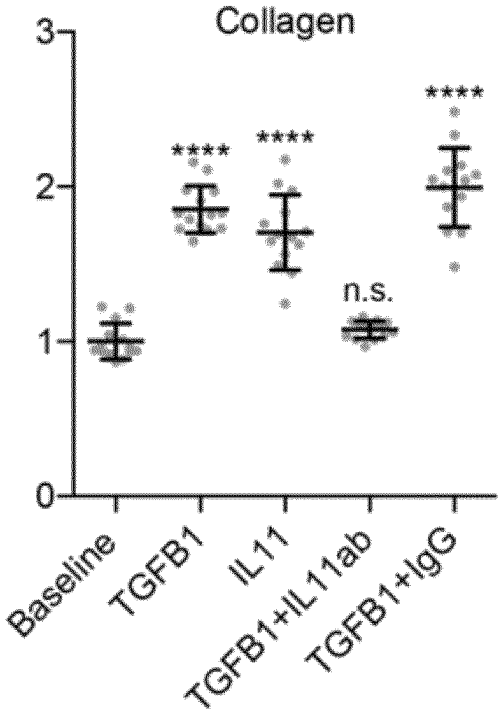


Figure 39C

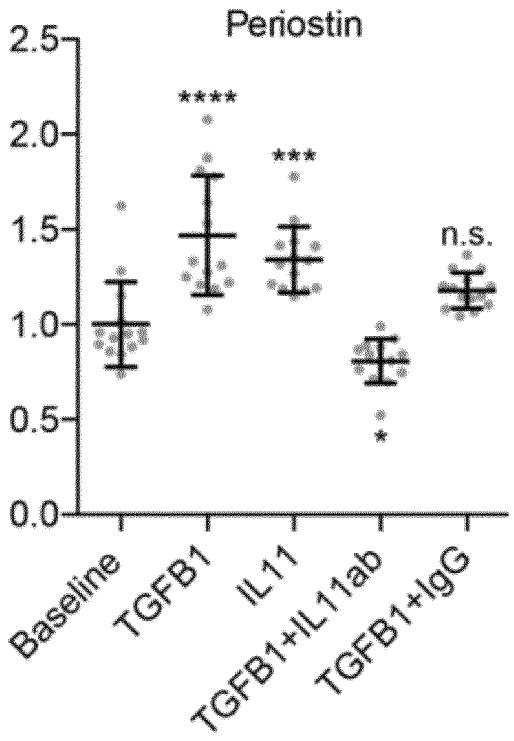


Figure 39D

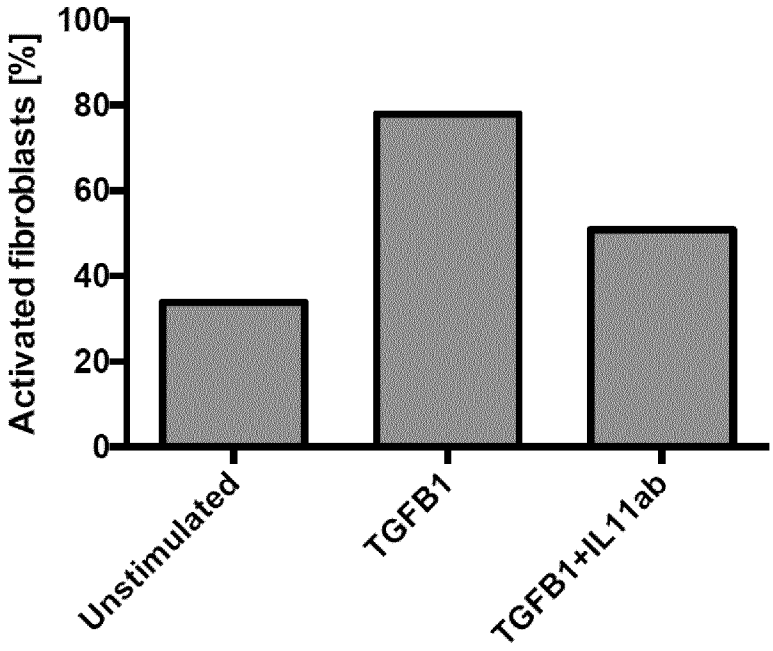


Figure 40

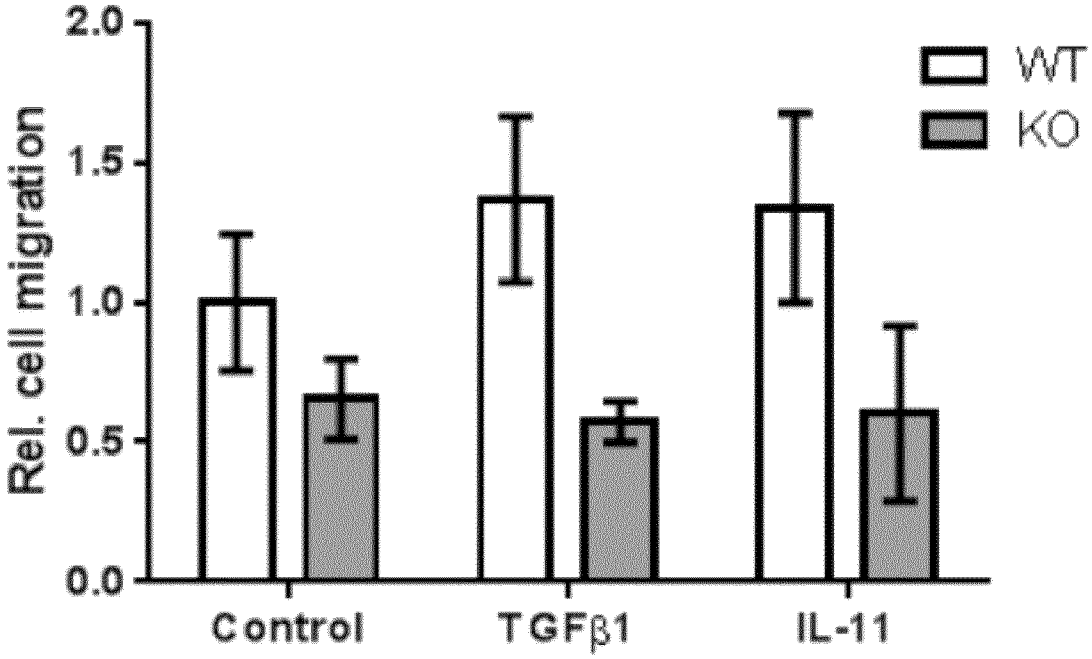


Figure 41

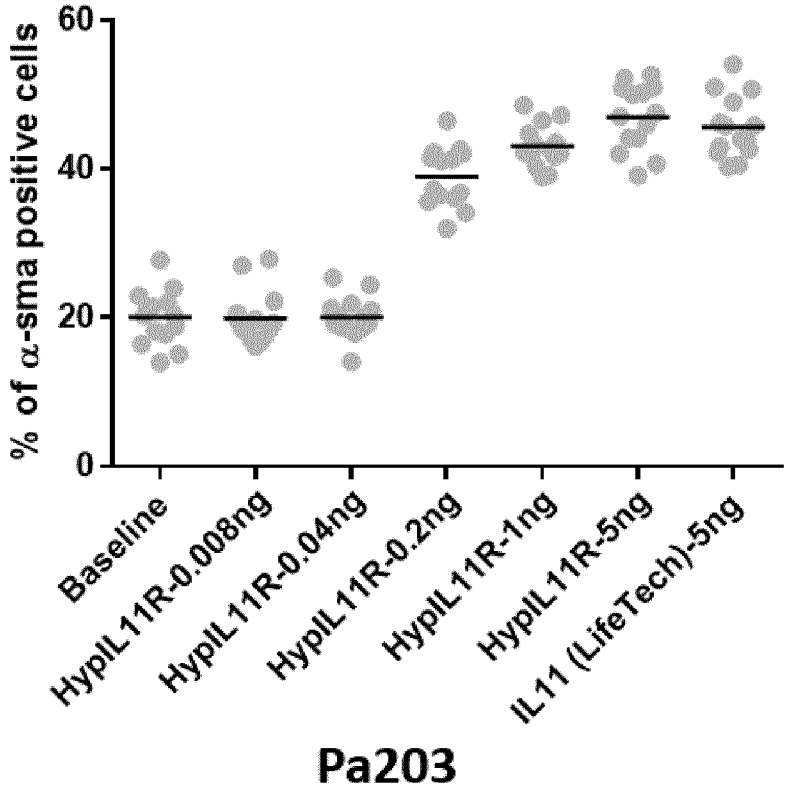


Figure 42A

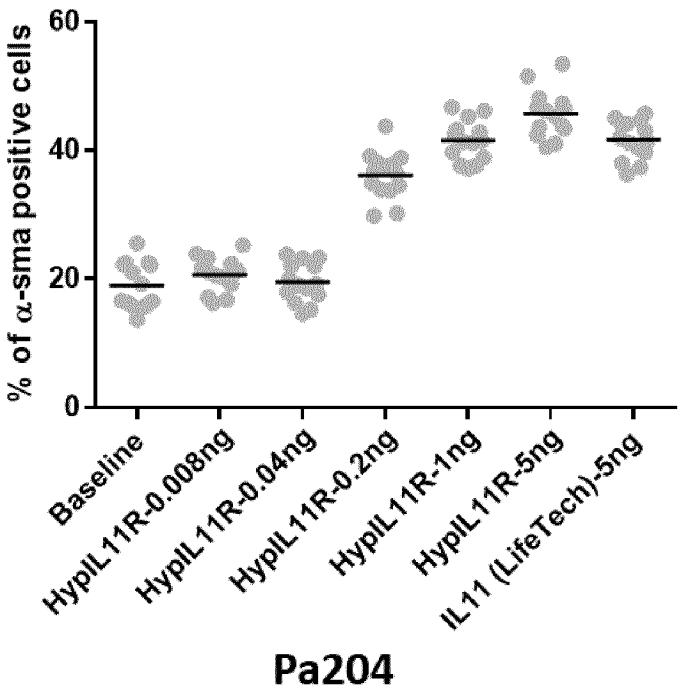


Figure 42B

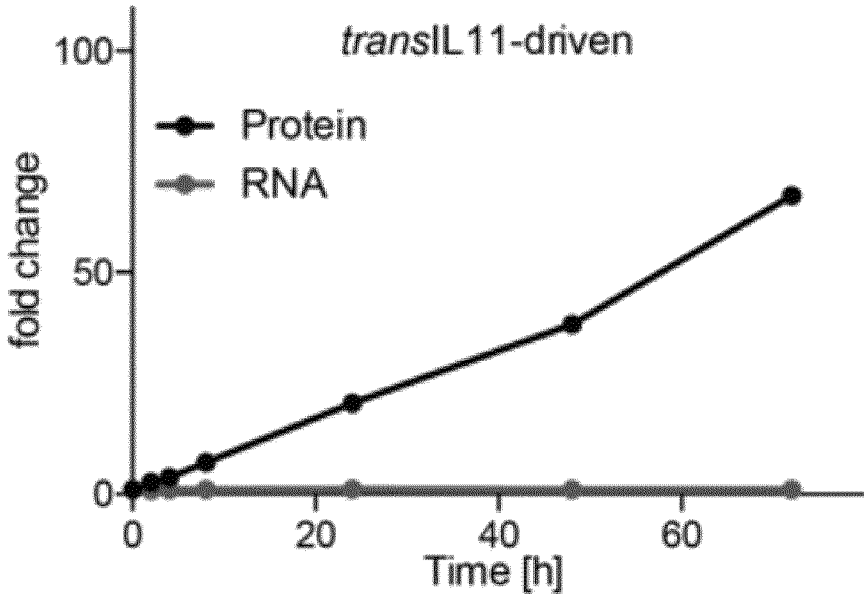


Figure 43

YU100-A10

LPVLTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHPGKAPELMIYDVSNRPSGVS NRFSGSKSGNTASLTISGLQPEDEADYYCSSFTTSIAWVFGGGTKLTVL (SEQ ID NO:267)

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTTSIAWV (SEQ ID NO:268)

YU100-A11

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:269)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-A12

LPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGDTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTKLTVL (SEQ ID NO:270)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU100-B01

QSALTQPRSVSGSPGQSVTISCTGTNTDVGAYNYVSWYQQYPGKAPKLIIYDVSKRPSGVP DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVL (SEQ ID NO:271)

LC-CDR1: NTDVGAYNY (SEQ ID NO:272)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273)

YU100-B03

QSVLTQPRSVSGSPGRSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLTLYDVVKRPSGV PDRYSGSKSGNTASLTISGLQAEDEADYYCCSYAGGYTWVFGGGTKVTVVCSYAGSYSW V (SEQ ID NO:274)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVV (SEQ ID NO:275)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276)

Figure 44

YU100-B06

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVL (SEQ ID NO:277)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278)

YU100-B07

QSALTQPRSVSGSPGQSVTMSCTGTSRDVGGYNYVSWYQHHPGKAPKLMIYDVSKRPSG VPDRFSGSKSGNTASLTISELQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:279)

LC-CDR1: SRDVGGYNY (SEQ ID NO:150)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-B08

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKVPRLLIYDVSNRPSGVS TRFSGSKSGNTASLTISGLQGEDEAEYYCSSFTSSTTWVFGGGTKLTVL (SEQ ID NO:280)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSFTSSTTWV (SEQ ID NO:281)

YU100-B09

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSDRPSGV SNRFSGSKSGNTASLTISGLQPEDEADYYCSSYRSGSTLGVRRRDQADRPR (SEQ ID NO:540)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282)

YU100-B12

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:269)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 44 (Cont.)

YU100-C02

QSALTQPRSVSGSPGQSVTISCTGTSSNVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYVWVFGGGTKLTVL (SEQ ID NO:283)

LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYVWV (SEQ ID NO:285)

YU100-C04

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHHPGKAPKLIIYDVTKRPSGVP DRFSGSKSGNTASLAISGLQAEEEADYYCCSYAGGYTWVFGGGTKLTVL (SEQ ID NO:286)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276)

YU100-C05

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGIS NRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSISWVFGGGTKLTVL (SEQ ID NO:287)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSISWV (SEQ ID NO:288)

YU100-C10

QSALTQPASVSGSPGQSITISCTGTRSDIGGYDYVSWYQQHPGKAPKLMIYDVNNRPSGVS NRFSGSKSGNTASLTISGLQAEDEAEYYCSSYTSSITWVFGGGTKVTVL (SEQ ID NO:289)

LC-CDR1: RSDIGGYDY (SEQ ID NO:290)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSYTSSITWV (SEQ ID NO:130)

YU100-C11

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQRPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQPDDEADYYCSSYTNSRTWVFGGGTKLTVL (SEQ ID NO:353)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTNSRTWV (SEQ ID NO:292)

Figure 44 (Cont.)

YU100-C12

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:269)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-D01

QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNFVSWYQQHPGKAPKLLIYDVDKRPSGV PDRFSGSKSGRTASLTISGLQTEDEAKYYCCSYAGRYTWIFGGGTKLTVL (SEQ ID NO:293)

LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVD (SEQ ID NO:295)
LC-CDR3: CSYAGRYTWI (SEQ ID NO:296)

YU100-D02

QSALTQPRSVSGSPGQSVTISCTGTSGDVGTYNYVSWYQQHPGKAPKLMIFDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVL (SEQ ID NO:297)

LC-CDR1: SGDVGTYNY (SEQ ID NO:298)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278)

YU100-D05

QSALTQPASVSGSPGQLITISCTGTNSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:299)

LC-CDR1: NSDVGGYNY (SEQ ID NO:300)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-D07

QSALTQPRSVSGSPGQSVTISCTGTSGDVGTYDYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVL (SEQ ID NO:301)

LC-CDR1: SGDVGTYDY (SEQ ID NO:302)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: NSYAGSYTWV (SEQ ID NO:278)

Figure 44 (Cont.)

YU100-D11

QSALTQPRSVSGSPGQSVTISCTGTSSNVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEANYYCASYAGNYNWVFGGGTKLTVL (SEQ ID NO:303)

LC-CDR1: SSNVGGYNY (SEQ ID NO:284)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: ASYAGNYNWV (SEQ ID NO:304)

YU100-E01

QSALTQPASVSGSPGQSITISCTGTSNDIGAYNYVSWYQQHPGKAPKLLIYDVNNRPSGVS DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVL (SEQ ID NO:305)

LC-CDR1: SNDIGAYNY (SEQ ID NO:306)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273)

YU100-E04

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKTPKLMIYDVTKRPSGV PDHFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSHIWVFGGGTKLTVL (SEQ ID NO:307)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSHIWV (SEQ ID NO:308)

YU100-E05

QAVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVL (SEQ ID NO:309)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYSWV (SEQ ID NO:273)

YU100-E06

QSALTQPASVSGFPEQSITISCTGTSSDVGGYDYVSWYQQHPGKAPKLMIYDVTNRPSGVS NRFSGSKSGNTASLTISGLQPEDEADYYCSSYTSNTTWVFGGGTKLTVLRQPKAAPSVTLF PPSS (SEQ ID NO:310)

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYTSNTTWV (SEQ ID NO:311)

Figure 44 (Cont.)

YU100-E07

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYDYVSWYQQHPGKAPELMIYDVTKRPSGV ADRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGRYTWVFGGGTKLTVL (SEQ ID NO:312)

LC-CDR1: SSDVGGYDY (SEQ ID NO:128)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGRYTWV (SEQ ID NO:313)

YU100-E08

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSRRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGNYTWMFGGGTKLTVL (SEQ ID NO:314)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGNYTWM (SEQ ID NO:315)

YU100-E09

QSALTQPRSVSGSPGQSVTISCTGTSSDVGDYDYVSWYQQHPGKAPKLIIYDVTKRPSGIP DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGRGTKLTVL (SEQ ID NO:316)

LC-CDR1: SSDVGDYDY (SEQ ID NO:317)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-E10

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIFDVSQRPSGV PDRFSASKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:318)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-E11

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:269)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 44 (Cont.)

YU100-E12

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGTAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSTTWVFGGGTKLTVL (SEQ ID NO:319)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSTTWV (SEQ ID NO:320)

YU100-F01

QSALTQPASVSGSPGQSITISCTGTGSDVGAYDYVSWYQQHPGKAPKLMIYDVNNRPSGV SNRFSGSKSGNTASLTISGLQAEDEAEYYCSSFATSISWVFGGGTRLTVL (SEQ ID NO:321)

LC-CDR1: GSDVGAYDY (SEQ ID NO:322)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: SSFATSISWV (SEQ ID NO:-408)

YU100-F02

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQADDEADYYCCSYAGSYTWIFGGGTKLTVL (SEQ ID NO:323)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWI (SEQ ID NO:324)

YU100-F05

QAVLTQPASVSGSPGQSITISCTGTSSDIGGYNYVSWYQQHPGTAPKLMIYDVSSRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKMTVL (SEQ ID NO:325)

LC-CDR1: SSDIGGYNY (SEQ ID NO:326)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-F06

QSALTQPRSVSGSPGQSVTISCTGSSSDVGGYNFVSWYRQHPGEAPKLVIFDVNKRPSGV PDRFSGSKSGNTASLTISGLQTEDEADYFCCSYAGGYTWVFGGGTKVTVV (SEQ ID NO:327)

LC-CDR1: SSDVGGYNF (SEQ ID NO:294)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276)

Figure 44 (Cont.)

YU100-F07

QSALTQPRSVSVSPGQSVTISCTGTSSDVGGYEYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQGEDAADYYCCSYAGSYTWVFGGGTTVTVL (SEQ ID NO:328)

LC-CDR1: SSDVGGYEY (SEQ ID NO:159)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-F11

QSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTQLTVL (SEQ ID NO:329)

LC-CDR1: SSDVAGYNY (SEQ ID NO:330)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-G01

QSALTQPRSVSASPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMLYDVNKRPSG VPDRFSGSKSGNTASLTISRLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:331)

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-G07

QSALTQPASVSGSPGQSITISCTGTSSDVGAYDYVSWYQQHPGKAPKLMIYDVTNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCASYTRSSVWVFGGGTKLTVL (SEQ ID NO:332)

LC-CDR1: SSDVGAYDY (SEQ ID NO:333)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: ASYTRSSVWV (SEQ ID NO:334)

YU100-G08

QSALTQPRSVSGSPGQSVTLSCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSG VPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGRYTWMFGGGTKVTVL (SEQ ID NO:335)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: CSYAGRYTWM (SEQ ID NO:336)

Figure 44 (Cont.)

YU100-G09

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTKLTVL (SEQ ID NO:337)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU100-G10

QSALTQPASVSGSLGQSITMSCTGTRRDVGGYDFVSWYQQYPGKAPKLIIYDVSNRPSGV SNRFTGSKSGNTASLTISGLQAEDEADYYCCSYAGTYTWVFGGGTKVTVL (SEQ ID NO:338)

LC-CDR1: RRDVGGYDF (SEQ ID NO:339)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340)

YU100-G11

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLTLYDVGKRPSG VPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGGYTWVFGGGTKVTVV (SEQ ID NO:341)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVG (SEQ ID NO:133)
LC-CDR3: CSYAGGYTWV (SEQ ID NO:276)

YU100-H01

QSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMIYDVSERPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:342)

LC-CDR1: SSDVGAYNY (SEQ ID NO:110)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-H02

QSALTQPRSVSRSPGQSVTISCTGTSSDVGTYNYVSWYQQHPGKAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGFYTWVFGGGTKLTVL (SEQ ID NO:343)

LC-CDR1: SSDVGTYNY (SEQ ID NO:344)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGFYTWV (SEQ ID NO:345)

Figure 44 (Cont.)

YU100-H04

QSALTQPASVSGSPGQSITISCTGTSSDIGVYNYVSWYQQHPGKAPKLMIYDVSKRPSGVP DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:346)

LC-CDR1: SSDIGVYNY (SEQ ID NO:347)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-H05

QAVLTQPRSVSGSPGQSITISCTGTGSNVGGYNYVSWYQQHPGQAPKLMIYDVSKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGTYTWVFGGGTKLTVL (SEQ ID NO:348)

LC-CDR1: GSNVGGYNY (SEQ ID NO:349)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGTYTWV (SEQ ID NO:340)

YU100-H06

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTKLTVL (SEQ ID NO: 214)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU100-H09

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:350)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

YU100-H11

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:350)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 44 (Cont.)

YU112-A07

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:13)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU112-B06

QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTIFGLQAEDEADYYCSSYTSSSSWVFGGGTKLTVL (SEQ ID NO:3)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: SSYTSSSSWV (SEQ ID NO:109)

YU112-C03

DSVMTQSPSSLSASVGDRVTITCRASQAINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISGLQPEDFATYYCQQSYSTPSWTFGQGTKVEIK (SEQ ID NO:351)

LC-CDR1: QAINSY (SEQ ID NO:352)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPSWT (SEQ ID NO:354)

YU112-C05

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:13)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU112-C09

ETTLTQSPATLSVSPGERATLSCRASQSFSSSYLAWYQQKPGQAPRLLIYGASRRAPGIPD RFSGSGSGTDFSLTISRLEPEDFAVYYCQQSSTSPTWAFGRGTKVEVK (SEQ ID NO:355)

LC-CDR1: QSFSSSY (SEQ ID NO:356)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSSTSPTWA (SEQ ID NO:357)

Figure 44 (Cont.)

YU112-D08

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:13)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

YU112-E07

EIVMTQSPDSLAVSLGERATINCKSSQSVNSAYLAWYQHKPGQPPRLLIYGASRRVTGVPD RFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSDPRWTFGQGTKVEIK (SEQ ID NO:358)

LC-CDR1: QSVNSAY (SEQ ID NO:359)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSYSDPRWT (SEQ ID NO:360)

YU112-E08

DIQMTQSPSFLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTWTFGQGTKVEIK (SEQ ID NO:35)

LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156)

YU112-F05

QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLIIYDVNNRPSGV SNRFSASKSGNTASLTISGLQAEDEADYYCNSYTSGSTWVFGGGTKLTVL (SEQ ID NO:361)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVN (SEQ ID NO:291)
LC-CDR3: NSYTSGSTWV (SEQ ID NO:362)

YU112-G01

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVL (SEQ ID NO:13)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGSYTWV (SEQ ID NO:124)

Figure 44 (Cont.)

YU112-G06

QSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRRSGV PDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGGYTWVFGGGTELTVL (SEQ ID NO:363)

LC-CDR1: ISDVGGYNY (SEQ ID NO:122)
LC-CDR2: DVT (SEQ ID NO:123)
LC-CDR3: SSYAGGYTWV (SEQ ID NO:364)

YU112-G09

DIQMTQSPSFLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPGRFCNLLLSTELQYPHV (SEQ ID NO:365)

LC-CDR1: QIISSY (SEQ ID NO:155)
LC-CDR2: AAS (SEQ ID NO:102)

YU112-H01

ETTLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISSLQPDDFATYYCQQSYSTPTWTFGQGTKVEIK (SEQ ID NO:366)

LC-CDR1: QSVSSSY (SEQ ID NO:367)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: QQSYSTPTWT (SEQ ID NO:156)

YU112-H02

QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKVMIYDVSKRPSG VPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL (SEQ ID NO:20)

LC-CDR1: SSDVGGYNY (SEQ ID NO:107)
LC-CDR2: DVS (SEQ ID NO:108)
LC-CDR3: CSYAGSYTWV (SEQ ID NO:131)

Figure 44 (Cont.)

YU100-A10

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:53)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-A11

EVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:368)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-A12

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B01

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B03

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

Figure 45

YU100-B06

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKSRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:371)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B07

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B08

EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:372)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B09

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-B12

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:373)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 45 (Cont.)

YU100-C02

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-C04

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-C05

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-C10

QVQLVESGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLITVSS
(SEQ ID NO:374)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-C11

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

Figure 45 (Cont.)

YU100-C12

EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:375)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-D01

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:376)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-D02

QVRLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:377)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-D05

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNK YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:378)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-D07

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRLTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:379)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 45 (Cont.)

YU100-D11

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E01

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:378)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E04

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:378)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E05

EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:372)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E06

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

Figure 45 (Cont.)

YU100-E07

QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNR YYADSVKGRFAISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:380)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNR (SEQ ID NO:381)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E08

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:382)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-E09

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:383)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-E10

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-E11

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:384)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 45 (Cont.)

YU100-E12

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-F01

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-F02

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:53)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-F05

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:378)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-F06

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:384)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 45 (Cont.)

YU100-F07

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:383)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-F11

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-G01

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-G07

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-G08

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

Figure 45 (Cont.)

YU100-G09

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:53)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-G10

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-G11

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:384)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-H01

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:382)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-H02

QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTL
VTVSS (SEQ ID NO:385)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

Figure 45 (Cont.)

YU100-H04

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:383)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-H05

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-H06

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU100-H09

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV TVSS (SEQ ID NO:382)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU100-H11

QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS (SEQ ID NO:370)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

Figure 45 (Cont.)

YU112-A07

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:386)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU112-B06

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:369)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU112-C03

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSS
(SEQ ID NO:387)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207)

YU112-C05

EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLV
TVSS (SEQ ID NO:62)

HC-CDR1: GFTFSSYA (SEQ ID NO:190)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: ARIMGYDYGDYDVVDY (SEQ ID NO:199)

YU112-C09

QVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSS
(SEQ ID NO:388)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235)

Figure 45 (Cont.)

YU112-D08

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVEGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:389)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU112-E07

QVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNK
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSS
(SEQ ID NO:388)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235)

YU112-E08

*VTLKESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSS
(SEQ ID NO:85)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207)

YU112-F05

EVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:390)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU112-G01

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS
(SEQ ID NO:73)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

Figure 45 (Cont.)

YU112-G06

QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSS
(SEQ ID NO:391)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKIGATDPLDY (SEQ ID NO:187)

YU112-G09

*VTLKESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSS
(SEQ ID NO:85)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGGKSYYGFDY (SEQ ID NO:207)

YU112-H01

QVQLVESGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSS
(SEQ ID NO:392)

HC-CDR1: GFTFGSYG (SEQ ID NO:234)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKGSYYFDY (SEQ ID NO:235)

YU112-H02

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKY
YADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSS
(SEQ ID NO:73)

HC-CDR1: GFTFSSYG (SEQ ID NO:186)
HC-CDR2: ISYDGSNK (SEQ ID NO:184)
HC-CDR3: AKLSGPNGVDY (SEQ ID NO:197)

Figure 45 (Cont.)

Clone	CDR 1	CDR 2	CDR 3
	Light Chain		
YU100-A10	SSDVGAYNY (SEQ ID NO:110)	DVS (SEQ ID NO:108)	SSFTTSIAWV (SEQ ID NO:268)
YU100-A11, YU100-B12, YU100-C12, YU100-E10, YU100-E11, YU100-H09, YU100-H11, YU112-H02	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-A12	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYAGSYTWV (SEQ ID NO:124)
YU100-B01	NTDVGAYNY (SEQ ID NO:272)	DVS (SEQ ID NO:108)	CSYAGSYSWV (SEQ ID NO:273)
YU100-B03	SSDVGGYNY (SEQ ID NO:107)	DVV (SEQ ID NO:275)	CSYAGGYTWV (SEQ ID NO:276)
YU100-B06	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	NSYAGSYTWV (SEQ ID NO:278)
YU100-B07	SRDVGGYNY (SEQ ID NO:150)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-B08	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSFTSSTTWV (SEQ ID NO:281)
YU100-B09	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282)
YU100-C02	SSNVGGYNY (SEQ ID NO:284)	DVS (SEQ ID NO:108)	CSYAGSYVWV (SEQ ID NO:285)
YU100-C04	SSDVGGYNY (SEQ ID NO:107)	DVT (SEQ ID NO:123)	CSYAGGYTWV (SEQ ID NO:276)
YU100-C05	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSISWV (SEQ ID NO:288)
YU100-C10	RSDIGGYDY (SEQ ID NO:290)	DVN (SEQ ID NO:291)	SSYTSSITWV (SEQ ID NO:130)
YU100-C11	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTNSRTWV (SEQ ID NO:292)
YU100-D01	SSDVGGYNF (SEQ ID NO:294)	DVD (SEQ ID NO:295)	CSYAGRYTWI (SEQ ID NO:296)
YU100-D02	SGDVGTYNY (SEQ ID NO:298)	DVS (SEQ ID NO:108)	NSYAGSYTWV (SEQ ID NO:278)
YU100-D05	NSDVGGYNY (SEQ ID NO:300)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-D07	SGDVGTYDY (SEQ ID NO:302)	DVS (SEQ ID NO:108)	NSYAGSYTWV (SEQ ID NO:278)
YU100-D11	SSNVGGYNY (SEQ ID NO:284)	DVS (SEQ ID NO:108)	ASYAGNYNWV (SEQ ID NO:304)
YU100-E01	SNDIGAYNY (SEQ ID NO:306)	DVN (SEQ ID NO:291)	CSYAGSYSWV (SEQ ID NO:273)
YU100-E04	SSDVGGYNY (SEQ ID NO:107)	DVT (SEQ ID NO:123)	CSYAGSHIWV (SEQ ID NO:308)
YU100-E05	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGSYSWV (SEQ ID NO:273)
YU100-E06	SSDVGGYDY (SEQ ID NO:128)	DVT (SEQ ID NO:123)	SSYTSNTTWV (SEQ ID NO:311)
YU100-E07	SSDVGGYDY (SEQ ID NO:128)	DVT (SEQ ID NO:123)	CSYAGRYTWV (SEQ ID NO:313)

Figure 46

Clone	CDR 1	CDR 2	CDR 3
Light Chain			
YU100-E08	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	CSYAGNYTWM (SEQ ID NO:315)
YU100-E09	SSDVGDYDY (SEQ ID NO:317)	DVT (SEQ ID NO:123)	CSYAGSYTWV (SEQ ID NO:131)
YU100-E12	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSTTWV (SEQ ID NO:320)
YU100-F01	GSDVGAYDY (SEQ ID NO:322)	DVN (SEQ ID NO:291)	SSFATSISWV (SEQ ID NO:408)
YU100-F02	SSDVGGYNY (SEQ ID NO:107)	DVT (SEQ ID NO:123)	CSYAGSYTWI (SEQ ID NO:324)
YU100-F05	SSDIGGYNY (SEQ ID NO:326)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-F06	SSDVGGYNF (SEQ ID NO:294)	DVN (SEQ ID NO:291)	CSYAGGYTWV (SEQ ID NO:276)
YU100-F07	SSDVGGYEY (SEQ ID NO:159)	DVT (SEQ ID NO:123)	CSYAGSYTWV (SEQ ID NO:131)
YU100-F11	SSDVAGYNY (SEQ ID NO:330)	DVT (SEQ ID NO:123)	CSYAGSYTWV (SEQ ID NO:131)
YU100-G01	SSDVGAYNY (SEQ ID NO:110)	DVN (SEQ ID NO:291)	CSYAGSYTWV (SEQ ID NO:131)
YU100-G07	SSDVGAYDY (SEQ ID NO:333)	DVT (SEQ ID NO:123)	ASYTRSSVWV (SEQ ID NO:334)
YU100-G08	SSDVGGYNY (SEQ ID NO:107)	DVN (SEQ ID NO:291)	CSYAGRYTWM (SEQ ID NO:336)
YU100-G09, YU112-A07, YU112-C05, YU112-D08, YU112-G01	ISDVGGYNY (SEQ ID NO:122)	DVT (SEQ ID NO:123)	SSYAGSYTWV (SEQ ID NO:124)
YU100-G10	RRDVGGYDF (SEQ ID NO:339)	DVS (SEQ ID NO:108)	CSYAGTYTWV (SEQ ID NO:340)
YU100-G11	SSDVGGYNY (SEQ ID NO:107)	DVG (SEQ ID NO:133)	CSYAGGYTWV (SEQ ID NO:276)
YU100-H01	SSDVGAYNY (SEQ ID NO:110)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-H02	SSDVGTYNY (SEQ ID NO:344)	DVS (SEQ ID NO:108)	CSYAGFYTWV (SEQ ID NO:345)
YU100-H04	SSDIGVYNY (SEQ ID NO:347)	DVS (SEQ ID NO:108)	CSYAGSYTWV (SEQ ID NO:131)
YU100-H05	GSNVGGYNY (SEQ ID NO:349)	DVS (SEQ ID NO:108)	CSYAGTYTWV (SEQ ID NO:340)
YU100-H06	SSDVGGYNY (SEQ ID NO:107)	DVT (SEQ ID NO:123)	SSYAGSYTWV (SEQ ID NO:124)
YU112-B06	SSDVGGYNY (SEQ ID NO:107)	DVS (SEQ ID NO:108)	SSYTSSSSWV (SEQ ID NO:109)
YU112-C03	QAINSY (SEQ ID NO:352)	AAS (SEQ ID NO:102)	QQSYSTPSWT (SEQ ID NO:354)
YU112-C09	QSFSSSY (SEQ ID NO:356)	GAS (SEQ ID NO:138)	QQSSTSPTWA (SEQ ID NO:357)

Figure 46 (Cont.)

Clone	CDR 1	CDR 2	CDR 3
Light Chain			
YU112-E07	QSVNSAY (SEQ ID NO:359)	GAS (SEQ ID NO:138)	QQSYSDPRWT (SEQ ID NO:360)
YU112-E08	QIISSY (SEQ ID NO:155)	AAS (SEQ ID NO:102)	QQSYSTPTWT (SEQ ID NO:156)
YU112-F05	SSDVGGYNY (SEQ ID NO:107)	DVN (SEQ ID NO:291	NSYTSGSTWV (SEQ ID NO:362)
YU112-G06	ISDVGGYNY (SEQ ID NO:122)	DVT (SEQ ID NO:123)	SSYAGGYTWV (SEQ ID NO:364)
YU112-G09	QIISSY (SEQ ID NO:155)	AAS (SEQ ID NO:102)	
YU112-H01	QSVSSSY (SEQ ID NO:367)	GAS (SEQ ID NO:138)	QQSYSTPTWT (SEQ ID NO:156)

Figure 46 (Cont.)

Clone	CDR 1	CDR 2	CDR 3
Heavy Chain			
YU100-A10, YU100-A11, YU100-A12, YU100-B01, YU100-B03, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-C02, YU100-C04, YU100-C05, YU100-C11, YU100-D02, YU100-D05, YU100-D11, YU100-E01, YU100-E04, YU100-E05, YU100-E06, YU100-E10, YU100-E12, YU100-F01, YU100-F02, YU100-F05, YU100-F11, YU100-G01, YU100-G07, YU100-G08, YU100-G09, YU100-G10, YU100-H05, YU100-H06, YU100-H11, YU112-A07, YU112-B06, YU112-D08, YU112-G06	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKIGATDPLDY (SEQ ID NO:187)
YU100-B12, YU100-C12, YU100-D01, YU100-D07, YU100-E08, YU100-E09, YU100-F07, YU100-H01, YU100-H04, YU100-H09, YU112-C05	GFTFSSYA (SEQ ID NO:190)	ISYDGSNK (SEQ ID NO:184)	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU100-C10, YU112-F05	GFTFGSYG (SEQ ID NO:234)	ISYDGSNK (SEQ ID NO:184)	AKIGATDPLDY (SEQ ID NO:187)

Figure 47

Clone	CDR 1	CDR 2	CDR 3
Heavy Chain			
YU100-E07	GFTFSSYG (SEQ ID NO:186)	ISYDGSNR (SEQ ID NO:381)	AKIGATDPLDY (SEQ ID NO:187)
YU100-E11, YU100-F06, YU100-G11, YU100-H02	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU112-C03, YU112-E08, YU112-G09	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKGGKSYYGFDY (SEQ ID NO:207)
YU112-C09, YU112-E07, YU112-H01	GFTFGSYG (SEQ ID NO:234)	ISYDGSNK (SEQ ID NO:184)	AKGSYYFDY (SEQ ID NO:235)
YU112-G01, YU112-H02	GFTFSSYG (SEQ ID NO:186)	ISYDGSNK (SEQ ID NO:184)	AKLSGPNGVDY (SEQ ID NO:197)

Figure 47 (Cont.)

Clone(s)	LC-CDR1	Sequence family	Family Consensus
YU100-D01, YU100-F06	SSDVGGYNF	matLC-CDR1-1	$X_{138}X_{139}$DVGGY$X_{140}X_{141}$ (SEQ ID NO:393) X_{138} = S, N or I X_{139} = S or R X_{140} = N, E or D X_{141} = Y or F
YU100-F07	SSDVGGYEY		
YU100-B07	SRDVGGYNY		
YU100-D05	NSDVGGYNY		
YU100-E06, YU100-E07	SSDVGGYDY		
YU100-A11, YU100-B12, YU100-C12, YU100-E10, YU100-E11, YU100-H09, YU100-H11, YU112-H02, YU100-A12, YU100-B03, YU100-B06, YU100-B08, YU100-B09, YU100-C04, YU100-C05, YU100-C11, YU100-E04, YU100-E05, YU100-E08, YU100-E12, YU100-F02, YU100-G08, YU100-G11, YU100-H06, YU112-B06, YU112-F05	SSDVGGYNY		
YU100-G09, YU112-A07, YU112-C05, YU112-D08, YU112-G01, YU112-G06	ISDVGGYNY		
YU100-E09	SSDVGDYDY	matLC-CDR1-2	SSDV$X_{142}X_{143}$YX_{144}Y (SEQ ID NO:394) X_{142} = G or A X_{143} = D, G or T X_{144} = N or D
YU100-F11	SSDVAGYNY		
YU100-H02	SSDVGTYNY		
YU100-B01	NTDVGAYNY	matLC-CDR1-3	$X_{145}X_{146}$DX_{147}GAYNY (SEQ ID NO:395) X_{145} = S or N X_{146} = N, T or S X_{147} = V or I
YU100-E01	SNDIGAYNY		
YU100-A10, YU100-G01, YU100-H01	SSDVGAYNY		

Figure 48A

Clone(s)	LC-CDR1	Sequence family	Family Consensus
YU100-H04	SSDIGVYNY	matLC-CDR1-4	SSDIGX_{148}YNY (SEQ ID NO:396) X_{148} = V or G
YU100-F05	SSDIGGYNY		
YU100-G07	SSDVGAYDY	matLC-CDR1-5	X_{149}SDVGAYDY (SEQ ID NO:397) X_{149} = S or G
YU100-F01	GSDVGAYDY		
YU100-D02	SGDVGTYNY	matLC-CDR1-6	SGDVGTYX_{150}Y (SEQ ID NO:398) X_{150} = N or D
YU100-D07	SGDVGTYDY		
YU112-C03	QAINSY	matLC-CDR1-7	QX_{151}IX_{152}SY (SEQ ID NO:399) X_{151} = A or I X_{152} = N or S
YU112-E08, YU112-G09	QIISSY		
YU112-C09	QSFSSSY	matLC-CDR1-8	QSX_{153}SSSY (SEQ ID NO:400) X_{153} = F or V
YU112-H01	QSVSSSY		
YU100-C10	RSDIGGYDY	matLC-CDR1-9	RX_{154}DX_{155}GGYDX_{156} (SEQ ID NO:401) X_{154} = S or R X_{155} = I or V X_{156} = Y or F
YU100-G10	RRDVGGYDF		
YU100-C02, YU100-D11	SSNVGGYNY	matLC-CDR1-10	SSNVGGYNY (SEQ ID NO:284)
YU100-H05	GSNVGGYNY	matLC-CDR1-11	GSNVGGYNY (SEQ ID NO:349)
YU112-E07	QSVNSAY	matLC-CDR1-12	QSVNSAY (SEQ ID NO:359)

Figure 48A (Cont.)

Clone(s)	LC-CDR2	Sequence family	Family Consensus
YU100-A10, YU100-A11, YU100-B12, YU100-C12, YU100-E10, YU100-E11, YU100-H09, YU100-H11, YU112-H02, YU100-A12, YU100-B01, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-C02, YU100-C05, YU100-C11, YU100-D02, YU100-D05, YU100-D07, YU100-D11, YU100-E05, YU100-E08, YU100-E12, YU100-F05, YU100-G10, YU100-H01, YU100-H02, YU100-H04, YU100-H05, YU112-B06	DVS	matLC-CDR2-1	DVX_{157} (SEQ ID NO:402) X_{157} = S, T, N, G, V or D
YU100-B03	DVV		
YU100-C04, YU100-E04, YU100-E06, YU100-E07, YU100-E09, YU100-F02, YU100-F07, YU100-F11, YU100-G07, YU100-G09, YU112-A07, YU112-C05, YU112-D08, YU112-G01, YU100-H06, YU112-G06,	DVT		

Figure 48B

Clone(s)	LC-CDR2	Sequence family	Family Consensus
YU100-D01	DVD	matLC-CDR2-1	DVX_{157} (SEQ ID NO:402) X_{157} = S, T, N, G, V or D
YU100-C10 **YU100-E01** **YU100-F01** **YU100-F06** **YU100-G01** **YU100-G08** **YU112-F05**	DVN		
YU100-G11	DVG		
YU112-C03, **YU112-E08,** **YU112-G09**	AAS	matLC-CDR2-2	X_{158}AS (SEQ ID NO:403) X_{158} = A or G
YU112-C09 **YU112-E07** **YU112-H01**	GAS		

Figure 48B (Cont.)

Clone(s)	LC-CDR3	Sequence family	Family Consensus
YU100-A11, YU100-B12, YU100-C12, YU100-E10, YU100-E11, YU100-H09, YU100-H11, YU112-H02, YU100-B07, YU100-D05, YU100-E09, YU100-F05, YU100-F07, YU100-F11, YU100-G01, YU100-H01, YU100-H04	CSYAGSYTWV	matLC-CDR3-1	X_{159}SYAG$X_{160}X_{161}X_{162}$WX_{163} (SEQ ID NO:404) X_{159} = C, S, A or N X_{160} = S, R, N, G, T or F X_{161} = Y or H X_{162} = T, N, I, S or V X_{163} = V, M or I
YU100-A12, YU100-G09, YU112-A07, YU112-C05, YU112-D08, YU112-G01, YU100-H06	SSYAGSYTWV		
YU100-B01, YU100-E01, YU100-E05	CSYAGSYSWV		
YU100-B03, YU100-C04, YU100-F06, YU100-G11	CSYAGGYTWV		
YU100-B06, YU100-D02, YU100-D07	NSYAGSYTWV		
YU100-C02	CSYAGSYVWV		
YU100-D01	CSYAGRYTWI		
YU100-G08	CSYAGRYTWM		
YU100-G10, YU100-H05	CSYAGTYTWV		
YU100-H02	CSYAGFYTWV		
YU100-E04	CSYAGSHIWV		
YU100-E07	CSYAGRYTWV		
YU100-E08	CSYAGNYTWM		
YU100-F02	CSYAGSYTWI		
YU100-D11	ASYAGNYNWV		
YU112-G06	SSYAGGYTWV		
YU100-C11	SSYTNSRTWV	matLC-CDR3-2	SSYT$X_{164}X_{165}X_{166}X_{167}$WV (SEQ ID NO:405) X_{164} = S or N X_{165} = S or N X_{166} = T, I, S or R X_{167} = T or S
YU100-E06	SSYTSNTTWV		
YU100-E12	SSYTSSTTWV		
YU112-B06	SSYTSSSSWV		
YU100-C05	SSYTSSISWV		
YU100-C10	SSYTSSITWV		

Figure 48C

Clone(s)	LC-CDR3	Sequence family	Family Consensus
YU112-C03	QQSYSTPSWT	matLC-CDR3-3	QQSYSX_{168}PX_{169}WT (SEQ ID NO:406) X_{168} = T or D X_{169} = S, R or T
YU112-E07	QQSYSDPRWT		
YU112-E08, YU112-H01	QQSYSTPTWT		
YU100-A10	SSFTTSIAWV	matLC-CDR3-4	SSF$X_{170}X_{171}$S$X_{172}X_{173}$WV (SEQ ID NO:407) X_{170} = T or A X_{171} = T or S X_{172} = I or T X_{173} = A or T
YU100-B08	SSFTSSTTWV		
YU100-F01	SSFATSISWV		
YU112-F05	NSYTSGSTWV	matLC-CDR3-5	NSYTSGSTWV (SEQ ID NO:362)
YU100-G07	ASYTRSSVWV	matLC-CDR3-6	ASYTRSSVWV (SEQ ID NO:334)
YU112-C09	QQSSTSPTWA	matLC-CDR3-7	QQSSTSPTWA (SEQ ID NO:357)
YU100-B09	SSYRSGSTLGVRRRDQADRPR	matLC-CDR3-8	SSYRSGSTLGVRRRDQADRPR (SEQ ID NO:282)

Figure 48C (Cont.)

Clone(s)	HC-CDR1	Sequence family	Family Consensus
YU100-A10, YU100-A11, YU100-A12, YU100-B01, YU100-B03, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-C02, YU100-C04, YU100-C05, YU100-C11, YU100-D02, YU100-D05, YU100-D11, YU100-E01, YU100-E04, YU100-E05, YU100-E06, YU100-E10, YU100-E12, YU100-F01, YU100-F02, YU100-F05, YU100-F11, YU100-G01, YU100-G07, YU100-G08, YU100-G09, YU100-G10, YU100-H05, YU100-H06, YU100-H11, YU112-A07, YU112-B06, YU112-D08, YU112-G06 YU100-E07, YU100-E11, YU100-F06, YU100-G11, YU100-H02, YU112-C03, YU112-E08, YU112-G09, YU112-G01, YU112-H02	GFTFSSYG	matHC-CDR1-1	GFTFX$_{174}$SYX$_{175}$ (SEQ ID NO:409) X$_{174}$ = S or G X$_{175}$ = G or A

Figure 49A

Clone(s)	HC-CDR1	Sequence family	Family Consensus
YU100-B12, YU100-C12, YU100-D01, YU100-D07, YU100-E08, YU100-E09, YU100-F07, YU100-H01, YU100-H04, YU100-H09, YU112-C05	GFTFSSYA	matHC-CDR1-1	$GFTFX_{174}SYX_{175}$ (SEQ ID NO:409) X_{174} = S or G X_{175} = G or A
YU100-C10, YU112-F05, YU112-C09, YU112-E07, YU112-H01	GFTFGSYG		

Figure 49A (Cont.)

Clone(s)	HC-CDR2	Sequence family	Family Consensus
YU100-A10, YU100-A11, YU100-A12, YU100-B01, YU100-B03, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-C02, YU100-C04, YU100-C05, YU100-C11, YU100-D02, YU100-D05, YU100-D11, YU100-E01, YU100-E04, YU100-E05, YU100-E06, YU100-E10, YU100-E12, YU100-F01, YU100-F02, YU100-F05, YU100-F11, YU100-G01, YU100-G07, YU100-G08, YU100-G09, YU100-G10, YU100-H05, YU100-H06, YU100-H11, YU112-A07, YU112-B06, YU112-D08, YU112-G06 YU100-B12, YU100-C12, YU100-D01, YU100-D07, YU100-E08, YU100-E09, YU100-F07, YU100-H01, YU100-H04, YU100-H09, YU112-C05,	ISYDGSNK	matHC-CDR2-1	ISYDGSNX_{176} (SEQ ID NO:410) X_{176} = K or R

Figure 49B

Clone(s)	HC-CDR2	Sequence family	Family Consensus
YU100-C10, YU112-F05, YU100-E11, YU100-F06, YU100-G11, YU100-H02, YU112-C03, YU112-E08, YU112-G09, YU112-C09, YU112-E07, YU112-H01, YU112-G01, YU112-H02	ISYDGSNK	matHC-CDR2-1	ISYDGSNX_{176} (SEQ ID NO:410) X_{176} = K or R
YU100-E07	ISYDGSNR		

Figure 49B (Cont.)

Clone(s)	HC-CDR3	Sequence family	Family Consensus
YU100-A10, YU100-A11, YU100-A12, YU100-B01, YU100-B03, YU100-B06, YU100-B07, YU100-B08, YU100-B09, YU100-C02, YU100-C04, YU100-C05, YU100-C11, YU100-D02, YU100-D05, YU100-D11, YU100-E01, YU100-E04, YU100-E05, YU100-E06, YU100-E10, YU100-E12, YU100-F01, YU100-F02, YU100-F05, YU100-F11, YU100-G01, YU100-G07, YU100-G08, YU100-G09, YU100-G10, YU100-H05, YU100-H06, YU100-H11, YU112-A07, YU112-B06, YU112-D08, YU112-G06, YU100-C10, YU112-F05, YU100-E07	AKIGATDPLDY	matHC-CDR3-1	AKIGATDPLDY (SEQ ID NO:187)

Figure 49C

Clone(s)	HC-CDR3	Sequence family	Family Consensus
YU100-B12, YU100-C12, YU100-D01, YU100-D07, YU100-E08, YU100-E09, YU100-F07, YU100-H01, YU100-H04, YU100-H09, YU112-C05, YU100-E11, YU100-F06, YU100-G11, YU100-H02	ARIMGYDYGDYDVVDY	matHC-CDR3-2	ARIMGYDYGDYDVVDY (SEQ ID NO:199)
YU112-G01, YU112-H02	AKLSGPNGVDY	matHC-CDR3-3	AKLSGPNGVDY (SEQ ID NO:197)
YU112-C03, YU112-E08, YU112-G09	AKGGKSYYGFDY	matHC-CDR3-4	AKG$X_{177}X_{178}$SYYX_{179}FDY (SEQ ID NO:411) X_{177} = absent or G X_{178} = absent or K X_{179} = absent or G
YU112-C09, YU112-E07, YU112-H01	AKGSYYFDY		

Figure 49C (Cont.)

YU100-A10
EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVLPVLTQPASVSGSPGQSITISCTGTSSDVGAYNYVSWYQQHPGKAPELMIYDVSNRPSGVSNR
FSGSKSGNTASLTISGLQPEDEADYYCSSFTTSIAWVFGGGTKLTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:412)

YU100-A11
EVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:413)

YU100-A12
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVLPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGDTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:414)

YU100-B01
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTNTDVGAYNYVSWYQQYPGKAPKLIIYDVSKRPSGVPDR
FSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:415)

YU100-B03
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSVLTQPRSVSGSPGRSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLTLYDVVKRPSGVPD
RYSGSKSGNTASLTISGLQAEDEADYYCCSYAGGYTWVFGGGTKVTVVGQPKAAPSVTLFPPSS
(SEQ ID NO:416)

YU100-B06
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
SRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:417)

YU100-B07
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTMSCTGTSRDVGGYNYVSWYQHHPGKAPKLMIYDVSKRPSGVP
DRFSGSKSGNTASLTISELQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:418)

Figure 50

YU100-B08
EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKVPRLLIYDVSNRPSGVSTR
FSGSKSGNTASLTISGLQGEDEAEYYCSSFTSSTTWVFGGGTKLTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:419)

YU100-B09
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSDRPSGVSN
RFSGSKSGNTASLTISGLQPEDEADYYCSSYRSGSTLGVRRRDQADRPRSAQGCPLGHSVPALL
(SEQ ID NO:420)

YU100-B12
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
DRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFP
PSS (SEQ ID NO:421)

YU100-C02
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSNVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYVWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:422)

YU100-C04
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQHHPGKAPKLIIYDVTKRPSGVPDR
FSGSKSGNTASLAISGLQAEEEADYYCCSYAGGYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:423)

YU100-C05
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGISNR
FSGSKSGNTASLTISGLQAEDEADYYCSSYTSSISWVFGGGTKLTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:424)

YU100-C10
QVQLVESGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLITVSSGSASAPKLEEGEFSE
ARVQSALTQPASVSGSPGQSITISCTGTRSDIGGYDYVSWYQQHPGKAPKLMIYDVNNRPSGVSNRF
SGSKSGNTASLTISGLQAEDEAEYYCSSYTSSITWVFGGGTKVTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:425)

Figure 50 (Cont.)

YU100-C11
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQRPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQPDDEADYYCSSYTNSRTWVFGGGTKLTVLSQPKAAPSVTLFPPSS
(SEQ ID NO:426)

YU100-C12
EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFP
PSS (SEQ ID NO:427)

YU100-D01
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPPSASGSPGQSVTISCTGTSSDVGGYNFVSWYQQHPGKAPKLLIYDVDKR
PSGVPDRFSGSKSGRTASLTISGLQTEDEAKYYCCSYAGRYTWIFGGGTKLTVLGQPKAAPSVILFPP
SS (SEQ ID NO:428)

YU100-D02
QVRLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSGDVGTYNYVSWYQQHPGKAPKLMIFDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:429)

YU100-D05
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQSALTQPASVSGSPGQLITISCTGTNSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVS
NRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:430)

YU100-D07
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRLTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSGDVGTYDYVSWYQQHPGKAPKLMIYDVSKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCNSYAGSYTWVFGGGTKLTVLGQPKTAPSVTLFP
PSS (SEQ ID NO:431)

YU100-D11
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSNVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEANYYCASYAGNYNWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:432)

Figure 50 (Cont.)

YU100-E01
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQSALTQPASVSGSPGQSITISCTGTSNDIGAYNYVSWYQQHPGKAPKLLIYDVNNRPSGVSD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVLGQPKANPTVTLFPPSS
(SEQ ID NO:433)

YU100-E04
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKTPKLMIYDVTKRPSGVP
DHFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSHIWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:434)

YU100-E05
EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQAVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYSWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:435)

YU100-E06
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGFPEQSITISCTGTSSDVGGYDYVSWYQQHPGKAPKLMIYDVTNRPSGVSN
RFSGSKSGNTASLTISGLQPEDEADYYCSSYTSNTTWVFGGGTKLTVLRQPKAAPSVTLFPPSS
(SEQ ID NO:436)

YU100-E07
QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNRYYADSVK
GRFAISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYDYVSWYQQHPGKAPELMIYDVTKRPSGVAD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGRYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:437)

YU100-E08
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSRR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGNYTWMFGGGTKLTVLGQPKAAPSVTLF
PPSS (SEQ ID NO:438)

YU100-E09
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGDYDYVSWYQQHPGKAPKLIIYDVTKRP
SGIPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGRGTKLTVLGQPKAAPSVTLFPP
ST (SEQ ID NO:439)

Figure 50 (Cont.)

YU100-E10
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIFDVSQRPSGVPD
RFSASKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:440)

YU100-E11
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFP
PSS (SEQ ID NO:441)

YU100-E12
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGTAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSTTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:442)

YU100-F01
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTGSDVGAYDYVSWYQQHPGKAPKLMIYDVNNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEAEYYCSSFATSISWVFGGGTRLTVLGQPKAAPSVTLFPPSS (SEQ
ID NO:443)

YU100-F02
EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQADDEADYYCCSYAGSYTWIFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:444)

YU100-F05
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQAVLTQPASVSGSPGQSITISCTGTSSDIGGYNYVSWYQQHPGTAPKLMIYDVSSRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKMTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:445)

YU100-F06
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGSSSDVGGYNFVSWYRQHPGEAPKLVIFDVNKR
PSGVPDRFSGSKSGNTASLTISGLQTEDEADYFCCSYAGGYTWVFGGGTKVTVVGQPKAAPSVTLF
PPSS (SEQ ID NO:446)

Figure 50 (Cont.)

YU100-F07
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSVSPGQSVTISCTGTSSDVGGYEYVSWYQQHPGKAPKLMIYDVTKR
PSGVPDRFSGSKSGNTASLTISGLQGEDAADYYCCSYAGSYTWVFGGGTTVTVLGQPKAAPSVTLF
PPSS (SEQ ID NO:447)

YU100-F11
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGSSSDVAGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTQLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:448)

YU100-G01
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSASPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMLYDVNKRPSGVP
DRFSGSKSGNTASLTISRLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:449)

YU100-G07
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGAYDYVSWYQQHPGKAPKLMIYDVTNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCASYTRSSVWVFGGGTKLTVLGQPKAASSVTLFPPSS
(SEQ ID NO:450)

YU100-G08
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTLSCTGTSSDVGGYNYVSWYQHYPGKAPKLMIFDVNERSSGVP
DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGRYTWMFGGGTKVTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:451)

YU100-G09
EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:452)

YU100-G10
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSLGQSITMSCTGTRRDVGGYDFVSWYQQYPGKAPKLIIYDVSNRPSGVSN
RFTGSKSGNTASLTISGLQAEDEADYYCCSYAGTYTWVFGGGTKVTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:453)

Figure 50 (Cont.)

YU100-G11
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLTLYDVGKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGGYTWVFGGGTKVTVVGQPKAAPSVTLF
PPSS (SEQ ID NO:454)

YU100-H01
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGAYNYVSWYQQHPGKAPKLMIYDVSER
PSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFP
PSS (SEQ ID NO:455)

YU100-H02
QVQLQQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPK
LEEGEFSEARVQSALTQPRSVSRSPGQSVTISCTGTSSDVGTYNYVSWYQQHPGKAPKLMIYDVSK
RPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGFYTWVFGGGTKLTVLGQPKAAPSVTLF
PPSS (SEQ ID NO:456)

YU100-H04
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPASVSGSPGQSITISCTGTSSDIGVYNYVSWYQQHPGKAPKLMIYDVSKRP
SGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPP
SS (SEQ ID NO:457)

YU100-H05
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQAVLTQPRSVSGSPGQSITISCTGTGSNVGGYNYVSWYQQHPGQAPKLMIYDVSKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGTYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:458)

YU100-H06
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARIQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEADYYCSSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:459)

YU100-H09
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNR
PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFP
PSS (SEQ ID NO:460)

Figure 50 (Cont.)

YU100-H11
QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:461)

YU112-A07
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYTDSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVLSQPKAAPSVTLFPPSS
(SEQ ID NO:462)

YU112-B06
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN
RFSGSKSGNTASLTIFGLQAEDEADYYCSSYTSSSSWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:463)

YU112-C03
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSSGSASAPKLEEGE
FSEARVDSVMTQSPSSLSASVGDRVTITCRASQAINSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISGLQPEDFATYYCQQSYSTPSWTFGQGTKVEIKRTVAAPSV (SEQ ID NO:464)

YU112-C05
EVQLVESGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIMGYDYGDYDVVDYWGQGTLVTVSSGSASAPKL
EEGEFSEARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKR
PSGVPDRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVLSQPKAAPSVTLFP
PSS (SEQ ID NO:465)

YU112-C09
QVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVETTLTQSPATLSVSPGERATLSCRASQSFSSSYLAWYQQKPGQAPRLLIYGASRRAPGIPDRF
SGSGSGTDFSLTISRLEPEDFAVYYCQQSSTSPTWAFGRGTKVEVKRTVAAPSV (SEQ ID NO:466)

YU112-D08
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVE
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVPD
RFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVLSQPKAAPSVTLFPPSS
(SEQ ID NO:467)

Figure 50 (Cont.)

YU112-E07
QVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVEIVMTQSPDSLAVSLGERATINCKSSQSVNSAYLAWYQHKPGQPPRLLIYGASRRVTGVPDRF
SGSGSGTDFTLTISSLQPEDFATYYCQQSYSDPRWTFGQGTKVEIKRTVAAPSV (SEQ ID NO:468)

YU112-E08
*VTLKESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSSGSASAPKLEEGE
FSEARVDIQMTQSPSFLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTWTFGQGTKVEIKRTVAAPSV (SEQ ID NO:469)

YU112-F05
EVQLVQSGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLIIYDVNNRPSGVSN
RFSASKSGNTASLTISGLQAEDEADYYCNSYTSGSTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:470)

YU112-G01
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRPSGVP
DRFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGSYTWVFGGGTELTVLSQPKAAPSVTLFPPSS
(SEQ ID NO:471)

YU112-G06
QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKIGATDPLDYWGQGTLVTVSSGSASAPKLEEGEFS
EARVQSALTQPRSVSGSPGQSVTISCTGTISDVGGYNYVSWYQQHPGKAPKLMIYDVTKRRSGVPD
RFSGSKSGNTASLTISGLQAEDEAGYYCSSYAGGYTWVFGGGTELTVLSQPKAAPSVTLFPPSS
(SEQ ID NO:472)

YU112-G09
*VTLKESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGGKSYYGFDYWGQGTLVTVSSGSASAPKLEEGE
FSEARVDIQMTQSPSFLSASVGDRVTITCRASQIISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFTLTISSLQPGRFCNLLLSTELQYPHV (SEQ ID NO:473)

YU112-H01
QVQLVESGGGVVQPGRSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKGSYYFDYWGQGTLVTVSSGSASAPKLEEGEFSE
ARVETTLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFS
GSGSGTDFTLTISSLQPDDFATYYCQQSYSTPTWTFGQGTKVEIKRTVAAPSV (SEQ ID NO:474)

Figure 50 (Cont.)

YU112-H02
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLSGPNGVDYWGQGTLVTVSSGSASAPKLEEGEF
SEARVQPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKVMIYDVSKRPSGVP
DRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVLGQPKAAPSVTLFPPSS
(SEQ ID NO:475)

Figure 50 (Cont.)

YU100-A10
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACTGCCTGTGCTGACTCAGCCCGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGCTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCGAACTCATGATTTATGATGTCAGTAATCGG
CCCTCCGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGCCTGAGGACGAGGCTGATTATTACTGCAGCTCATTTACGACCAGCATCGCTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:476)

YU100-A11
GAGGTGCAGCTGCAGCAGTCGGGGGGGGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTT
GGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCACCCTCCTCT (SEQ ID NO:477)

YU100-A12
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACTGCCTGTGCTGACTCAGCCCCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCGACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGTTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:478)

Figure 51

YU100-B01
CAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAACACTGATGTTGGTGCTTATAACTATG
TCTCCTGGTACCAACAGTACCCAGGCAAAGCCCCCAAACTCATCATTTATGATGTCAGTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACTCTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCGTCCTCT (SEQ ID NO:479)

YU100-B03
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGTGCTGACTCAGCCCCGCTCAGTGTCCGGGTC
TCCTGGGCGGTCAGTCACCATCTCATGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTAT
GTCTCCTGGTACCAACAGCACCCAGGCAAGGCCCCCAAACTCACACTTTATGATGTCGTTAAGC
GGCCCTCAGGGGTCCCTGATCGCTACTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCAT
CTCTGGGCTCCAGGCTGAGGATGAGGCCGATTATTACTGCTGCTCATATGCAGGCGGCTACACT
TGGGTGTTCGGCGGAGGGACCAAGGTGACCGTCGTTGGTCAGCCCAAGGCTGCCCCCTCGGTC
ACTCTGTTCCCACCCTCCTCT (SEQ ID NO:480)

YU100-B06
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGAGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGTAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCAACTCATATGCAGGCAGCTACACTT
GGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCACCCTCCTCT (SEQ ID NO:481)

Figure 51 (Cont.)

YU100-B07
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATACGATGGAAGTAATAAATACTATGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAG
CCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGAC
TACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAA
GAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGT
CTCCTGGACAGTCAGTCACCATGTCCTGCACTGGAACCAGCAGAGATGTTGGTGGTTATAATTAT
GTCTCCTGGTACCAACATCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGAGCTCCAGGCTGAGGATGAGGCTGATTATTACTGTTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:482)

YU100-B08
GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGGCAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTAT
GTCTCCTGGTACCAACAACACCCAGGCAAAGTCCCCAGACTCTTGATTTATGATGTCAGTAACCG
GCCCTCAGGGGTTTCTACTCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGGTGAGGACGAGGCTGAGTATTACTGCAGTTCATTTACGAGTAGTACCACTT
GGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTGGGTCAGCCCAAGGCTGCCCCCTCGGTC
ACTCTGTTCCCACCGTCCTCT (SEQ ID NO:483)

YU100-B09
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTTATGATTTATGATGTCAGTGATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGCCTGAGGACGAGGCTGATTATTACTGCAGTTCATATAGAAGCGGCAGCACTTT
GGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCGCCCTCCTCT (SEQ ID NO:484)

Figure 51 (Cont.)

YU100-B12
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGACCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCT (SEQ ID NO:485)

YU100-C02
CAGGTGCAGCTGGTGGAGTCGGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTAATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCAGTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACGTTT
GGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTCGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCGCCGTCCTCT (SEQ ID NO:486)

YU100-C04
CAGGTGCAGCTGGTGGAGTCGGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
TTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACACCACCCAGGCAAAGCCCCCAAACTCATAATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGGCCATCT
CTGGGCTCCAGGCTGAGGAAGAGGCTGATTATTACTGCTGCTCATATGCAGGCGGGTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCGTCCTCT (SEQ ID NO:487)

Figure 51 (Cont.)

YU100-C05
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGGGGTTATAATTAT
GTCTCCTGGTATCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAATCG
GCCCTCAGGGATTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATACACAAGCAGCATTTCTT
GGGTGTTCGGCGGAGGGACCAAACTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCGCCCTCCTCT (SEQ ID NO:488)

YU100-C10
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCGGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGATCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCCGCAGTGACATTGGTGGTTATGACTAT
GTCTCCTGGTATCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGACGTCAATAATCG
GCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGACGAGGCTGAGTATTACTGCTCCTCATATACAAGCAGCATCACTT
GGGTGTTCGGCGGAGGGACCAAGGTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCACCCTCCTCT (SEQ ID NO:489)

YU100-C11
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCGCCCAGGCAAGGCCCCCAAACTCATGATTTATGATGTCAGTAATCG
GCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGCCTGACGACGAGGCTGATTATTACTGCAGCTCATATACAAACAGCAGGACTT
GGGTGTTCGGCGGAGGGACCAAGTTGACCGTCCTAAGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCACCGTCCTCT (SEQ ID NO:490)

Figure 51 (Cont.)

YU100-C12
GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCGTCCTCT (SEQ ID NO:491)

YU100-D01
CAGGTGCAGCTGCAGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCC
CTCCGCGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTC
GGTGGTTACAACTTTGTCTCCTGGTATCAACAACACCCCGGCAAAGCCCCCAAACTCTTGATTTA
TGATGTCGATAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAGAACG
GCCTCCCTGACCATCTCTGGGCTCCAGACTGAGGATGAGGCTAAATATTATTGCTGCTCATATGC
AGGCAGGTACACTTGGATATTCGGCGGAGGGACCAAGCTGACCGTCCTCGGTCAGCCCAAGGC
TGCCCCCTCGGTCATTCTGTTCCCACCGTCCTCT (SEQ ID NO:492)

YU100-D02
CAGGTGCGGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCGGTGATGTTGGTACTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTTTGATGTCAGTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCAACTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:493)

Figure 51 (Cont.)

YU100-D05
CAGGTGCAGCTGCAGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTTGATCACCATCTCCTGCACTGGAACCAACAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCGTCCTCT (SEQ ID NO:494)

YU100-D07
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGACTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAG
CCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGAC
TACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCC
GCCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTC
GCTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCGGTGATGT
TGGTACTTATGACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTT
ATGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACAC
GGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCAACTCATAT
GCAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAG
ACTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCT (SEQ ID NO:495)

YU100-D11
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTAATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAAGATGAGGCTAATTATTACTGCGCCTCATATGCAGGCAACTACAATTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTTGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:496)

Figure 51 (Cont.)

YU100-E01
CAGGTGCAGCTGCAGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAATGACATAGGTGCTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCCTGATTTATGATGTCAATAATCGG
CCCTCAGGGGTTTCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACTCTTG
GGTGTTCGGCGGAGGGACCAAACTGACCGTCCTAGGTCAGCCCAAGGCCAACCCCACTGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:497)

YU100-E04
CAGGTGCAGCTGCAGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAACCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCACTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGTCACATTTG
GGTGTTCGGCGGAGGGACCAAGTTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:498)

YU100-E05
GAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGGCTGTGCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGCG
GCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACTCCT
GGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCGCCCTCCTCT (SEQ ID NO:499)

Figure 51 (Cont.)

YU100-E06
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTT
TCCTGAACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATGACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGCCTCCAACCTGAGGACGAGGCTGATTATTATTGCAGCTCATATACAAGCAACACCACTTGG
GTGTTCGGCGGAGGGACCAAGCTGACCGTCCTACGTCAGCCCAAGGCTGCCCCCTCGGTCACT
CTGTTCCCACCGTCCTCT (SEQ ID NO:500)

YU100-E07
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAGATACTATGCAGACTCCG
TGAAGGGCCGATTCGCCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAG
CCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGAC
TACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAA
GAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGT
CTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATGACTAT
GTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCGAACTCATGATTTATGATGTCACTAAGC
GGCCCTCAGGGGTCGCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCAT
CTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGGTACACT
TGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTC
ACTCTGTTCCCACCCTCCTCT (SEQ ID NO:501)

YU100-E08
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAGGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAATTACACTTGGATGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCGTCCTCT (SEQ ID NO:502)

Figure 51 (Cont.)

YU100-E09
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGGTTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGATTATGACTATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATTATTTA
TGATGTCACTAAACGGCCCTCAGGGATCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAGTTACACTTGGGTGTTCGGCAGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCCTCCACT (SEQ ID NO:503)

YU100-E10
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTTTGATGTCAGTCAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGCCTCCAAGTCCGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:504)

YU100-E11
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCT (SEQ ID NO:505)

Figure 51 (Cont.)

YU100-E12
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCACAGCCCCCAAACTCATGATTTATGATGTCAGTAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCAGCACCACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:506)

YU100-F01
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCGGCAGTGACGTTGGTGCTTATGACTAT
GTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAATAATCG
GCCCTCAGGAGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAAGCTGAGGACGAGGCTGAATATTACTGCAGTTCATTTGCAACTAGCATTTCTTG
GGTGTTCGGCGGAGGGACCAGACTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:507)

YU100-F02
GAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGACGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GATATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:508)

Figure 51 (Cont.)

YU100-F05
CAGGTGCAGCTGCAGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGGCCGTGCTGACTCAGCCCGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATTTCCTGCACTGGAACCAGCAGTGACATTGGTGGTTATAACTATG
TCTCCTGGTACCAGCAACACCCAGGCACAGCCCCCAAACTCATGATTTATGATGTCAGTAGTCG
GCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGTTACACTT
GGGTGTTCGGCGGAGGGACCAAGATGACCGTCCTGGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCACCCTCCTCT (SEQ ID NO:509)

YU100-F06
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGATCCAGCAGTGATGTT
GGTGGTTATAACTTTGTCTCCTGGTACCGACAACACCCAGGCGAAGCCCCCAAACTCGTGATTTT
TGATGTCAATAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCAGGGCTGCAAACTGAGGATGAGGCTGATTATTTCTGCTGCTCATATGC
AGGCGGCTACACTTGGGTGTTCGGCGGAGGGACCAAGGTGACCGTCGTTGGTCAGCCCAAGGC
TGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCT (SEQ ID NO:510)

YU100-F07
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGTGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGACGTT
GGCGGTTATGAATATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCACTAAGAGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGGTGAAGATGCGGCTGATTATTACTGCTGTTCATATG
CAGGCTCTTACACTTGGGTATTCGGCGGAGGCACCACGGTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCGTCCTCT (SEQ ID NO:511)

Figure 51 (Cont.)

YU100-F11
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGGAGCAGTAGTGACGTTGCTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGTTACACTTG
GGTTTTCGGCGGAGGGACCCAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCGTCCTCT (SEQ ID NO:512)

YU100-G01
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGCGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGCTTATAACTATG
TCTCCTGGTACCAACAACACCCCGGCAAAGCCCCCAAACTCATGCTTTATGATGTCAATAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTAGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:513)

YU100-G07
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGCTTATGACTAT
GTCTCCTGGTATCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAATCG
GCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCGCCTCATACACACGCAGCAGCGTTT
GGGTGTTCGGCGGAGGGACCAAACTGACCGTCTTAGGTCAGCCCAAGGCTGCCTCCTCGGTCA
CTCTGTTCCCACCCTCCTCT (SEQ ID NO:514)

Figure 51 (Cont.)

YU100-G08
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCCTCTCCTGTACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACACTACCCAGGCAAAGCCCCCAAACTCATGATTTTTGATGTCAATGAGCGG
TCCTCAGGAGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGGTACACTTG
GATGTTCGGCGGAGGGACCAAAGTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:515)

YU100-G09
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:516)

YU100-G10
CAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGT
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCTTGGACAGTCGATCACCATGTCCTGCACTGGAACCAGAAGAGACGTTGGTGGTTATGACTTTG
TCTCCTGGTACCAACAGTACCCCGGCAAAGCCCCCAAGCTCATCATTTACGATGTCAGCAATCG
GCCCTCGGGGGTTTCTAATCGCTTCACTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATC
TCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCACCTACACTT
GGGTGTTCGGCGGAGGGACCAAGGTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCA
CTCTGTTCCCGCCCTCCTCT (SEQ ID NO:517)

Figure 51 (Cont.)

YU100-G11
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGGCAGTCAGTCACCATCTCATGCACTGGAACCAGCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAGGCCCCCAAACTCACGCTTT
ATGATGTCGGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACAC
GGCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATAT
GCAGGCGGCTACACTTGGGTGTTCGGCGGAGGGACCAAGGTGACCGTCGTAGGTCAGCCCAAG
GCTGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCT (SEQ ID NO:518)

YU100-H01
CAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTGCTTATAACTATGTCTCCTGGTACCAGCAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTGAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCGTCCTCT (SEQ ID NO:519)

YU100-H02
CAGGTGCAGCTGCAGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCAGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTT
GGTACTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CAGGCTTCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCACCGTCCTCT (SEQ ID NO:520)

Figure 51 (Cont.)

YU100-H04
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGC
CTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACGGGAACCAGCAGTGACATT
GGTGTTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATG
CGGGCAGCTACACCTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCT (SEQ ID NO:521)

YU100-H05
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGGCTGTGCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAATCACCATCTCCTGCACTGGAACCGGCAGTAATGTTGGTGGTTATAACTATG
TCTCCTGGTATCAACAACACCCAGGCCAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGAGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTATTGCTGCTCATATGCAGGCACCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:522)

YU100-H06
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGNATACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAATTGATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAAGATGAGGCTGATTATTATTGCTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:523)

Figure 51 (Cont.)

YU100-H09
CAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGATTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGC
CTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCAGTAATCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCTGTTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCGCCGTCCTCT (SEQ ID NO:524)

YU100-H11
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCACCCTCCTCT (SEQ ID NO:525)

YU112-A07
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATACAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCGAGCTGACCGTCCTGAGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:526)

Figure 51 (Cont.)

YU112-B06
CAGGTGCAGCTGGTGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTC
TCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTT
TGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCAGTAGCAGTTGG
GTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACT
CTGTTCCCGCCCTCCTCT (SEQ ID NO:527)

YU112-C03
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGGGGGAAGAGCTACTACGGATTTG
ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTG
AAGAAGGTGAATTTTCAGAAGCACGCGTAGACAGCGTGATGACCCAGTCTCCATCCTCCCTGTC
TGCATCTGTAGGGGACAGAGTCACCATCACTTGCCGGGCAAGTCAGGCCATTAACAGCTATTTA
AATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCA
GAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
GGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTTCGTGGAC
GTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTC (SEQ ID
NO:528)

YU112-C05
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCG
TGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAGAATCATGGGCTATGACTACGGTGACT
ACGACGTAGTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCG
CCCCAAAGCTTGAAGAAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCG
CTCAGTGTCCGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTT
GGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTA
TGATGTCACTAAGCGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACG
GCCTCCCTGACCATCTCTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATG
CAGGCAGCTACACTTGGGTGTTCGGCGGAGGGACCGAGCTGACCGTCCTGAGTCAGCCCAAGG
CTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCT (SEQ ID NO:529)

Figure 51 (Cont.)

YU112-C09
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCGGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGTTCGTACTACTTTGACTACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAGAAGGTG
AATTTTCAGAAGCACGCGTAGAAACGACACTCACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCA
GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTTTTAGCAGCAGCTACTTAGCCTGGT
ACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGAAGAGCCCCTG
GCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCAGTCTCACCATCAGCAGACT
GGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTCTAGCACCTCACCCACGTGGGCGTTC
GGCCGAGGGACCAAGGTGGAAGTCAAACGAACTGTGGCTGCACCATCTGTC (SEQ ID NO:530)

YU112-D08
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GGAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCGAGCTGACCGTCCTGAGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:531)

YU112-E07
CAGGTGCAGCTGGTGCAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCGGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGTTCGTACTACTTTGACTACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAGAAGGTG
AATTTTCAGAAGCACGCGTAGAAATTGTGATGACTCAGTCTCCAGACTCCCTGGCTGTGTCTCTG
GGCGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTAACAGCGCCTACTTAGCCTGGT
ACCAGCACAAACCTGGCCAGCCTCCCAGACTCCTCATTTATGGTGCATCTCGCAGGGTCACTGG
CGTCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGTCTG
CAACCAGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTGACCCTCGGTGGACGTTCGG
CCAAGGGACCAAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTC (SEQ ID NO:532)

Figure 51 (Cont.)

YU112-E08
TAGGTCACCTTGAAGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCC
TGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCA
AGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGGGGGAAGAGCTACTACGGATTTG
ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTG
AAGAAGGTGAATTTTCAGAAGCACGCGTAGACATCCAGATGACCCAGTCTCCATCCTTCCTGTCT
GCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGATCATTAGCAGCTATTTAAA
TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTATGCTGCATCCAGTTTGCAAA
GTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAG
TCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCCACGTGGACGT
TCGGCCAAGGGACCAAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTC (SEQ ID
NO:533)

YU112-F05
GAGGTGCAGCTGGTGCAGTCGGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCGGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAACTCATCATTTATGATGTCAATAATCGG
CCCTCAGGGGTTTCTAATCGCTTCTCTGCCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAACTCATATACAAGCGGTAGCACTTG
GGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:534)

YU112-G01
CAGGTGCAGCTGGTGGAGTCGGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGGTTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAACTTTCCGGGCCCAACGGTGTGGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCGAGCTGACCGTCCTGAGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:535)

Figure 51 (Cont.)

YU112-G06
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACACTGTACCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAATAGGAGCTACTGACCCCCTTGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCATCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCACTAAGCGG
CGCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGGTTATTACTGCTCCTCATATGCAGGCGGCTACACTTG
GGTGTTCGGCGGAGGGACCGAGCTGACCGTCCTGAGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:536)

YU112-G09
TAGGTCACCTTGAAGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCC
TGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCA
AGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGGGGGAAGAGCTACTACGGATTTG
ACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTG
AAGAAGGTGAATTTTCAGAAGCACGCGTAGACATCCAGATGACCCAGTCTCCATCCTTCCTGTCT
GCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGATCATTAGCAGCTATTTAAA
TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAACTCCTGATCTATGCTGCATCCAGTTTGCAAA
GTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAG
TCTGCAACCTGGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCCACGTG (SEQ
ID NO:537)

YU112-H01
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCGGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAGGTTCGTACTACTTTGACTACTGGG
GCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAGAAGGTG
AATTTTCAGAAGCACGCGTAGAAACGACACTCACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCA
GGGGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTAGCCTGG
TACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCAGCAGGGCCACTG
GCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGTCT
GCAACCTGATGATTTTGCAACTTACTACTGTCAACAGAGTTACAGCACTCCTACGTGGACATTCG
GCCAAGGGACCAAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTC (SEQ ID NO:538)

Figure 51 (Cont.)

YU112-H02
CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGT
GAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGC
CTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAACTTTCCGGGCCCAACGGTGTGGACT
ACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGGGAGTGCATCCGCCCCAAAGCTTGAAG
AAGGTGAATTTTCAGAAGCACGCGTACAGCCTGTGCTGACTCAGCCCCGCTCAGTGTCCGGGTC
TCCTGGACAGTCAGTCACCATCTCCTGCACTGGAACCAGCAGTGATGTTGGTGGTTATAACTATG
TCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAAGTCATGATTTATGATGTCAGTAAGCGG
CCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCT
CTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCTGCTCATATGCAGGCAGCTACACTTG
GGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCAC
TCTGTTCCCGCCCTCCTCT (SEQ ID NO:539)

Figure 51 (Cont.)

Strategy No	Round 1	Round 2	soluble competition with	No of first hits (lambda sublibrary)	No of first hits (kappa sublibrary)
1	h-IL11	h-IL11	h-IL11	27	14
2	m-IL11	m-IL11	m-IL11	103	36
3	h-IL11	m-IL11	h-IL11/m-IL11	11	21

Figure 52

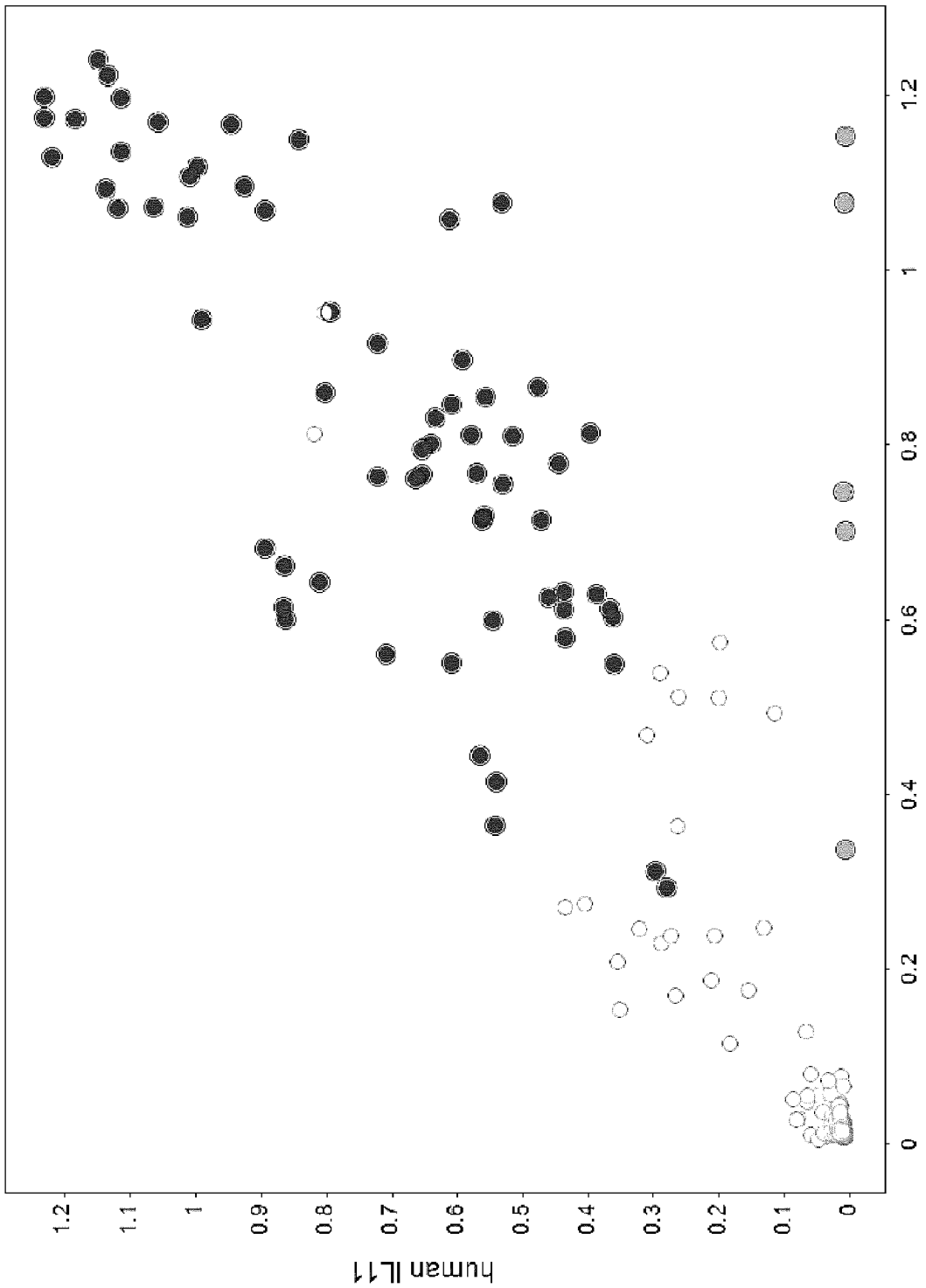

human IL11
mouse IL11
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
1.1
1.2
0
0.2
0.4
0.6
0.8
1
1.2

Figure 53

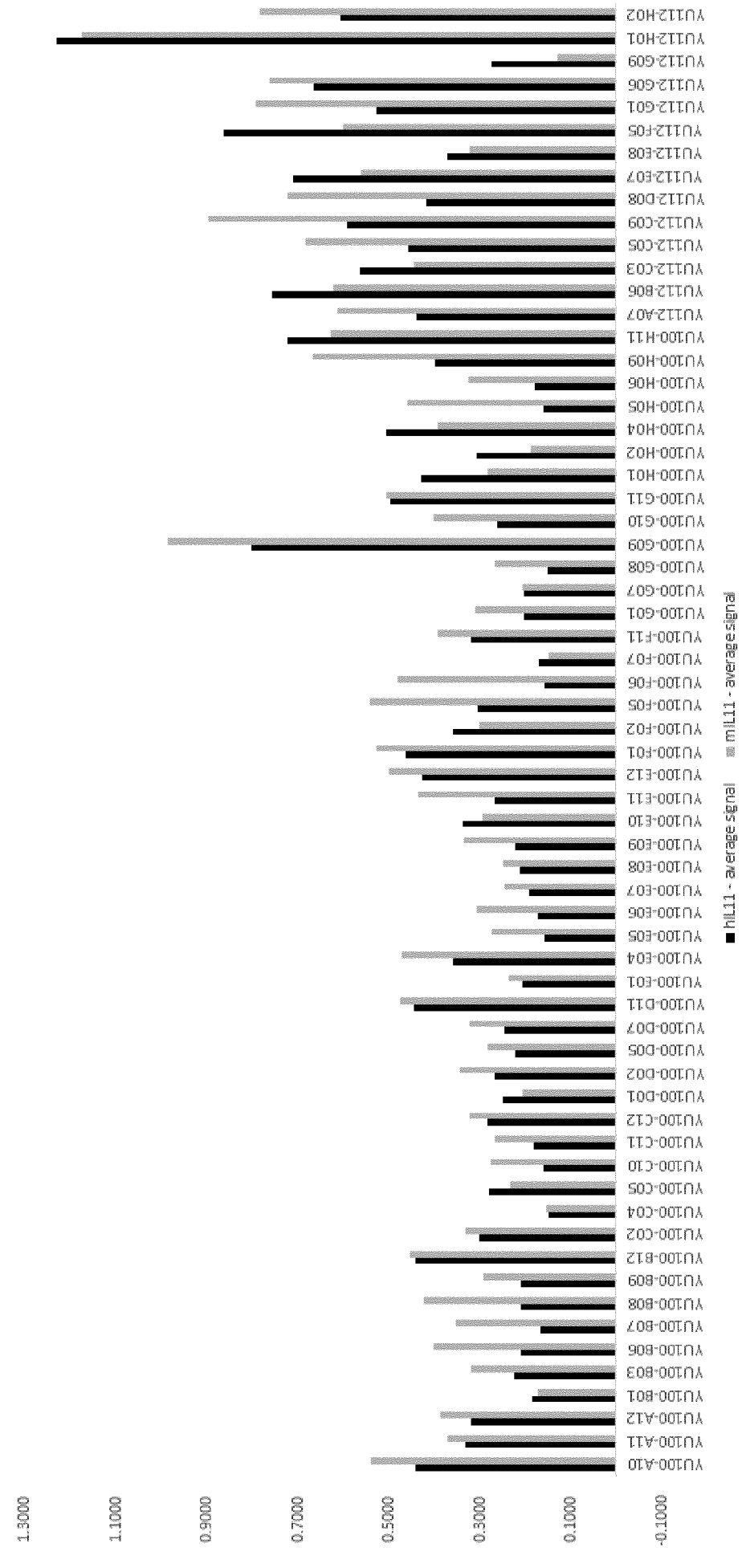

YU112-H02
YU112-H01
YU112-G09
YU112-G06
YU112-G01
YU112-F05
YU112-E08
YU112-E07
YU112-D08
YU112-C09
YU112-C05
YU112-C03
YU112-B06
YU112-A07
YU100-H11
YU100-H09
YU100-H06
YU100-H05
YU100-H04
YU100-H02
YU100-H01
YU100-G11
YU100-G10
YU100-G09
YU100-G08
YU100-G07
YU100-G01
YU100-F11
YU100-F07
YU100-F06
YU100-F05
YU100-F02
YU100-F01
YU100-E12
YU100-E11
YU100-E10
YU100-E09
YU100-E08
YU100-E07
YU100-E06
YU100-E05
YU100-E04
YU100-E01
YU100-D11
YU100-D07
YU100-D05
YU100-D02
YU100-D01
YU100-C12
YU100-C11
YU100-C10
YU100-C05
YU100-C04
YU100-C02
YU100-B12
YU100-B09
YU100-B08
YU100-B07
YU100-B06
YU100-B03
YU100-B01
YU100-A12
YU100-A11
YU100-A10
1.3000
1.1000
0.9000
0.7000
0.5000
0.3000
0.1000
-0.1000
hIL11 - average signal
mIL11 - average signal

Figure 54A

Clone	hIL11 - average signal	mIL11 - average signal
YU100-A10	0.4430	0.5400
YU100-A11	0.3328	0.3716
YU100-A12	0.3200	0.3883
YU100-B01	0.1870	0.1750
YU100-B03	0.2270	0.3210
YU100-B06	0.2090	0.4040
YU100-B07	0.1670	0.3540
YU100-B08	0.2090	0.4230
YU100-B09	0.2100	0.2930
YU100-B12	0.4430	0.4540
YU100-C02	0.3010	0.3330
YU100-C04	0.1480	0.1550
YU100-C05	0.2810	0.2350
YU100-C10	0.1610	0.2770
YU100-C11	0.1830	0.2670
YU100-C12	0.2829	0.3226
YU100-D01	0.2510	0.2060
YU100-D02	0.2680	0.3460
YU100-D05	0.2230	0.2840
YU100-D07	0.2460	0.3220
YU100-D11	0.4470	0.4750
YU100-E01	0.2070	0.2380
YU100-E04	0.3600	0.4720
YU100-E05	0.1600	0.2750
YU100-E06	0.1730	0.3090
YU100-E07	0.1930	0.2470
YU100-E08	0.2140	0.2510
YU100-E09	0.2240	0.3350
YU100-E10	0.3380	0.2970
YU100-E11	0.2675	0.4350
YU100-E12	0.4260	0.5000
YU100-F01	0.4640	0.5280
YU100-F02	0.3610	0.3030
YU100-F05	0.3040	0.5420
YU100-F06	0.1600	0.4810
YU100-F07	0.1720	0.1480
YU100-F11	0.3190	0.3950
YU100-G01	0.2050	0.3100
YU100-G07	0.2030	0.2060
YU100-G08	0.1530	0.2700
YU100-G09	0.8023	0.9846
YU100-G10	0.2620	0.4040
YU100-G11	0.4980	0.5070
YU100-H01	0.4300	0.2830
YU100-H02	0.3090	0.1880
YU100-H04	0.5080	0.3930
YU100-H05	0.1630	0.4610
YU100-H06	0.1810	0.3280
YU100-H09	0.4000	0.6680
YU100-H11	0.7240	0.6290
YU112-A07	0.4380	0.6120
YU112-B06	0.7563	0.6217
YU112-C03	0.5660	0.4450
YU112-C05	0.4576	0.6850
YU112-C09	0.5930	0.8980
YU112-D08	0.4180	0.7230
YU112-E07	0.7100	0.5610
YU112-E08	0.3733	0.3233
YU112-F05	0.8630	0.6010
YU112-G01	0.5280	0.7937
YU112-G06	0.6640	0.7620
YU112-G09	0.2760	0.1310
YU112-H01	1.2290	1.1750
YU112-H02	0.6060	0.7850

Figure 54B

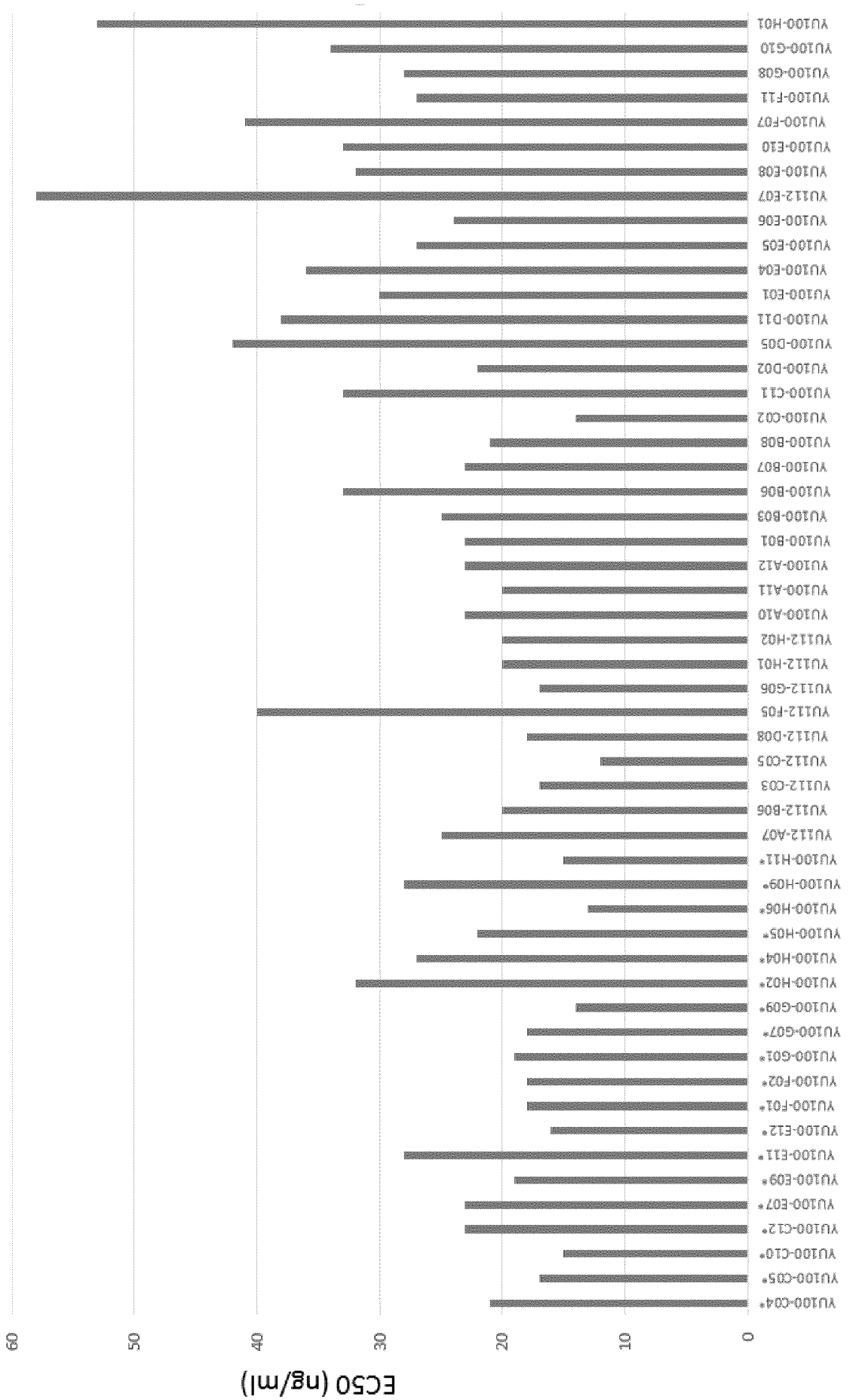

EC50 (ng/ml)
0
10
20
30
40
50
60
YU100-C04*
YU100-C05*
YU100-C10*
YU100-C12*
YU100-E07*
YU100-E09*
YU100-E11*
YU100-E12*
YU100-F01*
YU100-F02*
YU100-G01*
YU100-G07*
YU100-G09*
YU100-H02*
YU100-H04*
YU100-H05*
YU100-H06*
YU100-H09*
YU100-H11*
YU112-A07
YU112-B06
YU112-C03
YU112-C05
YU112-D08
YU112-F05
YU112-G06
YU112-H01
YU112-H02
YU100-A10
YU100-A11
YU100-A12
YU100-B01
YU100-B03
YU100-B06
YU100-B07
YU100-B08
YU100-C02
YU100-C11
YU100-D02
YU100-D05
YU100-D11
YU100-E01
YU100-E04
YU100-E05
YU100-E06
YU112-E07
YU100-E08
YU100-E10
YU100-F07
YU100-F11
YU100-G08
YU100-G10
YU100-H01

Figure 55

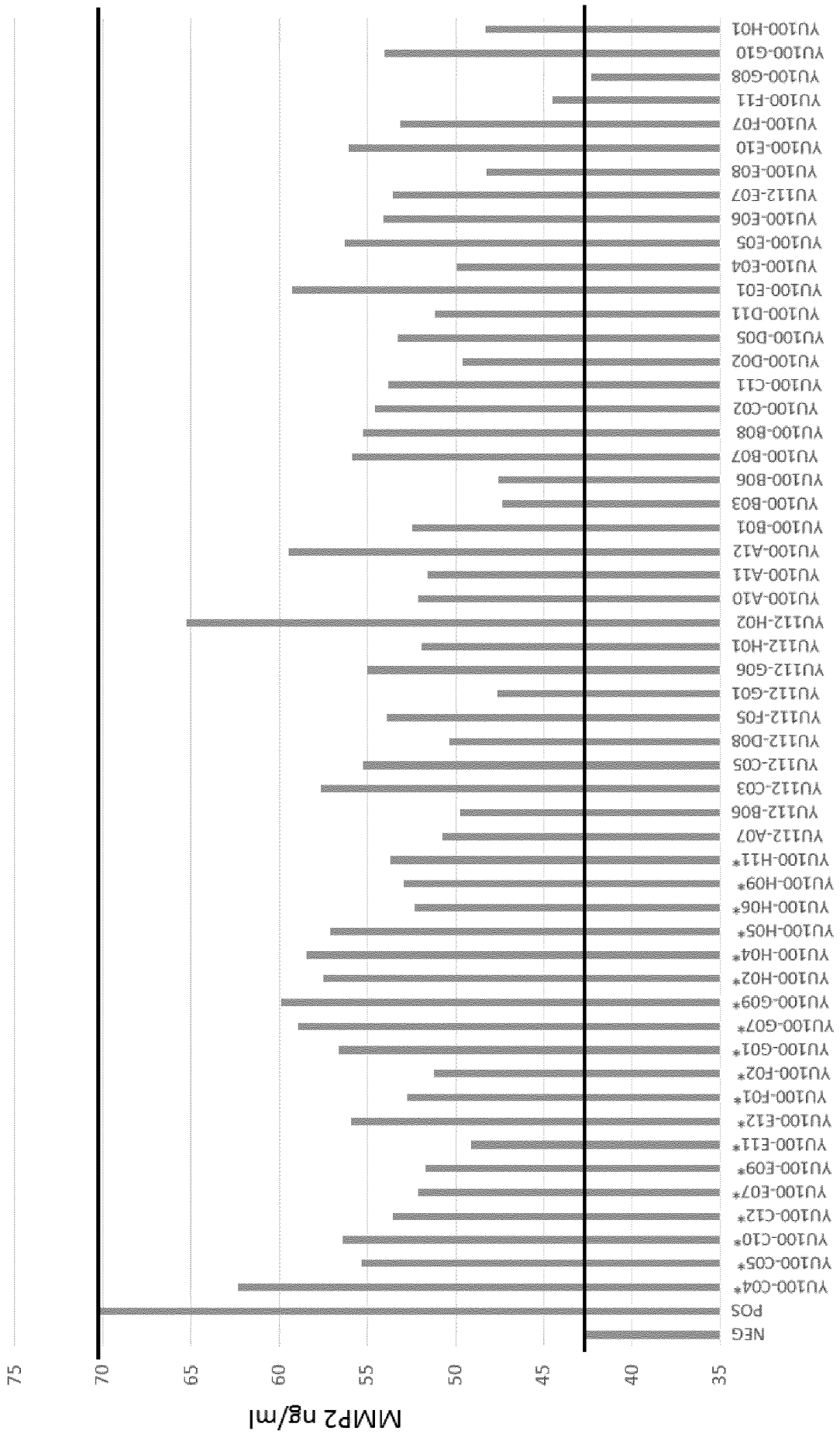
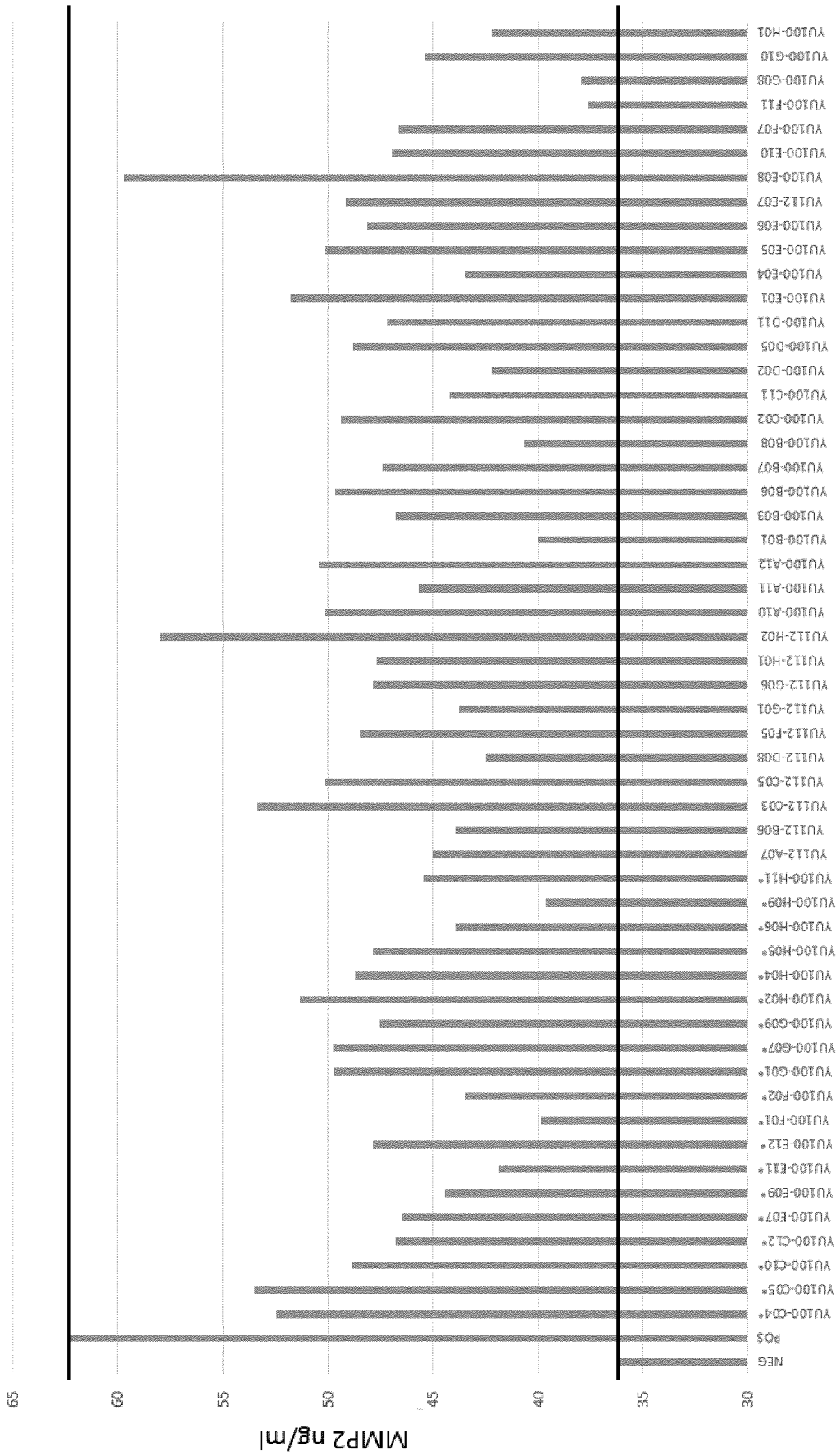

MMP2 ng/ml
75
70
65
60
55
50
45
40
35
NEG
POS
YU100-C04*
YU100-C05*
YU100-C10*
YU100-C12*
YU100-E07*
YU100-E09*
YU100-E11*
YU100-E12*
YU100-F01*
YU100-F02*
YU100-G01*
YU100-G07*
YU100-G09*
YU100-H02*
YU100-H04*
YU100-H05*
YU100-H06*
YU100-H09*
YU100-H11*
YU112-A07
YU112-B06
YU112-C03
YU112-C05
YU112-D08
YU112-F05
YU112-G01
YU112-G06
YU112-H01
YU112-H02
YU100-A10
YU100-A11
YU100-A12
YU100-B01
YU100-B03
YU100-B06
YU100-B07
YU100-B08
YU100-C02
YU100-C11
YU100-D02
YU100-D05
YU100-D11
YU100-E01
YU100-E04
YU100-E05
YU100-E06
YU112-E07
YU100-E08
YU100-E10
YU100-F07
YU100-F11
YU100-G08
YU100-G10
YU100-H01

Figure 56A


MMP2 ng/ml
65
60
55
50
45
40
35
30
NEG
POS
YU100-C04*
YU100-C05*
YU100-C10*
YU100-C12*
YU100-E07*
YU100-E09*
YU100-E11*
YU100-E12*
YU100-F01*
YU100-F02*
YU100-G01*
YU100-G07*
YU100-G09*
YU100-H02*
YU100-H04*
YU100-H05*
YU100-H06*
YU100-H09*
YU100-H11*
YU112-A07
YU112-B06
YU112-C03
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YU112-D08
YU112-F05
YU112-G01
YU112-G06
YU112-H01
YU112-H02
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YU100-A11
YU100-A12
YU100-B01
YU100-B03
YU100-B06
YU100-B07
YU100-B08
YU100-C02
YU100-C11
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YU100-D05
YU100-D11
YU100-E01
YU100-E04
YU100-E05
YU100-E06
YU112-E07
YU100-E08
YU100-E10
YU100-F07
YU100-F11
YU100-G08
YU100-G10
YU100-H01

Figure 56B

	Affinity *EC50 (ng/ml)*	**MMP2 production (ng/ml)** *(Experiment 1)*	**MMP2 production (ng/ml)** *(Experiment 2)*
No TGFB1, IgG1 control (NEG)	-	42.7	36.2
+ TGFB1, IgG1 control (POS)	-	70.2	62.3
YU100-C04*	21	62.3	52.5
YU100-C05*	17	55.3	53.5
YU100-C10*	15	56.4	48.9
YU100-C12*	23	53.5	46.8
YU100-E07*	23	52.1	46.5
YU100-E09*	19	51.7	44.4
YU100-E11*	28	49.1	41.9
YU100-E12*	16	56.0	47.9
YU100-F01*	18	52.8	39.9
YU100-F02*	18	51.2	43.5
YU100-G01*	19	56.6	49.7
YU100-G07*	18	59.0	49.7
YU100-G09*	14	59.9	47.5
YU100-H02*	32	57.5	51.3
YU100-H04*	27	58.5	48.7
YU100-H05*	22	57.1	47.8
YU100-H06*	13	52.3	43.9
YU100-H09*	28	52.9	39.6
YU100-H11*	15	53.7	45.5
YU112-A07	25	50.7	45.0
YU112-B06	20	49.7	43.9
YU112-C03	17	57.6	53.3
YU112-C05	12	55.2	50.1
YU112-D08	18	50.3	42.5
YU112-F05	40	53.9	48.5
YU112-G01	N.D.	47.6	43.8
YU112-G06	17	55.0	47.8
YU112-H01	20	51.9	47.7
YU112-H02	20	65.3	58.0
YU100-A10	23	52.1	50.1
YU100-A11	20	51.6	45.7
YU100-A12	23	59.5	50.4
YU100-B01	23	52.5	40.0
YU100-B03	25	47.3	46.8
YU100-B06	33	47.6	49.6
YU100-B07	23	55.9	47.4
YU100-B08	21	55.3	40.6
YU100-C02	14	54.6	49.4
YU100-C11	33	53.8	44.2
YU100-D02	22	49.6	42.2
YU100-D05	42	53.3	48.8
YU100-D11	38	51.2	47.2
YU100-E01	30	59.3	51.8
YU100-E04	36	50.0	43.5
YU100-E05	27	56.3	50.2
YU100-E06	24	54.1	48.2
YU112-E07	58	53.5	49.1
YU100-E08	32	48.2	59.7
YU100-E10	33	56.1	47.0
YU100-F07	41	53.1	46.6
YU100-F11	27	44.5	37.6
YU100-G08	28	42.3	38.0
YU100-G10	34	54.0	45.4
YU100-H01	53	48.3	42.2

Figure 57

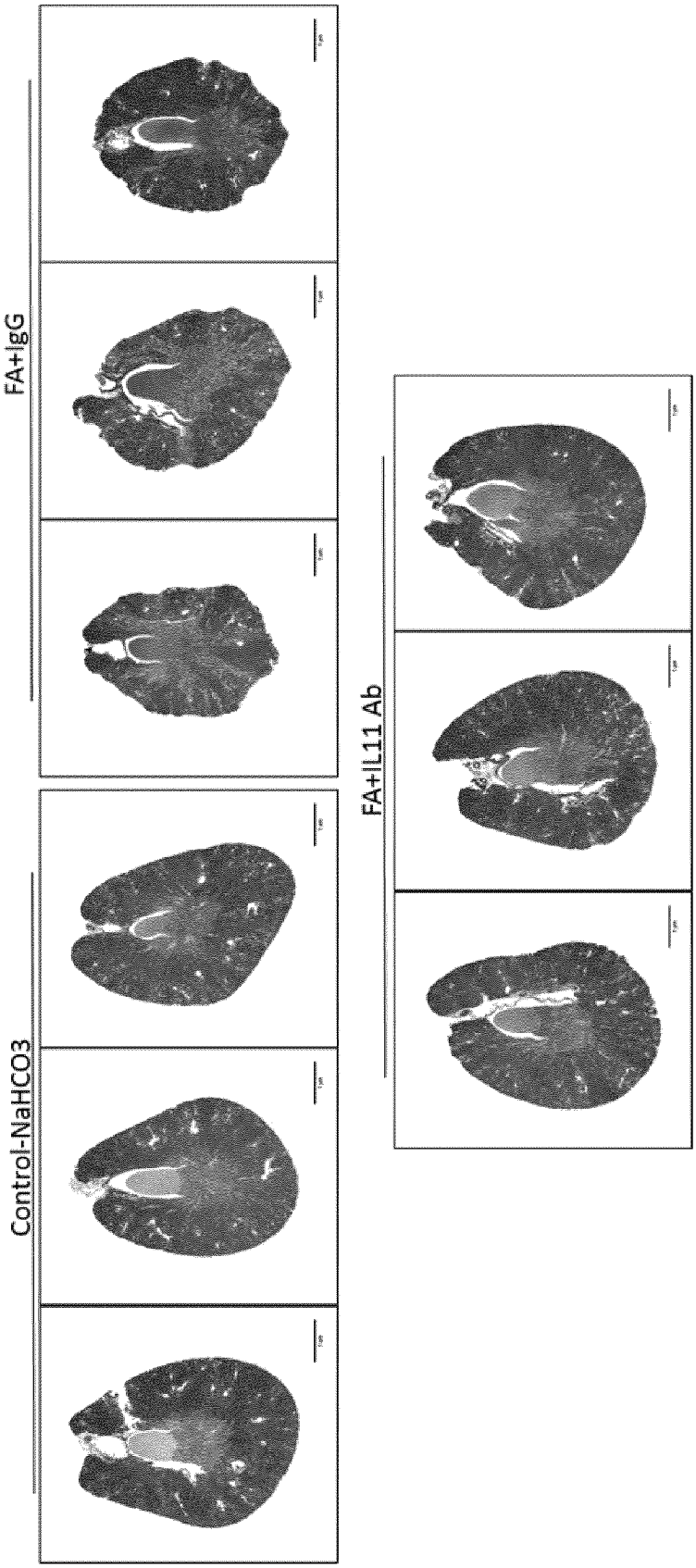

Figure 58A

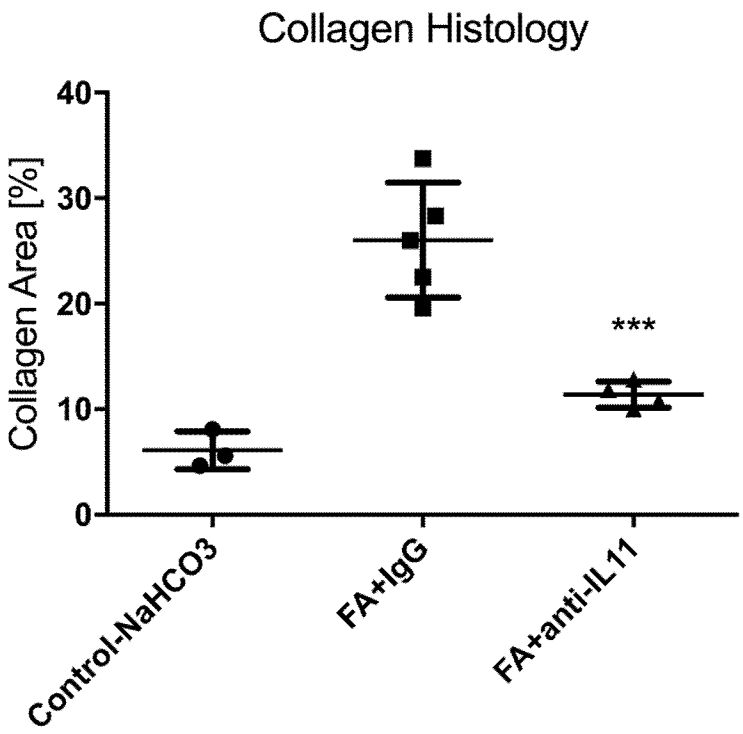

Figure 58B

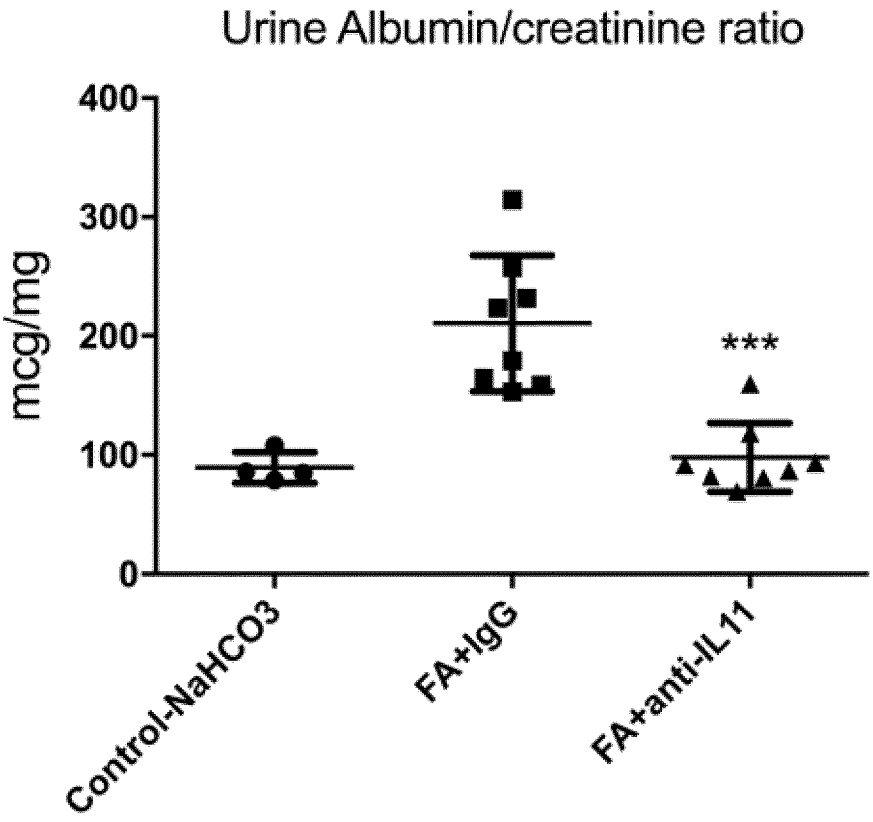

Figure 59

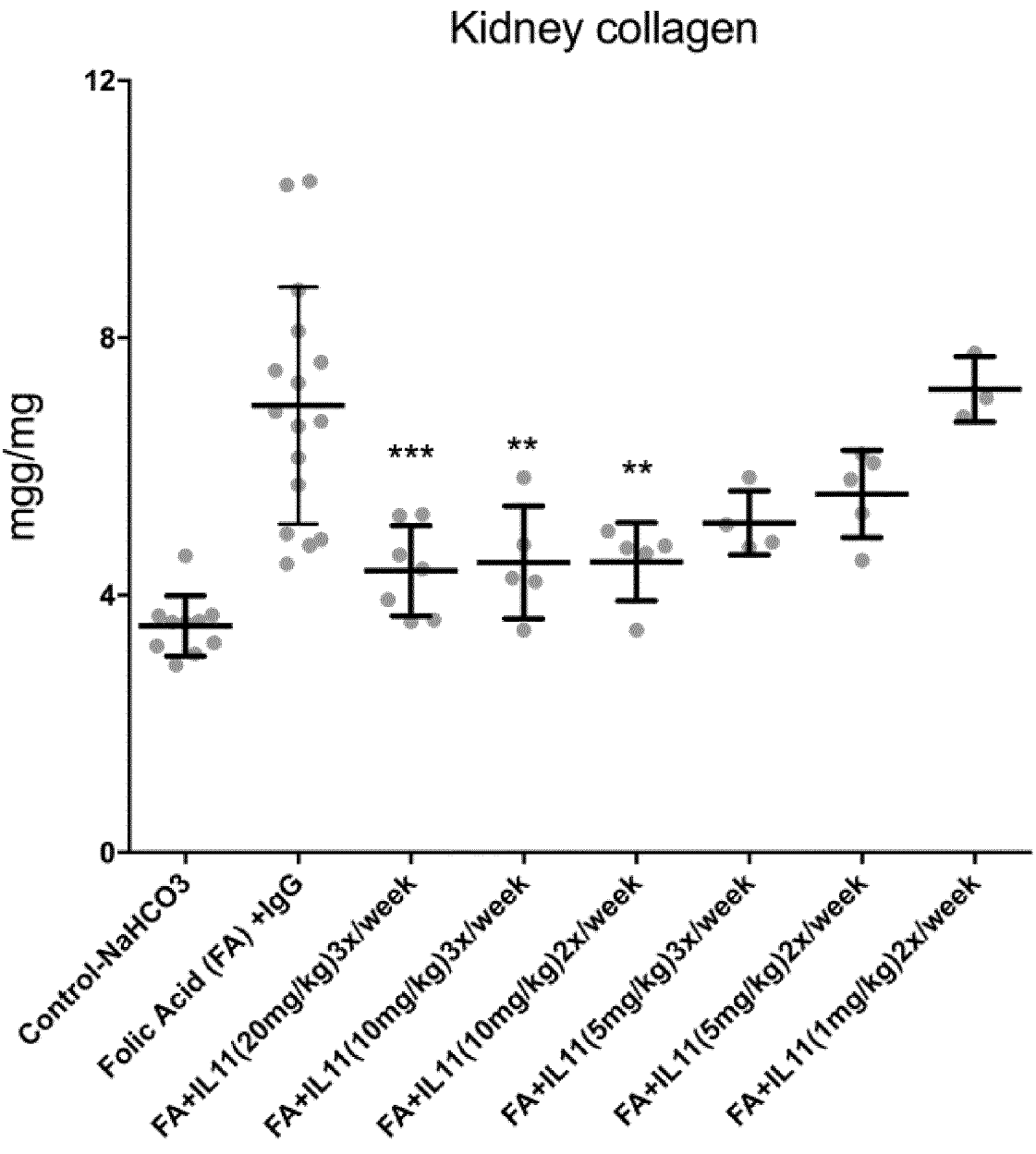
Kidney collagen
mgg/mg
12
8
4
0
***
**
**
Control-NaHCO3
Folic Acid (FA) +IgG
FA+IL11(20mg/kg)3x/week
FA+IL11(10mg/kg)3x/week
FA+IL11(10mg/kg)2x/week
FA+IL11(5mg/kg)3x/week
FA+IL11(5mg/kg)2x/week
FA+IL11(1mg/kg)2x/week

Figure 60

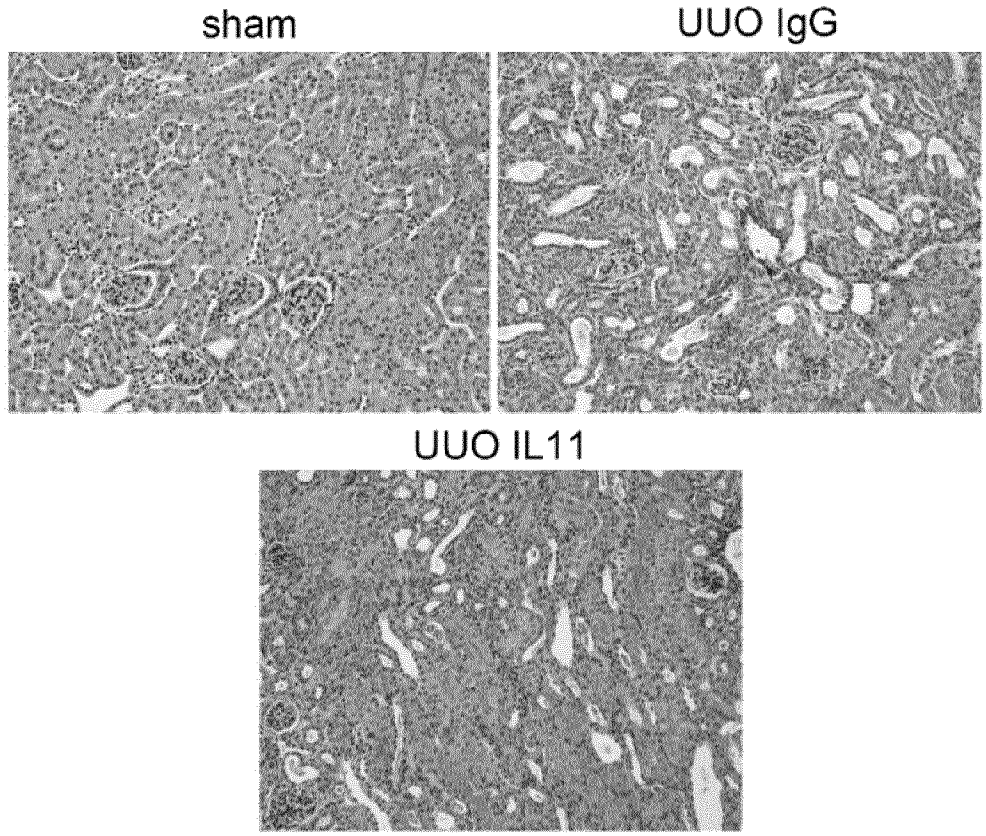

Figure 61A

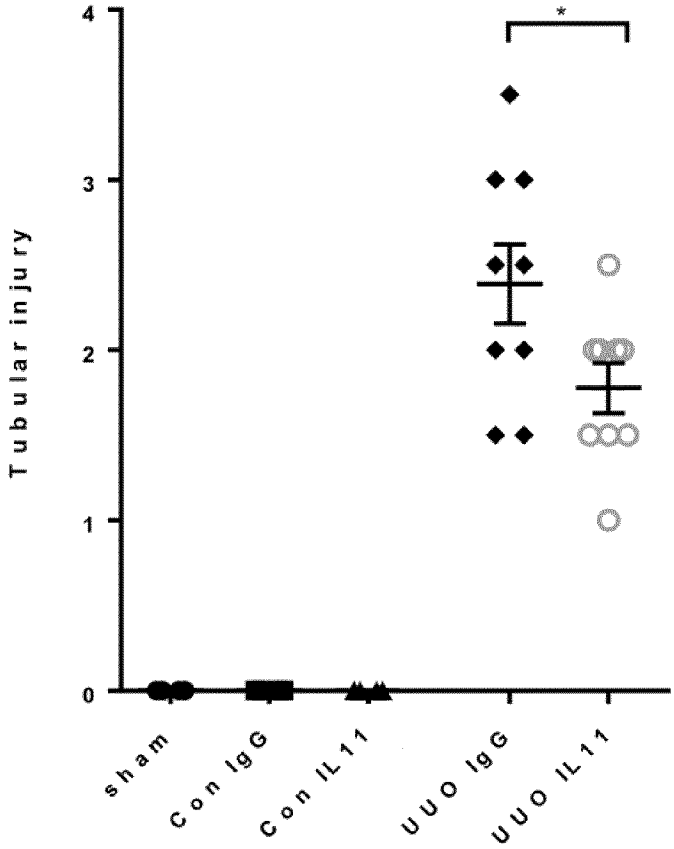

Figure 61B

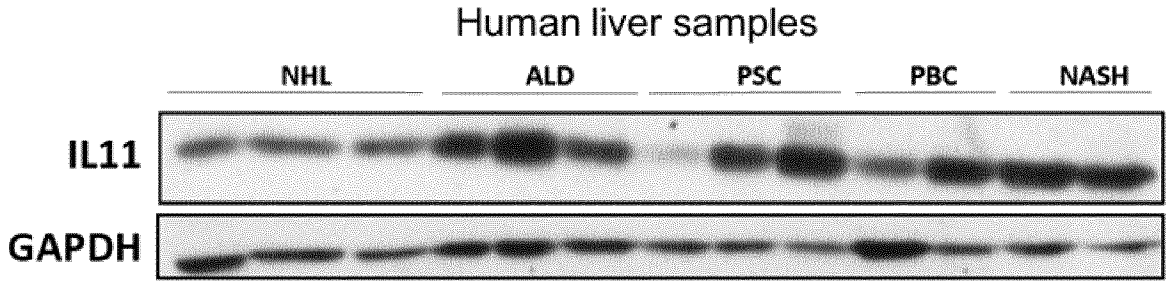

Figure 62

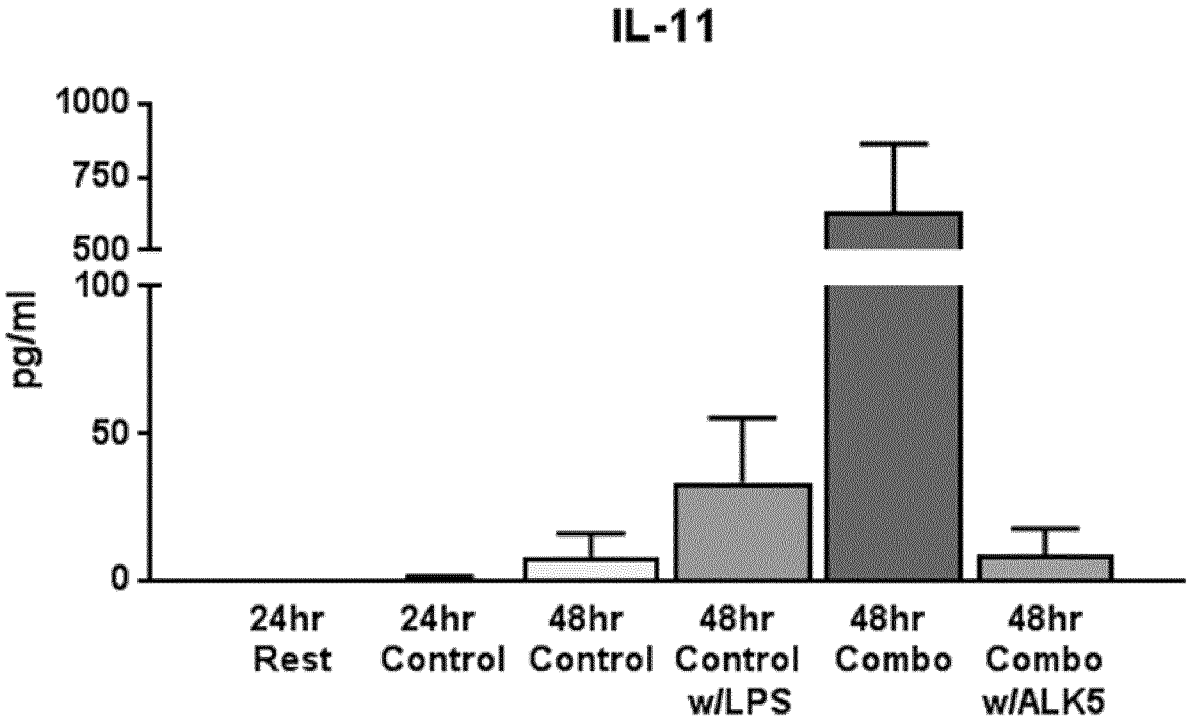

Figure 63

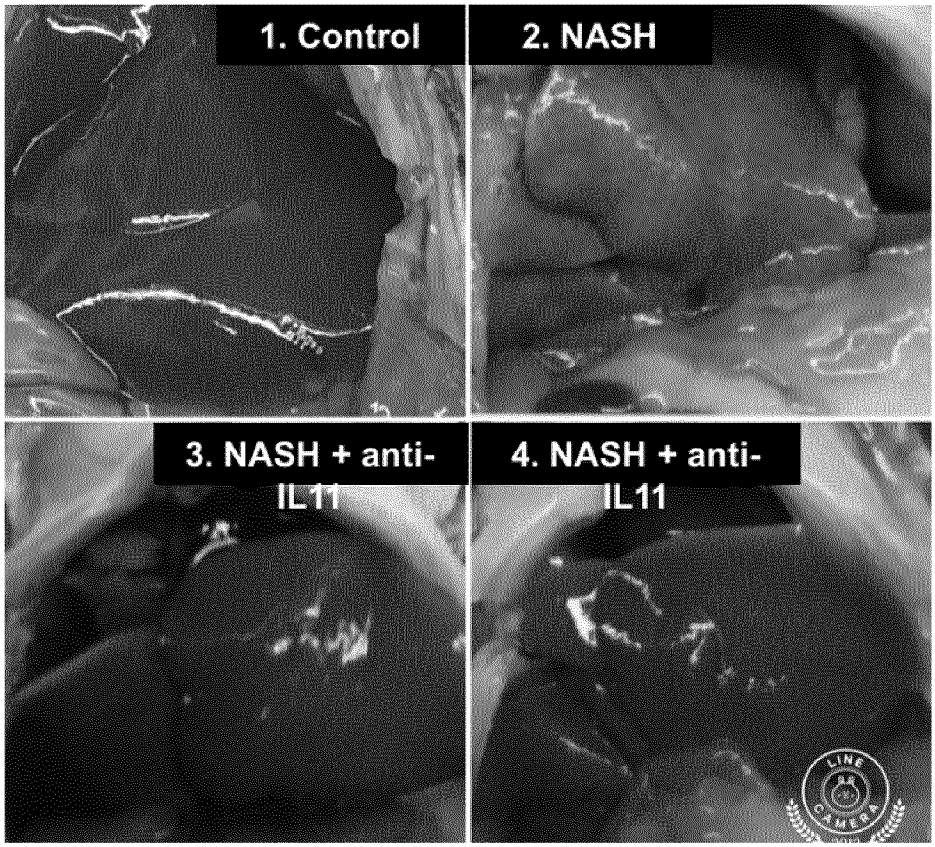

Figure 64A

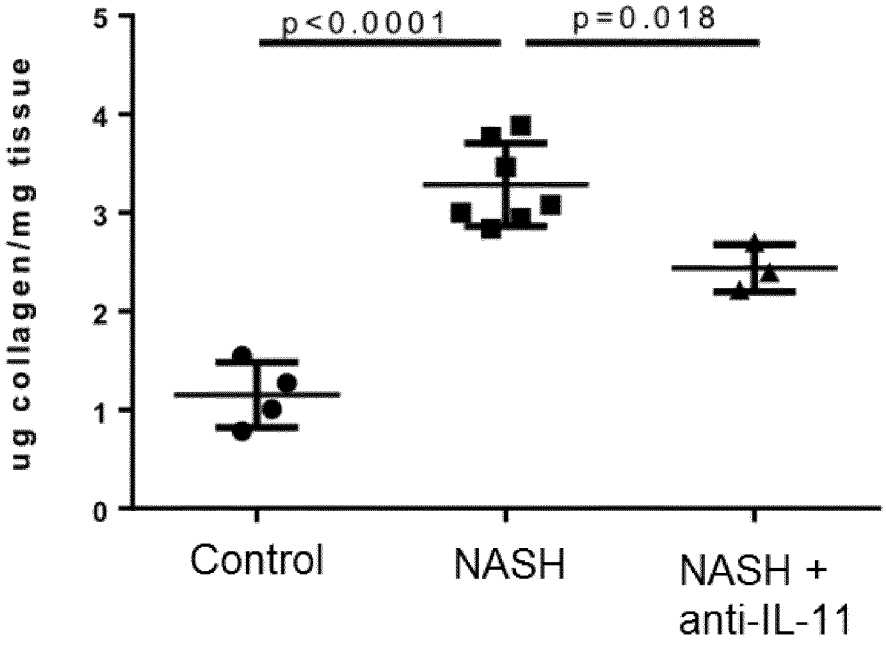

Figure 64B

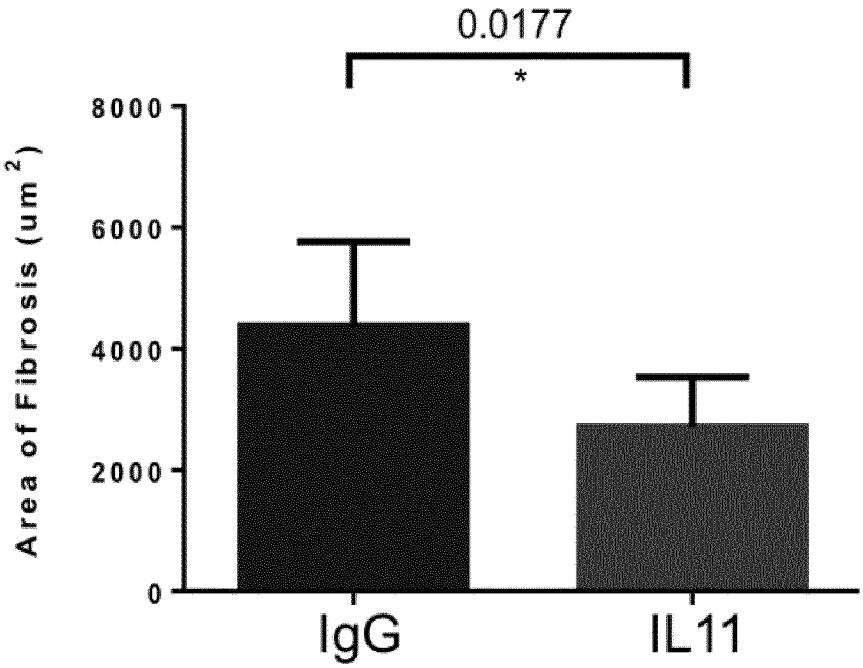

Figure 65A

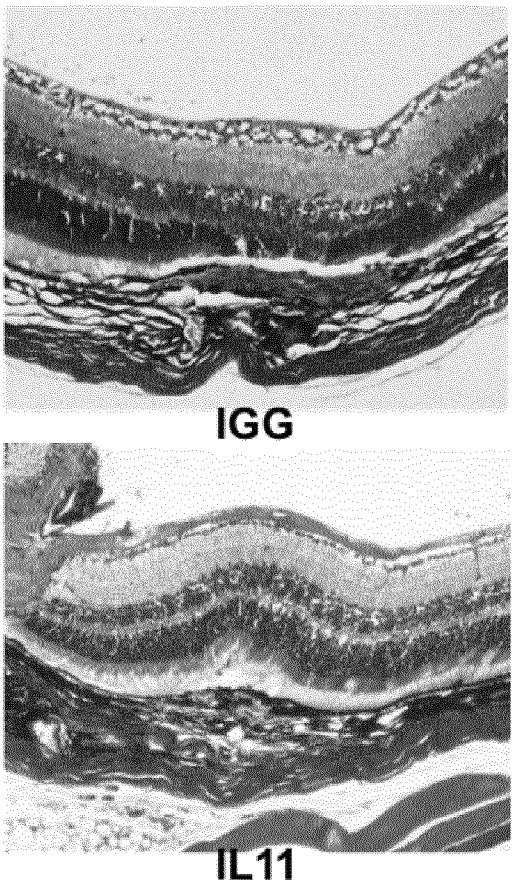

Figure 65B

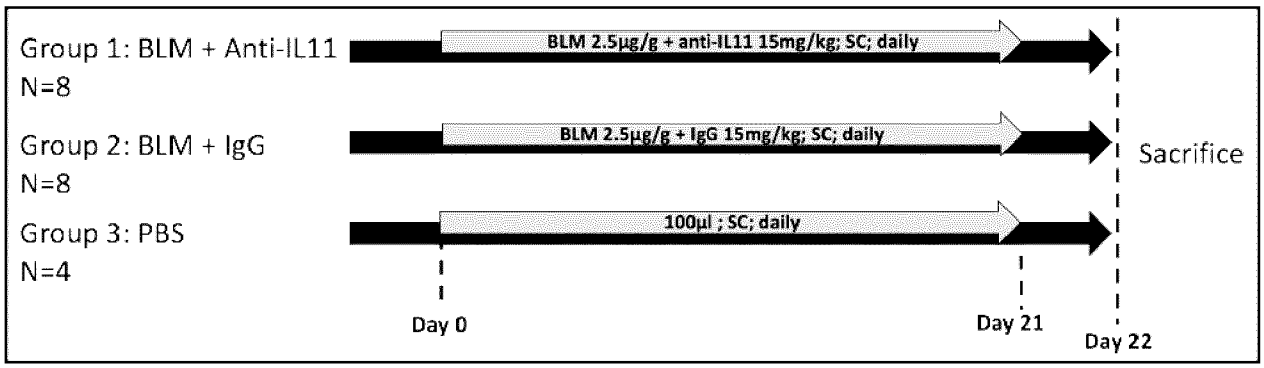

Figure 66A

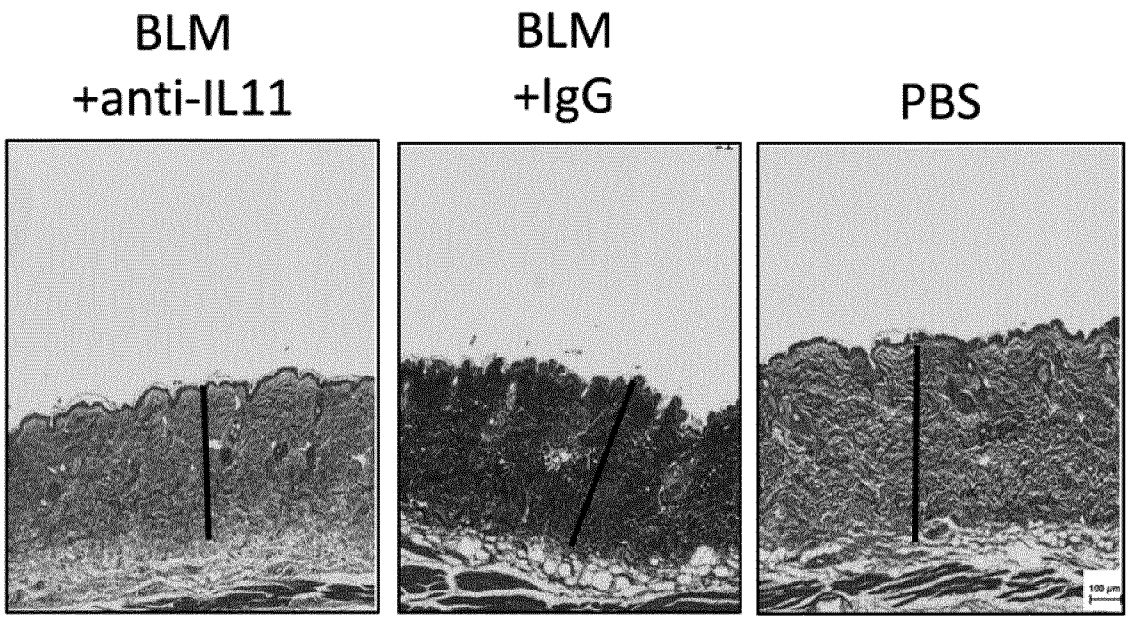

Figure 66B

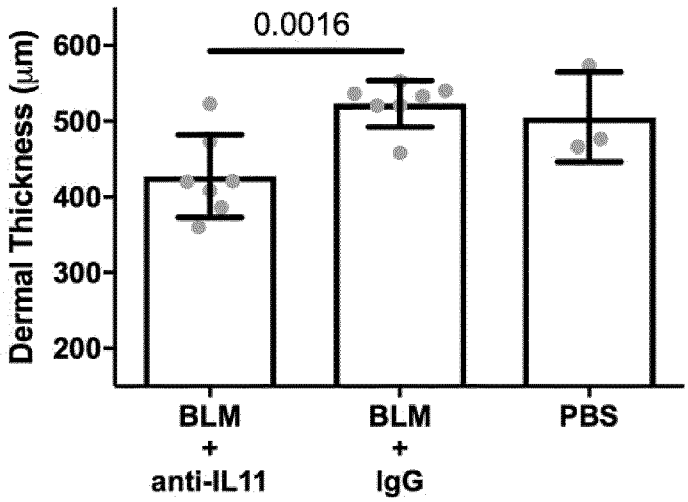

Figure 66C

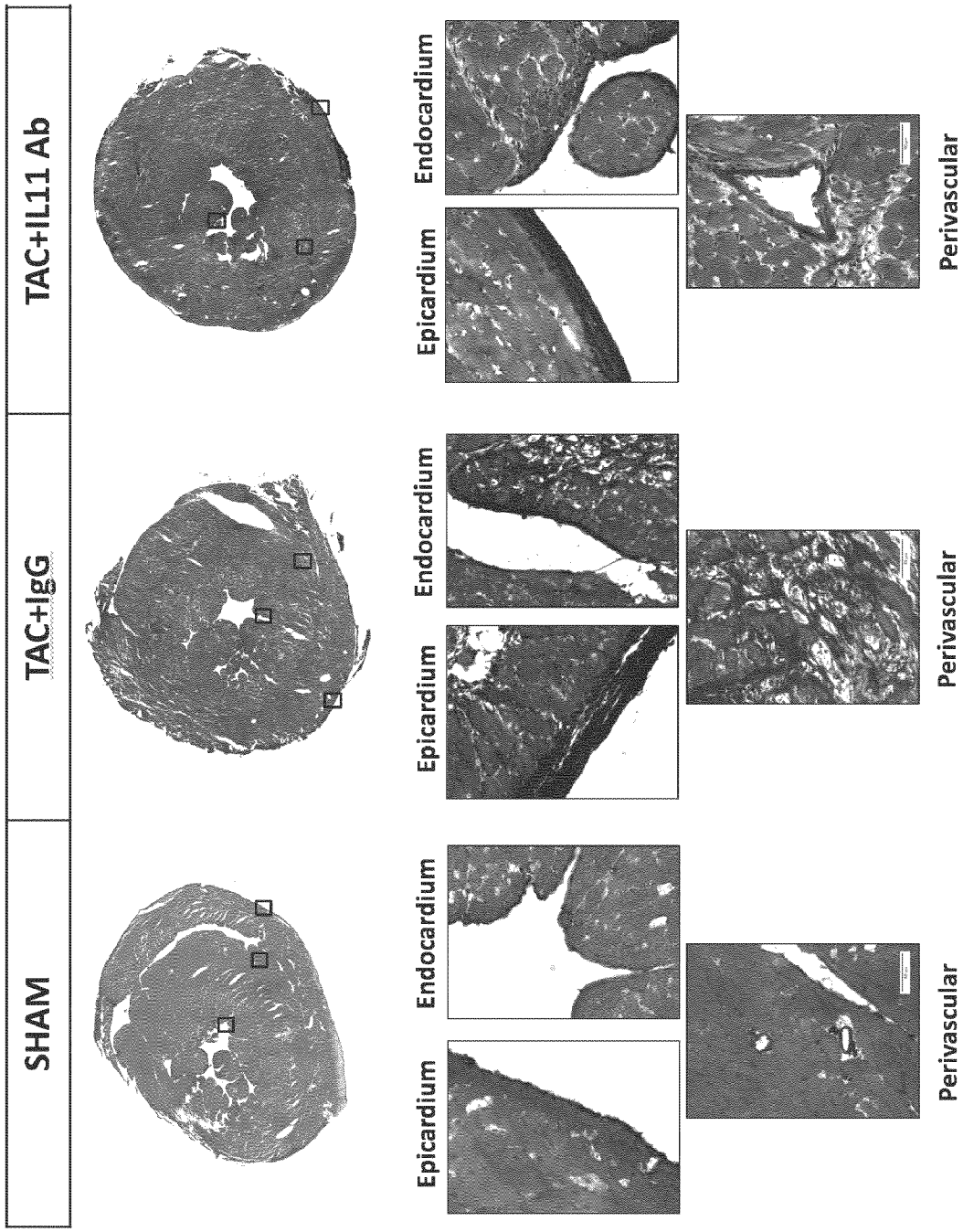
SHAM
TAC+IgG
TAC+IL11 Ab
Epicardium
Endocardium
Perivascular
Epicardium
Endocardium
Perivascular
Epicardium
Endocardium
Perivascular

Figure 67

BSN-2E1
QVQLQESGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHGKSLEWIGDINPHNGGPIYNQKFTG
KATLTVDKSSSTAYMELRSLTSEDTAVYYCARGELGHWYFDVWGTGTTVTVSS (SEQ ID NO:541)

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPHNGGP (SEQ ID NO:543)
HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544)

BSN-2G6
QVQLQESGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHGKSLEWIGNINPDNGGTIYNQKFKG
KATLTVDKSSSTAYMELRSLTSEDTAVYFCAREGPYGYTWFAYWGQGTLDTVSA (SEQ ID NO:545)

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPDNGGT (SEQ ID NO:546)
HC-CDR3: AREGPYGYTWFAY (SEQ ID NO:547)

BSN-3C6
QVQLQESGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHGKSLEWIGDINPHNGGPIYNQKFTG
KATLTVDKSSSTAYMELRSLTSEDTAVYYCARGELGHWYFDVWGTGTTVTVSS (SEQ ID NO:541)

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPHNGGP (SEQ ID NO:543)
HC-CDR3: ARGELGHWYFDV (SEQ ID NO:544)

BSN-5A6
EVQLQQSGPELVKPGASVKIPCKASGYTFTDYNMDWVKQSHGKSLEWIGNINPNNGGIIYNQKFKGK
ATLTVDKSSSTAYMVLRSLTSEDTAVYYCARNPSLYDGYLDCWGQGTTLTVSS (SEQ ID NO:548)

HC-CDR1: GYTFTDYN (SEQ ID NO:542)
HC-CDR2: INPNNGGI (SEQ ID NO:549)
HC-CDR3: ARNPSLYDGYLDC (SEQ ID NO:550)

BSN-5B8
QVQLQQSGAELARPGTSVKLSCKASGYTFTSYGISWVKQRTGQGLEWIGEIYPRSSNTYYNEKFKGK
ATLTADKSSSTAYMELRSLTSEDSADYFCARANWVGYFDVWGTGTTVTVSS (SEQ ID NO:551)

HC-CDR1: GYTFTSYG (SEQ ID NO:228)
HC-CDR2: IYPRSSNT (SEQ ID NO:552)
HC-CDR3: ARANWVGYFDV (SEQ ID NO:553)

Figure 68

BSN-2E1
NIVMTQSPKSMSMSVGERVTLTCKASENVVTYVSWYQQKPEQSPKLLIYGASNRYTGVPDRFTGSG
SATDFTLTISSVQAEDLADYHCGQGYSYPYTFGGGTKLEIK (SEQ ID NO:554)

LC-CDR1: ENVVTY (SEQ ID NO:555)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: GQGYSYPYT (SEQ ID NO:556)

BSN-2G6
DILLTQSPAILSVSPGERVSFSCRASQSIGTSIHWYQQRTNGSPRLLIKYASESISGIPSRFSGSGSGTD
FTLSINSVESEDIADYYCQQSNSWPLTFGAGTKLELK (SEQ ID NO:557)

LC-CDR1: QSIGTS (SEQ ID NO:558)
LC-CDR2: YAS (SEQ ID NO:559)
LC-CDR3: QQSNSWPLT (SEQ ID NO:560)

BSN-3C6
NIVMTQSPKSMSMSVGERVTLTCKASENVVTYVSWYQQKPEQSPKLLIYGASNRYTGVPDRFTGSG
SATDFTLTISSVQAEDLADYHCGQGYSYPYTFGGGTKLEIK (SEQ ID NO:554)

LC-CDR1: ENVVTY (SEQ ID NO:555)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: GQGYSYPYT (SEQ ID NO:556)

BSN-5A6_1
NIVMTQSPKSMSMSVGERVTLTCKASENVVTYVSWYQQKPEQSPKLLIYGASNRYTGVPDRFTGSG
SATDFTLTISSVQAEDLADYHCGQGYSYPYTFGGGTKLEIK (SEQ ID NO:554)

LC-CDR1: ENVVTY (SEQ ID NO:555)
LC-CDR2: GAS (SEQ ID NO:138)
LC-CDR3: GQGYSYPYT (SEQ ID NO:556)

BSN-5A6_2
DIVMSQSPSSLAVSVGEKVTMNCKSSQSLLYNSSQKNYLAWYQQKPGQSPKLLIYWASTRESGVPD
RFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYSYPLTFGAGTNLELK (SEQ ID NO:561)

LC-CDR1: QSLLYNSSQKNY (SEQ ID NO:562)
LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYYSYPLT (SEQ ID NO:581)

BSN-5B8
DIVMTQSHKFMSTSVGDRVTITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRLTGVPDRFTGSG
SGTYFTLTINNVQSEDLADYFCQQYSSYRTFGGGTKLEIK (SEQ ID NO:564)

LC-CDR1: QDVGTA (SEQ ID NO:565)
LC-CDR2: WAS (SEQ ID NO:563)
LC-CDR3: QQYSSYRT (SEQ ID NO:566)

Figure 69

Clone	CDR 1	CDR 2	CDR 3
	Heavy Chain		
BSN-2E1 and BSN-3C6	GYTFTDYN (SEQ ID NO:542)	INPHNGGP (SEQ ID NO:543)	ARGELGHWYFDV (SEQ ID NO:544)
BSN-2G6	GYTFTDYN (SEQ ID NO:542)	INPDNGGT (SEQ ID NO:546)	AREGPYGYTWFAY (SEQ ID NO:547)
BSN-5A6	GYTFTDYN (SEQ ID NO:542)	INPNNGGI (SEQ ID NO:549)	ARNPSLYDGYLDC (SEQ ID NO:550)
BSN-5B8	GYTFTSYG (SEQ ID NO:228)	IYPRSSNT (SEQ ID NO:552)	ARANWVGYFDV (SEQ ID NO:553)

Figure 70

Clone	CDR 1	CDR 2	CDR 3
	Light Chain		
BSN-2E1, BSN-3C6 and BSN-5A6_1	ENVVTY (SEQ ID NO:555)	GAS (SEQ ID NO:138)	GQGYSYPYT (SEQ ID NO:556)
BSN-2G6	QSIGTS (SEQ ID NO:558)	YAS (SEQ ID NO:559)	QQSNSWPLT (SEQ ID NO:560)
BSN-5A6_2	QSLLYNSSQKNY (SEQ ID NO:562)	WAS (SEQ ID NO:563)	QQYYSYPLT (SEQ ID NO:581)
BSN-5B8	QDVGTA (SEQ ID NO:565)	WAS (SEQ ID NO:563)	QQYSSYRT (SEQ ID NO:566)

Figure 71

Clone(s)	HC-CDR1	Sequence family	Family Consensus
BSN-2E1 and BSN-3C6 BSN-2G6 BSN-5A6	GYTFTDYN (SEQ ID NO:542)	mHC-CDR1-1	GYTFTX$_{180}$YX$_{181}$ (SEQ ID NO:567) X$_{180}$ = D or S X$_{181}$ =N or G
BSN-5B8	GYTFTSYG (SEQ ID NO:228)		

Figure 72A

Clone(s)	HC-CDR2	Sequence family	Family Consensus
BSN-2E1 and BSN-3C6	INPHNGGP (SEQ ID NO:543)	mHC-CDR2-1	INPX$_{182}$NGGX$_{183}$ (SEQ ID NO:568) X$_{182}$ = H, D or N X$_{183}$ = P, T or I
BSN-2G6	INPDNGGT (SEQ ID NO:546)		
BSN-5A6	INPNNGGI (SEQ ID NO:549)		
BSN-5B8	IYPRSSNT (SEQ ID NO:552)	mHC-CDR2-2	IYPRSSNT (SEQ ID NO:552)

Figure 72B

Clone(s)	HC-CDR3	Sequence family	Family Consensus
BSN-2E1 and BSN-3C6	ARGELGHWYFDV (SEQ ID NO:544)	mHC-CDR3-1	ARGELGHWYFDV (SEQ ID NO:544)
BSN-2G6	AREGPYGYTWFAY (SEQ ID NO:547)	mHC-CDR3-2	AREGPYGYTWFAY (SEQ ID NO:547)
BSN-5A6	ARNPSLYDGYLDC (SEQ ID NO:550)	mHC-CDR3-3	ARNPSLYDGYLDC (SEQ ID NO:550)
BSN-5B8	ARANWVGYFDV (SEQ ID NO:553)	mHC-CDR3-4	ARANWVGYFDV (SEQ ID NO:553)

Figure 72C

Clone(s)	LC-CDR1	Sequence family	Family Consensus
BSN-2E1, BSN-3C6 and BSN-5A6_1	ENVVTY (SEQ ID NO:555)	mLC-CDR1-1	ENVVTY (SEQ ID NO:555)
BSN-2G6	QSIGTS (SEQ ID NO:558)	mLC-CDR1-2	QSIGTS (SEQ ID NO:558)
BSN-5A6_2	QSLLYNSSQKNY (SEQ ID NO:562)	mLC-CDR1-3	QSLLYNSSQKNY (SEQ ID NO:562)
BSN-5B8	QDVGTA (SEQ ID NO:565)	mLC-CDR1-4	QDVGTA (SEQ ID NO:565)

Figure 73A

Clone(s)	LC-CDR2	Sequence family	Family Consensus
BSN-2E1, BSN-3C6 and BSN-5A6_1	GAS (SEQ ID NO:138)	mLC-CDR2-1	X_{184}AS (SEQ ID NO:569) X_{184} = G, Y or W
BSN-2G6	YAS (SEQ ID NO:559)		
BSN-5A6_2 and BSN-5B8	WAS (SEQ ID NO:563)		

Figure 73B

Clone(s)	LC-CDR3	Sequence family	Family Consensus
BSN-2E1, BSN-3C6 and BSN-5A6_1	GQGYSYPYT (SEQ ID NO:556)	mLC-CDR3-1	$X_{185}QX_{186}X_{187}SX_{188}X_{189}X_{190}T$ (SEQ ID NO:570) X_{185} = Q or G X_{186} = Y, G or S X_{187} = Y, N or S X_{188} = Y or W X_{189} = P or absent X_{190} = L, Y or R
BSN-2G6	QQSNSWPLT (SEQ ID NO:560)		
BSN-5A6_2	QQYYSYPLT (SEQ ID NO:581)		
BSN-5B8	QQYSSYRT (SEQ ID NO:566)		

Figure 73C

BSN-2E1_VH
CAGGTCCAGCTGCAGGAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATACCC
TGCAAGGCTTCTGGATACACATTCACTGACTACAACATGGACTGGGTGAAGCAGAGCCATGGAA
AGAGCCTTGAGTGGATTGGAGATATTAATCCTCACAATGGTGGTCCTATCTACAACCAGAAGTTC
ACGGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCCGCAGC
CTGACATCTGAGGACACTGCAGTCTATTACTGTGCAAGAGGGGAACTGGGTCACTGGTACTTCG
ATGTCTGGGGCACAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:571)

BSN-2E1_VL
AACATTGTAATGACCCAATCTCCCAAATCCATGTCCATGTCAGTAGGAGAGAGGGTCACCTTGAC
CTGCAAGGCCAGTGAGAATGTGGTTACTTATGTTTCCTGGTATCAACAGAAACCAGAGCAGTCTC
CTAAACTGCTGATATACGGGGCATCCAACCGGTACACTGGGGTCCCCGATCGCTTCACAGGCAG
TGGATCTGCAACAGATTTCACTCTGACCATCAGCAGTGTGCAGGCTGAAGACCTTGCAGATTATC
ACTGTGGACAGGGTTACAGCTATCCGTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA
(SEQ ID NO:572)

BSN-2G6_VH
CAGGTCCAGCTGCAGGAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATACCC
TGCAAGGCTTCTGGATACACGTTCACTGACTACAACATGGACTGGGTGAAGCAGAGCCATGGAA
AGAGCCTTGAGTGGATTGGAAATATTAATCCTGACAATGGTGGTACTATCTACAACCAGAAGTTC
AAGGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCCGCAGCC
TGACATCTGAGGACACTGCAGTCTATTTCTGTGCAAGAGAGGGGCCTTATGGTTACACCTGGTTT
GCTTACTGGGGCCAAGGGACTCTGGACACTGTCTCTGCA (SEQ ID NO:573)

BSN-2G6_VL
GACATCTTGCTGACTCAGTCTCCAGCCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGTTTCTC
CTGCAGGGCCAGTCAGAGCATTGGCACAAGCATACACTGGTATCAGCAAAGAACAAATGGTTCT
CCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATCTCTGGGATCCCTTCCAGGTTTAGTGGCAG
TGGATCAGGGACAGATTTTACTCTTAGCATCAACAGTGTGGAGTCTGAAGATATTGCAGATTATTA
CTGTCAACAAAGTAATAGCTGGCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA
(SEQ ID NO:574)

BSN-3C6_VH
CAGGTCCAGCTGCAGGAGTCTGGACCTGAGCTGGTGAAGCCTGGGGCTTCAGTGAAGATACCC
TGCAAGGCTTCTGGATACACATTCACTGACTACAACATGGACTGGGTGAAGCAGAGCCATGGAA
AGAGCCTTGAGTGGATTGGAGATATTAATCCTCACAATGGTGGTCCTATCTACAACCAGAAGTTC
ACGGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGAGCTCCGCAGC
CTGACATCTGAGGACACTGCAGTCTATTACTGTGCAAGAGGGGAACTGGGTCACTGGTACTTCG
ATGTCTGGGGCACAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:574)

BSN-3C6_VL
AACATTGTAATGACCCAATCTCCCAAATCCATGTCCATGTCAGTAGGAGAGAGGGTCACCTTGAC
CTGCAAGGCCAGTGAGAATGTGGTTACTTATGTTTCCTGGTATCAACAGAAACCAGAGCAGTCTC
CTAAACTGCTGATATACGGGGCATCCAACCGGTACACTGGGGTCCCCGATCGCTTCACAGGCAG
TGGATCTGCAACAGATTTCACTCTGACCATCAGCAGTGTGCAGGCTGAAGACCTTGCAGATTATC
ACTGTGGACAGGGTTACAGCTATCCGTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA
(SEQ ID NO:575)

Figure 74

BSN-5A6_VH
GAGGTCCAGCTGCAACAGTCTGGACCTGAACTGGTGAAGCCTGGGGCTTCAGTGAAGATACCCT
GCAAGGCTTCTGGATACACATTCACTGACTACAACATGGACTGGGTGAAGCAGAGCCATGGAAA
GAGCCTTGAGTGGATTGGAAATATTAATCCTAACAATGGTGGTATTATCTACAACCAGAAGTTCAA
GGGCAAGGCCACATTGACTGTAGACAAGTCCTCCAGCACAGCCTACATGGTACTCCGCAGCCTG
ACATCTGAGGACACTGCAGTCTATTACTGTGCAAGAAACCCAAGTCTCTATGATGGTTACCTTGA
CTGCTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA (SEQ ID NO:576)

BSN-5A6_VL1
AACATTGTAATGACCCAATCTCCCAAATCCATGTCCATGTCAGTAGGAGAGAGGGTCACCTTGAC
CTGCAAGGCCAGTGAGAATGTGGTTACTTATGTTTCCTGGTATCAACAGAAACCAGAGCAGTCTC
CTAAACTGCTGATATACGGGGCATCCAACCGGTACACTGGGGTCCCCGATCGCTTCACAGGCAG
TGGATCTGCAACAGATTTCACTCTGACCATCAGCAGTGTGCAGGCTGAAGACCTTGCAGATTATC
ACTGTGGACAGGGTTACAGCTATCCGTACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA
(SEQ ID NO:577)

BSN-5A6_VL2
GACATTGTGATGTCACAGTCTCCATCCTCCCTAGCTGTGTCAGTTGGAGAGAAGGTTACTATGAA
CTGCAAGTCCAGTCAGAGCCTTTTATATAATAGCAGTCAAAAGAACTACTTGGCCTGGTACCAGC
AGAAACCAGGGCAGTCTCCTAAATTGCTGATTTACTGGGCATCCACTAGGGAATCTGGGGTCCC
TGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTGTGAAGGCT
GAAGACCTGGCAGTTTATTACTGTCAGCAATATTATAGTTATCCGCTCACGTTCGGTGCTGGGAC
CAACCTGGAGCTGAAA (SEQ ID NO:578)

BSN-5B8_VH
CAGGTCCAGCTGCAGCAGTCTGGAGCTGAGCTGGCGAGGCCTGGGACTTCAGTGAAACTGTCC
TGCAAGGCTTCTGGCTACACCTTCACAAGCTATGGTATAAGCTGGGTGAAACAGAGAACTGGAC
AGGGCCTTGAGTGGATTGGAGAAATTTATCCTCGAAGTAGTAATACTTACTACAATGAGAAGTTC
AAGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCGTACATGGAGCTCCGCAGC
CTGACATCTGAGGACTCTGCGGACTATTTCTGTGCAAGGGCTAACTGGGTAGGGTACTTCGATG
TCTGGGGCACAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO:579)

BSN-5B8_VL
GACATTGTGATGACCCAGTCTCACAAATTCATGTCCACATCAGTCGGAGACAGGGTCACCATCAC
CTGCAAGGCCAGTCAGGATGTGGGTACTGCTGTAGCCTGGTATCAACAGAAACCAGGACAATCT
CCTAAACTACTGATTTACTGGGCATCCACCCGGCTCACTGGAGTCCCTGATCGCTTCACAGGCA
GTGGATCTGGGACATATTTCACTCTCACCATTAACAATGTGCAGTCTGAAGACTTGGCAGATTATT
TCTGTCAGCAATATAGCAGCTATCGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAG (SEQ
ID NO:580)

Figure 74 (Cont.)