



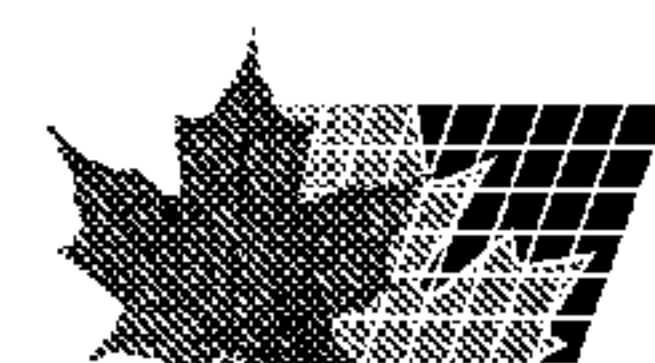
(86) **Date de dépôt PCT/PCT Filing Date:** 2015/05/28
(87) **Date publication PCT/PCT Publication Date:** 2015/12/03
(85) **Entrée phase nationale/National Entry:** 2016/11/22
(86) **N° demande PCT/PCT Application No.:** US 2015/032895
(87) **N° publication PCT/PCT Publication No.:** 2015/184099
(30) **Priorités/Priorities:** 2014/05/28 (US62/004,071);
2015/05/13 (US62/161,250)

(51) **Cl.Int./Int.Cl. C07K 16/28** (2006.01),
A61K 39/395 (2006.01), **A61P 31/12** (2006.01),
A61P 35/00 (2006.01), **A61P 37/02** (2006.01),
C12N 15/13 (2006.01), **C12P 21/08** (2006.01),
C12Q 1/00 (2006.01), **G01N 33/48** (2006.01)
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(54) **Titre : ANTICORPS ANTI-GITR ET LEURS PROCEDES D'UTILISATION**
(54) **Title: ANTI-GITR ANTIBODIES AND METHODS OF USE THEREOF**

(57) **Abrégé/Abstract:**

The present disclosure provides antibodies that specifically bind to human glucocorticoid-induced TNFR family related receptor (GITR) and compositions comprising such antibodies. In a specific aspect, the antibodies specifically bind to human GITR and modulate GITR activity, e.g., enhance, activate or induce GITR activity, utilizing such antibodies. The present disclosure also provides methods for treating disorders, such as cancer and infectious diseases, by administering an antibody that specifically binds to human GITR and modulates GITR activity e.g., enhances, activates or induces GITR activity.



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(51) **International Patent Classification:**
A61K 39/395 (2006.01) *C07K 16/28* (2006.01)

(21) **International Application Number:**
PCT/US2015/032895

(22) **International Filing Date:**
28 May 2015 (28.05.2015)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
62/004,071 28 May 2014 (28.05.2014) US
62/161,250 13 May 2015 (13.05.2015) US

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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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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).

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

(54) **Title:** ANTI-GITR ANTIBODIES AND METHODS OF USE THEREOF

(57) **Abstract:** The present disclosure provides antibodies that specifically bind to human glucocorticoid-induced TNFR family related receptor (GITR) and compositions comprising such antibodies. In a specific aspect, the antibodies specifically bind to human GITR and modulate GITR activity, *e.g.*, enhance, activate or induce GITR activity, utilizing such antibodies. The present disclosure also provides methods for treating disorders, such as cancer and infectious diseases, by administering an antibody that specifically binds to human GITR and modulates GITR activity *e.g.*, enhances, activates or induces GITR activity.

WO 2015/184099 A1

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JUMBO APPLICATIONS/PATENTS

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NOTE POUR LE TOME / VOLUME NOTE:

ANTI-GITR ANTIBODIES AND METHODS OF USE THEREOF

SEQUENCE LISTING

[0001] The instant application contains a sequence listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 27, 2015, is named 3617.009PC02_SL_PatentIn_ST25.txt and is 747,129 bytes in size.

1. FIELD

[0002] The present disclosure provides antibodies that specifically bind to human glucocorticoid-induced TNFR family related receptor (GITR) and compositions comprising such antibodies. In a specific aspect, the antibodies specifically bind to human GITR and modulate GITR activity, *e.g.*, enhance, activate or induce GITR activity, utilizing such antibodies. The present disclosure also provides methods for treating disorders, such as cancer and infectious diseases, by administering an antibody that specifically binds to human GITR and modulates GITR activity, *e.g.*, enhances, activates or induces GITR activity.

2. BACKGROUND

[0003] Glucocorticoid-induced TNFR-related protein (GITR), a member of the TNFR superfamily, is expressed in many components of the innate and adaptive immune system and stimulates both acquired and innate immunity (Nocentini G *et al.*, (1994) PNAS 94: 6216-6221; Hanabuchi S *et al.*, (2006) Blood 107:3617-3623; Nocentini G & Riccardi C (2005) Eur J Immunol 35: 1016-1022; Nocentini G *et al.*, (2007) Eur J Immunol 37:1165-1169). It is expressed in several cells and tissues, including T, B, dendritic (DC) and Natural Killer (NK) cells and is activated by its ligand, GITRL, mainly expressed on Antigen Presenting Cells (APCs), on endothelial cells, and also in tumor cells. The GITR/GITRL system participates in the development of autoimmune/inflammatory responses and potentiates response to infection and tumors. For example, treating animals with GITR-Fc fusion protein ameliorates autoimmune/inflammatory diseases while GITR triggering is effective in treating viral, bacterial, and parasitic infections, as well in boosting immune response against tumors (Nocentini G *et al.*, (2012) Br J Pharmacol 165: 2089-99). These effects are due to several concurrent mechanisms including: co-activation of effector T-cells, inhibition of regulatory T (Treg) cells, NK-cell co-activation, activation of macrophages, modulation of dendritic cell function and regulation of the extravasation process. The membrane expression of GITR is increased following T cell

activation (Hanabuchi S *et al.*, (2006) *supra*; Nocentini G & Riccardi C *supra*). Its triggering coactivates effector T lymphocytes (McHugh RS *et al.*, (2002) *Immunity* 16: 311-323; Shimizu J *et al.*, (2002) *Nat Immunol* 3: 135-142; Ronchetti S *et al.*, (2004) *Eur J Immunol* 34: 613-622; Tone M *et al.*, (2003) *PNAS* 100: 15059-15064). GITR activation increases resistance to tumors and viral infections, is involved in autoimmune/inflammatory processes and regulates leukocyte extravasation (Nocentini G & Riccardi C (2005) *supra*; Cuzzocrea S *et al.*, (2004) *J Leukoc Biol* 76: 933-940; Shevach EM & Stephens GL (2006) *Nat Rev Immunol* 6: 613-618; Cuzzocrea S *et al.*, (2006) *J Immunol* 177: 631-641; Cuzzocrea S *et al.*, (2007) *FASEB J* 21: 117-129).

[0004] Human GITR is expressed at very low levels in peripheral (non-activated) T cells. After T cell activation, GITR is strongly up-regulated for several days in both CD4⁺ and CD8⁺ cells (Kwon B *et al.*, (1999) *J Biol Chem* 274: 6056-6061; Gurney AL *et al.*, (1999) *Curr Biol* 9: 215-218; Ronchetti S *et al.*, (2004) *supra*; Shimizu J *et al.*, (2002) *supra*; Ji HB *et al.*, (2004) *supra*; Ronchetti S *et al.*, (2002) *Blood* 100: 350-352; Li Z *et al.*, (2003) *J Autoimmun* 21: 83-92), with CD4⁺ cells having a higher GITR expression than CD8⁺ cells (Kober J *et al.*, (2008) *Eur J Immunol* 38(10): 2678-88; Bianchini R *et al.*, (2011) *Eur J Immunol* 41(8): 2269-78).

[0005] Given the role of human GITR in modulating immune responses, provided herein are antibodies that specifically bind to GITR and the use of those antibodies to modulate GITR activity.

3. SUMMARY

[0006] In one aspect, provided herein are antibodies and fragments thereof that specifically bind to GITR (*e.g.*, human GITR). In one embodiment, an antibody or antigen-binding fragment thereof that specifically binds to GITR (*e.g.*, human GITR) partially inhibits GITR ligand (*e.g.*, human GITRL) from binding to GITR as assessed by a method known to one of skill in the art or described herein (see, *e.g.*, Sections 6.2.5.2 and 6.2.5.4, *infra*). In a specific embodiment, the antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM GITRL (*e.g.*, human GITRL) from binding to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL to the GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In certain embodiments, the antibody or antigen-binding fragment thereof inhibits 40% to 70%, 50% to 70%, 50% to 80%, or 40% to 80% of the GITRL (*e.g.*, human GITRL) from binding to GITR (*e.g.*, human GITR). In another specific embodiment, at least 20% of the amount of GITRL (*e.g.*, human GITRL) that binds to GITR (*e.g.*, human GITR) in the absence of the antibody or antigen-

binding fragment thereof binds to GITR (e.g., human GTR) in the presence of the antibody or antigen-binding fragment thereof in an assay: (a) coupling GTR (e.g., human GTR) to beads at a concentration of 5pg/ml/bead; (b) incubating the GTR (e.g., human GTR) coupled beads at a concentration of 40 beads/ μ l with or without the antibody in a well; (c) adding labeled GITRL (e.g., labeled human GITRL) to the well to obtain a final concentration of 0.5nM of the GITRL (e.g., human GITRL) and 20 beads/ μ l of the GTR coupled beads; and (d) detecting the labeled GITRL (e.g., human GITRL) bound to the GTR (e.g., human GTR) coupled beads by, e.g., a suspension array assay. In some embodiments, 20% to 60%, 20% to 50%, 30% to 60% or 30% to 50% of the amount of GITRL (e.g., human GITRL) that binds to GTR (e.g., human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (e.g., human GTR) in the presence of the antibody or antigen-binding fragment thereof.

[0007] In certain embodiments, the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region (VH) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 1), wherein

X_1 is D, E, G or A;

X_2 is A, V, L, I, P, F, M or Y; and

X_3 is Y, G, N, Q, S, T, C, W, F or H;

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of $X_1IX_2X_3X_4SGX_5X_6X_7YX_8QKFX_9X_{10}$ (SEQ ID NO: 2), wherein

X_1 is V, A, L, I, P, F, M or T;

X_2 is R, K, H, Q or A;

X_3 is T, G, N, Q, S, C, W, Y, V, I or P;

X_4 is Y, G, N, Q, S, T, C, W, F, H, or A;

X_5 is D, E, G or A;

X_6 is V, A, L, I, P, F, M or T;

X_7 is T, G, N, Q, S, C, W, Y, V, I, P or A;

X_8 is N, G, Q, S, T, C, W, Y or A;

X_9 is K, R, H, Q or A; and

X_{10} is D, E, G or A;

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of $SGTVRGX_1X_2X_3$ (SEQ ID NO: 3), wherein

X_1 is F, A, V, L, I, P, M, Y, W, H or S;

X_2 is A or D; and

X₃ is Y, G, N, Q, S, T, C, W, F, H or V;

(d) a light chain variable region (VL) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YX₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M;

X₂ is L, A, V, I, P, F, M or S;

X₃ is N, G, Q, S, T, C, W, Y or A;

X₄ is S, G, N, Q, T, C, W, Y or A;

X₅ is G, N, Q, S, T, C, W, Y or A;

X₆ is N, G, Q, S, T, C, W, Y or A;

X₇ is Q, G, N, S, T, C, W, Y or A;

X₈ is N, G, Q, S, T, C, W, Y or A; and

X₉ is T, G, N, Q, S, C, W, Y, V, I or A;

(e) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A;

X₂ is E, D or A; and

X₃ is S, G, N, Q, T, C, W, Y or A; and

(f) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y;

X₂ is D, E or Y; and

X₃ is S, G, N, Q, T, C, W, Y or A, and

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A.

In other embodiments, the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region (VH) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G;

X₂ is A or V; and

X₃ is Y or H;

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L;

X₂ is R, K or Q;

X₃ is Y or F;

X₄ is D, E or G;

X₅ is V or L;

X₆ is T or S;

X₇ is K, R or Q; and

X₈ is D, E or G;

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of SGTVRGFAY (SEQ ID NO: 9);

(d) a light chain variable region (VL) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S; and

X₂ is T or S;

(e) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of WASTRES (SEQ ID NO: 11); and

(f) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E; and

X₂ is Y, F or S.

[0008] In some embodiments, provided herein is an antibody or antigen-binding fragment thereof that specifically binds to GITR (e.g., human GITR), comprising:

(a) a heavy chain variable region (VH) complementarity determining region (CDR) 1 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A;

X₂ is A, V, L, I, P, F, M or Y; and

X₃ is Y, G, N, Q, S, T, C, W, F or H;

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T;

X₂ is R, K, H, Q or A;

X₃ is T, G, N, Q, S, C, W, Y, V, I or P;

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A;

X₅ is D, E, G or A;

X₆ is V, A, L, I, P, F, M or T;

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A;

X₈ is N, G, Q, S, T, C, W, Y or A;

X₉ is K, R, H, Q or A; and

X₁₀ is D, E, G or A;

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S;

X₂ is A, or D; and

X₃ is Y, G, N, Q, S, T, C, W, F, H or V;

(d) a light chain variable region (VL) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YLY₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M;

X₂ is L, A, V, I, P, F, M or S;

X₃ is N, G, Q, S, T, C, W, Y or A;

X₄ is S, G, N, Q, T, C, W, Y or A;

X₅ is G, N, Q, S, T, C, W, Y or A;

X₆ is N, G, Q, S, T, C, W, Y or A;

X₇ is Q, G, N, S, T, C, W, Y or A;

X₈ is N, G, Q, S, T, C, W, Y or A; and

X₉ is T, G, N, Q, S, C, W, Y, V, I or A;

(e) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A;

X₂ is E, D or A; and

X₃ is S, G, N, Q, T, C, W, Y or A; and

(f) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y;

X₂ is D, E or Y; and

X₃ is S, G, N, Q, T, C, W, Y or A, and

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR1 comprising, consisting of, or consisting

essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 13, 19-23, and 117-119. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 35 and SEQ ID NO:116. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 24-33, and 120-188. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 114, 115, and 194. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 34 and 189. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 16 and 101-104. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 17 and 105. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 18, 106-109, 192, and 193. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antibody in Table 2. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the amino acid sequences of the VH CDR1, VH CDR2, and VH CDR3 of an antibody in Table 6. In another specific embodiment, the antibody or antigen-binding fragment thereof comprises the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in Table 1. In another specific embodiment, the antibody or antigen-binding fragment thereof comprises the amino acid sequences of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in Table 5. In some embodiments, the antibody or antigen-binding fragment thereof partially inhibits GITRL (*e.g.*, human GITRL) from binding to GTR (*e.g.*, human GTR) as assessed by a method known to one of skill in the art or described herein (see, *e.g.*, Sections 6.2.5.2 and 6.2.5.4, *infra*). In certain embodiments, the antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM GITRL (*e.g.*, human GITRL) from binding to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of

0.5nM GITRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay. In certain embodiments, the antibody or antigen-binding fragment thereof inhibits 40% to 70%, 50% to 70%, 50% to 80%, or 40% to 80% of the GITRL (*e.g.*, human GITRL) from binding to GTR (*e.g.*, human GTR). In specific embodiments, at least 20% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof in an assay comprising the following steps: (a) coupling GTR (*e.g.*, human GTR) to beads at a concentration of 5pg/ml/bead; (b) incubating the GTR (*e.g.*, human GTR) coupled beads at a concentration of 40 beads/ μ l with or without the antibody in a well; (c) adding labeled GITRL (*e.g.*, labeled human GITRL) to the well to obtain a final concentration of 0.5nM of the GITRL (*e.g.*, human GITRL) 20 beads/ μ l of the GTR coupled beads; and (d) detecting the labeled GITRL (*e.g.*, human GITRL) bound to the GTR (*e.g.*, human GTR) coupled beads by, *e.g.*, a suspension array assay. In some embodiments, 20% to 60%, 20% to 50%, 30% to 60% or 30% to 50% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof.

[0009] In another embodiment, provided herein is an antibody or antigen-binding fragment thereof that specifically binds to GTR (*e.g.*, human GTR), comprising:

(a) a heavy chain variable region (VH) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 7), wherein

X_1 is D, E or G;

X_2 is A or V; and

X_3 is Y or H;

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO: 8), wherein

X_1 is V or L;

X_2 is R, K or Q;

X_3 is Y or F;

X_4 is D, E or G;

X_5 is V or L;

X_6 is T or S;

X_7 is K, R or Q; and

X_8 is D, E or G;

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of SGTVRGFAY (SEQ ID NO: 9);

(d) a light chain variable region (VL) CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence of KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X_1 is G or S; and

X_2 is T or S;

(e) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence of WASTRES (SEQ ID NO: 11); and

(f) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X_1 is D or E; and

X_2 is Y, F or S.

In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 13, 19-23, and 117-119. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of 35 and 116. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 24-33, and 120-188. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 114, 115, and 194. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR3 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 34 and 189. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR1 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 16, and 101-104. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR2 comprising, consisting of, or consisting essentially of an amino acid sequence selected from the group consisting of SEQ ID NO: 17 and 105. In some embodiments, the antibody or antigen-binding fragment thereof comprises a VL CDR3 comprising, consisting of, or consisting essentially of an amino acid sequence selected

from the group consisting of SEQ ID NO: 18, 106-109, 192, and 193. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antibody in Table 2. In another specific embodiment, the antibody or antigen-binding fragment thereof comprises the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof does not prevent GITRL (*e.g.*, human GITRL) from binding to GTR (*e.g.*, human GTR) as assessed by a method known to one of skill in the art or described herein (see, *e.g.*, Sections 6.2.5.2 and 6.2.5.4, *infra*). In certain embodiments, the antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM GITRL (*e.g.*, human GITRL) from binding to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay. In certain embodiments, the antibody or antigen-binding fragment thereof inhibits 40% to 70%, 50% to 70%, 50% to 80%, or 40% to 80% of the GITRL (*e.g.*, human GITRL) from binding to GTR (*e.g.*, human GTR). In specific embodiments, at least 20% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof in an assay comprising the following steps: (a) coupling GTR (*e.g.*, human GTR) to beads at a concentration of 5pg/ml/bead; (b) incubating the GTR (*e.g.*, human GTR) coupled beads at a concentration of 40 beads/ μ l with or without the antibody in a well; (c) adding labeled GITRL (*e.g.*, labeled human GITRL) to the well to obtain a final concentration of 0.5nM of the GITRL (*e.g.*, human GITRL) and 20 beads/ μ l of the GTR coupled beads; and (d) detecting the labeled GITRL (*e.g.*, human GITRL) bound to the GTR (*e.g.*, human GTR) coupled beads by, *e.g.*, a suspension array assay. In some embodiments, 20% to 60%, 20% to 50%, 30% to 60% or 30% to 50% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof.

[0010] In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to human GTR, comprising: (a) a heavy chain variable region (VH) CDR1 comprising the amino acid sequence of DYAMY (SEQ ID NO: 13); (b) a VH CDR2 comprising the amino acid sequence of VIRTYSGDVTYNQKFKD (SEQ ID NO: 14); (c) a VH CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO: 15); (d) a light chain

variable region (VL) CDR1 comprising the amino acid sequence of KSSQSLLNSGNQKNYLT (SEQ ID NO: 16); (e) a VL CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 17); and (f) a VL CDR3 comprising the amino acid sequence of QNDYSYPYT (SEQ ID NO: 18). In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to human GTR, comprising the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR 3 of an antibody 22 in Table 1 and Table 2. In some embodiments, the antibody or antigen-binding fragment thereof partially inhibits GITRL (*e.g.*, human GITRL) from binding to GTR (*e.g.*, human GTR) as assessed by a method known to one of skill in the art or described herein (see, *e.g.*, Sections 6.2.5.2 and 6.2.5.4, *infra*). In certain embodiments, the antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% of GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL (*e.g.*, human GITRL) to the GTR coupled beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay. In some embodiments, the antibody or antigen-binding fragment thereof inhibits 50% to 70% of human GITRL binding to human GTR. In specific embodiments, at least 20% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof in an assay comprising the following steps: (a) coupling GTR (*e.g.*, human GTR) to beads at a concentration of 5pg/ml/bead; (b) incubating the GTR (*e.g.*, human GTR) coupled beads at a concentration of 40 beads/ μ l with or without the antibody in a well; (c) adding labeled GITRL (*e.g.*, labeled human GITRL) to the well to obtain a final concentration of 0.5nM of the GITRL (*e.g.*, human GITRL) and 20 beads/ μ l of the GTR coupled beads; and (d) detecting the labeled GITRL (*e.g.*, human GITRL) bound to the GTR (*e.g.*, human GTR) coupled beads by, *e.g.*, a suspension array assay. In some embodiments, 20% to 60%, 20% to 50%, 30% to 60% or 30% to 50% of the amount of GITRL (*e.g.*, human GITRL) that binds to GTR (*e.g.*, human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (*e.g.*, human GTR) in the presence of the antibody or antigen-binding fragment thereof. In some embodiments, 30% to 50% of the amount of human GITRL that binds to human GTR in the absence of the antibody or antigen-binding fragment thereof binds to human GTR in the presence of the antibody or antigen-binding fragment thereof. In certain embodiments, the antibody or antigen-binding fragment thereof is agonistic.

[0011] In certain embodiments, an antibody or fragment thereof provided herein, which

specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable region sequence comprising one, two, three or four of the framework regions of the heavy chain variable region sequence of SEQ ID NO: 203. In some embodiments, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of a heavy chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95% or 100% identical to one, two, three or four of the framework regions of a heavy chain variable region sequence selected from the group consisting of SEQ ID NO: 201, SEQ ID NO: 206, and SEQ ID NOs: 215 to 389. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable region having human derived framework regions. In another embodiment, an antibody or antigen-binding fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGHV1-2*02 (SEQ ID NO: 601), IGHV1-3*01 (SEQ ID NO: 602), IGHV1-46*01 (SEQ ID NO: 603), IGHV1-18*01 (SEQ ID NO: 604), IGHV1-69*01 (SEQ ID NO: 605), and IGHV7-4-1*02 (SEQ ID NO: 606). In specific embodiments, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human heavy chain variable framework region. In a specific embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable framework region that is derived from amino acid sequence SEQ ID NO: 601, wherein at least one, two, three, four, or five (in certain embodiments up to 10) amino acids of amino acid sequence SEQ ID NO: 601 is substituted with an amino acid found in an analogous position in a corresponding non-human heavy chain variable framework region. In certain embodiments, the amino acid substitution is at an amino acid position selected from the group consisting of 24, 48, 67, 71, 73, and 94, wherein the amino acid position of each group member is indicated according to the Kabat numbering. In specific embodiments, the amino acid substitution is selected from the group consisting of 24G, 48I, 67A, 71V, 73K, and 94K, wherein the amino acid position of each group member is indicated according to the Kabat numbering

[0012] In another embodiment, provided herein is an antibody or fragment thereof that

specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, and SEQ ID NOS: 215 to 389. In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 203. In another specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 206.

[0013] In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 553, 554 and 567 to 570. In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 581 and 582.

[0014] In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region sequence comprising one, two, three or four framework regions of the light chain variable region sequence of SEQ ID NO: 204 or SEQ ID NO: 205. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of a light chain variable region sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NOS: 400-518. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of the light chain variable region sequence of SEQ ID NO: 519. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable sequence having human derived framework regions. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGKV4-1*01 (SEQ ID NO: 607) and IGKV3-7*02 (SEQ ID NO: 608). In specific embodiments, the light

chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human light chain variable framework region. In another embodiment, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable framework region that is or is derived from amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608 wherein at least one, two, three, four, or five (in certain embodiments up to 10) amino acids of amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608 is substituted with an amino acid found in an analogous position in a corresponding non-human light chain variable framework region. In certain embodiments, the amino acid substitution is at amino acid position 87, wherein the amino acid position is indicated according to the Kabat numbering. In specific embodiments, the amino acid substitution is an amino acid substitution of 87H, wherein the amino acid position is indicated according to the Kabat numbering.

[0015] In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208 and SEQ ID NOs: 400 to 518. In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 519. In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 204 or SEQ ID NO: 205. In another specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 207. In another specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 208.

[0016] In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 555, 556 and 571 to 576.

[0017] In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences of an antibody in the table of Figure 23 or any one of Figures 24A-24C. In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region and a light chain variable region comprising the amino acid sequences of an antibody in Table 17. In an specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 206; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 207. In another specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 206; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 208.

[0018] In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, a VH CDR3 and framework regions derived from a human immunoglobulin, wherein VH CDR1 comprises, consists of, or consists essentially of the amino acid sequence of DYAMY (SEQ ID NO: 13), VH CDR2 comprises, consists of, or consists essentially of the amino acid sequence of VIRTYSGDVTYNQKFKD (SEQ ID NO: 14) and VH CDR3 comprises, consists of, or consists essentially of the amino acid sequence of SGTVRGFAY (SEQ ID NO: 15). In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, a VL CDR3 and framework regions derived from a human immunoglobulin, wherein VL CDR1 comprises, consists of, or consists essentially of the amino acid sequence of KSSQSLLNSGNQKNYLT (SEQ ID NO: 16), VL CDR2 comprises, consists of, or consists essentially of the amino acid sequence of WASTRES (SEQ ID NO: 17) and VL CDR3 comprises, consists of, or consists essentially of the amino acid sequence of QNDYSYPYT (SEQ ID NO: 18). In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a heavy chain variable region (VH) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 201, 203, 206 and 215-389. In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising a light chain variable region (VL) comprising an amino acid sequence selected from

the group consisting of SEQ ID NO: 202, 204, 205, 207, 208 and 400-518. In another embodiment, provided herein is an antibody or fragment thereof that specifically binds to GTR (e.g., human GTR) comprising a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 519. In some embodiments, the antibody or antigen-binding fragment thereof partially inhibits GTRL (e.g., human GTRL) from binding to GTR (e.g., human GTR) as assessed by a method known to one of skill in the art or described herein (see, e.g., Sections 6.2.5.2 and 6.2.5.4, *infra*). In certain embodiments, the antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM GTRL (e.g., human GTRL) from binding to GTR coupled to beads (e.g., human GTR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GTRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay. In specific embodiments, at least 20% of the amount of GTRL (e.g., human GTRL) that binds to GTR (e.g., human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (e.g., human GTR) in the presence of the antibody or antigen-binding fragment thereof in an assay comprising the following steps: (a) coupling GTR (e.g., human GTR) to beads at a concentration of 5pg/ml/bead; (b) incubating the GTR (e.g., human GTR) coupled beads at a concentration of 40 beads/ μ l with or without the antibody in a well; (c) adding labeled GTRL (e.g., labeled human GTRL) to the well to obtain a final concentration of 0.5nM of the GTRL (e.g., human GTRL) and 20 beads/ μ l of the GTR coupled beads; and (d) detecting the labeled GTRL (e.g., human GTRL) bound to the GTR (e.g., human GTR) coupled beads by, e.g., a suspension array assay. In some embodiments, 20% to 60%, 20% to 50%, 30% to 60% or 30% to 50% of the amount of GTRL (e.g., human GTRL) that binds to GTR (e.g., human GTR) in the absence of the antibody or antigen-binding fragment thereof binds to GTR (e.g., human GTR) in the presence of the antibody or antigen-binding fragment thereof.

[0019] In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GTR (e.g., human GTR) comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the amino acid sequence of an antibody in Figure 23 or any one of Figures 24A-24C. In a specific embodiment, provided herein is an antibody or fragment thereof that specifically binds to GTR (e.g., human GTR) comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the amino acid sequence of an antibody in Table 17.

[0020] In certain embodiments, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises heavy and/or light chain constant regions. In some

embodiments, the heavy chain constant region is selected from the group of human immunoglobulins consisting of IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. In certain embodiments, the light chain constant region is selected from the group of human immunoglobulins consisting of IgGκ and IgGλ. In a specific embodiment, the IgG₁ is non-fucosylated IgG₁. In another specific embodiment, the antibody is an IgG₁ which comprises a N297A or N297Q mutation. In another specific embodiment, the antibody is an IgG₄ which comprises a S228P mutation. In another specific embodiment, the antibody is an IgG₂ which comprises a C127S mutation. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain constant region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 557-562. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain constant region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 583 and 584. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain constant region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 557-560 with an amino acid substitution of N to A or Q at amino acid position 180. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain constant region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 588-591. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain constant region comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 563-566.

[0021] In a specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 553, 554, and 567 to 570; and (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising the amino acid

sequence of SEQ ID NO: 581; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 573. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 581; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.

[0022] In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising the

amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555.

[0023] In another embodiment, provided herein is an antibody or fragment thereof that binds to the same epitope of GITR (*e.g.*, human GITR) as the antibody described herein. In another embodiment, provided herein is an isolated antibody that specifically binds to each of i) human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701 and ii) a variant of cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 699, wherein the antibody does not specifically bind to cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 704. In another embodiment, provided herein is an isolated antibody that specifically binds to each of i) human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701 and ii) a variant of cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 699, wherein the antibody does not exhibit substantial binding to cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 704. In another embodiment, provided herein is an isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, wherein the binding between the antibody and a variant GITR is substantially weakened relative to the binding between the antibody and the human GITR, and wherein the variant GITR comprises residues 26-241 of SEQ ID NO: 701 except for an amino acid substitution selected from the group consisting of D60A and G63A. In one embodiment, the substitution is D60A. In another embodiment, the substitution is G63A. In another embodiment, provided herein is an isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the antibody binds to an epitope comprising residues 60-63 of SEQ ID NO: 701. In another embodiment, provided herein is an isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the antibody binds to at least one residue within the amino acid sequence set forth by residues 60-63 of SEQ ID NO: 701. In one embodiment, the antibody binds to at least one residue selected from the group consisting of residues 60, 62, and 63 of SEQ ID NO: 701. In one embodiment, the antibody binds to at least one residue selected from the group consisting of residues 62 and 63 of SEQ ID NO: 701. In one embodiment, the antibody activates or enhances an activity of the human GITR. In another embodiment, provided herein is an isolated antibody that specifically binds human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the

antibody binds an epitope of the human GITR comprising at least one of residues 60 or 63 of SEQ ID NO:701. In another embodiment provided herein is an isolated antibody that specifically binds to human GITR, wherein the antibody exhibits, as compared to binding to human GITR, reduced or absent binding to a protein identical to human GITR except for the presence of a D60A or G63A amino acid substitution. In one embodiment, the antibody induces, activates or enhances an activity of the human GITR. In another embodiment, provided herein is an antibody or antigen-binding fragment thereof that competes with an antibody or antigen-binding fragment thereof described herein for binding to GITR (*e.g.*, human GITR). In a specific embodiment, provided herein is an antibody or antigen-binding fragment thereof that competes with antibody or antigen-binding fragment thereof described herein for binding to GITR (*e.g.*, human GITR) to the extent that the antibody or antigen-binding fragment thereof described herein self-competes for binding to GITR (*e.g.*, human GITR). In another specific embodiment, provided herein is a first antibody or antigen-binding fragment thereof that competes with an antibody or antigen-binding fragment thereof described herein for binding to GITR (*e.g.*, human GITR), wherein the first antibody or antigen-binding fragment thereof competes for binding in an assay comprising the following steps: (a) incubating GITR-transfected cells with the first antibody or antigen-binding fragment thereof in unlabeled form in a container; (b) adding the antibody or antigen-binding fragment thereof described herein in labeled form to the cells in the container and incubating the cells in the container; and (c) detecting the binding of the antibody or antigen-binding fragment thereof described herein in labeled form to the cells. In another specific embodiment, provided herein is a first antibody or antigen-binding fragment thereof competes with an antibody or antigen-binding fragment thereof described herein for binding to GITR (*e.g.*, human GITR), wherein the competition is exhibited as reduced binding of first antibody or antigen-binding fragment thereof to GITR (*e.g.*, human GITR) by more than 80% (*e.g.*, 85%, 90%, 95%, or 98%, or between 80% to 85%, 80% to 90%, 85% to 90%, or 85% to 95%).

[0024] In certain embodiments, an antibody or fragment thereof provided herein, which specifically binds to GITR (*e.g.*, human GITR), activates, induces or enhances an activity of GITR (*e.g.*, human GITR). In specific embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), is a humanized antibody, murine antibody or chimeric antibody. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), binds to GITR (*e.g.*, human GITR) with a K_D in the range of about 0.5 nM to 5 nM. In certain embodiments, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a detectable label. In specific embodiments, an

antibody provided herein is isolated.

[0025] In certain embodiments, an antibody or fragment described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, activates or enhances an activity of human GITR in a cell independent of TCR triggering. In specific embodiments, the cell is a T cell. In specific embodiments, the cell is not a T cell. In specific embodiments, the cell is selected from the group consisting of a B cell, a plasma cell, a memory cell, a natural killer cell, a granulocyte, a neutrophil, an eosinophil, a basophil, a mast cell, a monocyte, a dendritic cell, a plasmacytoid dendritic cell, an NKT cell, and a macrophage. In specific embodiments, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, activates, or enhances an activity of NF- κ B independent of TCR triggering. In certain embodiments, the activity of NF- κ B can be assessed in, *e.g.*, an assay comprising the following steps: (a) incubating T cells (*e.g.*, Jurkat cells) expressing a NF- κ B-luciferase reporter construct (*e.g.*, GloResponse NF- κ B-luc2P construct) and GITR (*e.g.*, human GITR) with the antibody described herein or an isotype control antibody at an antibody concentration of, *e.g.*, 12.5, 10, 5, 2.5, 1.25, or 0.625 μ g/ml, in the absence of an anti-CD3 antibody; and (b) reading luciferase signal after, *e.g.*, 2, 5, 6, 8 or 18 hours of incubation using, *e.g.*, an EnVision multilabel reader 2100, wherein a positive luciferase signal relative to the isotype control antibody indicates activity of NF- κ B. In a particular embodiment, the luciferase signal is read after 5 hours of incubation.

[0026] In certain embodiments, an antibody or fragment described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells. In specific embodiments, the increase in the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells can be assessed in, *e.g.*, an assay comprising the following steps: (a) incubating, *e.g.*, human PBMCs with, *e.g.*, an anti-CD3 antibody at various suboptimal concentrations (*e.g.*, 0.3-5 μ g/ml); and, *e.g.*, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), at, *e.g.*, 5 μ g/ml or an isotype control antibody, for, *e.g.*, 3-4 days at 37°C and 5% CO₂; (b) treating cells with, *e.g.*, Brefeldin A for, *e.g.*, 6 hours at 37°C and 5% CO₂; (c) staining the surface of the cells using, *e.g.*, an anti-CD3 antibody, an anti-CD4 antibody, and an anti-CD8 α antibody; (d) staining intracellularly using, *e.g.*, an anti-IFN γ antibody and an anti-TNF α antibody; and (e) determining the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells relative to the isotype control antibody. In specific embodiments, the polyfunctional (IFN γ ⁺ TNF α ⁺) T cells are selected from the group consisting of polyfunctional (IFN γ ⁺ TNF α ⁺) CD4⁺ T cells and polyfunctional (IFN γ ⁺ TNF α ⁺) CD8⁺ T

cells.

[0027] In specific embodiments, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), when bound to activated regulatory T cells, binds to activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64 to a greater extent (*e.g.*, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold) than the antibody, when bound to activated effector T cells, binds to the activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64, as assessed by methods described herein or known to one of skill in the art (*e.g.*, an Fc gamma receptor IIIA (CD16) reporter assay or as described in the Examples, *infra*). In specific embodiments, the activating Fc gamma receptors are expressed on a cell selected from the group consisting of myeloid-derived effector cells and lymphocyte-derived effector cells. In a particular embodiment, the activating Fc gamma receptor is CD16.

[0028] In specific embodiments, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), when bound to activated regulatory T cells, causes stronger activation of activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64 than the antibody, when bound to activated effector T cells, causes activation of activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64. In particular embodiments, the activation of the activating Fc gamma receptors, when the antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), is bound to activated regulatory T cells, is at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold stronger than the activation of the activating Fc gamma receptors, when the antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), is bound to activated effector T cells, as assessed by methods described herein or known to one of skill in the art (*e.g.*, an Fc gamma receptor IIIA (CD16) reporter assay or as described in the Examples, *infra*). In specific embodiments, the activating Fc gamma receptors are expressed on a cell selected from the group consisting of myeloid-derived effector cells and lymphocyte-derived effector cells. In a particular embodiment, the activating Fc gamma receptor is CD16.

[0029] In certain embodiments, an antibody or fragment described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases surface expression of OX40 and/or PD-1 in activated T cells by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20

fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, or 1000 fold as assessed by methods described herein and/or known to one of skill in the art, relative to surface expression of OX40 and/or PD-1 in activated T cells without the antibody described herein.

[0030] In another embodiment, provided herein are nucleic acid molecules encoding a heavy chain variable region and/or a light chain variable region, or a light chain and/or a heavy chain of an antibody described herein. In a specific embodiment, the nucleic acid molecule encodes a heavy chain variable region comprising the nucleic acid sequence of SEQ ID NO: 209. In another specific embodiment, the nucleic acid molecule encodes a light chain variable region comprising the nucleic acid sequence of SEQ ID NO: 210 or SEQ ID NO: 211. In specific embodiments, the nucleic acid molecule is isolated. In certain embodiments, a vector (*e.g.*, an isolated vector) comprises a nucleic acid molecule encoding a heavy chain variable region and/or a light chain variable region, or a light chain and/or a heavy chain of an antibody described herein. In certain embodiments, a host cell comprises the nucleic acid molecule or vector. Examples of host cells include *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cells, plant cells, insect cells, and human cells in tissue culture. In a specific embodiment, provided herein is a method of producing an antibody or antigen-binding fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprising culturing a host cell so that the nucleic acid molecule is expressed and the antibody is produced.

[0031] In another embodiment, provided herein is a method for enhancing the co-stimulation of T cells comprising incubating *ex vivo* T cells, which have been stimulated with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), with an antibody or antigen-binding fragment thereof described herein. In another embodiment, provided herein is a method for activating T cells comprising incubating *ex vivo* T cells with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the method further comprises, prior to, simultaneously with, or subsequent to the incubation with the anti-GITR antibody or antigen-binding fragment thereof, incubating *ex vivo* the T cells with a TCR complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In some embodiments, the T cells were isolated from a subject. In certain embodiments, the stimulated and/or activated T cells are infused into a subject. In some embodiments, the T cells being infused into the subject are autologous or

allogenic. In a specific embodiment, the subject is a human. In another embodiment, provided herein is a method for preferential expansion of effector T-cells over that of T-regulatory cells in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein. In a specific embodiment, the subject is human.

[0032] In another embodiment, provided herein is a method for enhancing the expansion of T cells (*e.g.*, CD4⁺ and/or CD8⁺ T cells) and/or T cell effector function, comprising incubating *ex vivo* the T cells with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the method further comprises, prior to, simultaneously with or subsequent to incubating the T cells with the antibody or antigen-binding fragment thereof, incubating the T cells with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In certain embodiments, the T cells were isolated from a subject. In some embodiments, the method further comprises infusing the T cells after their expansion and/or after their effector function is enhanced into a subject. In certain embodiments, the T cells being infused into the subject are autologous or allogenic. In a specific embodiment, the subject is a human.

[0033] In another embodiment, provided herein is a method for enhancing the expansion of CD8⁺ T cells, comprising incubating *ex vivo* the T cells with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the method further comprises, prior to, simultaneously with or subsequent to incubating the T cells with the antibody or antigen-binding fragment thereof, incubating the T cells with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In certain embodiments, the T cells were isolated from a subject. In some embodiments, the method further comprises infusing the T cells after their expansion and/or after their effector function is enhanced into a subject. In certain embodiments, the T cells being infused into the subject are autologous or allogenic. In a specific embodiment, the subject is a human.

[0034] In another embodiment, provided herein is a method for enhancing the expansion of CD4⁺ T cells, comprising incubating *ex vivo* the T cells with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the method further comprises, prior to, simultaneously with or subsequent to incubating the T cells with the antibody or antigen-binding fragment thereof, incubating the T cells with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In certain

embodiments, the T cells were isolated from a subject. In some embodiments, the method further comprises infusing the T cells after their expansion and/or after their effector function is enhanced into a subject. In certain embodiments, the T cells being infused into the subject are autologous or allogenic. In a specific embodiment, the subject is a human.

[0035] In another embodiment, provided herein is a method of activating GITR or activating NF- κ B comprising incubating *ex vivo* T cells, which have not been stimulated with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the T cells were isolated from a subject. In certain embodiments, the activated T cells are infused into a subject. In some embodiments, the T cells being infused into the subject are autologous or allogenic. In a specific embodiment, the subject is a human.

[0036] In another embodiment, provided herein is a method of activating T cells independent of TCR triggering comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein.

[0037] In another embodiment, provided herein is a method of inducing, activating or enhancing an activity of NF- κ B independent of TCR triggering comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein.

[0038] In another embodiment, provided herein is a method of increasing the percentage of polyfunctional (IFN γ + TNF α +) T cells comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein.

[0039] In another embodiment, provided herein is a method of increasing surface expression of OX40 and/or PD-1 in activated T cells comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein.

[0040] In another embodiment, provided herein are pharmaceutical compositions comprising an antibody or antigen-binding fragment thereof, a nucleic acid molecule, a vector, or a host cell described herein, and a pharmaceutically acceptable carrier. The pharmaceutical composition can be used to modulate immune response and/or to treat and/or prevent a disorder, such as cancer or an infectious disease. In a specific embodiment, provided herein is a method of modulating an immune response in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein. In a particular embodiment, the immune response is enhanced or induced. In another specific embodiment, provided herein is a method for enhancing the expansion of T cells and/or T cell effector function in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition

described herein. In another specific embodiment, provided herein is a method for enhancing the expansion of CD8⁺ T cells in a subject, comprising administering to the subject an effective amount of a pharmaceutical composition described herein. In some embodiments, the disclosure provides use of an antibody as described herein in the manufacture of a medicament for the treatment of cancer. In certain embodiments, the disclosure provides an antibody as described herein for use in the treatment of cancer. In certain embodiments, the disclosure provides use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of cancer. In certain embodiments, the disclosure provides a pharmaceutical composition as described herein for use in the treatment of cancer. In another specific embodiment, provided herein is a method of treating cancer in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein. In certain embodiments, the method of treating cancer further comprises administering an anti-cancer agent to the subject. Examples of anti-cancer agents that can be administered to a subject in combination with a pharmaceutical composition described herein are described in Section 5.4, *infra* (e.g., Sections 5.4.1 and 5.4.1.1). In a specific embodiment, the anti-cancer agent is a vaccine. In a particular embodiment, the vaccine comprises a heat shock protein peptide complex (HSPPC), in which the HSPPC comprises a heat shock protein (e.g., a gp96 protein) complexed with one or more antigenic peptides (e.g., tumor-associated antigenic peptides). In certain embodiments, the cancer treated is squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's or non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, salivary gland carcinoma, kidney cancer, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, or a type of head or neck cancer. In certain embodiments, the cancer treated is desmoplastic melanoma, inflammatory breast cancer, thymoma, rectal cancer, anal cancer, or surgically treatable or non-surgically treatable brain stem glioma. In a specific embodiment, the subject treated is a human.

[0041] In another embodiment, provided herein is a method for activating T cells independent of TCR triggering in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein.

[0042] In another embodiment, provided herein is a method for inducing, activating or enhancing an activity of NF- κ B independent of TCR triggering in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein.

[0043] In another embodiment, provided herein is a method for increasing the percentage of polyfunctional (IFN γ + TNF α +) T cells in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein.

[0044] In another embodiment, provided herein is a method for increasing surface expression of OX40 and/or PD-1 in activated T cells in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein.

[0045] The antibody as described herein can be used in combination with an IDO inhibitor for treating cancer. In one embodiment, provided herein is a method of treating cancer in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein, wherein the method further comprises administering to the subject an inhibitor of indoleamine-2,3-dioxygenase (IDO). The IDO inhibitor as described herein for use in treating cancer is present in a solid dosage form of a pharmaceutical composition such as a tablet, a pill or a capsule, wherein the pharmaceutical composition includes an IDO inhibitor and a pharmaceutically acceptable excipient. As such, the antibody as described herein and the IDO inhibitor as described herein can be administered separately, sequentially or concurrently as separate dosage forms. In one embodiment, the antibody is administered parenterally and the IDO inhibitor is administered orally. In particular embodiments, the inhibitor is selected from the group consisting of epacadostat (Incyte Corporation), F001287 (Flexus Biosciences), indoximod (NewLink Genetics), and NLG919 (NewLink Genetics). Epacadostat has been described in PCT Publication No. WO 2010/005958, which is incorporated herein by reference in its entirety for all purposes. In one embodiment, the inhibitor is epacadostat. In another embodiment, the inhibitor is F001287. In another embodiment, the inhibitor is indoximod. In another embodiment, the inhibitor is NLG919.

[0046] The antibody as described herein can be used in combination with a checkpoint targeting agent for treating cancer. In one embodiment, provided herein is a method of treating cancer in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein, wherein the method further comprises administering to the subject a checkpoint targeting agent. In some embodiments, the checkpoint targeting agent is selected from the group consisting of an antagonist of PD-1 (*e.g.*, an antagonist anti-PD-1 antibody), an antagonist of PD-L1 (*e.g.*, an antagonist anti-PD-L1 antibody), an antagonist of PD-L2 (*e.g.*, an antagonist anti-PD-L2 antibody), an antagonist of CTLA-4 (*e.g.*, an antagonist anti-CTLA-4 antibody), an antagonist of TIM-3 (*e.g.*, an antagonist anti-TIM-3 antibody), an antagonist of LAG-3 (*e.g.*, an antagonist anti-LAG-3 antibody), and an agonist of OX40 (*e.g.*, an agonist anti-OX40 antibody). In some embodiments, a checkpoint targeting

agent, *e.g.*, an antagonist of PD-1 (*e.g.*, an antagonist anti-PD-1 antibody) or an agonist of OX40 (*e.g.*, an agonist anti-OX40 antibody) is administered simultaneously with the anti-GITR antibody. In some embodiments, a checkpoint targeting agent, *e.g.*, an antagonist of PD-1 (*e.g.*, an antagonist anti-PD-1 antibody) or an agonist of OX40 (*e.g.*, an agonist anti-OX40 antibody) is administered prior to the administration of the anti-GITR antibody. In some embodiments, a checkpoint targeting agent, *e.g.*, an antagonist of PD-1 (*e.g.*, an antagonist anti-PD-1 antibody) or an agonist of OX40 (*e.g.*, an agonist anti-OX40 antibody) is administered subsequent to the administration of the anti-GITR antibody.

[0047] The antibody as described herein can be used in combination with an anti-CD25 antibody. In some embodiments, an anti-CD25 antibody is administered simultaneously with the anti-GITR antibody. In some embodiments, an anti-CD25 antibody is administered prior to the administration of the anti-GITR antibody. In some embodiments, an anti-CD25 antibody is administered subsequent to the administration of the anti-GITR antibody.

[0048] In another specific embodiment, provided herein is a method of treating cancer in a subject comprising administering an antagonist anti-PD-1 antibody to a subject in need thereof who has received an anti-GITR antibody, wherein the PD-1 antibody is administered at a time at which the anti-GITR antibody has increased expression of PD-1 in the subject relative to expression of PD-1 in the subject at the time of the administering. In another specific embodiment, provided herein is a method of treating cancer in a subject comprising administering an agonist anti-OX40 antibody to a subject in need thereof who has received an anti-GITR antibody, wherein the OX40 antibody is administered at a time at which the anti-GITR antibody has increased expression of OX40 in the subject relative to expression of OX40 in the subject at the time of the administering. In certain embodiments, the anti-GITR antibody induces, activates, or enhances an activity of GITR.

[0049] In another specific embodiment, provided herein is a method of treating cancer in a subject comprising administering an anti-GITR antibody to a subject in need thereof, wherein the anti-GITR antibody increases expression of PD-1 in the subject relative to expression of PD-1 in the subject at the time of the administering, and administering an antagonist anti-PD-1 antibody to the subject when expression of PD-1 is increased. In another specific embodiment, provided herein is a method of treating cancer in a subject comprising administering an anti-GITR antibody to a subject in need thereof, wherein the anti-GITR antibody increases expression of OX40 in the subject relative to expression of OX40 in the subject at the time of the administering, and administering an agonist OX40 antibody to the subject when expression of OX40 is increased. In certain embodiments, the anti-GITR antibody induces, activates, or

enhances an activity of GITR.

[0050] In another specific embodiment, provided herein is a method of treating cancer or a viral infection in a subject, the method comprising the steps of: (a) incubating T cells *ex vivo* with an antibody or antigen-binding fragment thereof described herein; and (b) infusing the T cells into the subject. In a specific embodiment, the T cells infused into the subject are autologous or allogenic. In certain embodiments, the T cells were isolated from a subject. In some embodiments, the T cells are not incubated with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In certain embodiments, the method further comprises, prior to step (a): (1) assaying the T cells for cell surface expression of GITR; and (2) if step (1) does not result in detection of GITR above a threshold value, inducing expression of GITR on the surface of the T cells by incubating the T cells with a T cell receptor (TCR) complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In some embodiments, the method further comprises, prior to, simultaneously with or subsequent to step (a), incubating the T cells with a T cell receptor (TCR) complex stimulating agent phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In a specific embodiment, the subject treated is a human.

[0051] In another embodiment, provided herein is a method of treating and/or preventing an infectious disease in a subject comprising administering to the subject an effective amount of a pharmaceutical composition described herein. See Section 5.4.1.2 below for examples of infectious diseases. In another specific embodiment, provided herein is a method of treating a viral infection in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition described herein. In certain embodiments, the viral infection treated is caused by a human papilloma virus (HPV), a Herpes simplex or other herpes virus, hepatitis B virus (HBV), hepatitis C virus (HCV) or other hepatitis virus, measles virus, HIV or Epstein Barr virus (EBV). In certain embodiments, the method of treating a viral infection further comprises administering an anti-viral agent to the subject. In a specific embodiment, the subject treated is a human.

[0052] In another specific embodiment, provided herein is a method of identifying an anti-GITR antibody that is capable of inducing, activating, or enhancing an activity of GITR in the absence of a TCR agonist comprising contacting a cell expressing GITR with an anti-GITR antibody in the absence of a TCR agonist and measuring GITR activity, wherein increased GITR

activity compared to GITR activity in the absence of the anti-GITR antibody indicates the anti-GITR antibody is capable of inducing, activating, or enhancing an activity of GITR in the absence of a TCR agonist. In certain embodiments, the GITR activity is assessed by measuring NF- κ B activity. In certain embodiments, the GITR activity is assessed by measuring activation of TRAF adaptor mediated signaling pathways, wherein the TRAF adaptor is selected from the group consisting of TRAF1, TRAF2, TRAF3, TRAF4, and TRAF5. In certain embodiments, the GITR activity is assessed by measuring activation of the MAPK/ERK pathway. In certain embodiments, the anti-GITR antibody increases the GITR activity at least two-fold compared to GITR activity in the absence of the anti-GITR antibody. In certain embodiments, the anti-GITR antibody increases the GITR activity two-fold to twenty-fold compared to GITR activity in the absence of the anti-GITR antibody. In certain embodiments, the anti-GITR antibody increases the GITR activity two-fold to ten-fold compared to GITR activity in the absence of the anti-GITR antibody. In certain embodiments, the cell is a T cell. In certain embodiments, the cell is not a T cell.

[0053] In another specific embodiment, provided herein is an anti-GITR antibody that specifically binds to human GITR, wherein said antibody is capable of inducing, activating, or enhancing an activity of GITR in a cell in the absence of TCR triggering. In another specific embodiment, provided herein is an anti-GITR antibody that specifically binds to human GITR, wherein said antibody induces, activates, or enhances an activity of NF- κ B in a cell in the absence of TCR triggering. In another specific embodiment, provided herein is a method of treating cancer comprising administering to a subject in need thereof an anti-GITR antibody that specifically binds to human GITR, wherein said antibody is capable of inducing, activating, or enhancing an activity of GITR and/or NF- κ B in the absence of TCR triggering.

3.1 Terminology

[0054] As used herein, the terms “about” and “approximately,” when used to modify a numeric value or numeric range, indicate that deviations of 5% to 10% above and 5% to 10% below the value or range remain within the intended meaning of the recited value or range.

[0055] As used herein, the binding between a test antibody and a first antigen is “substantially weakened” relative to the binding between the test antibody and a second antigen if the binding between the test antibody and the first antigen is reduced by at least 30%, 40%, 50%, 60%, 70%, or 80% relative to the binding between the test antibody and the second antigen, *e.g.*, in a given experiment, or using mean values from multiple experiments, as assessed by, *e.g.*,

an assay comprising the following steps: (a) expressing on the surface of cells (*e.g.*, 1624-5 cells) the first antigen or the second antigen; (b) staining the cells expressing the first antigen or the second antigen using, *e.g.*, 2 $\mu\text{g/ml}$ of the test antibody or a polyclonal antibody in a flow cytometry analysis and recording mean fluorescence intensity (MFI) values, *e.g.*, as the mean from more than one measurement, wherein the polyclonal antibody recognizes both the first antigen and the second antigen; (c) dividing the MFI value of the test antibody for the cells expressing the second antigen by the MFI value of the polyclonal antibody for the cells expressing the second antigen (MFI ratio₂); (d) dividing the MFI value of the test antibody for the cells expressing the first antigen by the MFI value of the polyclonal antibody for the cells expressing the first antigen (MFI ratio₁); and (e) determining the percentage of reduction in binding by calculating $100\% \times (1 - (\text{MFI ratio}_1 / \text{MFI ratio}_2))$.

[0056] As used herein, an antibody does not exhibit “substantial binding” to an antigen if when measured in a flow cytometry analysis, the mean fluorescence intensity (MFI) value of the antibody to the antigen is not significantly higher than the MFI value of an isotype control antibody to the antigen or the MFI value in the absence of any antibody.

[0057] As used herein, the terms “antibody” and “antibodies” are terms of art and can be used interchangeably herein and refer to a molecule with an antigen binding site that specifically binds an antigen.

[0058] Antibodies can include, for example, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, heteroconjugate antibodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affybodies, Fab fragments, F(ab')₂ fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-anti-Id antibodies), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ or IgA₂), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (*e.g.*, human IgG₁ or IgG₄) or subclass thereof. In a specific embodiment, the antibody is a humanized monoclonal antibody. In another specific embodiment, the antibody is a human monoclonal antibody,

preferably that is an immunoglobulin. In certain embodiments, an antibody described herein is an IgG₁, or IgG₄ antibody.

[0059] As used herein, the terms “antigen-binding domain,” “antigen-binding region,” “antigen-binding fragment,” and similar terms refer to a portion of an antibody molecule which comprises the amino acid residues that confer on the antibody molecule its specificity for the antigen (*e.g.*, the complementarity determining regions (CDR)). The antigen-binding region can be derived from any animal species, such as rodents (*e.g.*, mouse, rat or hamster) and humans.

[0060] As used herein, the terms “variable region” or “variable domain” are used interchangeably and are common in the art. The variable region typically refers to a portion of an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids in the mature heavy chain and about 90 to 115 amino acids in the mature light chain, which differ extensively in sequence among antibodies and are used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR).

Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.*, non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.*, non-human primate) framework regions (FRs).

[0061] The terms “VL” and “VL domain” are used interchangeably to refer to the light chain variable region of an antibody.

[0062] The terms “VH” and “VH domain” are used interchangeably to refer to the heavy chain variable region of an antibody.

[0063] The term “Kabat numbering” and like terms are recognized in the art and refer to a system of numbering amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen-binding portion thereof. In certain aspects, the CDRs of an antibody can be determined according to the Kabat numbering system (see, *e.g.*, Kabat EA & Wu TT (1971) *Ann NY Acad Sci* 190: 382-391 and Kabat EA *et al.*, (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). Using the Kabat numbering system, CDRs within an antibody heavy chain molecule are typically present at amino acid positions 31 to 35, which optionally can

include one or two additional amino acids, following 35 (referred to in the Kabat numbering scheme as 35A and 35B) (CDR1), amino acid positions 50 to 65 (CDR2), and amino acid positions 95 to 102 (CDR3). Using the Kabat numbering system, CDRs within an antibody light chain molecule are typically present at amino acid positions 24 to 34 (CDR1), amino acid positions 50 to 56 (CDR2), and amino acid positions 89 to 97 (CDR3). In a specific embodiment, the CDRs of the antibodies described herein have been determined according to the Kabat numbering scheme.

[0064] As used herein, the term “constant region” or “constant domain” are interchangeable and have its meaning common in the art. The constant region is an antibody portion, *e.g.*, a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain.

[0065] As used herein, the term “heavy chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG and IgM classes of antibodies, respectively, including subclasses of IgG, *e.g.*, IgG₁, IgG₂, IgG₃ and IgG₄.

[0066] As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, *e.g.*, kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain.

[0067] “Binding affinity” generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D is calculated from the quotient of k_{off}/k_{on} , whereas K_A is calculated from the quotient of k_{on}/k_{off} . k_{on} refers to the association rate constant of, *e.g.*, an antibody to an antigen, and k_{off} refers to the dissociation of, *e.g.*, an antibody to an antigen. The k_{on} and k_{off} can be determined by techniques known to one of ordinary skill in the art, such as BIAcore[®] or KinExA.

[0068] As used herein, a “conservative amino acid substitution” is one in which the amino

acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). In certain embodiments, one or more amino acid residues within a CDR(s) or within a framework region(s) of an antibody or antigen-binding fragment thereof can be replaced with an amino acid residue with a similar side chain.

[0069] As used herein, an “epitope” is a term in the art and refers to a localized region of an antigen to which an antibody can specifically bind. An epitope can be, for example, contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, for example, come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope to which an antibody binds can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson A (1990) *Eur J Biochem* 189: 1-23; Chayen NE (1997) *Structure* 5: 1269-1274; McPherson A (1976) *J Biol Chem* 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see *e.g.* *Meth Enzymol* (1985) volumes 114 & 115, eds Wyckoff HW *et al.*; U.S. 2004/0014194), and BUSTER (Bricogne G (1993) *Acta Crystallogr D Biol Crystallogr* 49(Pt 1): 37-60; Bricogne G (1997) *Meth Enzymol* 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) *Acta Crystallogr D Biol Crystallogr* 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.*, (1995) *J Biol Chem* 270: 1388-1394 and Cunningham BC & Wells JA (1989) *Science* 244: 1081-1085 for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. In a specific embodiment, the epitope of an antibody or antigen-binding fragment thereof is determined using alanine scanning mutagenesis studies, such as described in Section 6,

infra.

[0070] As used herein, the terms “immunospecifically binds,” “immunospecifically recognizes,” “specifically binds,” and “specifically recognizes” are analogous terms in the context of antibodies and refer to molecules that bind to an antigen (*e.g.*, epitope or immune complex) as such binding is understood by one skilled in the art. For example, a molecule that specifically binds to an antigen may bind to other peptides or polypeptides, generally with lower affinity as determined by, *e.g.*, immunoassays, BIAcore[®], KinExA 3000 instrument (Sapidyne Instruments, Boise, ID), or other assays known in the art. In a specific embodiment, molecules that immunospecifically bind to an antigen bind to the antigen with a K_A that is at least 2 logs, 2.5 logs, 3 logs, 4 logs or greater than the K_A when the molecules bind to another antigen.

[0071] In another specific embodiment, molecules that immunospecifically bind to an antigen do not cross react with other proteins under similar binding conditions. In another specific embodiment, molecules that immunospecifically bind to an antigen do not cross react with other non-GITR proteins. In a specific embodiment, provided herein is an antibody or fragment thereof that binds to GITR with higher affinity than to another unrelated antigen. In certain embodiments, provided herein is an antibody or fragment thereof that binds to GITR (*e.g.*, human GITR) with a 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or higher affinity than to another, unrelated antigen as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, the extent of binding of an anti-GITR antibody or antigen-binding fragment thereof described herein to an unrelated, non-GITR protein is less than 10%, 15%, or 20% of the binding of the antibody to GITR protein as measured by, *e.g.*, a radioimmunoassay.

[0072] In a specific embodiment, provided herein is an antibody or fragment thereof that binds to human GITR with higher affinity than to another species of GITR. In certain embodiments, provided herein is an antibody or fragment thereof that binds to human GITR with a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70% or higher affinity than to another species of GITR as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay. In a specific embodiment, an antibody or fragment thereof described herein, which binds to human GITR, will bind to another species of GITR protein with less than 10%, 15%, or 20% of the binding of the antibody or fragment thereof to the human GITR protein as measured by, *e.g.*, a radioimmunoassay, surface plasmon resonance, or kinetic exclusion assay.

[0073] As used herein, the terms “glucocorticoid-induced TNFR family related receptor” or “GITR” or “GITR polypeptide” refer to GITR including, but not limited to, native GITR, an

isoform of GITR, or an interspecies GITR homolog of GITR. GITR is a 26 kDa type I transmembrane protein. GenBank™ accession numbers BC152381 and BC152386 provide exemplary human GITR nucleic acid sequences. Swiss-Prot accession number Q9Y5U5-1 (TNR18_HUMAN; SEQ ID NO: 701) and GenBank™ accession number NP_004186 provide exemplary human GITR amino acid sequences for isoform 1. This amino acid sequence is 241 amino acids in length with the first 25 amino acid residues encoding the signal sequence. Isoform 1 is a type I membrane protein. An exemplary mature amino acid sequence of human GITR is provided as SEQ ID NO: 700. In contrast, isoform 2 is a secreted form of human GITR and is approximately 255 amino acids in length. Swiss-Prot accession number Q9Y5U5-2 and GenBank™ accession number NP_683699 provide exemplary human GITR amino acid sequences for isoform 2. Isoform 3 of human GITR is approximately 234 amino acids in length. Swiss-Prot accession number Q9Y5U5-3 and GenBank™ accession number NP_683700 (isoform 3 precursor) provide exemplary human GITR amino acid sequences for isoform 3. In a specific embodiment, the GITR is human GITR. In another specific embodiment, the GITR is human GITR isoform 1 (SEQ ID NO: 701). In certain embodiments, the GITR is human isoform 2 (SEQ ID NO: 702) or isoform 3 (SEQ ID NO: 703). GITR is also known as tumor necrosis factor receptor superfamily member 18 (TNFRSF18), activation-inducible TNFR family receptor (AITR), GITR-D, and CD357. Human GITR is designated GeneID: 8784 by Entrez Gene.

[0074] The amino acid sequence of an immature form of an exemplary GITR protein from cynomolgus monkey is provided in SEQ ID NO: 704. The mature form of this exemplary protein is amino acids 26-234 of SEQ ID NO: 704.

[0075] As used herein, the terms “GITR ligand” and “GITRL” refer to glucocorticoid-induced TNFR-related protein ligand. GITRL is otherwise known as activation-induced TNF-related ligand (AITRL) and tumor necrosis factor ligand superfamily member 18 (TNFSF18). GenBank™ accession number AF125303 provides an exemplary human GITRL nucleic acid sequence. GenBank™ accession number NP_005083 and Swiss-Prot accession number Q9UNG2 provide exemplary human GITRL amino acid sequences. In a particular embodiment, the GITRL is a human GITRL of SEQ ID NO: 716.

[0076] As used herein, the term “host cell” can be any type of cell, e.g., a primary cell, a cell in culture, or a cell from a cell line. In specific embodiments, the term “host cell” refers to a cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny of such a cell may not be identical to the parent cell transfected with the nucleic acid molecule, e.g., due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0077] As used herein, the term “effective amount” in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect. Examples of effective amounts are provided in Section 5.4.1.3, *infra*.

[0078] As used herein, the terms “subject” and “patient” are used interchangeably. The subject can be an animal. In some embodiments, the subject is a mammal such as a non-primate (*e.g.*, cow, pig, horse, cat, dog, rat etc.) or a primate (*e.g.*, monkey or human), most preferably a human. In certain embodiments, such terms refer to a non-human animal (*e.g.*, a non-human animal such as a pig, horse, cow, cat or dog). In some embodiments, such terms refer to a pet or farm animal. In specific embodiments, such terms refer to a human.

4. BRIEF DESCRIPTION OF THE FIGURES

[0079] **Figure 1** is a Western Blot under non-reducing conditions showing specificity of anti-GITR antibody 231-32-15 versus an isotype control. Antibody is blotted against human GITR recombinant protein (Hu GITR recomb protein), mouse GITR recombinant protein (Mu GITR recomb protein), CMS5A cells expressing recombinant human GITR (CMS5A-huGITR), wild-type CMS5A cells (CMS5A-wt), protein from CD4⁺ Activated cells (CD4⁺ Activated) and protein from CD4⁺ Untreated cells (CD4⁺ Untreated). 231-32-15 reactivity is seen against human GITR, recombinant human GITR in CMS5A cells, and natural human GITR in activated CD4⁺ cells.

[0080] **Figures 2A and 2B** show FACS analysis of competitive binding of the anti-GITR antibodies versus commercial (R&D Systems) anti-GITR mAb. In Figure 2A blocking of the R&D Systems mAb is tested using the R&D mAb and the test antibodies (antibody 1042-7, antibody 1039-45, antibody 1333-21 and antibody 32-15) as indicated in the figure. The condition ‘no antibody’ shows binding of the R&D Systems mAb alone, in the absence of test antibodies. Figure 2B shows blocking of the anti-GITR antibody 231-1039-45 using no mAb, the R&D Systems mAb and the test antibodies (antibody 1042-7, antibody 1039-45, antibody 1333-21 and antibody 32-14) as indicated in the figure. The condition ‘no antibody’ shows binding of antibody 231-1039-45 alone, in the absence of test antibodies.

[0081] **Figures 3A, 3B and 3C:** Figure 3A depicts staining of CMS5A-GITR by antibodies 1333-21 batch 1, 1333-21 batch 2 and R&D antibody at varying concentrations of antibody. Figure 3B graphs the fluorescence intensity of ex-vivo PBMC CD3-CD19-GITR⁺ and CD4⁺CD25⁺GITR⁺ cells on staining with antibodies 1042-7, 32-15, 1039-45, 1333-21 and R&D antibody. Figure 3C provides FACS analysis of CD3-CD19-GITR⁺ and

CD4+CD25+GITR+ cells by antibody 1333-21 and the R&D Systems antibody.

[0082] **Figure 4** depicts an assessment of the costimulatory effect of anti-GITR antibody on CD4+ T cells in combination with varying concentrations of anti-CD3 (OKT3) antibody. In the top panel the % CFSE-low cells is plotted for each antibody tested (PBS control, R&D, 1042-7, 32-15, 1039-45 and 1333-21) in combination with decreasing concentrations of OKT3 antibody (5µg/ml, 1µg/ml, 0.2µg/ml, 0.04µg/ml and 0µg/ml). In the bottom panel the concentration of IFNγ (pg/ml) is plotted for each antibody tested (PBS control, R&D, 1042-7, 32-15, 1039-45 and 1333-21) in combination with decreasing concentrations of the OKT3 antibody (5µg/ml, 1µg/ml, 0.2µg/ml, 0.04µg/ml and 0µg/ml).

[0083] **Figure 5** shows GITRL-PE binding to GITR in the presence of anti-GITR antibodies chimeric parental 231-32-15 and m6C8. A further antibody SK48E26, which recognizes IL-1β, was used as a negative control. The percentage of GITRL-PE binding was measured by suspension array technology (Luminex® 200 system) in the presence of increasing antibody concentrations (12, 37, 111, 333, 1000, 3000 and 9000ng/ml). Figure 5 shows the results from four independent repeats of this assay performed in duplicate and standard deviation was determined from n=8.

[0084] **Figure 6** is a similar graph to that shown in Figure 5 where the percentage of GITRL-PE binding was measured by suspension array technology (Luminex® 200 system) in the presence of increasing antibody concentrations (12, 37, 111, 333, 1000, 3000 and 9000ng/ml). The anti-GITR antibodies tested were the chimeric parental 231-32-15 antibody and the two humanized variants Hum231#1 and Hum231#2. This figure shows the results from one experiment performed in duplicate.

[0085] **Figure 7** shows GITR ligand binding to GITR in the presence of mAbs as measured by surface plasmon resonance (BIAcore® T100/200). The anti-GITR antibodies tested were chimeric parental 231-32-15, humanized variants Hum231#1 and Hum231#2 and m6C8. The negative control was the anti-IL-1β antibody SK48E26.

[0086] **Figures 8A and 8B** show FACS plots of the results of a suboptimal CD3 stimulation assay to assess the effects of stimulation of anti-GITR antibodies on enriched CD4⁺ T cells from two different buffy coats. Figure 8A shows the FACS analysis of cell number and proliferation of CD4 T cells from a high responder to stimulation (buffy coat 6), whereas Figure 8B shows the FACS analysis for a low responder (buffy coat 8). Cell proliferation (CFSE; x-axis) is shown for 10µg/ml of anti-GITR antibody (chimeric parental 231-32-15 antibody and humanized variants Hum231#1 and Hum231#2). The controls used were either anti-CD3/anti-CD28 antibody alone

or no stimulation. The assay was performed in triplicate.

[0087] **Figures 9A and 9B** are histograms showing the effect of anti-GITR humanized variant antibodies Hum231#1 and Hum231#2 on enriched CD4 T cell proliferation (Figure 9A) and cell number (Figure 9B), compared to the antibody m6C8, in a suboptimal CD3 stimulation assay. The antibodies were used at a concentration of 10µg/ml. The end column (solid black fill; Figures 9A and 9B) indicates anti-CD3/anti-CD28 stimulation without the addition of any anti-GITR antibodies.

[0088] **Figures 10A, 10B, 10C and 10D** show the analysis of cytokine production for IFNγ, IL-6, IL-10 and TNFα, respectively induced by the administration of anti-GITR antibodies in a suboptimal CD3 stimulation assay. The anti-GITR antibodies tested were chimeric parental 231-32-15 and humanized variants Hum231#1 and Hum231#2 at concentrations of 10µg/ml and 5µg/ml.

[0089] **Figure 11** is a histogram showing the further titration of anti-GITR antibodies and their effect on cell proliferation in a suboptimal CD3 stimulation assay. The chimeric parental 231-32-15 antibody and humanized variants Hum231#1 and Hum231#2 were used at concentrations of 10µg/ml, 5µg/ml and 2.5µg/ml.

[0090] **Figures 12A and 12B** show the further titration of anti-GITR antibodies and their effect on IFNγ production in a suboptimal CD3 stimulation assay. The chimeric parental 231-32-15 antibody and humanized variants Hum231#1 and Hum231#2 were used at concentrations of 10µg/ml, 5µg/ml and 2.5µg/ml as plate bound (Figure 12A) or 20µg/ml, 10µg/ml and 5µg/ml as soluble antibodies (Figure 12B).

[0091] **Figure 13** is a set of bar graphs showing the results of co-stimulation with 5 µg/ml, plate-bound Hum231#2 on cytokine secretion by PBMCs in a suboptimal CD3 stimulation assay. The data shown in Figure 13 are from two donors tested on day 2 and day 4 post-stimulation. The max fold induction over isotype control was plotted for six different cytokines (IFNγ, IL-2, TNFα, IL-10, IL-13 and IL-4). The error bars represent standard deviation for a replicate of two for each cytokine. Each donor has been tested in at least three individual experiments.

[0092] **Figures 14A, 14B and 14C** are results of intracellular cytokine staining assays measuring the production of IFNγ and TNFα, induced by plate-bound Hum231#2, Hum231#2w or pab1989 (the IgG4 counterpart of Hum231#2w) under suboptimal CD3 stimulation. Figure 14A is a set of flow cytometry plots showing the co-staining of IFNγ and TNFα for CD4+ and CD8+ T cells. The percentage of IFNγ+ monofunctional T cells, TNFα+ monofunctional T cells or IFNγ+ TNFα+ polyfunctional T cells was plotted for Hum231#2, Hum231#2w, pab1989 or

isotype control over a range of suboptimal anti-CD3 antibody concentrations (Figures 14B and 14C). Each dot in Figures 14B and 14C represents a replicate of two for the condition tested. The error bars represent standard deviation. The anti-GITR antibodies were used at a concentration of 5 $\mu\text{g/ml}$. The graphs are representative of experiments using PBMCs from six (Figures 14A and 14B) and four (Figure 14C) different donors, respectively.

[0093] **Figures 15A, 15B and 15C** are a set of bar graphs showing results of experiments comparing the anti-GITR antibody Hum231#2 under different cross-linking conditions. Figure 15A is a bar graph showing the maximum fold induction from isotype control for the percentage of IFN γ ⁺ TNF α ⁺ polyfunctional CD8⁺ T cells using PBMCs co-stimulated by 5 $\mu\text{g/ml}$ plate-bound (PB) or soluble Hum231#2 or isotype control. The error bars represent standard deviation. * represents $p < 0.05$ and ** represents $p < 0.005$ (unpaired T-test). In Figures 15B and 15C, the maximum fold induction over isotype control for six different cytokines was plotted for either plate-bound Hum231#2 (Figure 15B) or anti-Fc cross-linked Hum231#2 (Figure 15C). The error bars represent standard deviation from a replicate of two for each cytokine.

[0094] **Figures 16A and 16B** show the results of anti-CD3/anti-CD28 and anti-GITR antibody stimulation on T effector (T-eff) and T regulatory cells (Tregs). Figure 16A shows that activated T-effector and T-regulatory cells express GITR on their cell surface following stimulation with anti-CD3/anti-CD28 alone or in conjunction with anti-GITR antibodies. However, as is shown in Figure 16B, costimulation with anti-GITR antibodies preferentially expands effector T-cells over T-regulatory cells. Cell expansion/proliferation (CFSE; y-axis) is shown for 10 $\mu\text{g/ml}$ of anti-GITR antibodies (chimeric parental 231-32-15 antibody and humanized variants Hum231#1 and Hum231#2) on buffy coat 8. The controls used were either anti-CD3/anti-CD28 antibody at 125ng/ml alone or no stimulation.

[0095] **Figures 17A and 17B** show the results on T cell proliferation by the anti-GITR antibodies tested. Figure 17A shows the proliferation of CD4 cells and Figure 17B shows the proliferation of CD8 cells in total PBMCs stimulated with 31.25ng/ml anti-CD3 antibody. Chimeric parental 231-32-15 antibody and humanized variants Hum231#1 and Hum231#2 were tested at a concentration of 10 $\mu\text{g/ml}$.

[0096] **Figures 18A, 18B and 18C** are graphs showing the results of a GITR NF- κ B-luciferase reporter assay in the absence or presence of 0.3 $\mu\text{g/ml}$ of a plate-bound anti-CD3 antibody (Clone SP34). Figure 18A is a graph showing the luciferase relative light units (RLU) at a range of anti-GITR antibody concentrations at 18-hour post-stimulation in the presence of the anti-CD3 antibody. Figure 18B is a graph showing luciferase RLU at different anti-GITR antibody concentrations at 5-hour post-stimulation in the absence of the anti-CD3 antibody.

Figure 18C is a graph showing the highest ratios of luciferase expression (GITR Ab/isotype control) at 0, 2, 5, 6, 8 and 18 hrs post-stimulation. The error bars represent standard deviation from duplicates. The anti-GITR antibodies tested were Hum231#2w and m6C8. The data shown are representative of four experiments with anti-CD3 antibody or two experiments without anti-CD3 antibody.

[0097] **Figure 19A** is a bar graph showing the normalized receptor density of human GITR on activated nTregs, CD4⁺ T cells or CD8⁺ T cells as measured by flow cytometry. The anti-GITR antibody used was a PE-conjugated mouse anti-human GITR antibody (Biolegend: 621; 311604/B171072). The error bars represent standard deviation. **Figure 19B** is a graph examining the anti-GITR antibody Hum231#2w using an Fc gamma receptor IIIA (CD16) reporter cell line. Jurkat NFAT-luciferase reporter cells overexpressing CD16A with the high affinity 158 V/V polymorphism were co-cultured with activated primary nTregs and T effector cells for 20 hours at 37°C in the presence of Hum231#2w or an isotype control. The relative light units (RLU) were recorded after 20 hours, representing CD16A binding. Δ RLU represents the RLU of the anti-GITR antibody minus that of the isotype control. The error bars represent standard deviation (n=2). The data shown are representative of experiments using cells from three donors. **Figure 19C** is a set of histograms showing the surface expression of GITR measured by flow cytometry. Samples were collected from the blood of healthy human donors (a-c, n=3) or from tumor tissues of non-small cell lung cancer patients (NSCLC) (d-f, n=3). The cell populations were defined as: Tconv (CD3⁺, CD4⁺, CD8a⁻, CD25^{low}, FOXP3⁻) or Treg (CD3⁺, CD4⁺, CD8a⁻, CD25^{high}, FOXP3⁺).

[0098] **Figures 20A, 20B and 20C** are results from experiments using PBMCs from African green monkey (AGM). Figure 20A is a set of flow cytometry plots of the staining of activated CD4⁺ and CD8⁺ T cells from African green monkey (AGM) using the anti-GITR antibody Hum231#2 and an anti-PD-1 antibody. Healthy AGM PBMCs were activated with anti-CD3 antibody (clone SP34.2) or ConA plus IL-2 (20 U/ml) for 3 days. The flow cytometry plots are representative of experiments using PBMCs from three different AGMs. Figures 20B and 20C are results of a CD3 substimulation assay using AGM PBMCs. Figure 20B is a pair of flow cytometry plots showing the co-staining of CD8 and IFN γ for cells co-stimulated by Hum231#2w or isotype control. In Figure 20C, the percentage of IFN γ ⁺ AGM CD8⁺ T cells was plotted for different anti-GITR antibody concentrations. Each dot represents a replicate of two wells and the error bars represent standard deviation. The data shown in Figures 20B and 20C are representative of experiments using PBMCs from two AGMs.

[0099] **Figures 21A and 21B** are results from the staining of surface OX40 and PD-1 on

CD4⁺ and CD8⁺ T cells stimulated with plate-bound 0.8 µg/ml of an anti-CD3 antibody and 5 µg/ml of the anti-GITR antibody Hum231#2. Figure 21A is a set of flow cytometry plots and histograms showing co-staining of OX40 and PD-1. In Figure 21B, each bar represents the MFI value for PD-1 and OX40 on CD4⁺ and CD8⁺ T cells stimulated with Hum231#2 (black bars), isotype control (gray bars) or media only (white bars). The error bars represent standard deviation. The flow cytometry plots and graphs are representative of experiments using PBMCs from one donor.

[00100] **Figures 22A and 22B** show the design of the mutated libraries for the generation of germlined antibody variants. The different framework and CDR positions included in the library based on the IGHV1-2*02 VH human germline are shown in Figure 22A (SEQ ID NOS 37-53, respectively, in order of appearance) and for the library based on the IGKV4-1*01 VL human germline in Figure 22B (SEQ ID NOS 54-71, respectively, in order of appearance).

[00101] **Figure 23** is a table listing 17 germlined antibody variants and detailing their heavy and light chain variable regions with corresponding SEQ ID numbers. The table shows the number of extra germline amino acids and the mean relative affinity of the variant antibodies compared to the chimeric parental 231-32-15 antibody.

[00102] **Figures 24A-C** are a table listing 107 germlined antibody variants and detailing their heavy and light chain variable regions with corresponding SEQ ID numbers.

[00103] **Figures 25A and 25B** show GITRL-PE binding to GITR in the presence of a selection of anti-GITR germlined antibody variants. The percentage of GITRL-PE binding was measured by suspension array technology (Luminex[®] 200 system) in the presence of increasing antibody concentrations (12, 37, 111, 333, 1000, 3000 and 9000ng/ml).

[00104] **Figures 26A and 26B** show the effect on cell proliferation (% CFSE Low) of the germlined antibody variants compared to the chimeric parental 231-32-15 antibody and the humanized variants Hum231#1 and Hum231#2 on enriched CD4 T cells from two buffy coats, BC4 (Figure 26A) and BC9 (Figure 26B). A suboptimal CD3 stimulation assay was performed using plate bound anti-CD3 antibody at 125ng/ml with either plate bound or soluble isotype control. Anti-GITR antibodies were used at a concentration of 10µg/ml.

[00105] **Figures 27A and 27B** show the effect on cytokine release of IFNγ and IL-10, respectively of the germlined antibody variants compared to the chimeric parental 231-32-15 antibody and the humanized variants Hum231#1 and Hum231#2 on enriched CD4 T cells from buffy coat BC4. A suboptimal CD3 stimulation assay was performed using plate bound anti-CD3 antibody at 125ng/ml with either plate bound or soluble isotype control. Anti-GITR antibodies were used at a concentration of 10µg/ml and the cytokine levels were measured in the

culture supernatant.

[00106] **Figures 28A and 28B** show the effect on cytokine release of IFN γ and IL-10, respectively of the germlined antibody variants compared to the chimeric parental 231-32-15 antibody and the humanized variants Hum231#1 and Hum231#2 on enriched CD4 T cells from buffy coat BC9. A suboptimal CD3 stimulation assay was performed using plate bound anti-CD3 antibody at 125ng/ml with either plate bound or soluble isotype control. Anti-GITR antibodies were used at a concentration of 10 μ g/ml and the cytokine levels were measured in the culture supernatant.

[00107] **Figures 29A and 29B** show the percentage of IFN γ positive CD4⁺ T-cells (as measured by intracellular staining) of germlined antibody variants compared to the chimeric parental 231-32-15 antibody and the humanized variants Hum231#1 and Hum231#2 on enriched CD4 T cells from two buffy coats. Figure 29A shows the results from buffy coat 13 (BC13) and Figure 29B shows the results from buffy coat 18 (BC18).

[00108] **Figures 30A-C** are a set of graphs showing the results of a GITR NF- κ B-luciferase reporter assay in the presence of 0.3 μ g/ml anti-CD3 antibody. The anti-GITR antibodies tested in this assay were Hum231#2w and 20 germline variants: pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, pab2159, pab2160 and pab2161. In Figures 30A-C, the luciferase RLU at 18-hour post-stimulation was plotted for different anti-GITR antibody concentrations tested. The error bars represent standard deviation. **Figures 30D-F** are a set of graphs showing the results of a GITR NF- κ B-luciferase reporter assay in the absence of an anti-CD3 antibody. The anti-GITR antibodies tested in this assay were m6C8, Hum231#2w and 20 germline variants: pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, pab2159, pab2160 and pab2161. In Figures 30D-F, the luciferase RLU at 6-hour post-stimulation was plotted for different anti-GITR antibody concentrations tested. The error bars represent standard deviation. The graphs and plots are representative of data from two experiments (Figures 30A-C) or one experiment (Figures 30D-F).

[00109] **Figure 31** shows the loss of binding of 1624-5 pre-B cells expressing the chimeric parental 231-32-15 antibody to biotinylated GITR (GITR-bio) when GITR-bio was pre-incubated with chimeric parental 231-32-15, Hum231#1 or Hum231#2 antibodies. Figure 31 right-hand profile depicts the binding of 1624-5 pre-B cells expressing the chimeric parental 231-32-15 antibody to GITR-bio. In the left-hand profile however, there is loss of binding of 1624-5 cells expressing the chimeric parental 231-32-15 antibody to GITR-bio following pre-incubation of

GITR-bio with either the chimeric parental 231-32-15, Hum231#1 or Hum231#2 antibodies.

[00110] **Figure 32** shows the results of an epitope competition assay measured by surface plasmon resonance (BIAcore[®] T100/200). GITR antigen was immobilized on a CM5 sensor chip and the anti-GITR antibodies applied at a concentration of 300nM. Chimeric parental 231-32-15 antibody was applied first followed by the application of the murine antibody 6C8.

[00111] **Figures 33A and 33B** are the results of an epitope mapping experiment using a cellular library expressing GITR variants generated by error prone PCR. Shown in Figures 33A and 33B is an alignment of sequences from the GITR variants that bind to a polyclonal anti-GITR antibody but do not bind to the anti-GITR chimeric parental 231-32-15 antibody.

[00112] **Figures 34A and B** are the result of an epitope mapping experiment using alanine scanning. The following positions in human GITR (numbered according to SEQ ID NO: 701) were separately mutated to an Alanine: P28A, T29A, G30A, G31A, P32A, T54A, T55A, R56A, C57A, C58A, R59A, D60A, Y61A, P62A, G63A, E64A, E65A, C66A, C67A, S68A, E69A, W70A, D71A, C72A, M73A, C74A, V75A and Q76A. The antibodies tested in the experiment shown in Figure 34A included: the monoclonal anti-GITR antibodies Hum231#2, three germline variants (pab1967, pab1975 and pab1979) and the m6C8 antibody; and a polyclonal anti-GITR antibody (AF689, R&D systems). Figure 34A is a table summarizing the binding of Hum231#2, three germline variants (pab1967, pab1975 and pab1979) and the reference antibody m6C8 to 1624-5 cells expressing human GITR alanine mutants. Figure 34B is a set of flow cytometry plots showing the staining of 1624-5 cells expressing wild type human GITR, D60A mutant, or G63A mutant using the monoclonal antibodies 231-32-15, Hum231#2, or m6C8, or a polyclonal antibody. The percentage of GITR positive cells is indicated in each plot.

[00113] **Figure 35A** is a sequence alignment of human GITR, V1M cynomolgus GITR, and V1M/Q62P/S63G cynomolgus GITR, highlighting the positions 62 and 63 where two amino acids from cynomolgus GITR (GlnSer) were replaced by corresponding residues in human GITR (ProGly). **Figure 35B** is a set of flow cytometry plots showing the staining of 1624-5 cells expressing human GITR, V1M cynomolgus GITR, or V1M/Q62P/S63G cynomolgus GITR using the monoclonal antibodies 231-32-15, Hum231#2, or m6C8, or a polyclonal anti-GITR antibody.

5. DETAILED DESCRIPTION

[00114] Provided herein are antibodies (*e.g.*, monoclonal antibodies), and antigen-binding fragments thereof, that specifically bind to GITR (*e.g.*, human GITR) and modulate GITR activity. For example, in one aspect, provided herein is an antibody(ies) or fragment(s) thereof

that specifically binds to GTR and enhances, induces, or increases one or more GTR activities.

In a specific embodiment, the antibody(ies) or antigen-binding fragment(s) is isolated.

[00115] Also provided are isolated nucleic acids (polynucleotides), such as complementary DNA (cDNA), encoding such antibodies, and antigen-binding fragments thereof. Further provided are vectors (*e.g.*, expression vectors) and cells (*e.g.*, host cells) comprising nucleic acids (polynucleotides) encoding such antibodies or antigen-binding fragments thereof. Also provided are methods of making such antibodies. In other aspects, provided herein are methods and uses for inducing, increasing or enhancing a GTR activity, and treating certain conditions, such as cancer and infectious diseases. Related compositions (*e.g.*, pharmaceutical compositions), kits, and detection methods are also provided.

5.1 Antibodies

[00116] In a specific aspect, provided herein are antibodies (*e.g.*, monoclonal antibodies, such as chimeric or humanized antibodies) and fragments thereof which specifically bind to GTR (*e.g.*, human GTR). In some embodiments, an antibody or antigen-binding fragment thereof described herein partially inhibits GTRL (*e.g.*, human GTRL) from binding to GTR (*e.g.*, human GTR). In certain embodiments, an antibody or antigen-binding fragment thereof described herein inhibits binding of GTRL (*e.g.*, human GTRL) to GTR (*e.g.*, human GTR) by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% as assessed by an assay known to one of skill in the art or described herein. In a specific embodiment, an antibody or antigen-binding fragment thereof described herein inhibits binding of GTRL (*e.g.*, human GTRL) to GTR (*e.g.*, human GTR) by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% as assessed by the assay described in Example 2, *infra* (*e.g.*, Sections 6.2.5.2 or 6.2.5.4, *infra*). In another specific embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 1000 ng/ml, 950 ng/ml, 900 ng/ml, 850 ng/ml, 800 ng/ml, 750 ng/ml, 700 ng/ml, 650 ng/ml, 600 ng/ml, 550 ng/ml, 500 ng/ml, 450 ng/ml, 400 ng/ml, 350 ng/ml, 333 ng/ml, 300 ng/ml, 250 ng/ml, 200 ng/ml, 100ng/ml, 50ng/ml or 10ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GTRL (*e.g.*, GTRL-PE) to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GTRL to the

GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, an antibody or antigen-binding fragment thereof described herein at concentration of 1000 ng/ml to 750 ng/ml, 1000 ng/ml to 500 ng/ml, 850 ng/ml to 500 ng/ml, 750 ng/ml to 500 ng/ml, 600 ng/ml to 500 ng/ml, 500 ng/ml to 400 ng/ml, 400 ng/ml to 300 ng/ml, or 300 ng/ml to 200 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM, 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, an antibody or antigen-binding fragment thereof at a concentration of 1000ng/ml inhibits less than 80% (in some embodiments, 40% to 70%, 50%, to 80%, or 40% to 80%) of 0.5nM labeled GITRL (*e.g.*, human GITRL) from binding to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay.

[00117] In another specific embodiment, an antibody or antigen-binding fragment thereof described herein at concentration of 3500 ng/ml, 3400 ng/ml, 3300 ng/ml, 3200 ng/ml, 3100 ng/ml, 3000 ng/ml, 2900 ng/ml, 2800 ng/ml, 2700 ng/ml, 2600 ng/ml, 2500 ng/ml, 2400 ng/ml, 2300 ng/ml, 2200 ng/ml, 2100 ng/ml, 2000 ng/ml, 1900 ng/ml, 1800 ng/ml, 1700 ng/ml, 1600 ng/ml, 1500 ng/ml, 1400 ng/ml, 1300 ng/ml, 1200 ng/ml, or 1100 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml,

5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, an antibody or antigen-binding fragment thereof described herein at concentration of 3500 ng/ml to 3200 ng/ml, 3500 ng/ml to 3000ng/ml, 3200 ng/ml to 2500 ng/ml, 3000 to 2200 ng/ml, 2500 ng/ml to 1800 ng/ml, 2000 ng/ml to 1500 ng/ml, 1700 ng/ml to 1200 ng/ml, or 1500 ng/ml to 1000 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00118] In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 3000ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 85% or less than 80% (in some embodiments, 60% to 85%, 60% to 80%, 70% to 85% or 70% to 80%) when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 1000ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 85%, less than 80% or less than 75% (in some embodiments, 60% to 85%, 60% to 80%, 70% to 85% or 70% to 80%) when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 333ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 70% or less than 65% (in some embodiments, 50% to 70%, 55% to 70%, 50% to 65% or 50% to 60%) when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*,

Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 111ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GTR (*e.g.*, human GTR) by less than 65%, less than 60% or less than 55% (in some embodiments, 40% to 65%, 40% to 60%, 40% to 55% or 30% to 60%) when GTR (*e.g.*, human GTR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 37ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GTR (*e.g.*, human GTR) by less than 40% (in some embodiments, 20% to 40%, 20% to 30%, or 15% to 35%) when GTR (*e.g.*, human GTR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 12ng/ml inhibits binding of 0.5nM GITRL (*e.g.*, human GITRL) to GTR (*e.g.*, human GTR) by less than 20% (in some embodiments, 10% to 20%) when GTR (*e.g.*, human GTR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00119] In certain embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of GITRL (*e.g.*, human GITRL) binds to GTR (*e.g.*, human GTR) in the presence of an antibody or antigen-binding fragment thereof described herein assessed by an assay known to one of skill in the art or described herein. In a specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of GITRL (*e.g.*, human GITRL) binds to GTR (*e.g.*, human GTR) in the presence of an antibody or antigen-binding fragment thereof described herein as assessed by the assay described in Example 2, *infra* (*e.g.*, Section 6.2.5.2 or 6.2.5.4, *infra*). In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of

1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the presence of 1000 ng/ml, 950 ng/ml, 900 ng/ml, 850 ng/ml, 800 ng/ml, 750 ng/ml, 700 ng/ml, 650 ng/ml, 600 ng/ml, 550 ng/ml, 500 ng/ml, 450 ng/ml, 400 ng/ml, 350 ng/ml, 333 ng/ml, 300 ng/ml, 250 ng/ml or 200 ng/ml of an antibody or antigen-binding fragment thereof described herein relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the presence of 1000 ng/ml to 900 ng/ml, 1000 ng/ml to 850 ng/ml, 900 ng/ml to 800 ng/ml, or 850 ng/ml to 750 ng/ml, or 800 to 750 ng/ml relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, at least 20%, at least 25% or at least 30% of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 1000ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay.

[00120] In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM, 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml,

4pg/ml or 3pg/ml per bead in the presence of 3500 ng/ml, 3400 ng/ml, 3300 ng/ml, 3200 ng/ml, 3100 ng/ml, 3000 ng/ml, 2900 ng/ml, 2800 ng/ml, 2700 ng/ml, 2600 ng/ml, 2500 ng/ml, 2400 ng/ml, 2300 ng/ml, 2200 ng/ml, 2100 ng/ml, 2000 ng/ml, 1900 ng/ml, 1800 ng/ml, 1700 ng/ml, 1600 ng/ml, 1500 ng/ml, 1400 ng/ml, 1300 ng/ml, 1200 ng/ml, 1100 ng/ml or 1000 ng/ml of an antibody or antigen-binding fragment thereof described herein relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the presence of 3500 ng/ml to 3200 ng/ml, 3500 ng/ml to 3000ng/ml, 3200 ng/ml to 2500 ng/ml, 3000 to 2200 ng/ml, 2500 ng/ml to 1800 ng/ml, 2000 ng/ml to 1500 ng/ml, 1700 ng/ml to 1200 ng/ml, or 1500 ng/ml to 1000 ng/ml of an antibody or antigen-binding fragment thereof described herein relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00121] In another specific embodiment, at least 20%, at least 25% or at least 30% of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 3000ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In another specific embodiment, at least 25%, at least 30%, at least 40%, or at least 50% (in some embodiments, 25% to 60%, 40% to 60%, 40% to 70%, or 25% to 50%) of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 1000ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the

absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In another specific embodiment, at least 30%, at least 40%, at least 50% or at least 60% (in some embodiments, 30% to 60%, 40% to 60%, 40% to 70%, or 30% to 50%) of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 333ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In another specific embodiment, at least 40%, at least 50%, at least 60% or at least 65% (in some embodiments, 40% to 70%, 40% to 60%, 40% to 65%, or 40% to 50%) of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 111ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In another specific embodiment, at least 60%, at least 70% or at least 80% (in some embodiments 60% to 80%, 70% to 80% or 75% to 85%) of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 37ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay. In another specific embodiment, at least 80%, at least 85% or at least 90% (in some embodiments 80% to 90% or 85% to 95%) of 0.5nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml/bead in the presence of 12ng/ml of an antibody or antigen-binding fragment thereof relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay.

[00122] In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 3000ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 15% or more than 20% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of

5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 1000ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 15%, more than 20% or more than 25% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 333ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 30% or more than 35% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 111ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 35%, more than 40% or more than 45% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 37ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 60% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200 system). In a certain embodiment, an antibody or antigen-binding fragment thereof described herein at a concentration of 12ng/ml does not inhibit binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 80% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof, in a suspension array assay (*e.g.*, Luminex[®] 200

system).

[00123] In another embodiment, a certain amount of labeled GITRL (*e.g.*, human GITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) in the presence of an antibody or antigen-binding fragment thereof described herein in a method comprising: (a) coupling GITR (*e.g.*, human GITR) to beads at a concentration of approximately 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead; (b) incubating the GITR coupled beads at a concentration of approximately 30 beads/ μ l, 40 beads/ μ l, or 50 beads/ μ l with 3000ng/ml, 2500ng/ml, 2000ng/ml, 1500ng/ml, 1000ng/ml, 750ng/ml, 500ng/ml, 250ng/ml, 100ng/ml, 50ng/ml, 25ng/ml or 10ng/ml of an antibody or an antigen-binding fragment thereof described herein in a well for a first period of time (*e.g.*, 30 minutes, 60 minutes, 1.5 hours, 2 hours, 2.5 hours or 3 hours); (c) adding labeled GITRL (*e.g.*, human GITRL-PE) to the well to obtain a final concentration of approximately 1.5nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of the labeled GITRL and approximately 15 beads/ μ l, 20 beads/ μ l, or 25 beads/ μ l, and incubating for a second period of time (*e.g.*, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours); and (d) detecting the labeled GITRL bound to the GITR coupled beads in, *e.g.*, a suspension array assay such as the Luminex[®] 200 system. In specific embodiments, the amount of the labeled GITRL bound to the GITR coupled beads in the presence of the anti-GITR antibody or antigen-binding fragment thereof is determined relative to the amount of labeled GITRL bound to the GITR coupled beads in the absence of the anti-GITR antibody or antigen-binding fragment thereof. In certain embodiments, the absence of the anti-GITR antibody or antigen-binding fragment thereof means that no antibody or antigen-binding fragment thereof is present in the well. In other embodiments, the absence of the anti-GITR antibody or antigen-binding fragment thereof means that an isotype control antibody that does not bind to GITR is present in the well. In accordance with these embodiments, the amount of labeled GITRL bound to the GITR coupled beads in the presence of the anti-GITR antibody or antigen-binding fragment thereof is determined to be, in some embodiments, at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% or 15% to 60%, 20% to 60%, 30% to 70%, or 20% to 50% of the amount of the labeled GITRL bound to the GITR coupled beads in the absence of the anti-GITR antibody or antigen-binding fragment thereof.

[00124] In another embodiment, a certain amount of labeled GITRL (*e.g.*, human GITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) in the presence of an antibody or antigen-binding fragment thereof described herein in a method comprising: (a) coupling GITR (*e.g.*, human GITR) to beads at a concentration of approximately 5pg/ml per bead; (b) incubating the GITR coupled beads at a concentration of approximately 40 beads/ μ l

with 3000ng/ml, 2500ng/ml, 2000ng/ml, 1500ng/ml, 1000ng/ml, 750ng/ml, 500ng/ml, 250ng/ml, 100ng/ml, 50ng/ml or 10ng/ml of an antibody or an antigen-binding fragment thereof described herein in a well for a first period of time (*e.g.*, 30 minutes, 60 minutes, 1.5 hours, 2 hours, 2.5 hours or 3 hours); (c) adding labeled GITRL (*e.g.*, human GITRL-PE) to the well to obtain a final concentration of 0.5nM of the labeled GITRL and approximately 20 beads/ μ l, and incubating for a second period of time (*e.g.*, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours); and (d) detecting the labeled GITRL bound to the GITR coupled beads in, *e.g.*, a suspension array assay such as the Luminex[®] 200 system. In specific embodiments, the amount of the labeled GITRL bound to the GITR coupled beads in the presence of the anti-GITR antibody or antigen-binding fragment thereof is determined relative to the amount of labeled GITRL bound to the GITR coupled beads in the absence of the anti-GITR antibody or antigen-binding fragment thereof. In certain embodiments, the absence of the anti-GITR antibody or antigen-binding fragment thereof means that no antibody or antigen-binding fragment thereof is present in the well. In other embodiments, the absence of the anti-GITR antibody or antigen-binding fragment thereof means that an isotype control antibody that does not bind to GITR is present in the well. In accordance with these embodiments, the amount of labeled GITRL bound to the GITR coupled beads in the presence of the anti-GITR antibody or antigen-binding fragment thereof is determined to be, in some embodiments, at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60% or 20 to 70%, 20% to 60%, 30% to 70%, or 20% to 50% of the amount of the labeled GITRL bound to the GITR coupled beads in the absence of the anti-GITR antibody or antigen-binding fragment thereof.

[00125] In certain embodiments, an antibody or antigen-binding fragment thereof described herein at a concentration of 150nM, 145nM, 140nM, 135nM, 130nM, 125nM, 120nM, 115nM, 110nM, 105nM or 100nM bound to GITR (*e.g.*, human GITR) immobilized on a chip (*e.g.*, CM5 sensor chip) inhibits binding of 150nM, 145nM, 140nM, 135nM, 130nM, 125nM, 120nM, 115nM, 110nM, 105nM or 100nM of GITRL (*e.g.*, non-covalently linked trimer of human GITRL) to the GITR immobilized on the chip by less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20% or less than 15%. In certain embodiments, an antibody or antigen-binding fragment thereof described herein at a concentration of 125nM bound to GITR (*e.g.*, human GITR) immobilized on a chip (*e.g.*, CM5 sensor chip) inhibits binding of 125nM of GITRL (*e.g.*, non-covalently linked trimer of human GITRL) to the GITR immobilized on the chip by less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20% or less than 15%.

[00126] In certain embodiments, an antibody or fragment thereof described herein binds to GPCR (e.g., human GPCR) with a dissociation rate constant (k_{off}) of $8.5 \times 10^{-3} \text{ s}^{-1}$ or less, $3.5 \times 10^{-3} \text{ s}^{-1}$ or less, $5 \times 10^{-3} \text{ s}^{-1}$ or less, $2.5 \times 10^{-3} \text{ s}^{-1}$ or less, $1 \times 10^{-3} \text{ s}^{-1}$ or less, $8.5 \times 10^{-4} \text{ s}^{-1}$ or less, $5 \times 10^{-4} \text{ s}^{-1}$ or less, $3.5 \times 10^{-4} \text{ s}^{-1}$ or less, $2.5 \times 10^{-4} \text{ s}^{-1}$ or less, $1 \times 10^{-4} \text{ s}^{-1}$ or less, $8.5 \times 10^{-5} \text{ s}^{-1}$ or less, $3.5 \times 10^{-5} \text{ s}^{-1}$ or less, $5 \times 10^{-5} \text{ s}^{-1}$ or less, $2.5 \times 10^{-5} \text{ s}^{-1}$ or less, $1 \times 10^{-5} \text{ s}^{-1}$ or less, $8.5 \times 10^{-6} \text{ s}^{-1}$ or less, $5 \times 10^{-6} \text{ s}^{-1}$ or less, $3.5 \times 10^{-6} \text{ s}^{-1}$ or less, $2.5 \times 10^{-6} \text{ s}^{-1}$ or less, $1 \times 10^{-6} \text{ s}^{-1}$ or less, $8.5 \times 10^{-7} \text{ s}^{-1}$ or less, $5 \times 10^{-7} \text{ s}^{-1}$ or less, $2.5 \times 10^{-7} \text{ s}^{-1}$ or less, $1 \times 10^{-7} \text{ s}^{-1}$ or less, $8.5 \times 10^{-8} \text{ s}^{-1}$ or less, $5 \times 10^{-8} \text{ s}^{-1}$ or less, $2.5 \times 10^{-8} \text{ s}^{-1}$ or less, $1 \times 10^{-8} \text{ s}^{-1}$ or less, $8.5 \times 10^{-9} \text{ s}^{-1}$ or less, $5 \times 10^{-9} \text{ s}^{-1}$ or less, $2.5 \times 10^{-9} \text{ s}^{-1}$ or less, or $1 \times 10^{-9} \text{ s}^{-1}$ or less. In some embodiments, an antibody or fragment thereof described herein binds to GPCR (e.g., human GPCR) with a k_{off} of between $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $8.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-8} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-8} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $5 \times 10^{-6} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $8.5 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-4} \text{ s}^{-1}$, $5 \times 10^{-3} \text{ s}^{-1}$ to $2.5 \times 10^{-4} \text{ s}^{-1}$, $8.5 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $8.5 \times 10^{-5} \text{ s}^{-1}$ to $5 \times 10^{-5} \text{ s}^{-1}$. In certain embodiments, the k_{off} is determined using a monovalent antibody, such as a Fab fragment, as measured by, e.g., BIAcore® surface plasmon resonance technology. In other embodiments, the k_{off} is determined using a bivalent antibody as measured by, e.g., BIAcore® surface plasmon resonance technology. In a particular embodiment, the k_{off} is determined using an assay described in Section 6, *infra*.

[00127] In certain embodiments, an antibody or fragment thereof described herein binds to GPCR (e.g., human GPCR) with an association rate constant (k_{on}) of at least $10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $2.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $2.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $3.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $10^7 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, at least $10^8 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ or at least $10^9 \text{ M}^{-1}\text{s}^{-1}$. In some embodiments, an antibody or fragment thereof described herein binds to GPCR (e.g., human GPCR) with a k_{on} of between $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $2.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $3.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$. In certain embodiments, the k_{on} is determined using a monovalent antibody, such as a Fab fragment, as measured by, e.g., BIAcore® surface plasmon resonance technology. In other embodiments, the k_{on} is determined using a bivalent antibody as measured by, e.g., BIAcore® surface plasmon resonance technology. In a particular embodiment, the k_{on} is determined using an assay described in Section 6, *infra*.

[00128] In certain embodiments, an antibody or fragment thereof described herein binds to GITR (*e.g.*, human GITR) with a K_D of less than 7 nM, 6 nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.75 nM, 0.5 nM, 0.25 nM, or 0.1 nM. In some embodiments, an antibody or fragment thereof described herein binds to GITR (*e.g.*, human GITR) with a K_D of about 7 nM, 6 nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.75 nM, 0.5 nM, 0.25 nM, or 0.1 nM. In certain embodiments, an antibody or fragment thereof described herein binds to GITR (*e.g.*, human GITR) with a K_D of 7 nM to 2 nM, 5 nM to 3 nM, 5 nM to 1 nM, 4 nM to 3 nM, 4 nM to 2 nM, 3 nM to 2 nM, 3 nM to 1 nM, 2 nM to 1 nM, 3 nM to 0.1 nM, 2 nM to 0.1 nM, 1 nM to 0.1 nM, or 0.5 nM to 0.1 nM. In certain embodiments, the K_D is calculated as the quotient of k_{off}/k_{on} , and the k_{on} and k_{off} are determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In other embodiments, the K_D is calculated as the quotient of k_{off}/k_{on} , and the k_{on} and k_{off} are determined using a bivalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In a specific embodiment, the K_D is determined as set forth in the Examples in Section 6, *infra* (*e.g.*, Example 2).

[00129] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) comprising:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YLY₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M

X₂ is L, A, V, I, P, F, M or S

X₃ is N, G, Q, S, T, C, W, Y or A

X₄ is S, G, N, Q, T, C, W, Y or A

X₅ is G, N, Q, S, T, C, W, Y or A

X₆ is N, G, Q, S, T, C, W, Y or A

X₇ is Q, G, N, S, T, C, W, Y or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is T, G, N, Q, S, C, W, Y, V, I or A; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A

X₂ is E, D or A

X₃ is S, G, N, Q, T, C, W, Y or A; and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y

X₂ is D, E or Y

X₃ is S, G, N, Q, T, C, W, Y or A

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, or all three of the VL CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL CDRs in one row of Table 1, for example, all of the VL CDRs are from antibody 231-32-15). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions (FRs) of an antibody set forth in Table 3 (*e.g.*, one, two, three, or four of the framework regions in one row of Table 3).

[00130] In another embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable region (VH) comprising:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A

X₂ is A, V, L, I, P, F, M or Y

X₃ is Y, G, N, Q, S, T, C, W, F or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T

X₂ is R, K, H, Q or A

X₃ is T, G, N, Q, S, C, W, Y, V, I or P

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A

X₅ is D, E, G or A

X₆ is V, A, L, I, P, F, M or T

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is K, R, H, Q or A

X₁₀ is D, E, G or A; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A, or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row of Table 2, for example, all of the VH CDRs are from the antibody 231-32-15). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH frameworks described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VH framework regions of an antibody set forth in Table 4 (*e.g.*, one, two, three or four of the framework regions in one row of Table 4).

[00131] Table 1. VL CDR Amino Acid Sequences ¹

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
231-32-15	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
Hum231#1	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
Hum231#2	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
pab1964	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
pab1965	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1966	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1967	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
pab1968	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1969	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
pab1970	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
pab1971	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
pab1972	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
pab1973	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1975	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1976	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1977	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1979	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1980	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1981	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1983	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab2159	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
pab2160	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab2161	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
1	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
2	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
3	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
4	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
5	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
6	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
7	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNEYSFPYT (108)
8	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSYPYT (106)
9	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
10	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
11	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSFPYT (109)
12	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
13	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
14	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
15	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
16	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
17	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
18	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
19	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSFPYT (109)
20	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
21	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
22	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDHSFPYT (191)
23	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSSPYT (192)
24	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
25	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
26	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
27	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSFPYT (109)
28	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
29	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
30	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
31	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
32	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
33	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
34	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
35	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
36	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
37	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSYPYT (106)
38	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
39	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
40	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
41	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
42	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
43	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
44	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
45	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
46	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
47	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
48	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
49	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
50	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
51	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSSPYT (192)
52	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
53	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
54	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
55	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
56	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
57	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
58	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
59	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
60	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSYPYT (106)
61	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
62	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
63	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
64	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNEYSYPYT (106)
65	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNEYSFPYT (108)
66	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSFPYT (109)
67	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
68	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
69	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
70	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
71	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
72	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
73	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
74	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
75	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
76	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
77	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
78	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
79	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
80	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
81	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
82	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
83	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
84	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
85	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
86	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
87	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
88	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
89	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
90	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSSPYT (193)
91	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
92	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
93	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
94	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
95	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
96	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
97	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
98	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
99	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
100	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSSPYT (192)
101	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
102	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
103	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSSPYT (192)
104	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
105	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
106	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
107	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)

¹The VL CDRs in Table 1 are determined according to Kabat.

[00132] Table 2. VH CDR Amino Acid Sequences ²

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
231-32-15	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
Hum231#1	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
Hum231#2	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
pab1964	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
pab1965	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
pab1966	GYAMY (19)	VIKTYSGGVTYNQKFRG (26)	SGTVRGFAY (34)
pab1967	GYAMH (20)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
pab1968	DYAMY (21)	VIRTFSGDLTYNQKFQD (28)	SGTVRGFAY (34)
pab1969	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1970	DYAMY (21)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
pab1971	DYAMY (21)	VIRTYSGDVSYNQKFRG (177)	SGTVRGFAY (34)
pab1972	EYAMY (23)	LIRTYSGGVSYNQKFRD (31)	SGTVRGFAY (34)

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
pab1973	GYAMY (19)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
pab1975	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1976	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1977	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1979	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1980	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1981	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1983	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
pab2159	GYAMY (19)	LIRTYSGEVSYNQKFRG (144)	SGTVRGFAY (34)
pab2160	GYVMH (119)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
pab2161	EYAMH (22)	LIQTYSGDVSYNQKFRG (121)	SGTVRGFAY (34)
1	EYAMY (23)	VIRTYSGGVTYNQKFQG (187)	SGTVRGFAY (34)
2	EYAMH (22)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
3	GYVMH (119)	VIRTYSGEVSYNQKFQE (181)	SGTVRGFAY (34)
4	EYAMY (23)	LIRTFSGDVSYNQKFQD (124)	SGTVRGFAY (34)
5	EYAMH (22)	LIRTYSGGVTYNQKFRG (151)	SGTVRGFAY (34)
6	EYAMY (23)	LIRTFSGGVSYNQKFKG (135)	SGTVRGFAY (34)
7	GYAMH (20)	LIRTFSGGLSYNQKFRE (132)	SGTVRGFAY (34)
8	GYVMY (116)	VIKTFSGGVSYNQKFQE (152)	SGTVRGFAY (34)
9	GYAMY (19)	LIRTYSGEVSYNQKFRG (144)	SGTVRGFAY (34)
10	EYAMY (23)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
11	DYAMH (117)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
12	GYAMY (19)	VIRTFSGEVSYNQKFKG (164)	SGTVRGFAY (34)
13	GYAMY (19)	LIRTFSGDVTYNQKFRG (127)	SGTVRGFAY (34)
14	GYVMH (119)	LIRTYSGDVSYNQKFRD (146)	SGTVRGFAY (34)
15	DYAMY (21)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
16	GYAMY (19)	LIRTFSGGVTYNQKFRE (140)	SGTVRGFAY (34)
17	EYAMY (23)	VIQTFSGGVTYNQKFRG (157)	SGTVRGFAY (34)
18	GYAMY (19)	LIRTFSGEVTYNQKFRG (130)	SGTVRGFAY (34)
19	GYAMY (19)	LIRTYSGGLSYNQKFQD (145)	SGTVRGFAY (34)
20	DYAMY (21)	VIRTFSGDLSYNQKFRG (114)	SGTVRGFAY (34)
21	GYVMH (119)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
22	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
23	GYAMY (19)	LIRTFSGDVTYNQKFRG (127)	SGTVRGFAY (34)
24	DYAMH (117)	LIRTYSGGVTYNQKFRG (151)	SGTVRGFAY (34)
25	EYAMY (23)	LIRTFSGGVSYNQKFRG (138)	SGTVRGFAY (34)
26	EYAMH (22)	LIRTFSGDVSYNQKFKG (123)	SGTVRGFAY (34)
27	DYAMY (21)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
28	DYAMY (21)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
29	DYAMY (21)	VIRTFSGGVTYNQKFKG (172)	SGTVRGFAY (34)
30	DYVMY (35)	VIRTFSGGLSYNQKFRG (165)	SGTVRGFAY (34)
31	EYAMY (23)	LIRTFSGGLTYNQFKD (133)	SGTVRGFAY (34)

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
32	DYAMY (21)	VIRTFSGGVTYNQKFKD (171)	SGTVRGFAY (34)
33	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
34	DYAMY (21)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
35	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
36	DYAMY (21)	VIRTFSGGVSYNQKFRD (168)	SGTVRGFAY (34)
37	EYAMY (23)	LIRTFSGEVTYNQKFKD (129)	SGTVRGFAY (34)
38	GYAMY (19)	VIKTYSGGVTYNQKFRG (26)	SGTVRGFAY (34)
39	GYAMH (20)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
40	EYAMY (23)	VIRTYSGDLSYNQKFRG (174)	SGTVRGFAY (34)
41	DYVMY (35)	VIRTFSGGVSYNQKFRG (170)	SGTVRGFAY (34)
42	DYAMY (21)	VIRTFSGDLTYNQKFQD (28)	SGTVRGFAY (34)
43	EYAMY (23)	LIRTFSGDVSYNQKFKG (123)	SGTVRGFAY (34)
44	EYAMH (22)	LIRTYSGDVSYNQKFQG (142)	SGTVRGFAY (34)
45	EYAMY (23)	LIRTYSGGVSYNQKFQG (147)	SGTVRGFAY (34)
46	EYAMY (23)	LIRTFSGDLSYNQKFRG (122)	SGTVRGFAY (34)
47	DYAMY (21)	VIRTYSGGVTYNQKFRD (188)	SGTVRGFAD (189)
48	DYAMY (21)	LIRTYSGGVTYNQKFKE (149)	SGTVRGFAY (34)
49	GYAMY (19)	VIRTYSGDVTYNQKFRE (179)	SGTVRGFAY (34)
50	DYAMY (21)	LIRTFSGGVSYNQKFKE (134)	SGTVRGFAY (34)
51	EYAMY (23)	VIRTFSGGVTYNQKFKG (172)	SGTVRGFAY (34)
52	DYAMY (21)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
53	EYAMH (22)	VIRTYSGGLSYNQKFRG (182)	SGTVRGFAY (34)
54	EYAMH (22)	LIRTYSGGVSYNQKFQG (147)	SGTVRGFAY (34)
55	DYAMY (21)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
56	DYAMY (21)	VIRTYSGDVSYNQKFRG (177)	SGTVRGFAY (34)
57	GYAMY (19)	LIRTYSGDVTYNQKFKD (143)	SGTVRGFAY (34)
58	DYAMY (21)	VIRTYSGGVTYNQKFKG (186)	SGTVRGFAY (34)
59	EYAMY (23)	LIRTYSGGVSYNQKFRD (31)	SGTVRGFAY (34)
60	DYAMY (21)	VIKTYSGGVSYNQKFRG (153)	SGTVRGFAY (34)
61	EYAMH (22)	LIRTYSGGVSYNQKFQE (115)	SGTVRGFAY (34)
62	GYVMY (116)	VIRTFSGGVSYNQKFQG (167)	SGTVRGFAY (34)
63	EYAMY (23)	VIRTFSGDVTYNQKFKG (163)	SGTVRGFAY (34)
64	DYAMY (21)	VIRTYSGDVTYNQKFRG (180)	SGTVRGFAY (34)
65	EYAMY (23)	VIKTYSGGVTYNQKFRG (26)	SGTVRGFAY (34)
66	DYVMY (35)	VIRTYSGEVSYNQKFRG (183)	SGTVRGFAY (34)
67	EYAMY (23)	VIQTFSGDVSYNQKFKG (156)	SGTVRGFAY (34)
68	GYAMY (19)	LIRTYSGGVTYNQKFRG (151)	SGTVRGFAY (34)
69	EYVMH (118)	VIRTFSGGVSYNQKFRE (169)	SGTVRGFAY (34)
70	GYAMY (19)	VIRTYSGDVTYNQKFKD (178)	SGTVRGFAY (34)
71	GYAMY (19)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
72	GYAMY (19)	VIRTYSGDVSYNQKFQE (175)	SGTVRGFAY (34)
73	GYVMH (119)	IIKTYSGGVSYNQKFQG (120)	SGTVRGFAY (34)

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
74	DYAMY (21)	VIKTYSGGVTYNQKFKD (154)	SGTVRGFAY (34)
75	GYAMY (19)	VIRTYSGGVTYNQKFQG (187)	SGTVRGFAY (34)
76	DYAMH (117)	LIRTFSGDVSYNQKFRE (125)	SGTVRGFAY (34)
77	EYAMH (22)	LIQTYSGDVSYNQKFRG (121)	SGTVRGFAY (34)
78	DYAMY (21)	VIKTYSGGVTYNQKFRD (155)	SGTVRGFAY (34)
79	EYAMH (22)	LIRTYSGGVTYNQKFRE (150)	SGTVRGFAY (34)
80	EYAMH (22)	LIRTFSGDVSYNQKFRG (126)	SGTVRGFAY (34)
81	DYAMY (21)	LIRTFSGEVSYNQKFQD (128)	SGTVRGFAY (34)
82	GYVMH (119)	VIRTFSGGVSYNQKFRG (170)	SGTVRGFAY (34)
83	GYAMY (19)	VIRTFSGDVSYNQKFRD (161)	SGTVRGFAY (34)
84	GYAMY (19)	LIRTFSGDVTYNQKFRG (127)	SGTVRGFAY (34)
85	EYAMY (23)	VIRTYSGGVTYNQKFKD (185)	SGTVRGFAY (34)
86	EYAMY (23)	VIRTYSGGVTYNQKFRD (188)	SGTVRGFAY (34)
87	GYAMY (19)	VIRTFSGDLSYNQKFKG (159)	SGTVRGFAY (34)
88	EYAMH (22)	VIRTYSGDVSYNQKFRG (177)	SGTVRGFAY (34)
89	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
90	EYAMY (23)	LIRTYSGDLSYNQKFKE (141)	SGTVRGFAY (34)
91	EYAMH (22)	LIRTYSGGVSYNQKFQE (115)	SGTVRGFAY (34)
92	EYAMY (23)	LIRTFSGGVTYNQKFQG (139)	SGTVRGFAY (34)
93	DYAMH (117)	VIQTYSGDVSYNQKFQG (158)	SGTVRGFAY (34)
94	GYAMY (19)	VIRTFSGGVTYNQKFRD (173)	SGTVRGFAY (34)
95	DYAMY (21)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
96	EYAMY (23)	VIRTYSGGLTYNQKFRD (184)	SGTVRGFAY (34)
97	EYAMH (22)	LIRTFSGGLSYNQKFRD (131)	SGTVRGFAY (34)
98	GYAMH (20)	VIRTFSGGVSYNQKFQE (166)	SGTVRGFAY (34)
99	DYAMH (117)	LIRTFSGDLSYNQKFRG (122)	SGTVRGFAY (34)
100	EYAMH (22)	VIRTFSGGVSYNQKFQG (167)	SGTVRGFAY (34)
101	DYAMH (117)	LIRTFSGGVSYNQKFQD (136)	SGTVRGFAY (34)
102	GYAMY (19)	VIRTYSGGVSYNQKFRD (194)	SGTVRGFAY (34)
103	GYAMY (19)	VIRTYSGDVSYNQKFRG (177)	SGTVRGFAY (34)
104	DYAMY (21)	LIRTFSGGVSYNQKFRD (137)	SGTVRGFAY (34)
105	EYAMY (23)	LIRTFSGGVSYNQKFKG (135)	SGTVRGFAY (34)
106	DYAMY (21)	VIRTFSGDVSYNQKFQE (160)	SGTVRGFAY (34)
107	GYAMY (19)	VIRTYSGDVSYNQKFRD (176)	SGTVRGFAY (34)

²The VH CDRs in Table 2 are determined according to Kabat.

[00133] Table 3. VL FR Amino Acid Sequences³

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
231-32-15	DIVMTQSPSSLTVTA GEKVIMSC (616)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDLAVYHC (637)	FGGGTKLEIK (641)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
Hum231 #1	DIVMTQSPPTLSLSP GERVTLSC (615)	WYQQKPGQA PRLLIY (622)	GIPARFSGSGSGTDFTLTIS SLQPEDFAVYHC (626)	FGQGTKLEIK (643)
Hum231 #2	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
pab1964	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1965	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
pab1966	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1967	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
pab1968	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1969	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
pab1970	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1971	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
pab1972	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1973	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSDTDFTLTI SSVQAEDVAVYHC (627)	FGQGTKLEIK (643)
pab1975	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1976	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1977	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
pab1979	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1980	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1981	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
pab1983	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab2159	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
pab2160	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab2161	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
1	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
2	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
3	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
4	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
5	DIVMTQSPDSLAAAPG ERATINC (610)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
6	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
7	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
8	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
9	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
10	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
11	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
12	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
13	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
14	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
15	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
16	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
17	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
18	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
19	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
20	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLLY (624)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (620)	FGQGTKLEIK (643)
21	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
22	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
23	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLT SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
24	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLT SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
25	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
26	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLT SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
27	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
28	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
29	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
30	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
31	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
32	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
33	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLT SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
34	DIVMTQSTD SLAVSL GERATINC (617)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
35	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
36	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLT SSVQEEDVAVYHC (634)	FGQGTKLEIK (643)
37	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
38	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
39	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
40	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
41	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
42	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLT SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
43	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
44	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFTGSGSGTDFTLT SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
45	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
46	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
47	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
48	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
49	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
50	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
51	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
52	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
53	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
54	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
55	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
56	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
57	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
58	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
59	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
60	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
61	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
62	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
63	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
64	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
65	DIVMTQSPDSLAVSL GERATINC (612)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SFVQAEDVAVYYC (628)	FGQGTKLEIK (643)
66	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
67	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
68	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
69	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
70	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
71	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
72	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
73	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
74	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
75	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
76	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
77	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
78	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
79	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
80	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYYC (642)	FGQGTKLEIK (643)
81	DIVMTQSPDSLAVSL GERATINC (613)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
82	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYYC (631)	FGQGTKLEIK (643)
83	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
84	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
85	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
86	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
87	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
88	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
89	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
90	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
91	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
92	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTNFTLTI SSVQAEDVAVYHC (635)	FGQGTKLEIK (643)
93	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFTGSGSGTDFTLTI SSLQAEDVAVYHC (636)	FGQGTKLEIK (643)
94	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
95	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
96	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
97	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
98	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYHC (638)	FGQGTKLEIK (643)
99	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKMLIY (624)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
100	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKMLIY (619)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
101	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
102	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)
103	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSLQAEDVAVYHC (630)	FGQGTKLEIK (643)
104	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFSGSGSGTDFTLTI SSFQAEDVAVYHC (629)	FGQGTKLEIK (643)
105	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKLLIY (623)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYYC (633)	FGQGTKLEIK (643)
106	DIVMTQSPDSLAVSL GERATINC (611)	WYQQKPGQP PKSLIY (625)	GVPDRFSGSGSGTDFTLTI SSVQAEDVAVYHC (632)	FGQGTKLEIK (643)
107	DIVMTQSPDSLAVSL GERATINC (611)	WYHQKPGQP PKLLIY (618)	GVPDRFTGSGSGTDFTLTI SSVQAEDVAVYYC (639)	FGQGTKLEIK (643)

³ The VL framework regions described in Table 3 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VL CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00134] Table 4. VH FR Amino Acid Sequences ⁴

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
231-32-15	QVQLQLQSGTELVKPGVSV KISCKGSGYTFT (645)	WVKQSHAKSLE WIG (652)	KATMTVDKSSSIAYMELAR LSSEDSAIYYCAK (658)	WGQGTLVTVSS (668)
Hum231#1	QVQLVQSGAEVKKPGAS VKVSCCKGSGYTFT (649)	WVRQAPGQGLE WIG (653)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
Hum231#2	QVQLVQSGAEVKKPGAS VKVSCCKGSGYTFT (649)	WVRQAPGQGLE WIG (653)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
pab1964	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1965	QVQLVQSGAEAKKPGAS VKVSCCKGSGYTFT (646)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1966	QVQLVQSGTEVKKPGAS VKVSCCKGSGYTFT (651)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
pab1967	QVQLVQSGAEVKKPGAS VKVSCCKGSGYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLITVSS (667)
pab1968	QVQLVQSGTEVKKPGAS VKVSCCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1969	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
pab1970	QVQLVQSGTEVKKPGAS VKVSCCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1971	QVQLVQSGTEVKKPGAS VKVSCCKGSGYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1972	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
pab1973	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
pab1975	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
pab1976	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
pab1977	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
pab1979	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1980	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1981	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab1983	QVQLVQSGAEVKKPGAS VKVSCCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
pab2159	QVQLVQSGAEVKKPGAS	WVRQAPGQGLE	RATMTVDKSISTAYMELSR	WGQGTLVTVSS

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
	VKVSCKASGYTFT (648)	WMG (654)	LRSDDTAVYYCAK (659)	(668)
pab2160	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
pab2161	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (653)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
1	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (653)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
2	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
3	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
4	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQSLE WMG (657)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
5	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
6	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
7	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
8	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
9	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
10	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
11	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
12	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
13	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
14	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
15	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (653)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
16	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
17	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
18	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
19	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
20	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
21	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
22	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
23	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
24	QVQLVQSGAEVKKPGAS VKASCKSGSYTFT (647)	WVRQAPGQGME WIG (655)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
25	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
26	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
27	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
28	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WIG (653)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
29	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WIG (653)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
30	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
31	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGIPVTVSS (664)
32	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
33	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
34	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
35	QVQLVQSGAEAKKPGAS VKVSCKSGSYTFT (646)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
36	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (655)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
37	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
38	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
39	QVQLVQSGAEVKKPGAS	WVRQAPGQGLE	RATMTVDTSISTAYMELSR	WGQGTLITVSS

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
	VKVSCKGSGYTFT (649)	WMG (654)	LRSDDTAVYYCAK (670)	(667)
40	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
41	QVQLVQSGAEVKKPGAS VKVSCKGSGYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
42	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
43	QVQLVQSGAEVKKPGAS VKVSCKGSGYTFT (649)	WVRQAPGQGME WIG (655)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
44	QVQLVQSGTEVKKPGAS VKVSCKGSGYTFT (651)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
45	QVQLVQSGAEVKKPGAS VKVSCKGSGYTFT (649)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTFVTVSS (665)
46	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
47	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
48	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
49	QVQLVQSGTEVKKPGAS VKVSCKGSGYTFT (651)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
50	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
51	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
52	QVQLVQSGTEVKKPGAS VKVSCKGSGYTFT (651)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
53	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WMG (656)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
54	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
55	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
56	QVQLVQSGTEVKKPGAS VKVSCKGSGYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
57	QVQLVQSGTEVKKPGAS VKVSCKGSGYTFT (651)	WVRQAPGQGME WIG (655)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
58	QVQLVQSGAEVKKPGAS VKVSCKGSGYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
59	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
60	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
61	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
62	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
63	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
64	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
65	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
66	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
67	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
68	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
69	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
70	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WIG (655)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
71	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
72	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
73	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (655)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
74	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
75	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
76	QVQLVQSGAGVKKPGAS VKVSCKSGSYTFT (644)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
77	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WIG (653)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLVTVSS (668)
78	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WIG (653)	RATMTVDTSISTAYMELSR LRGDDTAVYYCAK (661)	WGRGTLVTVSS (669)
79	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
80	QVQLVQSGTEVKKPGAS	WVRQAPGQGME	RVTMTVDTSISTAYMELSR	WGQGTLVTVSS

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
	VKVSCKASGYTFT (650)	WMG (656)	LRSDDTAVYYCAK (663)	(668)
81	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
82	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
83	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
84	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
85	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
86	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
87	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WIG (655)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
88	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLLTVSS (668)
89	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
90	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WIG (653)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
91	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
92	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RATMTVDTSISTAYMELSR LQSDDTAVYYCAK (660)	WGQGTLLTVSS (668)
93	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
94	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGLE WIG (653)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTFVTVSS (666)
95	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTFVTVSS (666)
96	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLLTVSS (668)
97	QVQLVQSGTEVKKPGAS VKVSCKSGSYTFT (651)	WVRQAPGQGME WIG (655)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
98	QVQLVQSGAEVKKPGAS VKVSCKSGSYTFT (649)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)
99	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLLTVSS (668)
100	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGME WMG (656)	RATMTVDTSISTAYMELSR LRSDDTAVYYCAK (670)	WGQGTLLTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
101	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGLE WMG (654)	RVTMTVDKSISTAYMELSR LRSDDTAVYYCAK (662)	WGQGTLVTVSS (668)
102	QVQLVQSGTEVKKPGAS VKVSCKASGYTFT (650)	WVRQAPGQGLE WIG (653)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
103	QVQLVQSGAEVKKPGAS VKVSCKASGYTFT (648)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
104	QVQLVQSGTEVKKPGAS VKVSCKSGGYTFT (651)	WVRQAPGQGME WMG (656)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
105	QVQLVQSGAEVKKPGAS VKVSCKSGGYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)
106	QVQLVQSGTEVKKPGAS VKVSCKSGGYTFT (651)	WVRQAPGQGLE WIG (653)	RATMTVDKSISTAYMELSR LRSDDTAVYYCAK (659)	WGQGTLVTVSS (668)
107	QVQLVQSGAEVKKPGAS VKVSCKSGGYTFT (649)	WVRQAPGQGLE WMG (654)	RVTMTVDTSISTAYMELSR LRSDDTAVYYCAK (663)	WGQGTLVTVSS (668)

⁴ The VH framework regions described in Table 4 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VH CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00135] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) comprising:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YLX₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M

X₂ is L, A, V, I, P, F, M or S

X₃ is N, G, Q, S, T, C, W, Y or A

X₄ is S, G, N, Q, T, C, W, Y or A

X₅ is G, N, Q, S, T, C, W, Y or A

X₆ is N, G, Q, S, T, C, W, Y or A

X₇ is Q, G, N, S, T, C, W, Y or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is T, G, N, Q, S, C, W, Y, V, I or A; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A

X₂ is E, D or A

X₃ is S, G, N, Q, T, C, W, Y or A; and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y

X₂ is D, E or Y

X₃ is S, G, N, Q, T, C, W, Y or A

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, or all three of the VL CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 5. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 5. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 5. In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 5 (*e.g.*, the VL CDRs in one row of Table 5, for example, all of the VL CDRs are from antibody 231-32-15). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions (FRs) of an antibody set forth in Table 7 (*e.g.*, one, two, three, or four of the framework regions in one row of Table 7).

[00136] In another embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable region (VH) comprising:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A

X₂ is A, V, L, I, P, F, M or Y

X₃ is Y, G, N, Q, S, T, C, W, F or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T

X₂ is R, K, H, Q or A

X₃ is T, G, N, Q, S, C, W, Y, V, I or P

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A

X₅ is D, E, G or A

X₆ is V, A, L, I, P, F, M or T

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is K, R, H, Q or A

X₁₀ is D, E, G or A; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A, or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 6. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 6. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 6. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of VH CDRs of one of the antibodies in Table 6 (*e.g.*, the VH CDRs in one row of Table 6, for example, all of the VH CDRs are from the antibody 231-32-15). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH frameworks described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VH framework regions of an antibody set forth in Table 8 (*e.g.*, one, two, three or four of the framework regions in one row of Table 8).

[00137] Table 5. VL CDR Amino Acid Sequences ¹

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
231-32-15	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
Hum231#1	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
Hum231#2	KSSQSLLNSGNQKNYLT (16)	WASTRES (17)	QNDYSYPYT (18)
pab1964	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
pab1965	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1966	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1967	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
pab1968	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1969	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
pab1970	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
pab1971	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1972	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
pab1973	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1975	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1976	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1977	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1979	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab1980	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
pab1981	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
pab1983	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab2159	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
pab2160	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
pab2161	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
1	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
2	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
4	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
5	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
6	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
9	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
10	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
11	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSFPYT (109)
15	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
16	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
18	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
20	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
21	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
25	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
29	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
31	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
33	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSYPYT (106)
34	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
35	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
36	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
37	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSYPYT (106)
38	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
39	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNEYSFPYT (108)
42	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
43	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
45	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
46	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
47	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
49	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
50	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
52	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
54	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
55	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)

Antibody	VL CDR1 (SEQ ID NO:)	VL CDR2 (SEQ ID NO:)	VL CDR3 (SEQ ID NO:)
58	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
59	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
61	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
68	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
70	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
71	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSYPYT (107)
75	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
76	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSFPYT (109)
78	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
79	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
80	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
85	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
86	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
91	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNEYSFPYT (108)
92	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
94	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSYPYT (107)
95	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNDYSFPYT (109)
96	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
97	KSSQSLLNSGNQKNYLT (102)	WASTRES (105)	QNEYSFPYT (108)
101	KSSQSLLNSSNQKNYLT (103)	WASTRES (105)	QNDYSFPYT (109)
102	KSSQSLLNSSNQKNYLS (104)	WASTRES (105)	QNDYSYPYT (107)
105	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)
107	KSSQSLLNSGNQKNYLS (101)	WASTRES (105)	QNDYSYPYT (107)

¹The VL CDRs in Table 5 are determined according to Kabat.

[00138] Table 6. VH CDR Amino Acid Sequences ²

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
231-32-15	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
Hum231#1	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
Hum231#2	DYAMY (13)	VIRTYSGDVTYNQKFKD (14)	SGTVRGFAY (15)
pab1964	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
pab1965	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
pab1966	GYAMY (19)	VIKTYSGGVTYNQKFRG (26)	SGTVRGFAY (34)
pab1967	GYAMH (20)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
pab1968	DYAMY (21)	VIRTFSGDLTYNQKFQD (28)	SGTVRGFAY (34)
pab1969	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1970	DYAMY (21)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
pab1971	DYAMY (21)	VIRTYSGDVSYNQKFRG (177)	SGTVRGFAY (34)
pab1972	EYAMY (23)	LIRTYSGGVSYNQKFRD (31)	SGTVRGFAY (34)
pab1973	GYAMY (19)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
pab1975	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1976	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1977	EYAMH (22)	LIRTYSGGVSYNQKFQG (29)	SGTVRGFAY (34)
pab1979	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1980	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1981	EYAMH (22)	VIRTYSGGVSYNQKFQE (33)	SGTVRGFAY (34)
pab1983	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
pab2159	GYAMY (19)	LIRTYSGEVSYNQKFRG (144)	SGTVRGFAY (34)
pab2160	GYVMH (119)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
pab2161	EYAMH (22)	LIQTYSGDVSYNQKFRG (121)	SGTVRGFAY (34)
1	EYAMY (23)	VIRTYSGGVTYNQKFQG (187)	SGTVRGFAY (34)
2	EYAMH (22)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
4	EYAMY (23)	LIRTFSGDVSYNQKFQD (124)	SGTVRGFAY (34)
5	EYAMH (22)	LIRTYSGGVTYNQKFRG (151)	SGTVRGFAY (34)
6	EYAMY (23)	LIRTFSGGVSYNQKFKG (135)	SGTVRGFAY (34)
9	GYAMY (19)	LIRTYSGEVSYNQKFRG (144)	SGTVRGFAY (34)
10	EYAMY (23)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
11	DYAMH (117)	LIRTYSGGVSYNQKFRG (148)	SGTVRGFAY (34)
15	DYAMY (21)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
16	GYAMY (19)	LIRTFSGGVTYNQKFRE (140)	SGTVRGFAY (34)
18	GYAMY (19)	LIRTFSGEVTYNQKFRG (130)	SGTVRGFAY (34)
20	DYAMY (21)	VIRTFSGDLSYNQKFRG (114)	SGTVRGFAY (34)
21	GYVMH (119)	VIRTFSGDVSYNQKFRE (162)	SGTVRGFAY (34)
25	EYAMY (23)	LIRTFSGGVSYNQKFRG (138)	SGTVRGFAY (34)
29	DYAMY (21)	VIRTFSGGVTYNQKFKG (172)	SGTVRGFAY (34)
31	EYAMY (23)	LIRTFSGGLTYNQKFKD (133)	SGTVRGFAY (34)
33	GYAMY (19)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
34	DYAMY (21)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
35	GYAMY (19)	VIRTFSGDVTYNQKFRG (25)	SGTVRGFAY (34)
36	DYAMY (21)	VIRTFSGGVSYNQKFRD (168)	SGTVRGFAY (34)
37	EYAMY (23)	LIRTFSGEVTYNQKFKD (129)	SGTVRGFAY (34)
38	GYAMY (19)	VIKTYSGGVTYNQKFRG (26)	SGTVRGFAY (34)
39	GYAMH (20)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
42	DYAMY (21)	VIRTFSGDLTYNQKFQD (28)	SGTVRGFAY (34)
43	EYAMY (23)	LIRTFSGDVSYNQKFKG (123)	SGTVRGFAY (34)
45	EYAMY (23)	LIRTYSGGVSYNQKFQG (147)	SGTVRGFAY (34)
46	EYAMY (23)	LIRTFSGDLSYNQKFRG (122)	SGTVRGFAY (34)
47	DYAMY (21)	VIRTYSGGVTYNQKFRD (188)	SGTVRGFAD (189)
49	GYAMY (19)	VIRTYSGDVTYNQKFRE (179)	SGTVRGFAY (34)
50	DYAMY (21)	LIRTFSGGVSYNQKFKE (134)	SGTVRGFAY (34)
52	DYAMY (21)	LIRTYSGGVSYNQKFRE (27)	SGTVRGFAY (34)
54	EYAMH (22)	LIRTYSGGVSYNQKFQG (147)	SGTVRGFAY (34)
55	DYAMY (21)	LIRTYSGGVTYNQKFQG (24)	SGTVRGFAY (34)
58	DYAMY (21)	VIRTYSGGVTYNQKFKG (186)	SGTVRGFAY (34)
59	EYAMY (23)	LIRTYSGGVSYNQKFRD (31)	SGTVRGFAY (34)
61	EYAMH (22)	LIRTYSGGVSYNQKFQE (115)	SGTVRGFAY (34)
68	GYAMY (19)	LIRTYSGGVTYNQKFRG (151)	SGTVRGFAY (34)
70	GYAMY (19)	VIRTYSGDVTYNQKFKD (178)	SGTVRGFAY (34)
71	GYAMY (19)	VIRTFSGGVTYNQKFRG (32)	SGTVRGFAY (34)
75	GYAMY (19)	VIRTYSGGVTYNQKFQG (187)	SGTVRGFAY (34)
76	DYAMH (117)	LIRTFSGDVSYNQKFRE (125)	SGTVRGFAY (34)
78	DYAMY (21)	VIKTYSGGVTYNQKFRD (155)	SGTVRGFAY (34)
79	EYAMH (22)	LIRTYSGGVTYNQKFRE (150)	SGTVRGFAY (34)
80	EYAMH (22)	LIRTFSGDVSYNQKFRG (126)	SGTVRGFAY (34)
85	EYAMY (23)	VIRTYSGGVTYNQKFKD (185)	SGTVRGFAY (34)
86	EYAMY (23)	VIRTYSGGVTYNQKFRD (188)	SGTVRGFAY (34)
91	EYAMH (22)	LIRTYSGGVSYNQKFQE (115)	SGTVRGFAY (34)
92	EYAMY (23)	LIRTFSGGVTYNQKFQG (139)	SGTVRGFAY (34)

Antibody	VH CDR1 (SEQ ID NO:)	VH CDR2 (SEQ ID NO:)	VH CDR3 (SEQ ID NO:)
94	GYAMY (19)	VIRTFSGGVVTYNQKFRD (173)	SGTVRGEFAY (34)
95	DYAMY (21)	LIRTYSGGVSYNQKFRG (148)	SGTVRGEFAY (34)
96	EYAMY (23)	VIRTYSGGLTYNQKFRD (184)	SGTVRGEFAY (34)
97	EYAMH (22)	LIRTFSGGLSYNQKFRD (131)	SGTVRGEFAY (34)
101	DYAMH (117)	LIRTFSGGVSYNQKFQD (136)	SGTVRGEFAY (34)
102	GYAMY (19)	VIRTYSGGVSYNQKFRD (194)	SGTVRGEFAY (34)
105	EYAMY (23)	LIRTFSGGVSYNQKFKG (135)	SGTVRGEFAY (34)
107	GYAMY (19)	VIRTYSGDVSYNQKFRD (176)	SGTVRGEFAY (34)

²The VH CDRs in Table 6 were determined according to Kabat.

[00139] Table 7. VL FR Amino Acid Sequences ³

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
231-32-15	DIVMTQSPSSLTVTAG EKVIMSC (616)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDLAVYHC (637)	FGGGTKLEIK (641)
Hum231 #1	DIVMTQSPPTLSLSPG ERVTLSC (615)	WYQQKPGQAPR LLIY (622)	GIPARFSGSGSGTDFTLTISS LQPEDFAVYHC (626)	FGQGTKLEIK (643)
Hum231 #2	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
pab1964	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1965	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
pab1966	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1967	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
pab1968	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1969	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
pab1970	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1971	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)
pab1972	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab1973	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSDTDFTLTISS VQAEDVAVYHC (627)	FGQGTKLEIK (643)
pab1975	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1976	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1977	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
pab1979	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1980	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab1981	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)
pab1983	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
pab2159	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
pab2160	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
pab2161	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
1	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
2	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYYC (633)	FGQGTKLEIK (643)
4	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
5	DIVMTQSPDSLAAPE RATINC (610)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
6	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
9	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
10	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
11	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
15	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
16	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
18	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
20	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLLY (624)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (620)	FGQGTKLEIK (643)
21	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
25	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
29	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
31	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
33	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
34	DIVMTQSTDSLAVSLG ERATINC (617)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
35	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
36	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFSGSGSGTDFTLTISS VQEEDVAVYHC (634)	FGQGTKLEIK (643)
37	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
38	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
39	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
42	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
43	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
45	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
46	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYHC (636)	FGQGTKLEIK (643)
47	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
49	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
50	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
52	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
54	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
55	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
58	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
59	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
61	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYYC (633)	FGQGTKLEIK (643)
68	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)

Antibody	VL FR1 (SEQ ID NO:)	VL FR2 (SEQ ID NO:)	VL FR3 (SEQ ID NO:)	VL FR4 (SEQ ID NO:)
70	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
71	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
75	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)
76	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
78	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
79	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYYC (631)	FGQGTKLEIK (643)
80	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS LQAEDVAVYYC (642)	FGQGTKLEIK (643)
85	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYYC (633)	FGQGTKLEIK (643)
86	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYYC (633)	FGQGTKLEIK (643)
91	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
92	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK MLIY (619)	GVPDRFSGSGSGTNFTLTISS VQAEDVAVYHC (635)	FGQGTKLEIK (643)
94	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
95	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK MLIY (624)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
96	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS LQAEDVAVYHC (630)	FGQGTKLEIK (643)
97	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYHC (638)	FGQGTKLEIK (643)
101	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYHC (632)	FGQGTKLEIK (643)
102	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)
105	DIVMTQSPDSLAVSLG ERATINC (611)	WYQQKPGQPPK LLIY (623)	GVPDRFSGSGSGTDFTLTISS VQAEDVAVYYC (633)	FGQGTKLEIK (643)
107	DIVMTQSPDSLAVSLG ERATINC (611)	WYHQKPGQPPK LLIY (618)	GVPDRFTGSGSGTDFTLTISS VQAEDVAVYYC (639)	FGQGTKLEIK (643)

³The VL framework regions described in Table 7 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VL CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00140] Table 8. VH FR Amino Acid Sequences ⁴

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
231-32-15	QVQLQLQSGTELVVRPGVSVKI SCKGSGYTFT (645)	WVKQSHAKSLEWI G (652)	KATMTVDKSSSIAYMELARLS SEDSAIYYCAK (658)	WGQGTLLVTVSS (668)
Hum231#1	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)
Hum231#2	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)
pab1964	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEMI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1965	QVQLVQSGAEAKKPGASVKV SCKGSGYTFT (646)	WVRQAPGQGMEMI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1966	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTLLVTVSS (668)
pab1967	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLITVSS (667)
pab1968	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1969	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
pab1970	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1971	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMEMI G (656)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1972	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTLLVTVSS (668)
pab1973	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEMI G (656)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
pab1975	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
pab1976	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
pab1977	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
pab1979	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1980	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1981	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab1983	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEMI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab2159	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
pab2160	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
pab2161	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
1	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
2	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEWI G (655)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)
4	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQSLEWM G (657)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTLLVTVSS (668)
5	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
6	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
9	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)
10	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTLLVTVSS (668)
11	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
15	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTLLVTVSS (668)
16	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTLLVTVSS (668)
18	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
20	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
21	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
25	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
29	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTLLVTVSS (668)
31	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGIPVTVSS (664)
33	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
34	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)
35	QVQLVQSGAEAKKPGASVKV SCKGSGYTFT (646)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTLLVTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
36	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGMEWI G (655)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
37	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMEWI G (655)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
38	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
39	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILITVSS (667)
42	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
43	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGMEWI G (655)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTILVTVSS (668)
45	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTFFVTVSS (665)
46	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
47	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEWM G (656)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
49	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
50	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
52	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
54	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
55	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
58	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTILVTVSS (668)
59	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
61	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
68	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
70	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGMEWI G (655)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
71	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGMEWM G (656)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
75	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)

Antibody	VH FR1 (SEQ ID NO:)	VH FR2 (SEQ ID NO:)	VH FR3 (SEQ ID NO:)	VH FR4 (SEQ ID NO:)
76	QVQLVQSGAGVKKPGASVKV SCKGSGYTFT (644)	WVRQAPGQGLEWM G (654)	RATMTVDKSISTAYMELSRLR SDDTAVYYCAK (659)	WGQGTILVTVSS (668)
78	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWI G (653)	RATMTVDTSISTAYMELSRLR GDDTAVYYCAK (661)	WGRGTLVTVSS (669)
79	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMWWM G (656)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
80	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGMWWM G (656)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
85	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
86	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGMWWM G (656)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
91	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMWWM G (656)	RATMTVDTSISTAYMELSRLR SDDTAVYYCAK (670)	WGQGTILVTVSS (668)
92	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RATMTVDTSISTAYMELSRLQ SDDTAVYYCAK (660)	WGQGTILVTVSS (668)
94	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGLEWI G (653)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTFTVTVSS (666)
95	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTFTVTVSS (666)
96	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGMWWM G (656)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
97	QVQLVQSGTEVKKPGASVKV SCKGSGYTFT (651)	WVRQAPGQGMWMI G (655)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
101	QVQLVQSGAEVKKPGASVKV SCKASGYTFT (648)	WVRQAPGQGLEWM G (654)	RVTMTVDKSISTAYMELSRLR SDDTAVYYCAK (662)	WGQGTILVTVSS (668)
102	QVQLVQSGTEVKKPGASVKV SCKASGYTFT (650)	WVRQAPGQGLEWI G (653)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
105	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)
107	QVQLVQSGAEVKKPGASVKV SCKGSGYTFT (649)	WVRQAPGQGLEWM G (654)	RVTMTVDTSISTAYMELSRLR SDDTAVYYCAK (663)	WGQGTILVTVSS (668)

⁴ The VH framework regions described in Table 8 are determined based upon the boundaries of the Kabat numbering system for CDRs. In other words, the VH CDRs are determined by Kabat and the framework regions are the amino acid residues surrounding the CDRs in the variable region in the format FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[00141] In another embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence

KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YX₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M

X₂ is L, A, V, I, P, F, M or S

X₃ is N, G, Q, S, T, C, W, Y or A

X₄ is S, G, N, Q, T, C, W, Y or A

X₅ is G, N, Q, S, T, C, W, Y or A

X₆ is N, G, Q, S, T, C, W, Y or A

X₇ is Q, G, N, S, T, C, W, Y or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is T, G, N, Q, S, C, W, Y, V, I or A; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence

X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A

X₂ is E, D or A

X₃ is S, G, N, Q, T, C, W, Y or A; and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence

QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y

X₂ is D, E or Y

X₃ is S, G, N, Q, T, C, W, Y or A

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A; and/or

(d) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence

X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A

X₂ is A, V, L, I, P, F, M or Y

X₃ is Y, G, N, Q, S, T, C, W, F or H; and/or

(e) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence

X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T

X₂ is R, K, H, Q or A

X₃ is T, G, N, Q, S, C, W, Y, V, I or P

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A

X₅ is D, E, G or A

X₆ is V, A, L, I, P, F, M or T

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is K, R, H, Q or A

X₁₀ is D, E, G or A; and/or

(f) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A, or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three, four, five or all six of the CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row of Table 2, for example, all of the VH CDRs are from the antibody 231-32-15). In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL CDRs in one row of Table 1, for example, all of the VLCDRs are from the antibody 231-32-15).

[00142] In another embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

(i) the VL comprises:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSX₁X₂X₃X₄X₅X₆X₇KX₈YLY₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M

X₂ is L, A, V, I, P, F, M or S

X₃ is N, G, Q, S, T, C, W, Y or A

X₄ is S, G, N, Q, T, C, W, Y or A

X₅ is G, N, Q, S, T, C, W, Y or A

X₆ is N, G, Q, S, T, C, W, Y or A

X₇ is Q, G, N, S, T, C, W, Y or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is T, G, N, Q, S, C, W, Y, V, I or A; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A

X₂ is E, D or A

X₃ is S, G, N, Q, T, C, W, Y or A; and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y

X₂ is D, E or Y

X₃ is S, G, N, Q, T, C, W, Y or A

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A; and

(ii) the VH comprises:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A

X₂ is A, V, L, I, P, F, M or Y

X₃ is Y, G, N, Q, S, T, C, W, F or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T

X₂ is R, K, H, Q or A

X₃ is T, G, N, Q, S, C, W, Y, V, I or P

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A

X₅ is D, E, G or A

X₆ is V, A, L, I, P, F, M or T

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is K, R, H, Q or A

X₁₀ is D, E, G or A; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A, or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

In specific embodiments, the VL comprises two or all three of the VL CDRs above and/or the VH comprises two or all three of the VH CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row of Table 2). In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL CDRs in one row in Table 1).

[00143] In another embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) comprising:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S

X₂ is T or S; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WASTRES (SEQ ID NO: 11); and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E

X₂ is Y, F or S.

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, or all three of the VL CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL CDRs in one row of Table 1). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions (FRs) of an antibody set forth in Table 3 (*e.g.*, one, two, three, or four of the framework regions in one row of Table 3).

[00144] In another embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain variable region (VH) comprising:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence $X_1YX_2MX_3$ (SEQ ID NO: 7), wherein

X_1 is D, E or G

X_2 is A or V

X_3 is Y or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence $X_1IX_2TX_3SGX_4X_5X_6YNQKFX_7X_8$ (SEQ ID NO: 8), wherein

X_1 is V or L

X_2 is R, K or Q

X_3 is Y or F

X_4 is D, E or G

X_5 is V or L

X_6 is T or S

X_7 is K, R or Q

X_8 is D, E or G; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGFAY (SEQ ID NO: 9).

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs above. In certain embodiments, the antibody or antigen-binding

fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row in Table 2). In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH frameworks described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises the VH framework regions of an antibody set forth in Tables 4 (*e.g.*, one, two, three or four of the framework regions in one row of Table 4).

[00145] In a particular embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S

X₂ is T or S; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WASTRES (SEQ ID NO: 11); and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E

X₂ is Y, F or S.

(d) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G

X₂ is A or V

X₃ is Y or H; and/or

(e) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L

X₂ is R, K or Q

X₃ is Y or F

X₄ is D, E or G

X₅ is V or L

X₆ is T or S

X₇ is K, R or Q

X₈ is D, E or G; and/or

(f) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence SGTVRGFAY (SEQ ID NO: 9).

In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three, four, five or all six of the CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row in Table 2). In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL CDRs in one row in Table 1).

[00146] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

(i) the VL comprises:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S

X₂ is T or S; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WASTRES (SEQ ID NO: 11); and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E

X₂ is Y, F or S; and

(ii) the VH comprises:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence

X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G

X₂ is A or V

X₃ is Y or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence

X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L

X₂ is R, K or Q

X₃ is Y or F

X₄ is D, E or G

X₅ is V or L

X₆ is T or S

X₇ is K, R or Q

X₈ is D, E or G; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence

SGTVRGFAY (SEQ ID NO: 9).

In specific embodiments, the VL comprises two or all three of the VL CDRs above and/or the VH comprises two or all three of the VH CDRs above. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR1 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR2 of one of the antibodies in Table 1. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VL CDR3 of one of the antibodies in Table 1. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR1 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR2 of one of the antibodies in Table 2. In certain embodiments, the antibody or antigen-binding fragment thereof comprises the VH CDR3 of one of the antibodies in Table 2. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VH CDRs of one of the antibodies in Table 2 (*e.g.*, the VH CDRs in one row in Table 2). In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two or all three of the VL CDRs of one of the antibodies in Table 1 (*e.g.*, the VL

CDRs in one row in Table 1).

[00147] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

(i) the VL comprises:

(a) a VL CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S

X₂ is T or S; and/or

(b) a VL CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence WASTRES (SEQ ID NO: 11); and/or

(c) a VL CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E

X₂ is Y, F, or S; and

(ii) the VH comprises:

(a) a VH CDR1 comprising, consisting of, or consisting essentially of the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G

X₂ is A or V

X₃ is Y or H; and/or

(b) a VH CDR2 comprising, consisting of, or consisting essentially of the amino acid sequence X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L

X₂ is R, K or Q

X₃ is Y or F

X₄ is D, E or G

X₅ is V or L

X₆ is T or S

X₇ is K, R or Q

X₈ is D, E or G; and/or

(c) a VH CDR3 comprising, consisting of, or consisting essentially of the amino acid sequence of SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

[00148] In certain embodiments, provided herein is an antibody or fragment thereof which specifically binds to GITR (*e.g.*, human GITR) and comprises one, two or three of the light chain variable region (VL) complementarity determining regions (CDRs) of an antibody in Table 1 (*e.g.*, the VL CDRs in one row of Table 1). In some embodiments, provided herein is an antibody or fragment thereof which specifically binds to GITR (*e.g.*, human GITR) and comprises one, two or three of the heavy chain variable region (VH) CDRs of any one of any one of antibodies in Table 2 (*e.g.*, the VH CDRs in one row of Table 2).

[00149] In certain embodiments, provided herein is an antibody or fragment thereof which specifically binds to GITR (*e.g.*, human GITR) and comprises a light chain variable region (VL) comprising one, two or all three of the VL CDRs of an antibody in Table 1 (*e.g.*, the VL CDRs in one row of Table 1). In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or all four of the VL framework regions described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or all four of the VL framework regions (FRs) set forth in Table 3 (*e.g.*, one, two, three or four of the framework regions in one row in Table 3).

[00150] In certain embodiments, provided herein is an antibody or fragment thereof which specifically binds to GITR (*e.g.*, human GITR) and comprises a heavy chain variable region (VH) comprising one, two or all three of the VH CDRs of an antibody in Table 2 (*e.g.*, the VH CDRs in one row of Table 2). In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or all four of the VH framework regions described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or all four of the VH framework regions (FRs) set forth in Table 4 (*e.g.*, one, two, three, or four of the framework regions in one row in Table 4).

[00151] In certain embodiments, provided herein is an antibody or fragment thereof which specifically binds to GITR (*e.g.*, human GITR) and comprises light chain variable region (VL) CDRs and heavy chain variable region (VH) CDRs of any one of antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, for example as set forth in Tables 1 and 2 (*e.g.*, the VH CDRs and VL CDRs in the same row are all from the same antibody as designated by the name of the antibody in the first column of Tables 1 and 2, for example, the VL CDRs and VH CDRs in the first row of Tables 1 and 2 respectively are all from

antibody 231-32-15). In some embodiments, the antibody or antigen-binding fragment thereof comprises the VL framework regions and VH frameworks described herein. In specific embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions (FRs) and VH framework regions set forth in Tables 3 and 4 (*e.g.*, the VL FRs and VH FRs are all from the same antibody).

[00152] In a particular embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GTR (*e.g.*, human GTR), comprises a light chain variable region (VL) comprising VL CDR1, VL CDR2, and VL CDR3 as set forth in Table 1, for example, VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.*, the VL CDRs are in one row of Table 1). In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, one, two, three, or four of the framework regions in one row in Table 3). In certain embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region sequence comprising one, two, three or four of the framework regions of the light chain variable region sequence of SEQ ID NO: 204 or SEQ ID NO: 205. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or four of the framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of a light chain variable region sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NOs: 400-518. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or four of the framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of the light chain variable region sequence of SEQ ID NO: 519. In certain embodiments, an antibody or antigen-binding fragment thereof comprises a light chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGKV4-1*01 (SEQ ID NO: 607) and IGKV3-7*02 (SEQ ID NO: 608). In specific embodiments, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the light chain variable framework region that is derived from said amino acid sequence consists of said

amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human light chain variable framework region. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain variable framework region that is derived from amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608, wherein at least one amino acid in amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608 is substituted with an amino acid in an analogous position in a corresponding non-human light chain variable framework region. In a specific embodiment, the amino acid substitution is at amino acid position 87, wherein the amino acid position is indicated according to the Kabat numbering. In particular embodiments, the amino acid substitution is 87H, wherein the amino acid position is indicated according to the Kabat numbering.

[00153] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of Hum231#1, for example, the VL CDR1, VL CDR2, and VL CDR3 of Hum231#1 as set forth in Table 1 (SEQ ID NOS: 16, 17, and 18, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of Hum231#1).

[00154] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of Hum231#2, for example, the VL CDR1, VL CDR2, and VL CDR3 of Hum231#2 as set forth in Table 1 (SEQ ID NOS: 16, 17, and 18, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of Hum231#2).

[00155] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1964, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1964 as set forth in Table 1 (SEQ ID NOS: 101, 105, and 106, respectively). In certain embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1964).

[00156] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of A pab1965, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1965 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1965).

[00157] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1966, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1966 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1966).

[00158] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1967, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1967 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 108, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the

antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1967).

[00159] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1968, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1968 as set forth in Table 1 (SEQ ID NOS: 101, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1968).

[00160] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1969, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1969 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 109, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1969).

[00161] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1970, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1970 as set forth in Table 1 (SEQ ID NOS: 101, 105, and 109, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1970).

[00162] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL

CDR3 of pab1971, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1971 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1971).

[00163] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1972, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1972 as set forth in Table 1 (SEQ ID NOS: 104, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1972).

[00164] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1973, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1973 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1973).

[00165] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1975, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1975 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1975).

[00166] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1976, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1976 as set forth in Table 1 (SEQ ID NOS: 101, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1976).

[00167] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1977, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1977 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1977).

[00168] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1979, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1979 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1979).

[00169] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1980, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1980 as set forth in Table 1 (SEQ ID NOS: 101, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1980).

[00170] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1981, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1981 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1981).

[00171] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab1983, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab1983 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (*e.g.*, the framework regions of pab1983).

[00172] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab2159, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab2159 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 109, respectively). In certain embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (e.g., the framework regions of pab2159). In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (e.g., human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab2160, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab2160 as set forth in Table 1 (SEQ ID NOS: 102, 105, and 107, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (e.g., the framework regions of pab2160).

[00173] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (e.g., human GITR), comprises the VL CDR1, VL CDR2, and VL CDR3 of pab2161, for example, the VL CDR1, VL CDR2, and VL CDR3 of pab2161 as set forth in Table 1 (SEQ ID NOS: 103, 105, and 109, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions of an antibody set forth in Table 3 (e.g., the framework regions of pab2161).

[00174] In a particular embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (e.g., human GITR), comprises a heavy chain variable region (VH) comprising VH CDR1, VH CDR2, and VH CDR3 as set forth in Table 2, for example, VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (e.g., the VH CDRs in one row in Table 2). In some embodiments, the antibody or antigen-binding fragment thereof

comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, one, two, three, or four of the framework regions in one row in Table 4). In certain embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three or all four of the framework regions of the heavy chain variable region sequence of SEQ ID NO: 203. In some embodiments, the antibody or antigen-binding fragment thereof comprises one, two, three, or four of the framework regions of a heavy chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95% or 100% identical to one, two, three or four of the framework regions of a heavy chain variable region sequence selected from the group consisting of SEQ ID NO: 201, SEQ ID NO: 206, and SEQ ID NOS: 215 to 389. In certain embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGHV1-2*02 (SEQ ID NO: 601), IGHV1-3*01 (SEQ ID NO: 602), IGHV1-46*01 (SEQ ID NO: 603), IGHV1-18*01 (SEQ ID NO: 604), IGHV1-69*01 (SEQ ID NO: 605), and IGHV7-4-1*02 (SEQ ID NO: 606). In specific embodiments, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human heavy chain variable framework region. In specific embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable framework region that is derived from amino acid sequence SEQ ID NO: 601, wherein at least one amino acid of amino acid sequence SEQ ID NO: 601 is substituted with an amino acid in an analogous position in a corresponding non-human heavy chain variable framework region. In certain embodiments, the amino acid substitution is at an amino acid position selected from the group consisting of 24, 48, 67, 71, 73, and 94, wherein the amino acid position of each group member is indicated according to the Kabat numbering. In specific embodiments, the amino acid substitution selected from the group consisting of 24G, 48I, 67A, 71V, 73K, and 94K, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

[00175] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of Hum231#1, for example, the VH CDR1, VH CDR2, and VH CDR3 of Hum231#1 as set forth in Table 2 (SEQ ID NOS: 13, 14, and 15, respectively). In certain embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of Hum231#1).

[00176] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of Hum231#2, for example, the VH CDR1, VH CDR2, and VH CDR3 of Hum231#2 as set forth in Table 2 (SEQ ID NOS: 13, 14, and 15, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of Hum231#2).

[00177] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1964, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1964 as set forth in Table 2 (SEQ ID NOS: 19, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1964).

[00178] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1965, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1965 as set forth in Table 2 (SEQ ID NOS: 19, 25, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1965).

[00179] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1966, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1966 as set forth in Table 2 (SEQ ID NOS: 19, 26, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1966).

[00180] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1967, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1967 as set forth in Table 2 (SEQ ID NOS: 20, 27, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1967).

[00181] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1968, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1968 as set forth in Table 2 (SEQ ID NOS: 21, 28, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1968).

[00182] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1969, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1969 as set forth in Table 2 (SEQ ID NOS: 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1969).

[00183] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1970, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1970 as set forth in Table 2 (SEQ ID NOS: 21, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1970).

[00184] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1971, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1971 as set forth in Table 2 (SEQ ID NOS: 21, 177, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1971).

[00185] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1972, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1972 as set forth in Table 2 (SEQ ID NOS: 23, 31, and 34, respectively). In certain embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1972).

[00186] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1973, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1973 as set forth in Table 2 (SEQ ID NOS: 19, 32, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1973).

[00187] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1975, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1975 as set forth in Table 2 (SEQ ID NOS: 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1975).

[00188] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1976, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1976 as set forth in Table 2 (SEQ ID NOS: 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1976).

[00189] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1977, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1977 as set forth in Table 2 (SEQ ID NOS: 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1977).

[00190] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1979, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1979 as set forth in Table 2 (SEQ ID NOS: 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1979).

[00191] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1980, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1980 as set forth in Table 2 (SEQ ID NOS: 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1980).

[00192] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH

CDR3 of pab1981, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1981 as set forth in Table 2 (SEQ ID NOS: 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1981).

[00193] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab1983, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab1983 as set forth in Table 2 (SEQ ID NOS: 19, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7).

In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab1983).

[00194] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab2159, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab2159 as set forth in Table 2 (SEQ ID NOS: 19, 144, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab2159).

[00195] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab2160, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab2160 as set forth in Table 2 (SEQ ID NOS: 119, 162, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the

antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab2160).

[00196] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VH CDR1, VH CDR2, and VH CDR3 of pab2161, for example, the VH CDR1, VH CDR2, and VH CDR3 of pab2161 as set forth in Table 2 (SEQ ID NOS: 22, 121, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In specific embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VH framework regions derived from a human heavy chain variable subfamily (*e.g.*, one of subfamilies 1 to 7). In some embodiments, the antibody or antigen-binding fragment thereof comprises VH framework regions of an antibody set forth in Table 4 (*e.g.*, the framework regions of pab2161).

[00197] In a particular embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises (i) a heavy chain variable region (VH) comprising VH CDR1, VH CDR2, and VH CDR3 as set forth in Table 2, for example, VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.* the VH CDRs in one row in Table 2), and (ii) a light chain variable region (VL) comprising VL CDR1, VL CDR2, and VL CDR3 as set forth in Table 1, for example, VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.*, the VL CDRs in one row in Table 1). In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of a single antibody as designated by its name, for example, all of the FRs are from Hum231#1 or Hum231#2).

[00198] In some embodiments, the antibody or antigen-binding fragment thereof described herein comprises one, two, three or four framework regions of a heavy chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95% or 100% identical to one, two, three or

four of the framework regions of a heavy chain variable region sequence selected from the group consisting of SEQ ID NO: 201, SEQ ID NO: 206, and SEQ ID NOS: 215 to 389. In certain embodiments, the antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGHV1-2*02 (SEQ ID NO: 601), IGHV1-3*01 (SEQ ID NO: 602), IGHV1-46*01 (SEQ ID NO: 603), IGHV1-18*01 (SEQ ID NO: 604), IGHV1-69*01 (SEQ ID NO: 605), and IGHV7-4-1*02 (SEQ ID NO: 606). In specific embodiments, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the heavy chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human heavy chain variable framework region. In specific embodiments, the antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable framework region that is derived from amino acid sequence SEQ ID NO: 601, wherein at least one amino acid in amino acid sequence SEQ ID NO: 601 is substituted with an amino acid in an analogous position in a corresponding non-human light chain variable framework region. In certain embodiments, the amino acid substitution is at an amino acid position selected from the group consisting of 24, 48, 67, 71, 73, and 94, wherein the amino acid position of each group member is indicated according to the Kabat numbering. In specific embodiments, the amino acid substitution is selected from the group consisting of 24G, 48I, 67A, 71V, 73K, and 94K, wherein the amino acid position of each group member is indicated according to the Kabat numbering.

[00199] In some embodiments, the antibody or antigen-binding fragment thereof described herein comprises VL framework regions of an antibody set forth in Table 3. In certain embodiments, the antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising one, two, three or four of the framework regions of the light chain variable region sequence of SEQ ID NO: 204 or SEQ ID NO: 205. In some embodiments, the antibody or antigen-binding fragment thereof described herein comprises one, two, three or four framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of a light chain variable region sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NOS: 400-518. In some

embodiments, the antibody or antigen-binding fragment thereof described herein comprises one, two, three or four framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of the light chain variable region sequence of SEQ ID NO: 519. In certain embodiments, an antibody or antigen-binding fragment thereof described herein comprises a light chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein the amino acid sequence is selected from the group consisting of IGKV4-1*01 (SEQ ID NO: 607) and IGKV3-7*02 (SEQ ID NO: 608). In specific embodiments, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In a particular embodiment, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human light chain variable framework region. In some embodiments, an antibody or antigen-binding fragment thereof described herein comprises a light chain variable framework region that is derived from amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608, wherein at least one amino acid of amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608 with an amino acid in an analogous position in a corresponding non-human light chain variable framework region. In a specific embodiment, the amino acid substitution is at amino acid position 87, wherein the amino acid position is indicated according to the Kabat numbering. In particular embodiments, the amino acid substitution is 87H, wherein the amino acid position is indicated according to the Kabat numbering.

[00200] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of Hum231#1, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of Hum231#1 as set forth in Tables 1 and 2 (SEQ ID NOS: 16, 17, 18, 13, 14, and 15, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VH of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of Hum231#1).

[00201] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of Hum231#2, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of Hum231#2 as set forth in Tables 1 and 2 (SEQ ID NOS: 16, 17, 18, 13, 14, and 15, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the frameworks of a single antibody as designated by its name, for example, the framework regions of Hum231#1 or Hum231#2).

[00202] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1964, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1964 as set forth in Tables 1 and 2 (SEQ ID NOS: 101, 105, 106, 19, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1964).

[00203] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1965, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1965 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 19, 25, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1965).

[00204] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1966, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1966 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 19, 26, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1966).

[00205] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1967, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1967 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 108, 20, 27, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1967).

[00206] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1968, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1968 as set forth in Tables 1 and 2 (SEQ ID NOS: 101, 105, 107, 21, 28, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1968).

[00207] In a particular embodiment, an antibody or fragment thereof described herein, which

specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1969, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1969 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 109, 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1969).

[00208] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1970, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1970 as set forth in Tables 1 and 2 (SEQ ID NOS: 101, 105, 109, 21, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1970).

[00209] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1971, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1971 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 107, 21, 177, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1971).

[00210] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3,

VH CDR1, VH CDR2, and VH CDR3 of pab1972, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1972 as set forth in Tables 1 and 2 (SEQ ID NOS: 104, 105, 107, 23, 31, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1972).

[00211] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1973, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1973 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 107, 19, 32, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1973).

[00212] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1975, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1975 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1975).

[00213] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1976, for example, the VL CDR1, VL CDR2, VL

CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1976 as set forth in Tables 1 and 2 (SEQ ID NOS: 101, 105, 107, 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1976).

[00214] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1977, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1977 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 107, 22, 29, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1977).

[00215] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1979, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1979 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1979).

[00216] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1980, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1980 as set forth in Tables 1 and 2 (SEQ ID

NOS: 101, 105, 107, 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1980).

[00217] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1981, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1981 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 107, 22, 33, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1981).

[00218] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1983, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab1983 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 19, 24, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab1983).

[00219] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2159, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2159 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 109, 19, 144, and 34, respectively). In certain embodiments, the antibody or

antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab2159).

[00220] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2160, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2160 as set forth in Tables 1 and 2 (SEQ ID NOS: 102, 105, 107, 119, 162, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab2160).

[00221] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2161, for example, the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of pab2161 as set forth in Tables 1 and 2 (SEQ ID NOS: 103, 105, 109, 22, 121, and 34, respectively). In certain embodiments, the antibody or antigen-binding fragment further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody and one, two, three or all four VH framework regions derived from the VH of a human or primate antibody. In some embodiments, the antibody or antigen-binding fragment thereof comprises VL framework regions and VH framework regions of an antibody set forth in Tables 3 and 4, respectively (*e.g.*, the framework regions of pab2161).

[00222] In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising the amino acid sequence of a VL domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VL domain in one row of Figure 23 or any one of Figures 24A-24C). In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising the amino acid sequence of a VL domain of an antibody listed in Table 17 (*e.g.*, the

VL domain in one row of Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 207 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 208 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 435 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 437 (*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 441 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 444 (*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 458 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 459 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 463 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 519 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 444 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID

NO: 444 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 408 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 423 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 486 (*e.g.*, antibody pab2161).

[00223] In some embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of the amino acid sequence of a VL domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VL domain in one row of Figure 23 or any one of Figures 24A-24C). In some embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of the amino acid sequence of a VL domain of an antibody listed in Table 17 (*e.g.*, the VL domain in one row of Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 207 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 208 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 435 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 437 (*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 440 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 441 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 444

(*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 458 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 459 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 453 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 463 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 519 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 440 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 444 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 453 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 440 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 444 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 453 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 440 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 408 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain consisting of or consisting essentially of SEQ ID NO: 423 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a

VL domain consisting of or consisting essentially of SEQ ID NO: 486 (*e.g.*, antibody pab2161).

[00224] In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising the amino acid sequence of a VH domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VH domain in one row in Figure 23 or any one of Figures 24A-24C). In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising the amino acid sequence of a VH domain of an antibody listed in Table 17 (*e.g.*, the VH domain in one row in Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 206 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 206 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 249 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 251 (*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 254 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 255 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 259 (*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 277 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 280 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 284 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 304 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof

that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 249 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 224 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 237 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain comprising SEQ ID NO: 315 (*e.g.*, antibody pab2161).

[00225] In some embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of the amino acid sequence of a VH domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VH domain in one row in Figure 23 or any one of Figures 24A-24C). In some embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of the amino acid sequence of a VH domain of an antibody listed in Table 17 (*e.g.*, the VH domain in one row in Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 206 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 206 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 249 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 251

(*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 254 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 255 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 259 (*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 277 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 280 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 284 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 304 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*,

human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 249 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 224 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 237 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain consisting of or consisting essentially of SEQ ID NO: 315 (*e.g.*, antibody pab2161).

[00226] In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain and a VL domain, wherein the VH domain and the VL domain comprise the amino acid sequence of a VH domain and a VL domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VH domain and VL domain in one row of Figure 23 or any one of Figures 24A-24C). In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain and a VL domain, wherein the VH domain and the VL domain comprise the amino acid sequence of a VH domain and a VL domain of an antibody listed in Table 17 (*e.g.*, the VH domain and VL domain in one row of Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 207 and a VH domain comprising SEQ ID NO: 206 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 208 and a VH domain comprising SEQ ID NO: 206 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 435 and a VH domain comprising SEQ ID NO: 249 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 437 and a VH domain comprising SEQ ID NO: 251 (*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 and a VH domain comprising SEQ ID NO: 254 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 441 and a VH domain comprising SEQ ID NO: 255 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO:

444 and a VH domain comprising SEQ ID NO: 259 (*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 458 and a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 459 and a VH domain comprising SEQ ID NO: 277 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 and a VH domain comprising SEQ ID NO: 280 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 463 and a VH domain comprising SEQ ID NO: 284 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 519 and a VH domain comprising SEQ ID NO: 304 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 and a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 444 and a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 and a VH domain comprising SEQ ID NO: 276 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 and a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 444 and a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 453 and a VH domain comprising SEQ ID NO: 345 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 440 and a VH domain comprising SEQ ID NO: 249 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 408 and a VH domain comprising SEQ ID NO: 224 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that

specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 423 and a VH domain comprising SEQ ID NO: 237 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain comprising SEQ ID NO: 486 and a VH domain comprising SEQ ID NO: 315 (*e.g.*, antibody pab2161).

[00227] In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain and a VL domain, wherein the VH domain and the VL domain consist of or consist essentially of the amino acid sequence of a VH domain and a VL domain of an antibody listed in Figure 23 or any one of Figures 24A-24C (*e.g.*, the VH domain and VL domain in one row of Figure 23 or any one of Figures 24A-24C). In certain embodiments, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VH domain and a VL domain, wherein the VH domain and the VL domain consist of or consist essentially of the amino acid sequence of a VH domain and a VL domain of an antibody listed in Table 17 (*e.g.*, the VH domain and VL domain in one row of Table 17). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 207 and the VH domain consisting of or consisting essentially of SEQ ID NO: 206 (*e.g.*, antibody Hum231#1). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 208 and the VH domain consists of or consists essentially of SEQ ID NO: 206 (*e.g.*, antibody Hum231#2). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 435 and the VH domain consists of or consists essentially of SEQ ID NO: 249 (*e.g.*, antibody pab1964). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 437 and the VH domain consists of or consists essentially of SEQ ID NO: 251 (*e.g.*, antibody pab1965). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 440 and the VH domain consists of or consists essentially of SEQ ID NO: 254 (*e.g.*, antibody pab1966). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or

consists essentially of SEQ ID NO: 441 and the VH domain consists of or consists essentially of SEQ ID NO: 255 (*e.g.*, antibody pab1967). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 444 and the VH domain consists of or consists essentially of SEQ ID NO: 259 (*e.g.*, antibody pab1968). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 458 and the VH domain consists of or consists essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1969). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 459 and the VH domain consists of or consists essentially of SEQ ID NO: 277 (*e.g.*, antibody pab1970). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 453 and the VH domain consists of or consists essentially of SEQ ID NO: 280 (*e.g.*, antibody pab1971). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 463 and the VH domain consists of or consists essentially of SEQ ID NO: 284 (*e.g.*, antibody pab1972). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 519 and the VH domain consists of or consists essentially of SEQ ID NO: 304 (*e.g.*, antibody pab1973). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 440 and the VH domain consists of or consists essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1975). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 444 and the VH domain consists of or consists essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1976). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 453 and the VH domain consists of or consists essentially of SEQ ID NO: 276 (*e.g.*, antibody pab1977). In a specific embodiment, an antibody or fragment thereof that specifically binds to GITR (*e.g.*,

human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 440 and the VH domain consists of or consists essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1979). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 444 and the VH domain consists of or consists essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1980). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 453 and the VH domain consists of or consists essentially of SEQ ID NO: 345 (*e.g.*, antibody pab1981). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 440 and the VH domain consists of or consists essentially of SEQ ID NO: 249 (*e.g.*, antibody pab1983). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 408 and the VH domain consists of or consists essentially of SEQ ID NO: 224 (*e.g.*, antibody pab2159). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 423 and the VH domain consists of or consists essentially of SEQ ID NO: 237 (*e.g.*, antibody pab2160). In a specific embodiment, an antibody or fragment thereof that specifically binds to GTR (*e.g.*, human GTR) comprises a VL domain and a VH domain, wherein the VL domain consists of or consists essentially of SEQ ID NO: 486 and the VH domain consists of or consists essentially of SEQ ID NO: 315 (*e.g.*, antibody pab2161).

[00228] In certain aspects, an antibody described herein may be described by its VL domain alone, or its VH domain alone, or by its 3 VL CDRs alone, or its 3 VH CDRs alone. *See*, for example, Rader C *et al.*, (1998) PNAS 95: 8910-8915, which is incorporated herein by reference in its entirety, describing the humanization of the mouse anti- $\alpha v \beta 3$ antibody by identifying a complementing light chain or heavy chain, respectively, from a human light chain or heavy chain library, resulting in humanized antibody variants having affinities as high or higher than the affinity of the original antibody. *See also*, Clackson T *et al.*, (1991) Nature 352: 624-628, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VL domain (or VH domain) and screening a library for the complementary variable domains. The screen produced 14 new partners for a

specific VH domain and 13 new partners for a specific VL domain, which were strong binders, as determined by ELISA. See also, Kim SJ & Hong HJ, (2007) J Microbiol 45: 572-577, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VH domain and screening a library (*e.g.*, human VL library) for complementary VL domains; the selected VL domains in turn could be used to guide selection of additional complementary (*e.g.*, human) VH domains.

[00229] In certain aspects, the CDRs of an antibody can be determined according to the Chothia numbering scheme, which refers to the location of immunoglobulin structural loops (see, *e.g.*, Chothia C & Lesk AM, (1987), J Mol Biol 196: 901-917; Al-Lazikani B *et al.*, (1997) J Mol Biol 273: 927-948; Chothia C *et al.*, (1992) J Mol Biol 227: 799-817; Tramontano A *et al.*, (1990) J Mol Biol 215(1): 175-82; and U.S. Patent No. 7,709,226). Typically, when using the Kabat numbering convention, the Chothia CDR-H1 loop is present at heavy chain amino acids 26 to 32, 33, or 34, the Chothia CDR-H2 loop is present at heavy chain amino acids 52 to 56, and the Chothia CDR-H3 loop is present at heavy chain amino acids 95 to 102, while the Chothia CDR-L1 loop is present at light chain amino acids 24 to 34, the Chothia CDR-L2 loop is present at light chain amino acids 50 to 56, and the Chothia CDR-L3 loop is present at light chain amino acids 89 to 97. The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34).

[00230] In certain aspects, provided herein are antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) and comprise one or more Chothia VL CDRs of a VL of any one of the antibodies described herein, (*e.g.*, any one of Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) and/or one or more Chothia VH CDRs of a VH of any one of the antibodies described herein (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161). In certain embodiments, antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) comprise one or more CDRs, in which the Chothia and Kabat CDRs have the same amino acid sequence. In certain embodiments, provided herein are antibodies or fragments thereof that specifically bind to

GITR (*e.g.*, human GITR) and comprise combinations of Kabat CDRs and Chothia CDRs. In a particular embodiment, provided herein are antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) and comprise Chothia CDRs of any of the antibodies described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161).

[00231] In certain aspects, the CDRs of an antibody can be determined according to the IMGT numbering system as described in Lefranc M-P, (1999) *The Immunologist* 7: 132-136 and Lefranc M-P *et al.*, (1999) *Nucleic Acids Res* 27: 209-212. According to the IMGT numbering scheme, VH-CDR1 is at positions 26 to 35, VH-CDR2 is at positions 51 to 57, VH-CDR3 is at positions 93 to 102, VL-CDR1 is at positions 27 to 32, VL-CDR2 is at positions 50 to 52, and VL-CDR3 is at positions 89 to 97. In a particular embodiment, provided herein are antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of any one of the antibodies described herein (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), which are determined by the IMGT numbering system, for example, as described in Lefranc M-P (1999) *supra* and Lefranc M-P *et al.*, (1999) *supra*).

[00232] In certain aspects, the CDRs of an antibody can be determined according to MacCallum RM *et al.*, (1996) *J Mol Biol* 262: 732-745. See also, *e.g.*, Martin A. "Protein Sequence and Structure Analysis of Antibody Variable Domains," in *Antibody Engineering*, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001). In a particular embodiment, provided herein are antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of any one of the antibodies described herein (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), which are determined by the method in MacCallum RM *et al.*

[00233] In certain aspects, the CDRs of an antibody can be determined according to the AbM numbering scheme, which refers AbM hypervariable regions which represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software (Oxford Molecular Group, Inc.). In a particular embodiment,

provided herein are antibodies or fragments thereof that specifically bind to GITR (*e.g.*, human GITR) and comprise CDRs of any one of the antibodies described herein (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161,), which are determined by the AbM numbering scheme.

[00234] In a specific embodiment, the position of one or more CDRs along the VH (*e.g.*, CDR1, CDR2, or CDR3) and/or VL (*e.g.*, CDR1, CDR2, or CDR3) region of an antibody described herein may vary by one, two, three, four, five, or six amino acid positions so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). For example, in one embodiment, the position defining a CDR of any of antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) may vary by shifting the N-terminal and/or C-terminal boundary of the CDR by one, two, three, four, five, or six amino acids, relative to the CDR position of any one of the antibodies described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, identified in, *e.g.*, Table 1), so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the length of one or more CDRs along the VH (*e.g.*, CDR1, CDR2, or CDR3) and/or VL (*e.g.*, CDR1, CDR2, or CDR3) region of an antibody described herein may vary (*e.g.*, be shorter or longer) by one, two, three, four, five, or more amino acids, so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%).

[00235] In one embodiment, a VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be one, two, three, four, five or more amino acids shorter than one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, a VL CDR1, VL CDR2, VL

CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be one, two, three, four, five or more amino acids longer than one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the amino terminus of a VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the carboxy terminus of a VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the amino terminus of a VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In one embodiment, the carboxy terminus of a VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and/or VH CDR3 described herein may be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, SEQ ID NO: 1-34, 101-109, or 114-189 or SEQ ID NO: 35 or 191-194) so long as immunospecific binding to GITR (*e.g.*, human GITR) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). Any method known in the art can be used to ascertain whether immunospecific binding to GITR (*e.g.*, human GITR) is maintained, for example, the binding assays and conditions described in the “Examples” section (Section 6) provided herein.

[00236] In specific aspects, provided herein is an antibody comprising an antibody light chain and heavy chain, *e.g.*, a separate light chain and heavy chain. With respect to the light chain, in a specific embodiment, the light chain of an antibody described herein is a kappa light chain. In

another specific embodiment, the light chain of an antibody described herein is a lambda light chain. In yet another specific embodiment, the light chain of an antibody described herein is a human kappa light chain or a human lambda light chain. In a particular embodiment, an antibody described herein, which immunospecifically binds to an GTR polypeptide (*e.g.*, human GTR) comprises a light chain wherein the amino acid sequence of the VL domain comprises any amino acid sequence described herein (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518), and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region. In a particular embodiment, an antibody described herein, which immunospecifically binds to an GTR polypeptide (*e.g.*, human GTR) comprises a light chain wherein the amino acid sequence of the VL domain comprises any amino acid sequence described herein (*e.g.*, SEQ ID NO: 519), and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region. In another particular embodiment, an antibody described herein, which immunospecifically binds an GTR (*e.g.*, human GTR) comprises a light chain wherein the amino acid sequence of the VL domain can comprise any amino acid sequence described herein (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518), and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. In another particular embodiment, an antibody described herein, which immunospecifically binds an GTR (*e.g.*, human GTR) comprises a light chain wherein the amino acid sequence of the VL domain can comprise any amino acid sequence described herein (*e.g.*, SEQ ID NO: 519), and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. In a specific embodiment, an antibody described herein, which immunospecifically binds to GTR (*e.g.*, human GTR) comprises a light chain wherein the amino acid of the VL domain comprises (SEQ ID NOs: 207 or 208) and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa or lambda light chain constant region. Non-limiting examples of human constant region sequences have been described in the art, *e.g.*, see U.S. Patent No. 5,693,780 and Kabat EA *et al.*, (1991) *supra*.

[00237] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GTR (*e.g.*, human GTR) comprises a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, 571-576, and 580. In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GTR (*e.g.*, human GTR) comprises a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 571-576.

[00238] With respect to the heavy chain, in a specific embodiment, the heavy chain of an

antibody described herein can be an alpha (α), delta (δ), epsilon (ϵ), gamma (γ) or mu (μ) heavy chain. In another specific embodiment, the heavy chain of an antibody described can comprise a human alpha (α), delta (δ), epsilon (ϵ), gamma (γ) or mu (μ) heavy chain. In a particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain wherein the amino acid sequence of the VH domain can comprise any amino acid sequence described herein (*e.g.*, any of SEQ ID NO: 201, 203, 206, or 215-389), and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region. In a specific embodiment, an antibody described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain wherein the amino acid sequence of the VH domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 553, 554, 567-570, and 579, and wherein the constant region of the heavy chain comprises the amino acid of a human heavy chain described herein or known in the art. In a specific embodiment, an antibody described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain wherein the amino acid sequence of the VH domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 581 and 582, and wherein the constant region of the heavy chain comprises the amino acid of a human heavy chain described herein or known in the art. Non-limiting examples of human constant region sequences have been described in the art, *e.g.*, see U.S. Patent No. 5,693,780 and Kabat EA *et al.*, (1991) *supra*.

[00239] In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 553, 554, 567-570, and 579. In a particular embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 581 and 582. In a specific embodiment, an antibody or fragment thereof, which binds to GITR (*e.g.*, human GITR), comprises a heavy chain comprising the amino acid sequence of SEQ ID NOs: 567-570.

[00240] In a specific embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule. In another specific embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain comprising any amino acid

sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule. In a particular embodiment, the constant regions comprise the amino acid sequences of the constant regions of a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (*e.g.*, IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule.

[00241] In another specific embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VL domain and a VH domain comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of a human IgG₁ (*e.g.*, allotypes G1m3, G1m17,1 or G1m17,1,2) or human IgG₄. In a particular embodiment, an antibody described herein, which immunospecifically binds to an GITR (*e.g.*, human GITR) comprises a VL domain and a VH domain comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant region of a human IgG₁ (allotype G1m3). Non-limiting examples of human constant regions are described in the art, *e.g.*, see Kabat EA *et al.*, (1991) *supra*.

[00242] In another embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR) comprises a light chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, 571-576, and 580 and a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 553, 554, 567-570, and 579. In another embodiment, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR) comprises a light chain comprising the amino acid sequence of SEQ ID NO:576 and a heavy chain comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 581 and 582. In a specific embodiment, an antibody or fragment thereof, which specifically binds to GITR (*e.g.*, human GITR), comprises a light chain comprising the amino acid sequence of SEQ ID NO: 555 or 556 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 554.

[00243] In certain embodiments, one, two or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody described herein or a fragment thereof (*e.g.*, CH2 domain (residues 231-340 of human IgG₁) and/or CH3 domain (residues 341-447 of human IgG₁) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular

cytotoxicity.

[00244] In certain embodiments, one, two or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, *e.g.*, U.S. Patent No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain may be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody.

[00245] In some embodiments, one, two or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of an antibody described herein or a fragment thereof (*e.g.*, CH2 domain (residues 231-340 of human IgG₁) and/or CH3 domain (residues 341-447 of human IgG₁) and/or the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to increase or decrease the affinity of the antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody or fragment thereof that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, *e.g.*, Smith P *et al.*, (2012) PNAS 109: 6181-6186, U.S. Patent No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[00246] In a specific embodiment, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of the antibody *in vivo*. *See, e.g.*, International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Patent Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the antibody *in vivo*. In other embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In a specific embodiment, the antibodies may have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of

human IgG₁) and/or the third constant (CH3) domain (residues 341-447 of human IgG₁), with numbering according to the EU index in Kabat (Kabat EA *et al.*, (1991) *supra*). In a specific embodiment, the constant region of the IgG₁ of an antibody or antigen-binding fragment thereof described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. *See* U.S. Patent No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as “YTE mutant” has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (*see* Dall’Acqua WF *et al.*, (2006) J Biol Chem 281: 23514-24). In certain embodiments, an antibody or antigen-binding fragment thereof comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[00247] In a further embodiment, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322, numbered according to the EU index as in Kabat, can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. *See, e.g.*, U.S. Patent Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In certain embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (*see, e.g.*, Shields RL *et al.*, (2001) J Biol Chem 276: 6591-604). In various embodiments, one or more of the following mutations in the constant region of an antibody described herein may be made: an N297A substitution; an N297Q substitution; a L235A substitution and a L237A substitution; a L234A substitution and a L235A substitution; a E233P substitution; a L234V substitution; a L235A substitution; a C236 deletion; a P238A substitution; a D265A substitution; a A327Q substitution; or a P329A substitution, numbered according to the EU index as in Kabat.

[00248] In a specific embodiment, an antibody or antigen-binding fragment thereof described herein comprises the constant domain of an IgG₁ with an N297Q or N297A amino acid substitution.

[00249] In certain embodiments, one or more amino acids selected from amino acid residues 329, 331 and 322 in the constant region of an antibody described herein, numbered according to the EU index as in Kabat, can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent No. 6,194,551 (Idusogie *et al*). In some embodiments, one or more amino acid residues within amino acid positions 231 to 238 in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In certain embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by mutating one or more amino acids (e.g., introducing amino acid substitutions) at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439, numbered according to the EU index as in Kabat. This approach is described further in International Publication No. WO 00/42072.

[00250] In certain embodiments, an antibody described herein comprises the constant region of an IgG₄ antibody and the serine at amino acid residue 228 of the heavy chain, numbered according to the EU index as in Kabat, is substituted for proline.

[00251] Antibodies with reduced fucose content have been reported to have an increased affinity for Fc receptors, such as, e.g., FcγRIIIa. Accordingly, in certain embodiments, the antibodies or antigen-binding fragments thereof described herein have reduced fucose content or no fucose content. Such antibodies can be produced using techniques known to one skilled in the art. For example, the antibodies can be expressed in cells deficient or lacking the ability of fucosylation. In a specific example, cell lines with a knockout of both alleles of α1,6-fucosyltransferase can be used to produce antibodies with reduced fucose content. The Potelligent[®] system (Lonza) is an example of such a system that can be used to produce antibodies with reduced fucose content. Alternatively, antibodies or antigen-binding fragments

with reduced fucose content or no fucose content can be produced by, *e.g.*: (i) culturing cells under conditions which prevent or reduce fucosylation; (ii) posttranslational removal of fucose (*e.g.*, with a fucosidase enzyme); (iii) post-translational addition of the desired carbohydrate, *e.g.*, after recombinant expression of a non-glycosylated glycoprotein; or (iv) purification of the glycoprotein so as to select for antibodies or antigen-binding fragments thereof which are not fucosylated. See, *e.g.*, Longmore GD & Schachter H (1982) *Carbohydr Res* 100: 365-92 and Imai-Nishiya H *et al.*, (2007) *BMC Biotechnol.* 7: 84 for methods for producing antibodies or antigen-binding fragments thereof with no fucose content or reduced fucose content.

[00252] In certain embodiments, antibodies or antigen-binding fragments thereof described herein have an increased affinity for CD32B (also known as Fc γ RIIB or FCGR2B), *e.g.*, as compared to an antibody with a wild-type Fc region, *e.g.*, an IgG1 Fc. In certain embodiments, antibodies or antigen-binding fragments thereof described herein have a selectively increased affinity for CD32B (Fc γ RIIB) over both CD32A (Fc γ RIIA) and CD16 (Fc γ RIIIA). Sequence alterations that result in increased affinity for CD32B are provided, for example, in Mimoto *et al.*, *Protein Engineering, Design & Selection* 10: 589-598 (2013), Chu *et al.*, *Molecular Immunology* 45: 3926-3933 (2008), and Strohl, *Current Opinion in Biology* 20: 685-691 (2009), each of which is herein incorporated by reference in its entirety. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising a mutation selected from the group consisting of: G236D, P238D, S239D, S267E, L328F, L328E, an arginine inserted after position 236, and combinations thereof, numbered according to EU index (Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, Bethesda (1991)). In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising S267E and L328F substitutions. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising P238D and L328E substitutions. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising a P238D substitution and substitution selected from the group consisting of E233D, G237D, H268D, P271G, A330R, and combinations thereof. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising P238D, E233D, G237D, H268D, P271G, and A330R

substitutions. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising G236D and S267E. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising S239D and S267E. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising S267E and L328F. In some embodiments, the antibody or antigen-binding fragment with an increased affinity for CD32B comprises a heavy chain constant region, *e.g.*, an IgG1 constant region, or fragment thereof comprising an arginine inserted after position 236 and L328R.

[00253] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of any one of Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, those listed in Table 1); (ii) the heavy chain comprises a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of any one of Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, those listed in Table 2); (iii) the light chain further comprises a constant light chain domain comprising the amino acid sequence of the constant domain of a human kappa light chain; and (iv) the heavy chain further comprises a constant heavy chain domain comprising the amino acid sequence of the constant domain of a human IgG₁ (optionally IgG₁ (allotype G1m3)) heavy chain.

[00254] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising the amino acid sequence of any one of the antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518 or SEQ ID NO:519); (ii) the

heavy chain comprises a VH domain comprising the amino acid sequence of and one of the antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.*, SEQ ID NO: 201, 203, 206, or 215-389); (iii) the light chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human kappa light chain; and (iv) the heavy chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₁ (optionally IgG₁ (allotype Glm3)) heavy chain.

[00255] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising the amino acid sequence of Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NO: 207 or 208); (ii) the heavy chain comprises a VH domain comprising the amino acid sequence of Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NO: 206); (iii) the light chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human kappa light chain; and (iv) the heavy chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₁ (optionally IgG₁ (allotype Glm3)) heavy chain.

[00256] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of any one of the antibodies described herein, *e.g.*, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, those listed in Table 1); (ii) the heavy chain comprises a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of any one of the antibodies described herein, *e.g.*, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, those listed in Table 2); (iii) the light chain further comprises a constant light chain domain comprising the amino acid sequence of the constant domain of a human IgG₄; and (iv) the heavy chain further comprises a constant heavy chain domain comprising the amino acid sequence of the constant domain of a human IgG₄ heavy chain.

[00257] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518 or SEQ ID NO: 519); (ii) the heavy chain comprises a VH domain comprising the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 201, 203, 206, or 215-389); (iii) the light chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₄ light chain; and (iv) the heavy chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₄ heavy chain.

[00258] In another particular embodiment, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a light chain and a heavy chain, wherein (i) the light chain comprises a VL domain comprising the amino acid sequence of either Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NO: 207 or 208); (ii) the heavy chain comprises a VH domain comprising the amino acid sequence of either Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NO: 206); (iii) the light chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₄ light chain; and (iv) the heavy chain further comprises a constant domain comprising the amino acid sequence of the constant domain of a human IgG₄ heavy chain.

[00259] In a specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 553, 554, and 567 to 570; and (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576. In a specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 581 or 582; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GITR (*e.g.*, human GITR), comprises (a) a heavy

chain comprising the amino acid sequence of SEQ ID NO: 553; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 581; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 573. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 581; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.

[00260] In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid

sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556. In another specific embodiment, an antibody provided herein, which specifically binds to GTR (e.g., human GTR), comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553 with an amino acid substitution of N to A or Q at amino acid position 298; and (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555.

[00261] In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GTR (e.g., human GTR), comprises one, two, three, or four VL framework regions (FRs) having the amino acid sequence described herein for any one of the antibodies described herein, e.g., Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (e.g., see Table 3). In some embodiments an antibody or fragment thereof, which specifically binds to GTR (e.g., human GTR) comprises one, two, three, or four VH framework regions (FRs) having the amino acid sequence described herein for any one of the antibodies described herein, e.g., Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (e.g., see Table 4). In certain embodiments, an antibody or fragment thereof, which specifically binds to GTR (e.g., human GTR), comprises one, two, three, four, five, six, seven, or eight of the FRs of one of the antibodies described herein (e.g., Hum231#1 Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161). In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GTR (e.g., human GTR), comprises framework regions (e.g., framework regions of the VL domain and/or VH domain) that are human framework regions or derived from human framework regions. Non-limiting examples of human framework regions are described in the art, e.g., see Kabat EA *et al.*, (1991) *supra*). In certain embodiment, an antibody described herein comprises framework

regions (*e.g.*, framework regions of the VL domain and/or VH domain) that are primate (*e.g.*, non-human primate) framework regions or derived from primate (*e.g.*, non-human primate) framework regions.

[00262] For example, CDRs from antigen-specific non-human antibodies, typically of rodent origin (*e.g.*, mouse or rat), are grafted onto homologous human or non-human primate acceptor frameworks. In one embodiment, the non-human primate acceptor frameworks are from Old World apes. In a specific embodiment, the Old World ape acceptor framework is from *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*. In a particular embodiment, the non-human primate acceptor frameworks are from the chimpanzee *Pan troglodytes*. In a particular embodiment, the non-human primate acceptor frameworks are Old World monkey acceptor frameworks. In a specific embodiment, the Old World monkey acceptor frameworks are from the genus *Macaca*. In a certain embodiment, the non-human primate acceptor frameworks are derived from the cynomolgus monkey *Macaca cynomolgus*. Non-human primate framework sequences are described in U.S. Patent Application Publication No. US 2005/0208625.

[00263] In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two or more VL framework regions (FRs) having the amino acid sequences described herein for any one of the antibodies set forth in Table 3, *supra*. In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two or more VH framework regions (FRs) having the amino acid sequences described herein for any one of the antibodies set forth in Table 4, *supra*. In specific embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two or more VL framework regions having the amino acid sequences described herein for any one of the antibodies set forth in Table 3, *supra*, and one, two or more VH framework regions having the amino acid sequences described herein for the antibodies set forth in Table 4, *supra*.

[00264] In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the framework regions of VL domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, or 515-518 and/or the framework regions of the VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 271-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, 362-368, 380, 384, or 387. In certain embodiments, an antibody or fragment

thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises the framework regions of VL domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-464, 467-477, 481-486, 488-513, or 515-519 and/or the framework regions of the VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 270-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, or 362-368. In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of the VL domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107 (*e.g.*, SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, or 515-518) with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions) and/or the framework regions of the VH domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107 (*e.g.*, SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 271-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, 362-368, 380, 384, or 387). In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of the VL domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-464, 467-477, 481-486, 488-513, or 515-519) with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions) and/or the framework regions of the VH domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971,

pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 270-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, or 362-368). In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of the VH domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, pab2161 (*e.g.*, SEQ ID NO: 201, 203, 206, or 215-389) with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions) and/or the framework regions of the VL domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 201, 203, 206, or 215-389). In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of the VL domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107 (*e.g.*, SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, or 515-518) with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions) and/or one, two, three or four framework regions of the VH domain having the amino acid sequence of SEQ ID NO: 201, 203, 206, or 215-389 with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions). In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises one, two, three or four framework regions of the VL domain having the amino acid sequence of any one of the antibodies described herein, *e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-

107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-464, 467-477, 481-486, 488-513, or 515-519) with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions) and/or one, two, three or four framework regions of the VH domain having the amino acid sequence of SEQ ID NO: 201, 203, 206, or 215-389 with 1, 2, 3, 4, 5, 6, 7, 8, 9 or more amino acid mutations (*e.g.*, amino acid substitutions, such as conservative amino acid substitutions).

[00265] In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises VL framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein in Table 3, *supra*. In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises VH framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein Table 4, *supra*. In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises VH framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein Table 4, *supra*, and VL framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein Table 3, *supra*.

[00266] In certain embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises VL framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein for antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, as set forth in Table 3). In some embodiments, an antibody or fragment thereof described herein, which specifically binds to GITR (*e.g.*, human GITR), comprises VH framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein for antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, as set forth in Table 4). In certain embodiments, an antibody or fragment thereof described

herein, which specifically binds to GITR (*e.g.*, human GITR), comprises: (i) VL framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VL framework regions described herein for Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, as set forth in Table 3); and (ii) VH framework regions (FRs) having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the VH framework regions described herein for Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, as set forth in Table 4).

[00267] The determination of percent identity between two sequences (*e.g.*, amino acid sequences or nucleic acid sequences) can also be accomplished using a mathematical algorithm. A specific, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin S & Altschul SF (1990) PNAS 87: 2264-2268, modified as in Karlin S & Altschul SF (1993) PNAS 90: 5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul SF *et al.*, (1990) J Mol Biol 215: 403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.*, for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.*, to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul SF *et al.*, (1997) Nuc Acids Res 25: 3389 3402. Alternatively, PSI BLAST can be used to perform an iterated search which detects distant relationships between molecules (*Id.*). When utilizing BLAST, Gapped BLAST, and PSI Blast programs, the default parameters of the respective programs (*e.g.*, of XBLAST and NBLAST) can be used (see, *e.g.*, National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov). Another specific, non limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

[00268] The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, typically only exact matches are counted.

[00269] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of any one of antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518 or SEQ ID NO:519). In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain of any one of antibodies Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, Hum231#1, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208, or 400-518 or SEQ ID NO:519), wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.*, VL CDRs) that are identical to the CDRs (*e.g.*, VL CDRs) of an antibody set forth in Table 1 and/or Table 2 (*e.g.*, the CDRs are identical to the CDRs of a particular antibody referred to by name in Tables 1 and/or 2).

[00270] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VL domain comprising VL framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the framework regions selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, 208, and 400-518. In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VL domain comprising VL framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO: 519. In a particular embodiment, the antibody comprises VL CDRs that are identical to the VL CDRs of an antibody set forth in Table 1 (*e.g.*, the VL CDRs in one row in Table 1).

[00271] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH

domain of SEQ ID NO: 201, 203, 206, or 215-389. In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of SEQ ID NO: 201, 203, 206, or 215-389, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.*, VL CDRs) that are identical to the CDRs (*e.g.*, VL CDRs) of an antibody set forth in Table 1 and/or Table 2 (*e.g.*, the CDRs are identical to the CDRs of a particular named antibody referred to by name in Tables 1 and/or 2).

[00272] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain comprising VH framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the framework regions selected from the group consisting of SEQ ID NO: 201, 203, 206, and 215-389. In a particular embodiment, the antibody comprises VH CDRs that are identical to the VH CDRs of an antibody set forth in Table 2 (*e.g.*, the VH CDRs in one row in Table 2).

[00273] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises: (i) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, 208, and 400-518; and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of SEQ ID NO: 201, 203, 206, or 215-389. In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises: (i) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO: 519; and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain of SEQ ID NO: 304. In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises: (i) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL domain selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, 208, and 400-518; and (ii) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain selected from the group of SEQ ID NO: 201, 203, 206, and 215-389, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.*, VL CDRs) that are identical to the

CDRs (*e.g.*, VL CDRs) of an antibody set forth in Table 1 and/or Table 2 (*e.g.*, the CDRs are identical to the CDRs of a particular antibody referred to by name in Tables 1 and/or 2). In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises: (i) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:519; and (ii) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:304, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.*, VL CDRs) that are identical to the CDRs (*e.g.*, VL CDRs) of an antibody set forth in Table 1 and/or Table 2 (*e.g.*, the CDRs are identical to the CDRs of a particular antibody referred to by name in Tables 1 and/or 2).

[00274] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises: (i) a VL domain comprising VL framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the framework regions selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, and 208; and (ii) a VH domain comprising VH framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the framework regions selected from the group consisting of SEQ ID NO: 201, 203, 206, and 215-389. In a particular embodiment, the antibody comprises VL CDRs that are identical to the VL CDRs of an antibody set forth in Table 3 and/or VH CDRs that are identical to the VH CDRs of an antibody set forth in Table 4.

[00275] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain selected from the group of SEQ ID NO: 201, 203, 206, and 215-389. In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH domain selected from the group of SEQ ID NO: 201, 203, 206, and 215-389, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.*, VL CDRs) that are identical to the CDRs (*e.g.*, VL CDRs) of an antibody set forth in Table 1 and/or Table 2 (*e.g.*, the CDRs are identical to the CDRs of a particular antibody referred to in Tables 1 and/or 2).

[00276] In certain embodiments, an antibody or fragment thereof, which immunospecifically binds to GITR (*e.g.*, human GITR), comprises a VH domain comprising VH framework regions having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to

the amino acid sequence of the framework regions selected from the group consisting of SEQ ID NO: 201, 203, 206, and 215-389. In a particular embodiment, the antibody comprises VH CDRs that are identical to the VH CDRs of an antibody set forth in Table 2 (*e.g.*, the VH CDRs in one row in Table 2).

[00277] In another aspect, provided herein are antibodies that bind the same or an overlapping epitope of GITR (*e.g.*, an epitope of human GITR) as an antibody described herein (*e.g.*, antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107), or antibodies pab2159, pab2160, pab2161, or Hum231#2w. In certain embodiments, the epitope of an antibody can be determined by, *e.g.*, NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.*, liquid chromatography electrospray mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.*, site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.*, Giegé R *et al.*, (1994) *Acta Crystallogr D Biol Crystallogr* 50(Pt 4): 339-350; McPherson A (1990) *Eur J Biochem* 189: 1-23; Chayen NE (1997) *Structure* 5: 1269-1274; McPherson A (1976) *J Biol Chem* 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see *e.g.* *Meth Enzymol* (1985) volumes 114 & 115, eds Wyckoff HW *et al.*; U.S. Patent Application No. 2004/0014194), and BUSTER (Bricogne G (1993) *Acta Crystallogr D Biol Crystallogr* 49(Pt 1): 37-60; Bricogne G (1997) *Meth Enzymol* 276A: 361-423, ed Carter CW; Roversi P *et al.*, (2000) *Acta Crystallogr D Biol Crystallogr* 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.*, Champe M *et al.*, (1995) *supra* and Cunningham BC & Wells JA (1989) *supra* for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. In a specific embodiment, the epitope of an antibody or antigen-binding fragment thereof is determined using alanine scanning mutagenesis studies, such as described in Section 6, *infra*. In addition, antibodies that recognize and bind to the same or overlapping epitopes of GITR (*e.g.*, human GITR) can be identified using routine techniques such as an immunoassay, for example, by showing the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competition binding assays also can be used to determine whether two antibodies have similar binding specificity for an epitope. Competitive binding can be determined in an assay in which the immunoglobulin under test inhibits specific

binding of a reference antibody to a common antigen, such as GITR. Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli C *et al.*, (1983) *Methods Enzymol* 9: 242-253); solid phase direct biotin-avidin EIA (see Kirkland TN *et al.*, (1986) *J Immunol* 137: 3614-9); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow E & Lane D, (1988) *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (see Morel GA *et al.*, (1988) *Mol Immunol* 25(1): 7-15); solid phase direct biotin-avidin EIA (Cheung RC *et al.*, (1990) *Virology* 176: 546-52); and direct labeled RIA. (Moldenhauer G *et al.*, (1990) *Scand J Immunol* 32: 77-82). Typically, such an assay involves the use of purified antigen (*e.g.*, GITR such as human GITR) bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition can be measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more. A competition binding assay can be configured in a large number of different formats using either labeled antigen or labeled antibody. In a common version of this assay, the antigen is immobilized on a 96-well plate. The ability of unlabeled antibodies to block the binding of labeled antibodies to the antigen is then measured using radioactive or enzyme labels. For further details see, for example, Wagener C *et al.*, (1983) *J Immunol* 130: 2308-2315; Wagener C *et al.*, (1984) *J Immunol Methods* 68: 269-274; Kuroki M *et al.*, (1990) *Cancer Res* 50: 4872-4879; Kuroki M *et al.*, (1992) *Immunol Invest* 21: 523-538; Kuroki M *et al.*, (1992) *Hybridoma* 11: 391-407 and *Antibodies: A Laboratory Manual*, Ed Harlow E & Lane D editors *supra*, pp. 386-389.

[00278] In one embodiment, a competition assay is performed using surface plasmon resonance (BIAcore[®]), *e.g.*, by an 'in tandem approach' such as that described by Abdiche YN *et al.*, (2009) *Analytical Biochem* 386: 172-180, whereby GITR antigen is immobilized on the chip surface, for example, a CM5 sensor chip and the anti-GITR antibodies are then run over the chip. To determine if an antibody competes with an anti-GITR antibody or antigen-binding fragment thereof described herein, the anti-GITR antibody is first run over the chip surface to achieve saturation and then the potential, competing antibody is added. Binding of the competing antibody can then be determined and quantified relative to a non-competing control.

[00279] In certain aspects, competition binding assays can be used to determine whether an

antibody is competitively blocked, *e.g.*, in a dose dependent manner, by another antibody for example, an antibody binds essentially the same epitope, or overlapping epitopes, as a reference antibody, when the two antibodies recognize identical or sterically overlapping epitopes in competition binding assays such as competition ELISA assays, which can be configured in all number of different formats, using either labeled antigen or labeled antibody. In a particular embodiment, an antibody can be tested in competition binding assays with an antibody described herein (*e.g.*, antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w), or a chimeric or Fab antibody thereof, or an antibody comprising VH CDRs and VL CDRs of an antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w).

[00280] In another aspect, provided herein are antibodies that compete (*e.g.*, in a dose dependent manner) for binding to GITR (*e.g.*, human GITR) with an antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107), or antibodies pab2159, pab2160, pab2161, or Hum231#2w, as determined using assays known to one of skill in the art or described herein (*e.g.*, ELISA competitive assays or surface plasmon resonance). In another aspect, provided herein are antibodies that competitively inhibit (*e.g.*, in a dose dependent manner) an antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w) from binding to GITR (*e.g.*, human GITR), as determined using assays known to one of skill in the art or described herein (*e.g.*, ELISA competitive assays, or suspension array or surface plasmon resonance assay described in Example 6, *infra*). In particular embodiments, such competitively blocking antibody activates, induces or enhances one or more GITR activities. In specific aspects, provided herein is an antibody which competes (*e.g.*, in a dose dependent manner) for specific binding to GITR (*e.g.*, human GITR), with an antibody comprising the amino acid sequences described herein (*e.g.*, VL and/or VH amino acid sequences of antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979,

pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161, or Hum231#2w), as determined using assays known to one of skill in the art or described herein (*e.g.*, ELISA competitive assays, or suspension array or surface plasmon resonance assay described in Example 6, *infra*).

[00281] In certain embodiments, provided herein is an antibody that competes with an antibody described herein for binding to GTR (e.g., human GTR) to the same extent that the antibody described herein self-competes for binding to GTR (*e.g.*, human GTR). In some embodiments, provided herein is a first antibody that competes with an antibody described herein for binding to GTR (e.g., human GTR), wherein the first antibody competes for binding in an assay comprising the following steps: (a) incubating GTR-transfected cells with the first antibody in unlabeled form in a container; and (b) adding an antibody described herein in labeled form in the container and incubating the cells in the container; and (c) detecting the binding of the antibody described herein in labeled form to the cells. In certain embodiments, provided herein is a first antibody that competes with an antibody described herein for binding to GTR (e.g., human GTR), wherein the competition is exhibited as reduced binding of the first antibody to GTR by more than 80% (*e.g.*, 85%, 90%, 95%, or 98%, or between 80% to 85%, 80% to 90%, 85% to 90%, or 85% to 95%).

[00282] In specific aspects, provided herein is an antibody which competes (*e.g.*, in a dose dependent manner) for specific binding to GTR (*e.g.*, human GTR), with an antibody comprising a VL domain having the amino acid sequence selected from the group consisting of SEQ ID 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, and 515-518, and a VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 271-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 350, 354-356, 358-360, 362-368, 380, 384 and 387. In specific aspects, provided herein is an antibody which competes (*e.g.*, in a dose dependent manner) for specific binding to GTR (*e.g.*, human GTR), with an antibody comprising a VL domain having the amino acid sequence selected from the group consisting of SEQ ID 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, and 515-519, and a VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 270-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, and 362-368.

[00283]

[00284] In specific aspects, provided herein is an antibody which competes (*e.g.*, in a dose dependent manner) for specific binding to GITR (*e.g.*, human GITR), with an antibody comprising (i) a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of the VL CDRs of an antibody listed in Table 1; and (ii) a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of the CDRs of an antibody listed in Table 2 (*e.g.*, the VH CDRs of a particular antibody referred to by name in Table 1, such as 231-32-15, Hum231#1, or Hum231#2).

[00285] In a particular embodiment, provided herein is an antibody that competes (*e.g.*, in a dose-dependent manner), for specific binding to GITR (*e.g.*, human GITR), with an antibody comprising the VH and VL CDRs of 231-32-15 (SEQ ID NO: 201 and 202).

[00286] In a specific embodiment, an antibody described herein is one that is competitively blocked (*e.g.*, in a dose dependent manner) by an antibody comprising a VL domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, and 515-518 and a VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 271-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, 362-368, 380, 384, and 387, for specific binding to GITR (*e.g.*, human GITR). In a specific embodiment, an antibody described herein is one that is competitively blocked (*e.g.*, in a dose dependent manner) by an antibody comprising a VL domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-464, 467-477, 481-486, 488-513, and 515-519 and a VH domain having the amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 270-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, and 362-368, for specific binding to GITR (*e.g.*, human GITR).

[00287] In one embodiment, an antibody described herein is one that is competitively blocked by an antibody comprising a VL domain having the amino acid sequence of SEQ ID NO: 207 or 208 and a VH domain having the amino acid sequence of SEQ ID NO: 206 for specific binding to GITR (*e.g.*, human GITR).

[00288] In another specific embodiment, an antibody described herein is one that is competitively blocked (*e.g.*, in a dose dependent manner) by an antibody comprising (i) a VL

domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of the CDRs of antibody listed in Table 1 (*e.g.*, the VL CDRs of a particular antibody referred by name in Table 1); and (ii) a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of the CDRs of antibody listed in Table 2.

[00289] In specific aspects, provided herein is an antibody, or an antigen-binding fragment thereof, which immunospecifically binds to the same epitope as that of an antibody (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w) comprising the amino acid sequences described herein (see, *e.g.*, Tables 1-4) for specific binding to GITR (*e.g.*, human GITR). Assays known to one of skill in the art or described herein (*e.g.*, X-ray crystallography, ELISA assays, etc.) can be used to determine if two antibodies bind to the same epitope.

[00290] In a specific embodiment, an antibody or an antigen-binding fragment thereof described herein immunospecifically binds to the same epitope as that of an antibody (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107) comprising a VL domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-452, 454-464, 467-477, 481-486, 488-513, and 515-518, and a VH domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 271-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306, 308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, 362-368, 380, 384, and 387). In a specific embodiment, an antibody or an antigen-binding fragment thereof described herein immunospecifically binds to the same epitope as that of an antibody (*e.g.*, any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w) comprising a VL domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 202, 207, 208, 400-411, 413-416, 418-421, 423-448, 450-464, 467-477, 481-486, 488-513, and 515-519, and a VH domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, 215, 217-234, 236-256, 258, 259, 261-265, 267, 268, 270-273, 276, 277, 280, 281, 283-285, 287, 288, 290, 291, 294, 296-299, 301, 304-306,

308, 313-316, 319, 320, 322-325, 327, 328, 333, 336, 338-340, 342, 343, 345, 350, 354-356, 358-360, and 362-368).

[00291] In a specific embodiment, an antibody or an antigen-binding fragment thereof described herein immunospecifically binds to the same epitope as that bound by an antibody comprising the VH domain and VL domain of antibody Hum231#1 or Hum231#2 (SEQ ID NOs: 206 and 207 or SEQ ID NOs: 206 and 208, respectively), or an epitope that overlaps the epitope of antibody comprising the VH domain and VL domain of antibody Hum231#1 or Hum231#2 (SEQ ID NOs: 206 and 207 or SEQ ID NOs: 206 and 208, respectively).

[00292] In another specific embodiment, an antibody or an antigen-binding fragment thereof described herein, immunospecifically binds to the same epitope as that of an antibody comprising (i) a VL domain comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of the CDRs of antibody listed in Table 1 (*e.g.*, the VL CDRs of a particular antibody referred to by name in Table 1) and (ii) a VH domain comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of the CDRs of antibody listed in Table 2 (*e.g.*, the VH CDRs of a particular antibody referred to by name in Table 2).

[00293] In a particular embodiment, an antibody described herein or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR) and competitively blocks (*e.g.*, in a dose dependent manner) antibody 231-32-15, Hum231#1, Hum231#2 or Hum231#2w from binding to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

(i) the VL comprises:

(a) a VL CDR1 comprising the amino acid sequence KSSQ₁SX₁X₂X₃X₄X₅X₆X₇KX₈YLX₉ (SEQ ID NO: 4), wherein:

X₁ is L, A, V, I, P, F or M

X₂ is L, A, V, I, P, F, M or S

X₃ is N, G, Q, S, T, C, W, Y or A

X₄ is S, G, N, Q, T, C, W, Y or A

X₅ is G, N, Q, S, T, C, W, Y or A

X₆ is N, G, Q, S, T, C, W, Y or A

X₇ is Q, G, N, S, T, C, W, Y or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is T, G, N, Q, S, C, W, Y, V, I or A; and/or

(b) a VL CDR2 comprising the amino acid sequence X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A

X₂ is E, D or A

X₃ is S, G, N, Q, T, C, W, Y or A; and/or

(c) a VL CDR3 comprising the amino acid sequence QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y

X₂ is D, E or Y

X₃ is S, G, N, Q, T, C, W, Y or A

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A; and (ii) the VH comprises:

(a) a VH CDR1 comprising the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 1), wherein

X₁ is D, E, G or A

X₂ is A, V, L, I, P, F, M or Y

X₃ is Y, G, N, Q, S, T, C, W, F or H; and/or

(b) a VH CDR2 comprising the amino acid sequence X₁IX₂X₃X₄SGX₅X₆X₇YX₈QKFX₉X₁₀ (SEQ ID NO: 2), wherein

X₁ is V, A, L, I, P, F, M or T

X₂ is R, K, H, Q or A

X₃ is T, G, N, Q, S, C, W, Y, V, I or P

X₄ is Y, G, N, Q, S, T, C, W, F, H, or A

X₅ is D, E, G or A

X₆ is V, A, L, I, P, F, M or T

X₇ is T, G, N, Q, S, C, W, Y, V, I, P or A

X₈ is N, G, Q, S, T, C, W, Y or A

X₉ is K, R, H, Q or A

X₁₀ is D, E, G or A; and/or

(c) a VH CDR3 comprising the amino acid sequence SGTVRGX₁X₂X₃ (SEQ ID NO: 3), wherein

X₁ is F, A, V, L, I, P, M, Y, W, H or S

X₂ is A, or D

X₃ is Y, G, N, Q, S, T, C, W, F, H or V.

[00294] In a particular embodiment, an antibody described herein, or an antigen-binding fragment thereof, which specifically binds to GITR (*e.g.*, human GITR) and competitively blocks (*e.g.*, in a dose dependent manner) antibody 231-32-15, Hum231#1, Hum231#2 or Hum231#2w from binding to GITR (*e.g.*, human GITR), comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

(i) the VL comprises:

(a) a VL CDR1 comprising the amino acid sequence KSSQSLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S

X₂ is T or S; and/or

(b) a VL CDR2 comprising the amino acid sequence WASTRES (SEQ ID NO: 11); and/or

(c) a VL CDR3 comprising the amino acid sequence QNX₁YSX₂PYT (SEQ ID NO: 12), wherein X₁ is D or E

X₂ is Y, F or S and (ii) the VH comprises:

(a) a VH CDR1 comprising the amino acid sequence X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G

X₂ is A or V

X₃ is Y or H; and/or

(b) a VH CDR2 comprising the amino acid sequence X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L

X₂ is R, K or Q

X₃ is Y or F

X₄ is D, E or G

X₅ is V or L

X₆ is T or S

X₇ is K, R or Q

X₈ is D, E or G; and/or

(c) a VH CDR3 comprising the amino acid sequence SGTVRGFAY (SEQ ID NO: 9).

[00295] In some embodiments, an antibody that competes for binding with an antibody described herein for binding GTR (e.g., human GTR) or binds to the same or an overlapping epitope of an antibody described herein (e.g., Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w) prevents binding of GITRL (e.g., human GITRL) to GTR (e.g., human GTR) by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% as assessed by an assay known to one of skill in the art or described herein. In a specific embodiment, an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (e.g., human GTR) or binds to the same epitope or overlapping epitope of an antibody described

herein, inhibits binding of GITRL (*e.g.*, human GITRL) to GTR (*e.g.*, human GTR) by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% as assessed by the assay described in Example 2, *infra* (*e.g.*, Section 6.2.5.2 or 6.2.5.4, *infra*). In another specific embodiment, an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or binds to the same epitope or overlapping epitope of an antibody described herein, at a concentration of 1000 ng/ml, 950 ng/ml, 900 ng/ml, 850 ng/ml, 800 ng/ml, 750 ng/ml, 700 ng/ml, 650 ng/ml, 600 ng/ml, 550 ng/ml, 500 ng/ml, 450 ng/ml, 400 ng/ml, 350 ng/ml, 333 ng/ml, 300 ng/ml, 250 ng/ml, 200 ng/ml, 100 ng/ml, 50 ng/ml or 10 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GTR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or binds to the same epitope or overlapping epitope of an antibody described herein, at concentration of 1000 ng/ml to 750 ng/ml, 1000 ng/ml to 500 ng/ml, 850 ng/ml to 500 ng/ml, 750 ng/ml to 500 ng/ml, 600 ng/ml to 500 ng/ml, 500 ng/ml to 400 ng/ml, 400 ng/ml to 300 ng/ml, or 300 ng/ml to 200 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GTR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00296] In another specific embodiment, an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or

binds to the same epitope or overlapping epitope of an antibody described herein, at concentration of 3500 ng/ml, 3400 ng/ml, 3300 ng/ml, 3200 ng/ml, 3100 ng/ml, 3000 ng/ml, 2900 ng/ml, 2800 ng/ml, 2700 ng/ml, 2600 ng/ml, 2500 ng/ml, 2400 ng/ml, 2300 ng/ml, 2200 ng/ml, 2100 ng/ml, 2000 ng/ml, 1900 ng/ml, 1800 ng/ml, 1700 ng/ml, 1600 ng/ml, 1500 ng/ml, 1400 ng/ml, 1300 ng/ml, 1200 ng/ml, or 1100 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, at concentration of 3500 ng/ml to 3200 ng/ml, 3500 ng/ml to 3000ng/ml, 3200 ng/ml to 2500 ng/ml, 3000 to 2200 ng/ml, 2500 ng/ml to 1800 ng/ml, 2000 ng/ml to 1500 ng/ml, 1700 ng/ml to 1200 ng/ml, or 1500 ng/ml to 1000 ng/ml inhibits binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, GITRL-PE) to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead by less than 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20% or 10% relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00297] In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 3000ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 85% or less than 80% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR

coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 1000ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 85%, less than 80% or less than 75% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 333ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 70% or less than 65% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 111ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 65%, less than 60% or less than 55% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 37ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 40% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for

binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 12ng/ml prevents binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by less than 20% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00298] In another embodiment, a certain amount of labeled GITRL (*e.g.*, human GITRL-PE) binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) in the presence of an antibody, which competes for binding with an antibody described herein for binding to GITR or binds to the same or an overlapping epitope of an antibody described herein, in a method comprising: (a) coupling GITR (*e.g.*, human GITR) to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 5pg/ml per bead; (b) incubating the GITR coupled beads at a concentration of 40 beads/ μ l with 3000ng/ml, 2500ng/ml, 2000ng/ml, 1500ng/ml, 1000ng/ml, 750ng/ml, 500ng/ml, 250ng/ml, 100ng/ml, 50ng/ml or 10ng/ml of the competing antibody or the antibody that binds to the same or overlapping epitope in a well for a first period of time (*e.g.*, 30 minutes, 60 minutes, 1.5 hours, 2 hours, 2.5 hours or 3 hours), wherein the well contains 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400 or 1500 beads; (c) adding labeled GITRL (*e.g.*, human GITRL-PE) to the well to obtain a final concentration of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM (in specific embodiments, 0.5nM) of the labeled GITRL and 20 beads/ μ l of the GITR coupled beads, and incubating for a second period of time (*e.g.*, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours or 3 hours); and (d) detecting the labeled GITRL bound to the GITR coupled beads in, *e.g.*, a suspension array assay such as the Luminex[®] 200 system. In specific embodiments, the amount of the labeled GITRL bound to the GITR coupled beads in the presence of the competing antibody or the antibody that binds to the same or overlapping epitope is determined relative to the amount of labeled GITRL bound to the GITR coupled beads in the absence of the competing antibody or the antibody that binds to the same or overlapping epitope. In certain embodiments, the absence of the competing antibody or the antibody that binds to the same or overlapping epitope means that no antibody or antigen-binding fragment thereof is present in the well. In other embodiments, the absence of the competing antibody or the antibody that binds to the same or overlapping epitope means that an isotype control antibody that does not bind to GITR is present in the well. In accordance with these embodiments, the amount of labeled GITRL bound to the GITR coupled beads in the presence of the competing antibody or

the antibody that binds to the same or overlapping epitope is determined to be, in some embodiments, at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55% or 60%, or 20% to 60%, 30% to 50%, or 20% to 70% of the amount of the labeled GITRL bound to the GTR coupled beads in the absence of the competing antibody or the antibody that binds to the same or overlapping epitope.

[00299] In certain embodiments, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of GITRL (*e.g.*, human GITRL) binds to GTR (*e.g.*, human GTR) in the presence of an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or binds to the same epitope or overlapping epitope of an antibody described herein, assessed by an assay known to one of skill in the art or described herein. In a specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of GITRL (*e.g.*, human GITRL) binds to GTR (*e.g.*, human GTR) in the presence of an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or binds to the same epitope or overlapping epitope of an antibody described herein, as assessed by the assay described in Example 2, *infra* (*e.g.*, Sections 6.2.5.2 or 6.2.5.4, *infra*). In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE) binds to GTR coupled to beads (*e.g.*, human GTR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the presence of 1000 ng/ml, 950 ng/ml, 900 ng/ml, 850 ng/ml, 800 ng/ml, 750 ng/ml, 700 ng/ml, 650 ng/ml, 600 ng/ml, 550 ng/ml, 500 ng/ml, 450 ng/ml, 400 ng/ml, 350 ng/ml, 333 ng/ml, 300 ng/ml, 250 ng/ml, 200 ng/ml, 100 ng/ml, 50 ng/ml or 10 ng/ml of an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GTR (*e.g.*, human GTR) or binds to the same epitope or overlapping epitope of an antibody described herein, relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GTR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GTR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In another specific embodiment, at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, or 75% of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL (*e.g.*, labeled human GITRL, such as hGITRL-PE)

binds to GITR coupled to beads (*e.g.*, human GITR coupled to Luminex[®] beads) at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the presence of 3500 ng/ml, 3400 ng/ml, 3300 ng/ml, 3200 ng/ml, 3100 ng/ml, 3000 ng/ml, 2900 ng/ml, 2800 ng/ml, 2700 ng/ml, 2600 ng/ml, 2500 ng/ml, 2400 ng/ml, 2300 ng/ml, 2200 ng/ml, 2100 ng/ml, 2000 ng/ml, 1900 ng/ml, 1800 ng/ml, 1700 ng/ml, 1600 ng/ml, 1500 ng/ml, 1400 ng/ml, 1300 ng/ml, 1200 ng/ml, or 1100 ng/ml of an antibody or antigen-binding fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, relative to the binding of 1.5nM, 1.4nM, 1.3nM, 1.2nM, 1.1nM, 1nM, 0.9nM, 0.8nM, 0.7nM, 0.6nM, 0.5nM, 0.4nM, 0.3nM, 0.2nM or 0.1nM of labeled GITRL to the GITR coupled beads at a concentration of 9pg/ml, 8pg/ml, 7pg/ml, 6pg/ml, 5pg/ml, 4pg/ml or 3pg/ml per bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00300] In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 3000ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 15% or more than 20% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 1000ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 15%, more than 20% or more than 25% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 333ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 30% or more than 35% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of

5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 111ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 35%, more than 40% or more than 45% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml per bead relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 37ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 60% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof per bead in a suspension array assay (*e.g.*, Luminex[®] 200 system). In certain embodiments, an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 12ng/ml does not prevent binding of 0.5nM GITRL (*e.g.*, human GITRL) to GITR (*e.g.*, human GITR) by more than 85% when GITR (*e.g.*, human GITR) is coupled to beads (*e.g.*, Luminex[®] beads) at a concentration of 5pg/ml relative to the binding of 0.5nM of labeled GITRL to GITR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GITR antibody or antigen-binding fragment thereof per bead in a suspension array assay (*e.g.*, Luminex[®] 200 system).

[00301] In certain embodiments, provided herein is an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, at a concentration of 150nM, 145nM, 140nM, 135nM, 130nM, 125nM, 120nM, 115nM, 110nM, 105nM or 100nM bound to GITR (*e.g.*, human GITR) immobilized on a chip (*e.g.*, CM5 sensor chip) inhibits binding of 150nM, 145nM, 140nM, 135nM, 130nM, 125nM, 120nM, 115nM, 110nM, 105nM or 100nM of GITRL (*e.g.*, non-covalently linked trimer of human GITRL) to the GITR immobilized on the chip by

less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20% or less than 15%. In certain embodiments, provided herein is an antibody, which competes for binding with an antibody described herein for binding GITR (*e.g.*, human GITR) or binds to the same or an overlapping epitope of an antibody described herein, wherein the competing antibody or the antibody that binds to the same or overlapping epitope at a concentration of 125nM bound to GITR (*e.g.*, human GITR) immobilized on a chip (*e.g.*, CM5 sensor chip) inhibits binding of 125nM of GITRL (*e.g.*, non-covalently linked trimer of human GITRL) to the GITR immobilized on the chip by less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20% or less than 15%.

[00302] In certain embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a dissociation rate constant (k_{off}) of $8.5 \times 10^{-3} \text{ s}^{-1}$ or less, $3.5 \times 10^{-3} \text{ s}^{-1}$ or less, $5 \times 10^{-3} \text{ s}^{-1}$ or less, $2.5 \times 10^{-3} \text{ s}^{-1}$ or less, $1 \times 10^{-3} \text{ s}^{-1}$ or less, $8.5 \times 10^{-4} \text{ s}^{-1}$ or less, $5 \times 10^{-4} \text{ s}^{-1}$ or less, $3.5 \times 10^{-4} \text{ s}^{-1}$ or less, $2.5 \times 10^{-4} \text{ s}^{-1}$ or less, $1 \times 10^{-4} \text{ s}^{-1}$ or less, $8.5 \times 10^{-5} \text{ s}^{-1}$ or less, $3.5 \times 10^{-5} \text{ s}^{-1}$ or less, $5 \times 10^{-5} \text{ s}^{-1}$ or less, $2.5 \times 10^{-5} \text{ s}^{-1}$ or less, $1 \times 10^{-5} \text{ s}^{-1}$ or less, $8.5 \times 10^{-6} \text{ s}^{-1}$ or less, $5 \times 10^{-6} \text{ s}^{-1}$ or less, $3.5 \times 10^{-6} \text{ s}^{-1}$ or less, $2.5 \times 10^{-6} \text{ s}^{-1}$ or less, $1 \times 10^{-6} \text{ s}^{-1}$ or less, $8.5 \times 10^{-7} \text{ s}^{-1}$ or less, $5 \times 10^{-7} \text{ s}^{-1}$ or less, $2.5 \times 10^{-7} \text{ s}^{-1}$ or less, $1 \times 10^{-7} \text{ s}^{-1}$ or less, $8.5 \times 10^{-8} \text{ s}^{-1}$ or less, $5 \times 10^{-8} \text{ s}^{-1}$ or less, $2.5 \times 10^{-8} \text{ s}^{-1}$ or less, $1 \times 10^{-8} \text{ s}^{-1}$ or less, $8.5 \times 10^{-9} \text{ s}^{-1}$ or less, $5 \times 10^{-9} \text{ s}^{-1}$ or less, $2.5 \times 10^{-9} \text{ s}^{-1}$ or less, or $1 \times 10^{-9} \text{ s}^{-1}$ or less. In some embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a k_{off} of between $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $8.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-9} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-8} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-8} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, $5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-7} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $5 \times 10^{-6} \text{ s}^{-1}$, $9.5 \times 10^{-5} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $8.5 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-4} \text{ s}^{-1}$, $5 \times 10^{-3} \text{ s}^{-1}$ to $2.5 \times 10^{-4} \text{ s}^{-1}$, $8.5 \times 10^{-3} \text{ s}^{-1}$ to $1 \times 10^{-5} \text{ s}^{-1}$, $8.5 \times 10^{-5} \text{ s}^{-1}$ to $5 \times 10^{-5} \text{ s}^{-1}$. In certain embodiments, the k_{off} is determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In other embodiments, the k_{off} is determined using a bivalent antibody as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In a particular embodiment, the k_{off} is determined using an assay described in Section 6, *infra*.

[00303] In certain embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope

or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with an association rate constant (k_{on}) of at least $10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $2.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, at least $10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $2.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $3.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, at least $10^7 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, at least $10^8 \text{ M}^{-1}\text{s}^{-1}$, at least $5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ or at least $10^9 \text{ M}^{-1}\text{s}^{-1}$. In some embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a k_{on} of between $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $2.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $3.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $3.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$, $1 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ to $1 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$. In certain embodiments, the k_{on} is determined using a monovalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In other embodiments, the k_{on} is determined using a bivalent antibody as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In a particular embodiment, the k_{on} is determined using an assay described in Section 6, *infra*.

[00304] In certain embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a K_D of less than 7 nM, 6nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.75 nM, 0.5 nM, 0.25 nM, or 0.1 nM. In some embodiments, an antibody or fragment thereof, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a K_D of about 7nM, 6nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, 0.75 nM, 0.5 nM, 0.25 nM, or 0.1 nM. In certain embodiments, an antibody or fragment thereof described herein, which competes with an antibody described herein for binding to GITR (*e.g.*, human GITR) or binds to the same epitope or overlapping epitope of an antibody described herein, binds to GITR (*e.g.*, human GITR) with a K_D of 7 nM to 4 nM, 7 nM to 5 nM, 6 nM to 4 nM, 5 nM to 3 nM, 5 nM to 1 nM, 5 nM to 0.5 nM, 4 nM to 3 nM, 4 nM to 2 nM, 4 nM to 1 nM, 4 nM to 0.5 nM, 3 nM to 2 nM, 3 nM to 1 nM, 3 nM to 0.5 nM, 2 nM to 1 nM, 2 nM to 0.5 nM, 3 nM to 0.1 nM, 2 nM to 0.1 nM, 1 nM to 0.1 nM, or 0.5 nM to 0.1 nM. In certain embodiments, the K_D is calculated as the quotient of k_{off}/k_{on} , and the k_{on} and k_{off} are determined using a monovalent antibody, such as a Fab fragment, as measured by,

e.g., BIAcore[®] surface plasmon resonance technology. In other embodiments, the K_D is calculated as the quotient of k_{off}/k_{on} , and the k_{on} and k_{off} are determined using a bivalent antibody, such as a Fab fragment, as measured by, *e.g.*, BIAcore[®] surface plasmon resonance technology. In a specific embodiment, the K_D is determined as set forth in the Examples in Section 6, *infra* (*e.g.*, Example 2).

[00305] In certain embodiments, the epitope of an antibody described herein is used as an immunogen to produce antibodies. See, *e.g.*, Section 5.2 *infra* for methods for producing antibodies.

[00306] In specific aspects, an antibody or fragment thereof described, which specifically binds to GITR (*e.g.*, human GITR), does not inhibit (*e.g.*, in a dose dependent manner) the binding of the murine antibody 6C8 to GITR (*e.g.*, human GITR) in an assay known to one of skill in the art or described herein. See, *e.g.*, U.S. Patent No. 7,812,135 for a description of the murine antibody 6C8. In certain embodiments, at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the murine antibody 6C8 binds to GITR (*e.g.*, human GITR) in the presence of an antibody or fragment thereof described, which specifically binds to GITR (*e.g.*, human GITR), as assessed in an assay known to one of skill in the art or described herein. In a specific embodiment, an antibody or fragment thereof described, which specifically binds to GITR (*e.g.*, human GITR), does not inhibit (*e.g.*, in a dose dependent manner) the binding of the murine antibody 6C8 to GITR (*e.g.*, human GITR) as assessed in the assay described in Example 6, *infra*. In certain embodiments, at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the murine antibody 6C8 binds to GITR (*e.g.*, human GITR) in the presence of an antibody or fragment thereof described, which specifically binds to GITR (*e.g.*, human GITR), as assessed in the assay described in Example 6, *infra*.

[00307] In some embodiments, anti-GITR antibodies described herein may be multispecific antibodies, *e.g.*, bispecific antibodies. In a particular embodiment, an anti-GITR antibody described herein is a bispecific antibody, wherein the antibody has specificities for at least two different, typically non-overlapping epitopes. In a particular embodiment, a bispecific antibody comprises one arm comprising of an antibody described herein with specificity for GITR (*e.g.*, human GITR), and a second arm comprising an antibody with specificity for a different epitope on GITR (*e.g.*, human GITR) or an epitope on a different molecule, *e.g.*, PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG-3 or OX40. For example, the bispecific antibody may comprise one arm comprising an antibody described herein with specificity for GITR (*e.g.*, human GITR) and a second arm comprising an antibody with specificity for CTLA-4, such as tremelimumab (Pfizer),

ipilimumab (Yervoy[®], Bristol-Meyers Squibb), an antibody that binds to the same epitope as tremelimumab or an overlapping epitope thereto, or an antibody that binds to the same epitope as ipilimumab or an overlapping epitope thereto.

[00308] In specific aspects, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), functions as an agonist.

[00309] In certain embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases GITR (*e.g.*, human GITR) activity by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein and/or known to one of skill in the art, relative to GITR (*e.g.*, human GITR) activity in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR). In certain embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases GITR (*e.g.*, human GITR) activity by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein and/or known to one of skill in the art, relative to GITR (*e.g.*, human GITR) activity in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR). Non-limiting examples of GITR (*e.g.*, human GITR) activity can include cell proliferation, GITR (*e.g.*, human GITR) signaling, cell survival, and cytokine production (*e.g.*, IL-2, IL-6, IL-10, TNF- α , and IFN- γ). In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces or increases a GITR (*e.g.*, human GITR) activity together with GITRL (*e.g.*, human GITRL). In certain embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, enhances, or increases a GITR (*e.g.*, human GITR) activity in the absence of GITRL (*e.g.*, human GITRL). In specific embodiments, the antibody or antibody-binding fragment induces, enhances, or increases a GITR activity and does not inhibit (*e.g.*, does not completely inhibit or only partially inhibits) GITRL from binding to GITR. In specific embodiments, an increase in a GITR activity is assessed as described in the Examples, *infra*.

[00310] In certain aspects, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, enhances, or increases the cellular proliferation of cells that express GITR and that respond to GITR signaling (*e.g.*, cells

that proliferate in response to GITR stimulation and GITR signaling, such as T cells). Cell proliferation assays are described in the art, such as a ^3H -thymidine incorporation assay, BrdU incorporation assay or CFSE assay, such as described in Example 3, and can be readily carried out by one of skill in the art. In specific embodiments, T cells (*e.g.*, CD4^+ or CD8^+ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). *See* Example 3, *infra*, which demonstrates an increase in T cell proliferation in the presence of an antibody described herein that immunospecifically binds to GITR.

[00311] In one embodiment, CD8^+ T cells stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In another embodiment, CD4^+ T cells stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In another embodiment, CD4^+ T cells and CD8^+ T cells stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which

immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody). In some embodiments, T cells that have not been stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR) have increased GITR activity and/or increased NF- κ B activity relative to T cells not in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR).

[00312] In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases cell proliferation (*e.g.*, T cells, such as CD4 and CD8 effector T cells) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein or known to one of skill in the art (*e.g.*, ^{3} H-thymidine incorporation assay, BrdU incorporation assay or CFSE assay, such as described in Example 3, *infra*), relative to GITR (*e.g.*, human GITR) activity in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR). In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases cell proliferation (*e.g.*, T cells, such as CD4 and CD8 effector T cells) by at least at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein or known to one of skill in the art (*e.g.*, ^{3} H-thymidine incorporation assay, BrdU incorporation assay or CFSE assay, such as described in Example 3, *infra*), relative to GITR (*e.g.*, human GITR) activity in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR).

[00313] In some embodiments, T cells (*e.g.*, CD4⁺ or CD8⁺ effector T cells) stimulated with a T cell mitogen (*e.g.*, an anti-CD3 antibody or phorbol ester) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20

fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to T cells only stimulated with the T cell mitogen, as assessed by methods described herein or known to one of skill in the art (*e.g.*, ^3H -thymidine incorporation assay, BrdU incorporation assay or CFSE assay, such as described in Example 3, *infra*). In some embodiments, T cells (*e.g.*, CD4^+ or CD8^+ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cellular proliferation by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), as assessed by methods described herein or known to one of skill in the art (*e.g.*, ^3H -thymidine incorporation assay, BrdU incorporation assay or CFSE assay, such as described in Example 3, *infra*). In a specific embodiment, cell proliferation is assessed as described in Example 3, *infra*.

[00314] In certain aspects, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases the survival of cells (*e.g.*, T cells, such as CD4 and CD8 effector T cells). In a specific embodiment, T cells (*e.g.*, CD4^+ or CD8^+ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased survival relative to T cells only stimulated with the T cell mitogen. Cell survival assays are described in the art (*e.g.*, a trypan blue exclusion assay) and can be readily carried out by one of skill in the art.

[00315] In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases cell survival (*e.g.*, T cells, such as CD4 and CD8 effector T cells) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein or known to one of skill in the art (*e.g.*, a trypan blue exclusion assay), relative to cell survival in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation

without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR). In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), increases cell survival (*e.g.*, T cells, such as CD4 and CD8 effector T cells) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein or known to one of skill in the art (*e.g.*, a trypan blue exclusion assay), relative to cell survival in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR).

[00316] In some embodiments, T cells (*e.g.*, CD4⁺ or CD8⁺ effector T cells) stimulated with a T cell mitogen (*e.g.*, an anti-CD3 antibody or phorbol ester) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cell survival by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), as assessed by methods described herein or known to one of skill in the art (*e.g.*, a trypan blue exclusion assay). In some embodiments, T cells (*e.g.*, CD4⁺ or CD8⁺ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cell survival by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% relative to T cells only stimulated with the T cell mitogen, as assessed by methods described herein or known to one of skill in the art (*e.g.*, a trypan blue exclusion assay).

[00317] In certain embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), protects effector T cells (*e.g.*, CD4⁺ and CD8⁺ effector T cells) from activation-induced cell death. In some embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces resistance of effector T cells (*e.g.*, CD4⁺ and CD8⁺ effector T cells) to Treg-mediated suppression.

[00318] In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, enhances, or increases cytokine production (*e.g.*, IL-2, IL-6, IL-10, TNF- α , and IFN- γ) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, as assessed by methods described herein (*see* the Examples, *infra*, such as Example 3) or known to one of skill in the art, relative to cytokine production in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR). In specific embodiments, an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces or enhances cytokine production (*e.g.*, IL-2, IL-6, IL-10, TNF- α , and IFN- γ) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold, as assessed by methods described herein (*see* the Examples, *infra*, such as Example 3) or known to one of skill in the art, relative to cytokine production in the presence or absence of GITRL (*e.g.*, human GITRL) stimulation without any antibody or with an unrelated antibody (*e.g.*, an antibody that does not immunospecifically bind to GITR).

[00319] In certain embodiments, T cells (*e.g.*, CD4⁺ or CD8⁺ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cytokine production (*e.g.*, IL-2, IL-6, IL-10, TNF- α , and IFN- γ) by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), as assessed by methods described herein or known to one of skill in the art (*e.g.*, an ELISA assay or as described in the Examples, *infra*). In some embodiments, T cells (*e.g.*, CD4⁺ or CD8⁺ effector T cells) stimulated with a T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) in the presence of an antibody or fragment thereof described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), have increased cytokine production (*e.g.*, IL-2, IL-6, IL-10, TNF- α ,

and IFN- γ) by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold relative to T cells only stimulated with the T cell mitogen or T cell receptor complex stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody), as assessed by methods described herein or known to one of skill in the art (*e.g.*, an ELISA assay or as described in the Examples, *infra*).

[00320] In certain embodiments, an anti-GITR antibody or antigen binding fragment thereof induces, enhances or activates an activity of GITR, in the absence of a TCR agonist (*e.g.*, an anti-CD3 antibody). GITR activity can be assessed by measuring activation of canonical and non-canonical NF- κ B pathways. GITR activity can be assessed by measuring activation of TRAF adapter mediated signaling pathways. The TRAF adapter is selected from the group consisting of TRAF1, TRAF2, TRAF3, TRAF4, and TRAF5. GITR activity can be assessed by measuring activation of MAPK/ERK pathway (also called the Ras-Raf-MEK-ERK pathway). Examples of “a TCR agonist” include, but are not limited to, antibodies targeting the T cell receptor complex (*e.g.*, an anti-CD3 antibody) and peptides bound to human leukocyte antigens, *e.g.*, MHC class I and MHC class II, wherein the peptides are derived from self, mutated self, or pathogen associated proteins (*e.g.*, viral or bacterial).

[00321] An anti-GITR antibody or antigen-binding fragment thereof can be fused or conjugated (*e.g.*, covalently or noncovalently linked) to a detectable label or substance. Examples of detectable labels or substances include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{121}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. Such labeled antibodies or antigen-binding fragments can be used to detect GITR (*e.g.*, human GITR) protein. See, *e.g.*, Section 5.4.2, *infra*.

5.2 Antibody Production

[00322] Antibodies or fragments thereof that immunospecifically bind to GITR (*e.g.*, human GITR) can be produced by any method known in the art for the synthesis of antibodies, for example, by chemical synthesis or by recombinant expression techniques. The methods described herein employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited

herein and are fully explained in the literature. See, *e.g.*, Maniatis T *et al.*, (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.*, (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B *et al.*, (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00323] In a specific embodiment, an antibody described herein is an antibody (*e.g.*, recombinant antibody) prepared, expressed, created or isolated by any means that involves creation, *e.g.*, via synthesis, genetic engineering of DNA sequences. In certain embodiments, such antibody comprises sequences (*e.g.*, DNA sequences or amino acid sequences) that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.*, human) *in vivo*.

[00324] In a certain aspect, provided herein is a method of making an antibody or an antigen-binding fragment thereof which immunospecifically binds to GITR (*e.g.*, human GITR) comprising culturing a cell or host cell described herein. In a certain aspect, provided herein is a method of making an antibody or an antigen-binding fragment thereof which immunospecifically binds to GITR (*e.g.*, human GITR) comprising expressing (*e.g.*, recombinantly expressing) the antibody or antigen-binding fragment thereof using a cell or host cell described herein (*e.g.*, a cell or a host cell comprising polynucleotides encoding an antibody described herein). In a particular embodiment, the cell is an isolated cell. In a particular embodiment, the exogenous polynucleotides have been introduced into the cell. In a particular embodiment, the method further comprises the step of purifying the antibody or antigen-binding fragment thereof obtained from the cell or host cell.

[00325] Methods for producing polyclonal antibodies are known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.*, eds., John Wiley and Sons, New York).

[00326] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow E & Lane D,

Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling GJ *et al.*, in: Monoclonal Antibodies and T-Cell Hybridomas 563 681 (Elsevier, N.Y., 1981). The term “monoclonal antibody” as used herein is not limited to antibodies produced through hybridoma technology. For example, monoclonal antibodies can be produced recombinantly from host cells exogenously expressing an antibody described herein or a fragment thereof, for example, light chain and/or heavy chain of such antibody.

[00327] In specific embodiments, a “monoclonal antibody,” as used herein, is an antibody produced by a single cell (*e.g.*, hybridoma or host cell producing a recombinant antibody), wherein the antibody immunospecifically binds to GITR (*e.g.*, human GITR) as determined, *e.g.*, by ELISA or other antigen-binding or competitive binding assay known in the art or in the Examples provided herein. In particular embodiments, a monoclonal antibody can be a chimeric antibody or a humanized antibody. In certain embodiments, a monoclonal antibody is a monovalent antibody or multivalent (*e.g.*, bivalent) antibody. In particular embodiments, a monoclonal antibody is a monospecific or multispecific antibody (*e.g.*, bispecific antibody). Monoclonal antibodies described herein can, for example, be made by the hybridoma method as described in Kohler G & Milstein C (1975) Nature 256: 495 or can, *e.g.*, be isolated from phage libraries using the techniques as described herein, for example. Other methods for the preparation of clonal cell lines and of monoclonal antibodies expressed thereby are well known in the art (see, for example, Chapter 11 in: Short Protocols in Molecular Biology, (2002) 5th Ed., Ausubel FM *et al.*, *supra*).

[00328] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. For example, in the hybridoma method, a mouse or other appropriate host animal, such as a sheep, goat, rabbit, rat, hamster or macaque monkey, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein (*e.g.*, GITR (*e.g.*, human GITR)) used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Additionally, a RIMMS (repetitive immunization multiple sites) technique can be used to immunize an animal (Kilpatrick KE *et al.*, (1997) Hybridoma 16:381-9, incorporated by reference in its entirety).

[00329] In some embodiments, mice (or other animals, such as rats, monkeys, donkeys, pigs, sheep, hamster, or dogs) can be immunized with an antigen (*e.g.*, GITR (*e.g.*, human GITR)) and once an immune response is detected, *e.g.*, antibodies specific for the antigen are detected in the

mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the American Type Culture Collection (ATCC[®]) (Manassas, VA), to form hybridomas. Hybridomas are selected and cloned by limited dilution. In certain embodiments, lymph nodes of the immunized mice are harvested and fused with NS0 myeloma cells.

[00330] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[00331] Specific embodiments employ myeloma cells that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these myeloma cell lines are murine myeloma lines, such as NS0 cell line or those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8.653 cells available from the American Type Culture Collection, Rockville, MD, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor D (1984) J Immunol 133: 3001-5; Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

[00332] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against GTR (e.g., human GTR). The binding specificity of monoclonal antibodies produced by hybridoma cells is determined by methods known in the art, for example, immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

[00333] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding JW (Ed), Monoclonal Antibodies: Principles and Practice, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI 1640 medium. In addition, the hybridoma cells may be grown *in vivo* as ascites tumors in an animal.

[00334] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis,

dialysis, or affinity chromatography.

[00335] Antibodies described herein include antibody fragments which recognize specific GTR (e.g., human GTR) and can be generated by any technique known to those of skill in the art. For example, Fab and F(ab')₂ fragments described herein can be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). A Fab fragment corresponds to one of the two identical arms of an antibody molecule and contains the complete light chain paired with the VH and CH1 domains of the heavy chain. A F(ab')₂ fragment contains the two antigen-binding arms of an antibody molecule linked by disulfide bonds in the hinge region.

[00336] Further, the antibodies described herein or antigen-binding fragments thereof can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of affected tissues). The DNA encoding the VH and VL domains are recombined together with a scFv linker by PCR and cloned into a phagemid vector. The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13, and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to a particular antigen can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies described herein include those disclosed in Brinkman U *et al.*, (1995) J Immunol Methods 182: 41-50; Ames RS *et al.*, (1995) J Immunol Methods 184: 177-186; Kettleborough CA *et al.*, (1994) Eur J Immunol 24: 952-958; Persic L *et al.*, (1997) Gene 187: 9-18; Burton DR & Barbas CF (1994) Advan Immunol 57: 191-280; PCT Application No. PCT/GB91/001134; International Publication Nos. WO 90/02809, WO 91/10737, WO 92/01047, WO 92/18619, WO 93/1 1236, WO 95/15982, WO 95/20401, and WO 97/13844; and U.S. Patent Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727, 5,733,743 and 5,969,108.

[00337] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described below. Techniques to recombinantly produce antibody fragments such as Fab, Fab' and F(ab')₂

fragments can also be employed using methods known in the art such as those disclosed in PCT publication No. WO 92/22324; Mullinax RL *et al.*, (1992) BioTechniques 12(6): 864-9; Sawai H *et al.*, (1995) Am J Reprod Immunol 34: 26-34; and Better M *et al.*, (1988) Science 240: 1041-1043.

[00338] In one aspect, to generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences from a template, *e.g.*, scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, *e.g.*, human kappa or lambda constant regions. The VH and VL domains can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00339] A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules. For example, a chimeric antibody can contain a variable region of a mouse or rat monoclonal antibody fused to a constant region of a human antibody. Methods for producing chimeric antibodies are known in the art. See, *e.g.*, Morrison SL (1985) Science 229: 1202-7; Oi VT & Morrison SL (1986) BioTechniques 4: 214-221; Gillies SD *et al.*, (1989) J Immunol Methods 125: 191-202; and U.S. Patent Nos. 5,807,715, 4,816,567, 4,816,397, and 6,331,415.

[00340] A humanized antibody is capable of binding to a predetermined antigen and which comprises a framework region having substantially the amino acid sequence of a human immunoglobulin and CDRs having substantially the amino acid sequence of a non-human immunoglobulin (*e.g.*, a murine immunoglobulin). In particular embodiments, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The antibody also can include the CH1, hinge, CH2, CH3, and CH4 regions of the heavy chain. A humanized antibody can be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG₁, IgG₂, IgG₃ and IgG₄. Humanized antibodies can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239400; International Publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (European Patent Nos. EP 592106 and EP 519596; Padlan EA (1991) Mol Immunol 28(4/5): 489-498; Studnicka GM *et al.*, (1994) Prot Engineering 7(6):

805-814; and Roguska MA *et al.*, (1994) PNAS 91: 969-973), chain shuffling (U.S. Patent No. 5,565,332), and techniques disclosed in, *e.g.*, U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, International Publication No. WO 93/17105; Tan P *et al.*, (2002) J Immunol 169: 1119-25; Caldas C *et al.*, (2000) Protein Eng. 13(5): 353-60; Morea V *et al.*, (2000) Methods 20(3): 267-79; Baca M *et al.*, (1997) J Biol Chem 272(16): 10678-84; Roguska MA *et al.*, (1996) Protein Eng 9(10): 895 904; Couto JR *et al.*, (1995) Cancer Res. 55 (23 Supp): 5973s-5977s; Couto JR *et al.*, (1995) Cancer Res 55(8): 1717-22; Sandhu JS (1994) Gene 150(2): 409-10 and Pedersen JT *et al.*, (1994) J Mol Biol 235(3): 959-73. See also U.S. Application Publication No. US 2005/0042664 A1 (Feb. 24, 2005), which is incorporated by reference herein in its entirety.

[00341] Methods for making multispecific (*e.g.*, bispecific antibodies) have been described, see, for example, U.S. Patent Nos. 7,951,917; 7,183,076; 8,227,577; 5,837,242; 5,989,830; 5,869,620; 6,132,992 and 8,586,713.

[00342] Single domain antibodies, for example, antibodies lacking the light chains, can be produced by methods well known in the art. See Riechmann L & Muyldermans S (1999) J Immunol 231: 25-38; Nuttall SD *et al.*, (2000) Curr Pharm Biotechnol 1(3): 253-263; Muyldermans S, (2001) J Biotechnol 74(4): 277-302; U.S. Patent No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591 and WO 01/44301.

[00343] Further, antibodies that immunospecifically bind to a GITR antigen can, in turn, be utilized to generate anti-idiotypic antibodies that “mimic” an antigen using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan NS & Bona CA (1989) FASEB J 7(5): 437-444; and Nissinoff A (1991) J Immunol 147(8): 2429-2438).

[00344] In particular embodiments, an antibody described herein, which binds to the same epitope of GITR (*e.g.*, human GITR) as an anti-GITR antibody described herein, is a human antibody or an antigen-binding fragment thereof. In particular embodiments, an antibody described herein, which competitively blocks (*e.g.*, in a dose-dependent manner) any one of the antibodies described herein, (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w) from binding to GITR (*e.g.*, human GITR), is a human antibody or an antigen-binding fragment thereof. Human antibodies can be produced using any method known in the art. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, can be used. In particular, the human heavy and light chain immunoglobulin gene complexes can be introduced randomly or by homologous recombination

into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region can be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes can be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of an antigen (*e.g.*, GITR). Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg N & Huszar D (1995) *Int Rev Immunol* 13:65-93. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, International Publication Nos. WO 98/24893, WO 96/34096 and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318 and 5,939,598. Examples of mice capable of producing human antibodies include the XenomouseTM (Abgenix, Inc.; U.S. Patent Nos. 6,075,181 and 6,150,184), the HuAb-MouseTM (Mederex, Inc./Gen Pharm; U.S. Patent Nos. 5,545,806 and 5,569, 825), the Trans Chromo MouseTM (Kirin) and the KM MouseTM (Medarex/Kirin).

[00345] Human antibodies which specifically bind to GITR (*e.g.*, human GITR) can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. *See also* U.S. Patent Nos. 4,444,887, 4,716,111, and 5,885,793; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[00346] In some embodiments, human antibodies can be produced using mouse-human hybridomas. For example, human peripheral blood lymphocytes transformed with Epstein-Barr virus (EBV) can be fused with mouse myeloma cells to produce mouse-human hybridomas secreting human monoclonal antibodies, and these mouse-human hybridomas can be screened to determine ones which secrete human monoclonal antibodies that immunospecifically bind to a target antigen (*e.g.*, GITR (*e.g.*, human GITR)). Such methods are known and are described in

the art, see, *e.g.*, Shinmoto H *et al.*, (2004) Cytotechnology 46: 19-23; Naganawa Y *et al.*, (2005) Human Antibodies 14: 27-31.

5.2.1 Polynucleotides

[00347] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding an antibody described herein or a fragment thereof (*e.g.*, a variable light chain region and/or variable heavy chain region) that immunospecifically binds to a GITR (*e.g.*, human GITR) antigen, and vectors, *e.g.*, vectors comprising such polynucleotides for recombinant expression in host cells (*e.g.*, *E. coli* and mammalian cells). Provided herein are polynucleotides comprising nucleotide sequences encoding any of the antibodies provided herein, as well as vectors comprising such polynucleotide sequences, *e.g.*, expression vectors for their efficient expression in host cells, *e.g.*, mammalian cells.

[00348] As used herein, an “isolated” polynucleotide or nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source (*e.g.*, in a mouse or a human) of the nucleic acid molecule. Moreover, an “isolated” nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. For example, the language “substantially free” includes preparations of polynucleotide or nucleic acid molecule having less than about 15%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (in particular less than about 10%) of other material, *e.g.*, cellular material, culture medium, other nucleic acid molecules, chemical precursors and/or other chemicals. In a specific embodiment, a nucleic acid molecule(s) encoding an antibody described herein is isolated or purified.

[00349] In particular aspects, provided herein are polynucleotides comprising nucleotide sequences encoding antibodies or antigen-binding fragments thereof, which immunospecifically bind to a GITR polypeptide (*e.g.*, human GITR) and comprises an amino acid sequence as described herein, as well as antibodies which compete with such antibodies for binding to a GITR polypeptide (*e.g.*, in a dose-dependent manner), or which binds to the same epitope as that of such antibodies.

[00350] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding the light chain or heavy chain of an antibody described herein. The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VL FRs and CDRs of antibodies described herein (see, *e.g.*, Tables 1 and 3). The polynucleotides

can comprise nucleotide sequences encoding a heavy chain comprising the VH FRs and CDRs of antibodies described herein (see, *e.g.*, Tables 2 and 4). In specific embodiments, a polynucleotide described herein encodes a VL domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, 208, and 400-518. In specific embodiments, a polynucleotide described herein encodes a VL domain comprising the amino acid sequence of SEQ ID NO: 519. In specific embodiments, a polynucleotide described herein encodes a VH domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 201, 203, 206, and 215-389. In specific embodiments, a polynucleotide described herein encodes a VL domain comprising the amino acid sequence of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 202, 207 or 208). In specific embodiments, a polynucleotide described herein encodes a VH domain comprising the amino acid sequence of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 201 or 206). In specific embodiments, a polynucleotide described herein encodes a VL domain and a VH domain comprising the amino acid sequence of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 201-202 and/or 206-208).

[00351] In particular embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-GITR antibody comprising three VL chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Table 1, for example, the VL CDRs in one row in Table 1). In specific embodiments, provided herein are polynucleotides comprising three VH chain CDRs, *e.g.*, containing VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies described herein (*e.g.*, see Table 2, for example, the VH CDRs in one row in Table 2). In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-GITR antibody comprising three VH chain CDRs, *e.g.*, containing VL CDR1, VL CDR2, and VL CDR3 of any one of antibodies described herein (*e.g.*, see Table 1, *e.g.*, the VL CDRs in one row in Table 1) and three VH chain CDRs, *e.g.*, containing VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies described herein (*e.g.*, see Table 2, *e.g.*, the VH CDRs in one row in Table 2). In specific embodiments, a polynucleotide described herein encodes the VL CDRs of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 16, 17, or 18). In specific embodiments, a polynucleotide described herein encodes the VH CDRs of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 13, 14, or 15). In specific embodiments, a polynucleotide described herein encodes VL CDRs and VH CDRs of any one of antibodies 231-32-15, Hum231#1 or Hum231#2 (*e.g.*, SEQ ID NOs: 13-18).

[00352] In particular embodiments, provided herein are polynucleotides comprising a

nucleotide sequence encoding an anti-GITR antibody comprising a VL domain, *e.g.*, containing FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, comprising an amino acid sequence described herein (*e.g.*, see Tables 1 and 3, *e.g.*, the VL CDRs and VLFRs of a particular antibody identified by name in the tables). In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-GITR antibody comprising a VH domain, *e.g.*, containing FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, comprising an amino acid sequence described herein (*e.g.*, see Tables 2 and 4, *e.g.*, the VH CDRs and VH FRs of a particular antibody identified by name in the Tables).

[00353] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding an antibody provided herein comprising a light chain variable region comprising an amino acid sequence described herein (*e.g.*, SEQ ID NOs: 202, 204, 205, 207, 208, and 400-518 or SEQ ID NO:519), wherein the antibody immunospecifically binds to GITR (*e.g.*, human GITR). In a certain embodiment, a polynucleotide described herein comprises a nucleotide sequence encoding antibodies Hum231#1 or Hum231#2 or Hum231#2w provided herein comprising a light chain variable region comprising an amino acid sequence described herein (*e.g.*, SEQ ID NOs: 207 or 208).

[00354] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding an antibody provided herein comprising a heavy chain variable region comprising an amino acid sequence described herein (*e.g.*, SEQ ID NO: 201, 203, 206, and 215-389), wherein the antibody immunospecifically binds to GITR (*e.g.*, human GITR). In a certain embodiment, a polynucleotide described herein comprises a nucleotide sequence encoding antibodies Hum231#1, Hum231#2 or Hum231#2w provided herein comprising a heavy chain variable region comprising an amino acid sequence described herein (*e.g.*, SEQ ID NO: 206).

[00355] In certain aspects, a polynucleotide comprises a nucleotide sequence encoding an antibody described herein comprising a VL domain comprising one or more VL FRs having the amino acid sequence described herein (*e.g.*, see Table 3, *e.g.*, the framework regions in one row of the table), wherein the antibody immunospecifically binds to GITR (*e.g.*, human GITR). In certain aspects, a polynucleotide comprises a nucleotide sequence encoding an antibody described herein comprising a VH domain comprising one or more VH FRs having the amino acid sequence described herein (*e.g.*, see Table 4, *e.g.*, the framework regions in one row of the table), wherein the antibody immunospecifically binds to GITR (*e.g.*, human GITR).

[00356] In specific embodiments, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein comprising: framework regions (*e.g.*, framework regions of the VL domain and VH domain) that are human framework regions,

wherein the antibody immunospecifically binds GITR (*e.g.*, human GITR). In certain embodiments, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody or fragment thereof (*e.g.*, CDRs or variable domain) described in Section 5.1 above.

[00357] In specific aspects, provided herein is a polynucleotide comprising a nucleotide sequence encoding an antibody comprising a light chain and a heavy chain, *e.g.*, a separate light chain and heavy chain. With respect to the light chain, in a specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a kappa light chain. In another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a lambda light chain. In yet another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein comprising a human kappa light chain or a human lambda light chain. In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a light chain, and wherein the amino acid sequence of the VL domain can comprise any amino acid sequence described herein (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208 and 400-518 or SEQ ID NO:519), and wherein the constant region of the light chain comprises the amino acid sequence of a human kappa light chain constant region. In another particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), and comprises a light chain, wherein the amino acid sequence of the VL domain can comprises any amino acid sequence described herein (*e.g.*, SEQ ID NO: 202, 204, 205, 207, 208 and 400-518 or SEQ ID NO:519), and wherein the constant region of the light chain comprises the amino acid sequence of a human lambda light chain constant region. For example, human constant region sequences can be those described in U.S. Patent No. 5,693,780.

[00358] In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), wherein the antibody comprises a heavy chain, wherein the amino acid sequence of the VH domain can comprise any amino acid sequence described herein (*e.g.*, SEQ ID NO: 201, 203, 206 and 215-389), and wherein the constant region of the heavy chain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region.

[00359] In a certain embodiment, a polynucleotide provided herein comprises a nucleotide sequence(s) encoding a VH domain and/or a VL domain of an antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981,

pab1983, 231-32-15, or antibodies 1-107 such as SEQ ID NO: 209 or 800-974 for the VH domain or SEQ ID NO: 210, 211 or 1001-1126 for the VL domain), which immunospecifically binds to GITR (*e.g.*, human GITR). In a certain embodiment, a polynucleotide provided herein comprises a nucleotide sequence(s) encoding a VH domain and/or a VL domain of an antibody described herein (*e.g.*, Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 such as SEQ ID NO: 209 or 800-974 for the VH domain or SEQ ID NO: 210, 211 or 1000-1118 for the VL domain), which immunospecifically binds to GITR (*e.g.*, human GITR). In a certain embodiment, a polynucleotide provided herein comprises a nucleotide sequence(s) encoding a VH domain and/or a VL domain of antibody Hum231#1 or Hum231# (*e.g.*, SEQ ID NOs: 209-211).

[00360] In yet another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding an antibody described herein (or an antigen-binding fragment thereof), which immunospecifically binds GITR (*e.g.*, human GITR), wherein the antibody comprises a VL domain and a VH domain comprising any amino acid sequences described herein, and wherein the constant regions comprise the amino acid sequences of the constant regions of a human IgG₁ (*e.g.*, allotype 1, 17, or 3) or human IgG₄.

[00361] In a specific embodiment, provided herein are polynucleotides comprising a nucleotide sequence encoding an anti-GITR antibody, or an antigen-binding fragment or domain thereof, designated herein, *see, e.g.*, Tables 1-4, for example antibody Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15, or antibodies 1-107, or antibodies pab2159, pab2160, pab2161, or Hum231#2w.

[00362] Also provided herein are polynucleotides encoding an anti-GITR antibody or a fragment thereof that are optimized, *e.g.*, by codon/RNA optimization, replacement with heterologous signal sequences, and elimination of mRNA instability elements. Methods to generate optimized nucleic acids encoding an anti-GITR antibody or a fragment thereof (*e.g.*, light chain, heavy chain, VH domain, or VL domain) for recombinant expression by introducing codon changes and/or eliminating inhibitory regions in the mRNA can be carried out by adapting the optimization methods described in, *e.g.*, U.S. Patent Nos. 5,965,726; 6,174,666; 6,291,664; 6,414,132; and 6,794,498, accordingly. For example, potential splice sites and instability elements (*e.g.*, A/T or A/U rich elements) within the RNA can be mutated without altering the amino acids encoded by the nucleic acid sequences to increase stability of the RNA for

recombinant expression. The alterations utilize the degeneracy of the genetic code, *e.g.*, using an alternative codon for an identical amino acid. In some embodiments, it can be desirable to alter one or more codons to encode a conservative mutation, *e.g.*, a similar amino acid with similar chemical structure and properties and/or function as the original amino acid. Such methods can increase expression of an anti-GITR antibody or fragment thereof by at least 1 fold, 2 fold, 3 fold, 4 fold, 5 fold, 10 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold or more relative to the expression of an anti-GITR antibody encoded by polynucleotides that have not been optimized.

[00363] In certain embodiments, an optimized polynucleotide sequence encoding an anti-GITR antibody described herein or a fragment thereof (*e.g.*, VL domain and/or VH domain) can hybridize to an antisense (*e.g.*, complementary) polynucleotide of an unoptimized polynucleotide sequence encoding an anti-GITR antibody described herein or a fragment thereof (*e.g.*, VL domain and/or VH domain). In specific embodiments, an optimized nucleotide sequence encoding an anti-GITR antibody described herein or a fragment hybridizes under high stringency conditions to antisense polynucleotide of an unoptimized polynucleotide sequence encoding an anti-GITR antibody described herein or a fragment thereof. In a specific embodiment, an optimized nucleotide sequence encoding an anti-GITR antibody described herein or a fragment thereof hybridizes under high stringency, intermediate or lower stringency hybridization conditions to an antisense polynucleotide of an unoptimized nucleotide sequence encoding an anti-GITR antibody described herein or a fragment thereof. Information regarding hybridization conditions has been described, see, *e.g.*, U.S. Patent Application Publication No. US 2005/0048549 (*e.g.*, paragraphs 72-73), which is incorporated herein by reference.

[00364] The polynucleotides can be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Nucleotide sequences encoding antibodies described herein, *e.g.*, antibodies described in Tables 1-4, and modified versions of these antibodies can be determined using methods well known in the art, *i.e.*, nucleotide codons known to encode particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody. Such a polynucleotide encoding the antibody can be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier G *et al.*, (1994), *BioTechniques* 17: 242-6), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[00365] Alternatively, a polynucleotide encoding an antibody described herein can be generated from nucleic acid from a suitable source (*e.g.*, a hybridoma) using methods well

known in the art (*e.g.*, PCR and other molecular cloning methods). For example, PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of a known sequence can be performed using genomic DNA obtained from hybridoma cells producing the antibody of interest. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the light chain and/or heavy chain of an antibody. Such PCR amplification methods can be used to obtain nucleic acids comprising the sequence encoding the variable light chain region and/or the variable heavy chain region of an antibody. The amplified nucleic acids can be cloned into vectors for expression in host cells and for further cloning, for example, to generate chimeric and humanized antibodies.

[00366] If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin can be chemically synthesized or obtained from a suitable source (*e.g.*, an antibody cDNA library or a cDNA library generated from, or nucleic acid, preferably poly A⁺ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody described herein) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, *e.g.*, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR can then be cloned into replicable cloning vectors using any method well known in the art.

[00367] DNA encoding anti-GITR antibodies described herein can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the anti-GITR antibodies). Hybridoma cells can serve as a source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells (*e.g.*, CHO cells from the CHO GS System™ (Lonza)), or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of anti-GITR antibodies in the recombinant host cells.

[00368] To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a heavy chain constant region, *e.g.*, the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a light chain constant region, *e.g.*, human kappa or lambda constant regions. In certain embodiments, the vectors for expressing the VH or VL

domains comprise an EF-1 α promoter, a secretion signal, a cloning site for the variable domain, constant domains, and a selection marker such as neomycin. The VH and VL domains can also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, *e.g.*, IgG, using techniques known to those of skill in the art.

[00369] The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the murine sequences, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

[00370] Also provided are polynucleotides that hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides that encode an antibody described herein. In specific embodiments, polynucleotides described herein hybridize under high stringency, intermediate or lower stringency hybridization conditions to polynucleotides encoding a VH domain (*e.g.*, SEQ ID NO: 201, 203, 206, and 215-389) and/or VL domain (*e.g.*, 202, 204, 205, 207, 208, and 400-518 or SEQ ID NO: 519) provided herein.

[00371] Hybridization conditions have been described in the art and are known to one of skill in the art. For example, hybridization under stringent conditions can involve hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C; hybridization under highly stringent conditions can involve hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C. Hybridization under other stringent hybridization conditions are known to those of skill in the art and have been described, see, for example, Ausubel FM *et al.*, eds., (1989) Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3.

5.2.2 Cells and Vectors

[00372] In certain aspects, provided herein are cells (*e.g.*, host cells) expressing (*e.g.*, recombinantly) antibodies described herein (or an antigen-binding fragment thereof) which specifically bind to GITR (*e.g.*, human GITR) and related polynucleotides and expression vectors. Provided herein are vectors (*e.g.*, expression vectors) comprising polynucleotides comprising nucleotide sequences encoding anti-GITR antibodies or a fragment for recombinant expression in host cells, preferably in mammalian cells. Also provided herein are host cells

comprising such vectors for recombinantly expressing anti-GITR antibodies described herein (*e.g.*, human or humanized antibody). In a particular aspect, provided herein are methods for producing an antibody described herein, comprising expressing such antibody from a host cell.

[00373] Recombinant expression of an antibody described herein (*e.g.*, a full-length antibody, heavy and/or light chain of an antibody, or a single chain antibody described herein) that specifically binds to GITR (*e.g.*, human GITR) involves construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule, heavy and/or light chain of an antibody, or a fragment thereof (*e.g.*, heavy and/or light chain variable domains) described herein has been obtained, the vector for the production of the antibody molecule can be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody or antibody fragment (*e.g.*, light chain or heavy chain) encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody or antibody fragment (*e.g.*, light chain or heavy chain) coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Also provided are replicable vectors comprising a nucleotide sequence encoding an antibody molecule described herein, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody or a fragment thereof, or a heavy or light chain CDR, operably linked to a promoter. Such vectors can, for example, include the nucleotide sequence encoding the constant region of the antibody molecule (see, *e.g.*, International Publication Nos. WO 86/05807 and WO 89/01036; and U.S. Patent No. 5,122,464) and variable domains of the antibody can be cloned into such a vector for expression of the entire heavy, the entire light chain, or both the entire heavy and light chains.

[00374] An expression vector can be transferred to a cell (*e.g.*, host cell) by conventional techniques and the resulting cells can then be cultured by conventional techniques to produce an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) or a fragment thereof. Thus, provided herein are host cells containing a polynucleotide encoding an antibody described herein or fragments thereof, or a heavy or light chain thereof, or fragment thereof, or a single chain antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968,

pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), operably linked to a promoter for expression of such sequences in the host cell. In certain embodiments, for the expression of double-chained antibodies, vectors encoding both the heavy and light chains, individually, can be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below. In certain embodiments, a host cell contains a vector comprising a polynucleotide encoding both the heavy chain and light chain of an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), or a fragment thereof. In specific embodiments, a host cell contains two different vectors, a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), or a fragment thereof, and a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), or a fragment thereof. In other embodiments, a first host cell comprises a first vector comprising a polynucleotide encoding a heavy chain or a heavy chain variable region of an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), or a fragment thereof, and a second host cell comprises a second vector comprising a polynucleotide encoding a light chain or a light chain variable region of an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161). In specific embodiments, a heavy

chain/heavy chain variable region expressed by a first cell associated with a light chain/light chain variable region of a second cell to form an anti-GITR antibody described herein (*e.g.*, antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) or an antigen-binding fragment thereof. In certain embodiments, provided herein is a population of host cells comprising such first host cell and such second host cell.

[00375] In a particular embodiment, provided herein is a population of vectors comprising a first vector comprising a polynucleotide encoding a light chain/light chain variable region of an anti-GITR antibody described herein (*e.g.*, antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161), and a second vector comprising a polynucleotide encoding a heavy chain/heavy chain variable region of an anti-GITR antibody described herein (*e.g.*, antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161).

[00376] A variety of host-expression vector systems can be utilized to express antibody molecules described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161 (see, *e.g.*, U.S. Patent No. 5,807,715). Such host-expression systems represent vehicles by which the coding sequences of interest can be produced and subsequently purified, but also represent cells which can, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule described herein *in situ*. These include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (*e.g.*, *Saccharomyces Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing antibody coding sequences;

plant cell systems (*e.g.*, green algae such as *Chlamydomonas reinhardtii*) infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing antibody coding sequences; or mammalian cell systems (*e.g.*, COS (*e.g.*, COS1 or COS), CHO, BHK, MDCK, HEK 293, NS0, PER.C6, VERO, CRL7030, HsS78Bst, HeLa, and NIH 3T3, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20 and BMT10 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter). In a specific embodiment, cells for expressing antibodies described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) or an antigen-binding fragment thereof are CHO cells, for example CHO cells from the CHO GS System™ (Lonza). In a particular embodiment, cells for expressing antibodies described herein are human cells, *e.g.*, human cell lines. In a specific embodiment, a mammalian expression vector is pOptiVEC™ or pcDNA3.3. In a particular embodiment, bacterial cells such as *Escherichia coli*, or eukaryotic cells (*e.g.*, mammalian cells), especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary (CHO) cells, in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking MK & Hofstetter H (1986) *Gene* 45: 101-5; and Cockett MI *et al.*, (1990) *Biotechnology* 8(7): 662-7). In certain embodiments, antibodies described herein are produced by CHO cells or NS0 cells. In a specific embodiment, the expression of nucleotide sequences encoding antibodies described herein which immunospecifically bind GITR (*e.g.*, human GITR) is regulated by a constitutive promoter, inducible promoter or tissue specific promoter.

[00377] In bacterial systems, a number of expression vectors can be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such an antibody is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified can be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruether U & Mueller-Hill B (1983) *EMBO J* 2: 1791-1794), in which the antibody coding sequence can be ligated individually into the

vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye S & Inouye M (1985) Nuc Acids Res 13: 3101-3109; Van Heeke G & Schuster SM (1989) J Biol Chem 24: 5503-5509); and the like. For example, pGEX vectors can also be used to express foreign polypeptides as fusion proteins with glutathione 5-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[00378] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV), for example, can be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence can be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[00379] In mammalian host cells, a number of viral-based expression systems can be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest can be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene can then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (*e.g.*, see Logan J & Shenk T (1984) PNAS 81(12): 3655-9). Specific initiation signals can also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, *etc.* (see, *e.g.*, Bitter G *et al.*, (1987) Methods Enzymol. 153: 516-544).

[00380] In addition, a host cell strain can be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products can be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and

processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product can be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, Hela, MDCK, HEK 293, NIH 3T3, W138, BT483, Hs578T, HTB2, BT2O and T47D, NS0 (a murine myeloma cell line that does not endogenously produce any immunoglobulin chains), CRL703O, COS (*e.g.*, COS1 or COS), PER.C6, VERO, HsS78Bst, HEK-293T, HepG2, SP210, R1.1, B-W, L-M, BSC1, BSC40, YB/20, BMT10 and HsS78Bst cells. In certain embodiments, anti-GITR antibodies described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) are produced in mammalian cells, such as CHO cells.

[00381] In a specific embodiment, the antibodies described herein or antigen-binding fragments thereof have reduced fucose content or no fucose content. Such antibodies can be produced using techniques known one skilled in the art. For example, the antibodies can be expressed in cells deficient or lacking the ability of to fucosylate. In a specific example, cell lines with a knockout of both alleles of α 1,6-fucosyltransferase can be used to produce antibodies or antigen-binding fragments thereof with reduced fucose content. The Potelligent[®] system (Lonza) is an example of such a system that can be used to produce antibodies or antigen-binding fragments thereof with reduced fucose content.

[00382] For long-term, high-yield production of recombinant proteins, stable expression cells can be generated. For example, cell lines which stably express an anti-GITR antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) or an antigen-binding fragment thereof can be engineered. In specific embodiments, a cell provided herein stably expresses a light chain/light chain variable domain and a heavy chain/heavy chain variable domain which associate to form an antibody described herein (*e.g.*, an antibody comprising the CDRs of any one of antibodies Hum231#1, Hum231#2, pab1964, pab1965, pab1966, pab1967, pab1968, pab1969, pab1970, pab1971, pab1972, pab1973, pab1975, pab1976, pab1977, pab1979, pab1980, pab1981, pab1983, 231-32-15 or antibodies 1-107, or antibodies pab2159, pab2160, or pab2161) or an antigen-binding fragment thereof.

[00383] In certain aspects, rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer, sequences, transcription terminators, polyadenylation sites, *etc.*), and a selectable marker. Following the introduction of the foreign DNA/polynucleotide, engineered cells can be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method can advantageously be used to engineer cell lines which express an anti-GITR antibody described herein or a fragment thereof. Such engineered cell lines can be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

[00384] A number of selection systems can be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler M *et al.*, (1977) Cell 11(1): 223-32), hypoxanthineguanine phosphoribosyltransferase (Szybalska EH & Szybalski W (1962) PNAS 48(12): 2026-2034) and adenine phosphoribosyltransferase (Lowy I *et al.*, (1980) Cell 22(3): 817-23) genes can be employed in tk-, hgp^{rt}- or ap^{rt}-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr*, which confers resistance to methotrexate (Wigler M *et al.*, (1980) PNAS 77(6): 3567-70; O'Hare K *et al.*, (1981) PNAS 78: 1527-31); *gpt*, which confers resistance to mycophenolic acid (Mulligan RC & Berg P (1981) PNAS 78(4): 2072-6); neo, which confers resistance to the aminoglycoside G-418 (Wu GY & Wu CH (1991) Biotherapy 3: 87-95; Tolstoshev P (1993) Ann Rev Pharmacol Toxicol 32: 573-596; Mulligan RC (1993) Science 260: 926-932; and Morgan RA & Anderson WF (1993) Ann Rev Biochem 62: 191-217; Nabel GJ & Felgner PL (1993) Trends Biotechnol 11(5): 211-5); and *hygro*, which confers resistance to hygromycin (Santerre RF *et al.*, (1984) Gene 30(1-3): 147-56). Methods commonly known in the art of recombinant DNA technology can be routinely applied to select the desired recombinant clone and such methods are described, for example, in Ausubel FM *et al.*, (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler M, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli NC *et al.*, (eds.), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colbère-Garapin F *et al.*, (1981) J Mol Biol 150: 1-14, which are incorporated by reference herein in their entireties.

[00385] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington CR & Hentschel CCG, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.

3 (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse GF *et al.*, (1983) Mol Cell Biol 3: 257-66).

[00386] The host cell can be co-transfected with two or more expression vectors described herein, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors can contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. The host cells can be co-transfected with different amounts of the two or more expression vectors. For example, host cells can be transfected with any one of the following ratios of a first expression vector and a second expression vector: 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, or 1:50.

[00387] Alternatively, a single vector can be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot NJ (1986) Nature 322: 562-565; and Köhler G (1980) PNAS 77: 2197-2199). The coding sequences for the heavy and light chains can comprise cDNA or genomic DNA. The expression vector can be monocistronic or multicistronic. A multicistronic nucleic acid construct can encode 2, 3, 4, 5, 6, 7, 8, 9, 10 or more, or in the range of 2-5, 5-10 or 10-20 genes/nucleotide sequences. For example, a bicistronic nucleic acid construct can comprise in the following order a promoter, a first gene (*e.g.*, heavy chain of an antibody described herein), and a second gene and (*e.g.*, light chain of an antibody described herein). In such an expression vector, the transcription of both genes can be driven by the promoter, whereas the translation of the mRNA from the first gene can be by a cap-dependent scanning mechanism and the translation of the mRNA from the second gene can be by a cap-independent mechanism, *e.g.*, by an IRES.

[00388] Once an antibody molecule described herein has been produced by recombinant expression, it can be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (*e.g.*, ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies described herein can be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[00389] In specific embodiments, an antibody or an antigen-binding fragment thereof

described herein is isolated or purified. Generally, an isolated antibody is one that is substantially free of other antibodies with different antigenic specificities than the isolated antibody. For example, in a particular embodiment, a preparation of an antibody described herein is substantially free of cellular material and/or chemical precursors. The language “substantially free of cellular material” includes preparations of an antibody in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, an antibody that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (by dry weight) of heterologous protein (also referred to herein as a “contaminating protein”) and/or variants of an antibody, for example, different post-translational modified forms of an antibody or other different versions of an antibody (*e.g.*, antibody fragments). When the antibody is recombinantly produced, it is also generally substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, 2%, 1%, 0.5%, or 0.1% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is generally substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, or 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a specific embodiment, antibodies described herein are isolated or purified.

5.3 Pharmaceutical Compositions

[00390] Provided herein are compositions comprising an antibody or antigen-binding fragment thereof described herein having the desired degree of purity in a physiologically acceptable carrier, excipient or stabilizer (Remington's Pharmaceutical Sciences (1990) Mack Publishing Co., Easton, PA). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or

dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[00391] In a specific embodiment, pharmaceutical compositions comprise an antibody or antigen-binding fragment thereof described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In a specific embodiment, pharmaceutical compositions comprise an effective amount of an antibody or antigen-binding fragment thereof described herein, and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. *See* Section 5.4, *infra*, for examples of prophylactic or therapeutic agents. In some embodiments, the antibody is the only active ingredient included in the pharmaceutical composition. Pharmaceutical compositions described herein can be useful in enhancing, inducing or activating a GTR activity and treating a condition, such as cancer and an infectious disease.

[00392] Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances. Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[00393] A pharmaceutical composition may be formulated for any route of administration to a subject. Specific examples of routes of administration include intranasal, oral, pulmonary, transdermal, intradermal, and parenteral. Parenteral administration, characterized by either

subcutaneous, intramuscular or intravenous injection, is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[00394] Preparations for parenteral administration of an antibody include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

[00395] If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[00396] Topical mixtures comprising an antibody are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions or the like and can be formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[00397] An antibody or antigen-binding fragment thereof described herein can be formulated as an aerosol for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209 and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[00398] An antibody or antigen-binding fragment thereof described herein can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for

transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the antibody alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[00399] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer an antibody. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010,715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

[00400] In certain embodiments, a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof described herein is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions and other mixtures. It may also be reconstituted and formulated as solids or gels. The lyophilized powder is prepared by dissolving an antibody or antigen-binding fragment thereof described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to room temperature.

[00401] Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

[00402] The antibodies or antigen-binding fragments thereof described herein and other compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, e.g., U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751,

6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874. In a specific embodiment, an antibody or antigen-binding fragment thereof described herein is targeted to a tumor.

[00403] The compositions to be used for *in vivo* administration can be sterile. This is readily accomplished by filtration through, *e.g.*, sterile filtration membranes.

5.4 Uses and Methods

5.4.1 Therapeutic Uses and Methods

[00404] In one aspect, presented herein are methods for modulating one or more immune functions or responses in a subject, comprising to a subject in need thereof administering an anti-GITR antibody or antigen-binding fragment thereof described herein, or a composition thereof. In a specific aspect, presented herein are methods for activating, enhancing or inducing one or more immune functions or responses in a subject, comprising to a subject in need thereof administering an anti-GITR antibody or antigen-binding fragment thereof, or a composition thereof. In a specific embodiment, presented herein are methods for preventing and/or treating diseases in which it is desirable to activate or enhance one or more immune functions or responses, comprising administering to a subject in need thereof an anti-GITR antibody or antigen-binding fragment thereof described herein or a composition thereof. In other specific embodiments, the method comprises combination therapy, wherein the anti-GITR antibody or antigen-binding fragment thereof is administered to a subject in combination with another therapy, such as those described below, to activate or enhance one or more immune functions or responses. In certain embodiments, the anti-GITR antibody or antigen-binding fragment thereof is administered as an adjuvant in combination with an antigenic composition. In certain embodiments, the antigenic composition comprises a cancer or tumor antigen (*e.g.*, the bcr/abl antigen in leukemia, HPVE6 and E7 antigens of the oncogenic virus associated with cervical cancer, the MAGE1 and MZ2-E antigens in or associated with melanoma, or the MVC-1 and HER-2 antigens in or associated with breast cancer). In some embodiments, the antigenic composition comprises an antigen derived from a pathogen (*e.g.*, a viral antigen, parasitic antigen, bacterial antigen or fungal antigen). Examples of viral antigens include the nucleoprotein (NP) of influenza virus, HIV antigens (*e.g.*, gag proteins of HIV, HIV env protein (*e.g.*, gp120 and/or gp41), HIV Nef protein, HIV Pol proteins, HIV reverse transcriptase, or HIV protease), Ebola virus (EBOV) antigens (*e.g.*, EBOV NP or glycoprotein), small pox antigens, hepatitis A, B or C virus antigens, human rhinovirus antigens, Herpes simplex virus antigens, poliovirus antigens, foot-and-mouth disease virus (FMDV) antigens, rabies virus antigens,

rotavirus antigens, coxsackie virus antigens, and human papilloma virus (HPV) antigens. Examples of bacterial antigens include *Bordetella pertussis* (e.g., P69 protein and filamentous haemagglutinin (FHA) antigens), *Vibrio cholerae*, *Bacillus anthracis*, and *E. coli* antigens such as *E. coli* heat Labile toxin B subunit (LT-B), *E. coli* K88 antigens, and enterotoxigenic *E. coli* antigens.

[00405] As used herein, the term “in combination” refers to the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). The use of the term “in combination” does not restrict the order in which therapies are administered to a subject with a disease or disorder, or the route of administration. A first therapy (e.g., a prophylactic or therapeutic agent) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to a subject with a disease or disorder or a symptom thereof. In certain embodiments, a therapy (e.g., an agent) administered in combination with an anti-GITR antibody or antigen-binding fragment thereof to a subject is administered in the same composition (e.g., pharmaceutical composition). In other embodiments, a therapy (e.g., an agent) administered in combination with an anti-GITR antibody or antigen-binding fragment thereof is administered to a subject in a different composition (e.g., two or more pharmaceutical compositions). The two compositions may be administered at the same or different times and/or by the same or different routes of administration. In a particular embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with a vaccine composition to induce, activate or enhance the immune response elicited by the vaccine composition. In one embodiment, the vaccine composition is a cancer vaccine. A cancer vaccine is an agent, molecule, or immunogen which stimulates or elicits an endogenous immune response in an individual or subject against one or more cancer antigens. The cancer antigen can be a tumor associated peptide, or protein that induces or enhances immune response and is derived from tumor associated genes and encoded proteins including, for example, MAGE-A1, MAGE-A2, MAGE-A3, MAGE-A4, MAGE-A5, MAGE-A6, MAGE-A7, MAGE-A8, MAGE-A9, MAGE-A10, MAGE-A11, MAGE-A12, MAGE-A13, GAGE-1, GAGE-2, GAGE-3, GAGE-4, GAGE-5, GAGE-6, GAGE-7, GAGE-8, BAGE-1, RAGE-1, LB33/MUM-1, PRAME, NAG, MAGE-Xp2 (MAGE-B2), MAGEXp3 (MAGE-B3), MAGE-

Xp4 (AGE-B4), tyrosinase, brain glycogen phosphorylase, Melan-A, MAGE-C1, MAGE-C2, NY-ESO-1, LAGE-1, SSX-1, SSX-2(HOM-MEL-40), SSX-1, SSX-4, SSX-5, SCP-1, CT-7, alpha-actinin-4, Bcr-Abl fusion protein, Casp-8, beta-catenin, cdc27, cdk4, cdkn2a, coa-1, dekan fusion protein, EF2, ETV6-AML1 fusion protein, LDLR-fucosyltransferaseAS fusion protein, HLA-A2, HLA-A11, hsp70-2, KIAA0205, Mart2, Mum-2, and 3, neo-PAP, myosin class I, OS-9, pml-RAR α fusion protein, PTPRK, K-ras, N-ras, Triosephosphate isomeras, GnTV, Herv-K-mel, Lage-1, Mage-C2, NA-88, /Lage-2, SP17, and TRP2-Int2, (MART-I), gp100 (Pmel 17), TRP-1, TRP-2, MAGE-1, MAGE-3, p15(58), CEA, NY-ESO (LAGE), SCP-1, Hom/Mel-40, p53, H-Ras, HER-2/neu, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR, Epstein Barr virus antigens, EBNA, human papillomavirus (HPV) antigens E6 and E7, TSP-180, MAGE-4, MAGE-5, MAGE-6, p185erbB2, p180erbB-3, c-met, nm-23H1, PSA, TAG-72-4, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, beta-Catenin, CDK4, Mum-1, p16, TAGE, PSMA, PSCA, CT7, telomerase, 43-9F, 5T4, 791Tgp72, .alpha.-fetoprotein, 13HCG, BCA225, BTAA, CA 125, CA 15-3 (CA 27.29\BCAA), CA 195, CA 242, CA-50, CAM43, CD68\KP1, CO-029, FGF-5, G250, Ga733 (EpCAM), HTgp-175, M344, MA-50, MG7-Ag, MOV18, NB\170K, NYCO-1, RCAS1, SDCCAG16, TA-90 (Mac-2 binding protein\cyclophilin C-associated protein), TAAL6, TAG72, TLP, and TPS. Cancer vaccines are useful to either increase recognition of cancer cells by the immune system or enhance the anti-tumor response through lymphocyte activation. Effector T cells have been successfully generated by immunization with intact tumor cells or extract, purified antigens, use of peptides optimized for binding to both MHC and TcR, immune dominant peptides, DNA encoding tumor antigens, recombinant viruses encoding tumor antigens or antigen pulsed antigen-presenting cells. In some embodiments, enhancement of immune recognition and cell expansion may be improved by the use of co-stimulators and cytokines, injection of vectors to express cytokines, *in vitro* antigen-pulsed and activated autologous dendritic cells and by blocking negative modulators (*e.g.*, using immune checkpoint targeting agents) and by depleting T-regulatory cells.

[00406] In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with a heat shock protein based tumor vaccine or a heat shock protein based pathogen vaccine. See Sections 5.4.1.1 and 5.4.1.2 below regarding heat shock protein based tumor vaccines or heat shock protein based pathogen vaccines for use in combination with an anti-GITR antibody or antigen-binding fragment thereof described herein.

[00407] In a particular embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an adjuvant to induce, activate or

enhance the agonistic effects of the anti-GITR antibody. Various adjuvants can be used depending on the treatment context. Non-limiting examples of appropriate adjuvants include, for example, Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), motanide ISA (incomplete seppic adjuvant), the Ribi adjuvant system (RAS), Titer Max, muramyl peptides, Syntex Adjuvant Formulation (SAF), alum (aluminum hydroxide and/or aluminum phosphate), aluminum salt adjuvants, Gerbu[®] adjuvants, nitrocellulose absorbed antigen, encapsulated or entrapped antigen, immuno-stimulating complexes such as saponins, Quil A, QS-21 and others. Other adjuvants include CpG oligonucleotides and double stranded RNA molecules, such as poly(A), poly(U). Combinations of the above adjuvants may also be used. In some embodiments, one or more adjuvants are a saponin, such as QS-21, QS-21 and 3 De-O-acylated monophosphoryl lipid A (3 D-MPL), and immunostimulatory oligonucleotides and saponin adjuvants as disclosed in U.S. Patent Nos. 6,645,495; 7,029,678 and 7,858,589, respectively.

[00408] In certain embodiments, provided herein are methods for enhancing the stimulation of GITR-responsive cells (*e.g.*, T cells, such as effector T-cells) comprising incubating *ex vivo* the GITR-responsive cells (*e.g.*, T cells) with an antibody or antigen-binding fragment thereof described herein. In some embodiments, the GITR-responsive cells are incubated with a stimulating agent (*e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) prior to, simultaneously with or subsequent to the incubation with the anti-GITR antibody or antigen-binding fragment thereof. In certain embodiments, the GITR-responsive cells (*e.g.*, T cells) were isolated from a subject (*e.g.*, a human). In some embodiments, the GITR-responsive cells following stimulation with the anti-GITR antibody or antigen binding fragment thereof are administered to a subject (*e.g.*, a human). The GITR-response cells (*e.g.*, T cells) may be administered to the same or a different subject than the cells were originally isolated from.

[00409] In some embodiments, provided herein are methods for activating GITR-responsive cells (*e.g.*, T cells) comprising incubating the GITR-responsive cells (*e.g.*, T cells) with an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the GITR-responsive cells are incubated with a stimulating agent (*e.g.*, a T cell receptor complex stimulating agent such as, *e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) prior to, simultaneously with or subsequent to the incubation with the anti-GITR antibody or antigen-binding fragment thereof. In some embodiments, the GITR-responsive cells (*e.g.*, T cells) were isolated from a subject (*e.g.*, a human). In certain embodiments, the GITR-

responsive cells following activation with the anti-GITR antibody or antigen-binding fragment thereof are administered to a subject (*e.g.*, a human). The GITR-responsive cells (*e.g.*, T cells) may be administered to the same or a different subject than the cells were originally isolated from.

[00410] In some embodiments, cells responsive to GITR (*i.e.*, GITR-responsive cells) are incubated in cell culture with an anti-GITR antibody or antigen-binding fragment thereof described herein, and administered to a subject to enhance immune function (*e.g.*, to enhance the expansion/proliferation of GITR-responsive cells, such as T cells, and/or enhance T cell effector function) and/or to treat cancer and/or prevent or treat an infectious disease. Examples of cancers and infectious diseases are provided herein. See, *e.g.*, Example 7 below for exemplary methods. In specific embodiments, the GITR-responsive cells are effector T cells (*e.g.*, CD4⁺ and CD8⁺). In some embodiments, the GITR-responsive cells are isolated from a subject. In some embodiments, the GITR-responsive cells are assessed for GITR expression prior to incubation with an anti-GITR antibody or antigen-binding fragment thereof described herein. In certain embodiments, the GITR-responsive cells are incubated with a mitogen (*e.g.*, a T cell mitogen, such as, *e.g.*, phytohaemagglutinin (PHA) and/or phorbol myristate acetate (PMA), or a TCR complex stimulating antibody, such as an anti-CD3 antibody and anti-CD28 antibody) prior to, simultaneously with or subsequent to the incubation with an anti-GITR antibody or antigen-binding fragment thereof described herein. The GITR responsive cells may be incubated with an anti-GITR antibody or antigen-binding fragment thereof described herein for, *e.g.*, 5 minutes, 10 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 12 hours, 18 hours, 24 hours or more. In certain embodiments, the GITR-responsive cells which are administered to a subject were derived from the subject (*i.e.*, the GITR-responsive cells are autologous). In other embodiments, the GITR-responsive cells which are administered to a subject were derived from a different subject. The GITR-responsive cells following incubation with anti-GITR antibody or antigen-binding fragment thereof may be administered locally or systemically to a subject via any route known to one of skill in the art (*e.g.*, parenteral administration, such as subcutaneous, intravenous, or intramuscular administration, or intratumoral administration). In certain embodiments, a suitable dose of GITR-responsive cells following incubation with anti-GITR antibody or an antigen-binding fragment thereof administered to subject may be at least 100, 200, 300, 400, 500, 700, 1,000, 5,000, 10,000, 25,000, 50,000, 100,000, 1×10^6 , 1×10^7 , or 1×10^8 cells. The GITR-responsive cells following incubation with anti-GITR antibody or antigen-binding fragment thereof may be administered 1, 2, 3, 4, 5, 6, 7, 8 or more times. The frequency and dose of GITR-responsive

cells following incubation with anti-GITR antibody or antigen-binding fragment thereof which are administered to a subject will vary depending on several factors, including, *e.g.*, the condition of the patient. In another embodiment, provided herein is a method for enhancing the expansion of T cells (*e.g.*, CD4⁺ and/or CD8⁺ T cells) in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In another embodiment, provided herein is a method for enhancing the expansion of CD8⁺ T cells in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In another embodiment, provided herein is a method for enhancing the expansion of CD4⁺ T cells in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In a specific embodiment, the subject is human.

[00411] In another embodiment, provided herein is a method for enhancing the expansion of T cells (*e.g.*, CD4⁺ and/or CD8⁺ T cells) and/or T cell effector function in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In another embodiment, provided herein is a method for enhancing the expansion of CD8⁺ T cells and/or T cell effector function in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In another embodiment, provided herein is a method for enhancing the expansion of CD4⁺ T cells and/or T cell effector function in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a pharmaceutical composition described herein. In a specific embodiment, the subject is human.

[00412] In another embodiment, provided herein is a method for preferential expansion of effector T-cells over the expansion of T-regulatory cells, comprising incubating *ex vivo* T-cells with an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the anti-GITR antibody or antigen-binding fragment thereof expands effector T-cells over T-regulatory cells by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80% or greater. In some embodiments, the anti-GITR antibody or antigen-binding fragment thereof expands effector T-cells over T-regulatory cells by 10% to 20%, 15% to 25%, 25% to 50%, 30% to 60%, 50% to 75% or 65% to 85%. The effector T-cells and T-regulatory cells can be distinguished from each other by cell surface markers, such as those disclosed in the

examples *infra*. In some embodiments, the T-cells were isolated from a subject (*e.g.*, a human). In certain embodiments, the T-cells after expansion are administered to a subject (*e.g.*, a human).

[00413] In another embodiment, provided herein is a method for preferential expansion of effector T-cells over the expansion of T-regulatory cells in a subject, comprising administering to the subject an effective amount of an antibody or antigen-binding fragment thereof described herein, or a composition thereof. In certain embodiments, the anti-GITR antibody or antigen-binding fragment thereof expands effector T-cells over T-regulatory cells by 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80% or greater. In some embodiments, the anti-GITR antibody or antigen-binding fragment thereof expands effector T-cells over T-regulatory cells by 10% to 20%, 15% to 25%, 25% to 50%, 30% to 60%, 50% to 75% or 65% to 85%. The effector T-cells and T-regulatory cells can be distinguished from each other by cell surface markers and/or intracellular markers, such as those disclosed in the examples *infra*. In a specific embodiment, the subject is human.

[00414] In certain embodiments, treatment of a subject with an anti-GITR antibody or antigen-binding fragment described herein, or a composition thereof achieves one, two, three, four or more of the following effects: (i) reduction or amelioration of the severity of a disease or symptom associated therewith; (ii) reduction in the duration of a symptom associated with a disease; (iii) inhibition of the progression of a disease or symptom associated therewith; (iv) regression of a disease or symptom associated therewith; (v) prevention of the development or onset of a symptom associated with a disease that is present in the patient; (vi) inhibition of the recurrence of a symptom associated with a disease; (vii) reduction in the hospitalization of a subject; (viii) reduction in the hospitalization length; (ix) an increase in the survival of a subject with a disease; (x) a reduction in the number of symptoms associated with a disease; and (xi) an enhancement, improvement, supplementation, complementation or augmentation of the therapeutic effect(s) of another therapy. In an alternative embodiment, an anti-GITR antibody or antigen-binding fragment thereof is used to prevent a disorder, such as an infectious disease.

[00415] In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof, or a composition thereof is administered to a subject in combination with an immunotherapeutic agent. Immunotherapeutic agents for use in the combination therapies disclosed herein include, but are not limited to, a Her2/neu receptor antibody such as trastuzumab (marketed as Herceptin[®]), an anti-CD52 antibody such as alemtuzumab (marketed as Campath[®], MabCampath[®] or Campath-1H), an anti-CD33 antibody such as gemtuzumab linked to calicheamicin (marketed as Mylotarg[®]), an anti-CD20 antibody such as rituximab (marketed as Rituxan[®] and MabThera[®]), Ibritumomab tiuxetan (marketed as Zevalin[®]), anti-TNF α antibodies

such as infliximab (marketed as Remicade[®]) or adalimumab (marketed as Humira[®]), a soluble TNFR2 molecule such as etanercept (marketed as Enbrel[®]), an antibody to the CD25 chain of the IL-2 receptor such as basiliximab (marketed as Simulect[®]), an anti-CD40/CD40L antibody such as humanized IgG₁ anti-human CD40 antibody (SGN-40), Toll-like receptor agonists such as monophosphoril lipid A (MPL[®]), CpG, single-stranded RNA, nucleotides, nucleotide analogue, CL087 (a TLR7-specific ligand), loxoribine, polyinosinepolycytidylic acid, flagellin, resiquimod, immiquimod, gardiquimod, NOD ligands such as muramyl dipeptide, murabutide, peptidoglycan and muramyldipeptide, CD1d agonists, such as α -galactosyl ceramide (α -GalCer) and threitol ceramide (ThrCer), an antibody such as Fresolimumab[®] (GC1008), an antibody targeting an inhibiting TGF-beta isoforms 1, 2 or 3, an Fc fusion, Dalantercept (Alk-Fc), and the small molecule LY2157299 (receptor kinase inhibitor).

[00416] Diseases that can be treated by an enhancement of immune function include cancer and infectious diseases. Various cancers and infectious diseases are described below. In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein can be used to treat a condition associated with cancer or a condition resulting from the administration of an anti-cancer therapy (such as, *e.g.*, chemotherapy or radiation). In a particular embodiment, an anti-GITR antibody or antigen-binding fragment thereof can be used to treat or manage lymphocytopenia. In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof is administered to a patient diagnosed with cancer to increase the proliferation and/or effector function of one or more immune cell populations (*e.g.*, T cell effector cells, such as CD4⁺ and CD8⁺ T cells) in the patient.

[00417] In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein activates or enhances or induces one or more immune functions or responses in a subject by at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative to the immune function in a subject not administered the anti-GITR antibody or antigen-binding fragment thereof described herein using assays well known in the art, *e.g.*, ELISPOT, ELISA, and cell proliferation assays. In a specific embodiment, the immune function is cytokine production (*e.g.*, interferon-gamma, IL-2, IL-5, IL-10, IL-12, or transforming growth factor (TGF) –alpha production). In another embodiment, the immune function is T cell proliferation/expansion, which can be assayed, *e.g.*, by flow cytometry to detect the number of cells expressing markers of T cells (*e.g.*, CD3, CD4, or CD8). In another embodiment, the immune function is antibody production, which can be

assayed, *e.g.*, by ELISA. In some embodiments, the immune function is effector function, which can be assayed, *e.g.*, by a cytotoxicity assay or other assays well known in the art. In another embodiment, the immune function is a Th1 response. In another embodiment, the immune function is a Th2 response. In another embodiment, the immune function is a memory response.

[00418] In specific embodiments, non-limiting examples of immune functions that may be enhanced or induced by an anti-GITR antibody or antigen-binding fragment thereof are proliferation/expansion of effector lymphocytes (*e.g.*, increase in the number of effector T lymphocytes), inhibition of apoptosis of effector lymphocytes (*e.g.*, effector T lymphocytes), and suppression of Tregs. In particular embodiments, an immune function enhanced or induced by an anti-GITR antibody or antigen-binding fragment thereof described herein is proliferation/expansion in the number of or activation of CD4⁺ T cells (*e.g.*, Th1 and Th2 helper T cells), CD8⁺ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, CD122⁺ T cells, natural killer (NK) cells), macrophages, monocytes, dendritic cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes. In one embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein activates or enhances the proliferation/expansion or number of lymphocyte progenitors. In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof described herein increases the number of CD4⁺ T cells (*e.g.*, Th1 and Th2 helper T cells), CD8⁺ T cells (*e.g.*, cytotoxic T lymphocytes, alpha/beta T cells, and gamma/delta T cells), B cells (*e.g.*, plasma cells), memory T cells, memory B cells, tumor-resident T cells, CD122⁺ T cells, natural killer cells (NK cells), macrophages, monocytes, dendritic cells, mast cells, eosinophils, basophils or polymorphonucleated leukocytes by approximately at least 99%, at least 98%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10%, or in the range of between 10% to 25%, 25% to 50%, 50% to 75%, or 75% to 95% relative a negative control (*e.g.*, number of the respective cells not treated, cultured, or contacted with an anti-GITR antibody or antigen-binding fragment thereof described herein).

[00419] In particular embodiments, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, activates or enhances an activity of human GITR independent of TCR triggering. In specific embodiments, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), induces, activates or enhances an activity of NF-κB independent of TCR triggering. In certain embodiments, the activity of NF-κB can be assessed in, *e.g.*, an assay comprising the following steps: (a) incubating T cells (*e.g.*,

Jurkat cells) expressing a NF- κ B-luciferase reporter construct (*e.g.*, GloResponse NF- κ B-luc2P construct) and GITR (*e.g.*, human GITR) with the antibody described herein or an isotype control antibody at an antibody concentration of, *e.g.*, 12.5, 10, 5, 2.5, 1.25, or 0.625 μ g/ml, in the absence of an anti-CD3 antibody; and (b) reading luciferase signal after, *e.g.*, 2, 5, 6, 8 or 18 hours of incubation using, *e.g.*, an EnVision multilabel reader 2100, wherein a positive luciferase signal relative to the isotype control antibody indicates the activity of NF- κ B. In a particular embodiment, the luciferase signal is read after 5 hours of incubation.

[00420] In another embodiment, provided herein is a method of activating T cells independent of TCR triggering comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein. In particular embodiments, provided herein is a method of inducing, activating or enhancing an activity of NF- κ B independent of TCR triggering comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein. In certain embodiments, the activity of NF- κ B can be assessed in, *e.g.*, an assay comprising the following steps: (a) incubating T cells (*e.g.*, Jurkat cells) expressing a NF- κ B-luciferase reporter construct (*e.g.*, GloResponse NF- κ B-luc2P construct) and GITR (*e.g.*, human GITR) with the antibody described herein or an isotype control antibody at an antibody concentration of, *e.g.*, 12.5, 10, 5, 2.5, 1.25, or 0.625 μ g/ml, in the absence of an anti-CD3 antibody; and (b) reading luciferase signal after, *e.g.*, 2, 5, 6, 8 or 18 hours of incubation using, *e.g.*, an EnVision multilabel reader 2100, wherein a positive luciferase signal relative to the isotype control antibody indicates the activity of NF- κ B. In a particular embodiment, the luciferase signal is read after 5 hours of incubation.

[00421] In particular embodiments, provided herein is a method of increasing the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein. An increase in the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells can be assessed in, *e.g.*, an assay comprising the following steps: (a) incubating, *e.g.*, human PBMCs with, *e.g.*, an anti-CD3 antibody at various suboptimal concentrations (*e.g.*, 0.3-5 μ g/ml); and, *e.g.*, an antibody described herein, which immunospecifically binds to GITR (*e.g.*, human GITR), at, *e.g.*, 5 μ g/ml or an isotype control antibody, for, *e.g.*, 3-4 days at 37°C and 5% CO₂; (b) treating cells with, *e.g.*, Brefeldin A for, *e.g.*, 6 hours at 37°C and 5% CO₂; (c) staining the surface of the cells using, *e.g.*, an anti-CD3 antibody, an anti-CD4 antibody, and an anti-CD8 α antibody; (d) staining intracellularly using, *e.g.*, an anti-IFN γ antibody and an anti-TNF α antibody; and (e) determining the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells relative to the isotype control antibody. In specific

embodiments, the polyfunctional (IFN γ + TNF α +) T cells are selected from the group consisting of polyfunctional (IFN γ + TNF α +) CD4+ T cells and polyfunctional (IFN γ + TNF α +) CD8+ T cells.

[00422] In particular embodiments, provided herein is a method of increasing surface expression of OX40 and PD-1 in activated T cells comprising contacting T cells with an antibody or antigen-binding fragment thereof described herein. The surface expression of OX40 and PD-1 in activated T cells can be increased by at least about 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 200 fold, 300 fold, 400 fold, 500 fold, 600 fold, 700 fold, 800 fold, 900 fold, or 1000 fold as assessed by methods described herein and/or known to one of skill in the art, relative to surface expression of OX40 and PD-1 in activated T cells without the antibody described herein.

5.4.1.1 Cancer

[00423] In a specific aspect, presented herein are methods for treating cancer, comprising administering to a subject in need thereof an effective amount of an anti-GITR antibody or antigen-binding fragment thereof described herein or a composition thereof. In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein or a composition thereof is the only active agent administered to a subject.

[00424] The effect of an anti-GITR antibody or antigen-binding fragment thereof described herein on proliferation of cancer cells can be detected by routine assays, such as by assays that measure the uptake of radiolabeled thymidine. Alternatively, cell viability can be measured by assays that measure lactate dehydrogenase (LDH), a stable cytosolic enzyme that is released upon cell lysis, or by the release of [^{51}Cr] upon cell lysis. In one embodiment, necrosis measured by the ability or inability of a cell to take up a dye such as neutral red, trypan blue, or ALAMARTM blue (Page B *et al.*, (1993) Intl J Oncology 3: 473-6). In such an assay, the cells are incubated in media containing the dye, the cells are washed, and the remaining dye, reflecting cellular uptake of the dye, is measured spectrophotometrically.

[00425] In another embodiment, the dye is sulforhodamine B (SRB), whose binding to proteins can be used as a measure of cytotoxicity (Skehan P *et al.*, (1990) J Nat Cancer Inst 82: 1107-12). In yet another embodiment, a tetrazolium salt, such as MTT, is used in a quantitative colorimetric assay for mammalian cell survival and proliferation by detecting living, but not dead, cells (see, *e.g.*, Mosmann T (1983) J Immunol Methods 65: 55-63).

[00426] In other embodiments, apoptotic cells are measured in both the attached and

“floating” compartments of the cultures. Both compartments are collected by removing the supernatant, trypsinizing the attached cells, and combining both preparations following a centrifugation wash step (10 minutes, 2000 rpm). The protocol for treating tumor cell cultures with sulindac and related compounds to obtain a significant amount of apoptosis has been described in the literature (see, *e.g.*, Piazza GA *et al.*, (1995) Cancer Res 55: 3110-6). Features of this method include collecting both floating and attached cells, identification of the optimal treatment times and dose range for observing apoptosis, and identification of optimal cell culture conditions.

[00427] In another embodiment, apoptosis is quantitated by measuring DNA fragmentation. Commercial photometric methods for the quantitative *in vitro* determination of DNA fragmentation are available. Examples of such assays, including TUNEL (which detects incorporation of labeled nucleotides in fragmented DNA) and ELISA-based assays, are described in Biochemica, (1999) 2: 34 37 (Roche Molecular Biochemicals). In yet another embodiment, apoptosis can be observed morphologically.

[00428] Cancer cell lines on which such assays can be performed are well known to those of skill in the art. Apoptosis, necrosis and proliferation assays can also be performed on primary cells, *e.g.*, a tissue explant.

[00429] In specific embodiments, the administration of an anti-GITR antibody or antigen-binding fragment thereof described herein or a composition thereof to a subject with cancer (in some embodiments, an animal model for cancer) achieves at least one, two, three, four or more of the following effects: (i) the reduction or amelioration of the severity of one or more symptoms of cancer; (ii) the reduction in the duration of one or more symptoms associated with cancer; (iii) the prevention in the recurrence of a symptom associated with cancer; (iv) the reduction in hospitalization of a subject; (v) a reduction in hospitalization length; (vi) the increase in the survival of a subject; (vii) the enhancement or improvement of the therapeutic effect of another therapy; (viii) the inhibition of the development or onset of one or more symptoms associated with cancer; (ix) the reduction in the number of symptoms associated with cancer; (x) improvement in quality of life as assessed by methods well known in the art; (xi) inhibition of the recurrence of a tumor; (xii) the regression of tumors and/or one or more symptoms associated therewith; (xiii) the inhibition of the progression of tumors and/or one or more symptoms associated therewith; (xiv) a reduction in the growth of a tumor; (xv) a decrease in tumor size (*e.g.*, volume or diameter); (xvi) a reduction in the formation of a newly formed tumor; (xvii) eradication, removal, or control of primary, regional and/or metastatic tumors; (xviii) a decrease in the number or size of metastases; (xix) a reduction in mortality; (xx) an increase in relapse

free survival; (xx) the size of the tumor is maintained and does not increase or increases by less than the increase of a tumor after administration of a standard therapy as measured by conventional methods available to one of skill in the art, such as magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI (DCE-MRI), X-ray, and computed tomography (CT) scan, or a positron emission tomography (PET) scan; and/or (xxi) an increase in the length of remission in patients.

[00430] In certain embodiments, two or more different anti-GITR antibodies or antigen-binding fragments thereof described herein are administered to a subject. In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with one or more other therapies, *e.g.*, anti-cancer agents, cytokines, cellular vaccines or anti-hormonal agents, to treat cancer.

[00431] In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with radiation therapy comprising, *e.g.*, the use of x-rays, gamma rays and other sources of radiation to destroy the cancer cells. In specific embodiments, the radiation treatment is administered as external beam radiation or teletherapy wherein the radiation is directed from a remote source. In other embodiments, the radiation treatment is administered as internal therapy or brachytherapy wherein a radioactive source is placed inside the body close to cancer cells or a tumor mass. In one aspect, an anti-GITR antibody or antigen-binding fragment thereof described herein can activate or enhance the immune function or response in a cancer patient with a compromised immune system due to anti-cancer therapy.

[00432] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with chemotherapy. In an embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein can be used before, during or after radiation therapy or chemotherapy. Examples of chemotherapeutic agents include cyclophosphamide, methotrexate, cyclosporin A, leflunomide, cisplatin, ifosfamide, taxanes such as taxol and paclitaxol, topoisomerase I inhibitors (*e.g.*, CPT 11, topotecan, 9 AC, and GG 211), gemcitabine, vinorelbine, oxaliplatin, 5-fluorouracil (5-FU), leucovorin, vinorelbine, temodal, cytochalasin B, gramicidin D, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1 dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin homologs, and cytoxan.

[00433] In one embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with cyclophosphamide, *e.g.*, a low

dose of cyclophosphamide. Cyclophosphamide (Elostan, Cytosan), is a chemotherapeutic agent that has an immunomodulatory function when used at low doses (*e.g.*, up to 300 mg/m², 300 mg/m² or about 300 mg/m² when administered intravenously). Specifically, low doses of cyclophosphamide can reduce the number and proliferative capacity of regulatory T cells (Treg) (*e.g.*, CD4+CD25+FoxP3+ cells or, alternatively, CD45+CD3+CD4+CD8-FOXP3+CD25hiCD127low cells) and modulate immune-suppressive networks. In some embodiments, the dosage of a cyclophosphamide administration is about 50 mg/m², 100 mg/m², 200 mg/m², 300 mg/m², 500 mg/m², or more. In some embodiments, the dosage of a cyclophosphamide administration is in a range of 10 mg/m² to 100 mg/m², 50 mg/m² to 200 mg/m², 50 mg/m² to 300 mg/m², 50 mg/m² to 500 mg/m². In some embodiments, cyclophosphamide is administered to the subject within 1 hour, 2 hours, 3 hours, 4 hours, 8 hours, 12 hours, 1 day, 5 days or more prior to or following an initial administration of an anti-GITR antibody or antigen-binding fragment thereof described herein. In some embodiments, anti-GITR antibody or antigen-binding fragment thereof described herein is used in combination with cyclophosphamide, *e.g.*, low dose cyclophosphamide, for the treatment of metastatic renal cell carcinoma (RCC).

[00434] In one embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with a Treg-inhibitory agent. Examples of Treg-inhibitory agents include Zenapax[®] (daclizumab) (Roche), which is a human anti-CD25 monoclonal antibody used, *e.g.*, for inducing immune suppression in organ transplantation. Daclizumab blocks IL-2 binding to CD25, which is also a signal for the maintenance of Tregs. Another agent that inhibits Tregs is Sutent[®] (Sunitinib) (Pfizer) which is a small molecule, multi-targeted tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma (RCC) and other cancers. Another agent that may inhibit Tregs is 1-Methyl-D-tryptophan (1-MT), a competitive inhibitor of indoleamine 2,3-dioxygenase (IDO). IDO is an immunosuppressive agent expressed in certain normal and neoplastic cells and may be associated with an increase in Tregs in cancer patients. Additional Treg inhibitors include agents that block trafficking of Tregs to the tumor microenvironment. Such agents may include antibodies against certain chemokines and chemokine receptors such as CCL17, CCL22 and CCR4.

[00435] Further examples of Treg-inhibitory agents that may be used in accordance with methods described herein are disclosed in the following patent applications, which are incorporated herein by reference in their entirety for all purposes: U.S. Patent Publication Nos. US 2009/0214533, US 2012/0142750, US 2011/0305713, US 2009/0004213, US 2012/0219559, US 2010/0278844, US 2013/0323283 and US 2008/0152665.

[00436] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein can be administered to a subject before, during or after surgery.

[00437] In certain embodiments, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with an immune modulator or antibody. Immune modulators or antibodies may be, but are not limited to, adjuvants, antigens, anti-CD3 (*e.g.*, OKT3), checkpoint targeting agents or modulators, or interleukins. The terms “checkpoint targeting agent” or “checkpoint modulator” can be used interchangeably and refer to an agent that selectively modulates expression or activity of a regulatory molecule (*e.g.*, a co-inhibitory checkpoint molecule (*e.g.*, protein) or a costimulatory checkpoint molecule (*e.g.*, protein), which may be, *e.g.*, a receptor or a ligand) of an immune system checkpoint.

Checkpoint targeting agents can be selected from the group consisting of an agonist of a checkpoint molecule, an antagonist of a checkpoint molecule, a polypeptide (*e.g.*, a peptide ligand, an antibody, an antibody fragment) that selectively targets a checkpoint molecule; a small molecule that selectively targets a checkpoint molecule; and a regulatory nucleic acid (*e.g.*, an siRNA, miRNA) that selectively modulates expression or activity of a checkpoint molecule. In one embodiment, a checkpoint targeting agent can be selected from the group consisting of an antagonist of PD-1, an antagonist of PD-L1, an antagonist of PD-L2, an antagonist of CTLA-4, an antagonist of TIM-3, an antagonist of LAG-3, an agonist of GITR, and an agonist of OX40. Thus, in some embodiments, an anti-GITR agonistic antibody (*e.g.*, Hum231#1, Hum231#2 or Hum231#2w) or antigen-binding fragment thereof, may be administered in combination with, *e.g.*, an anti-CTLA-4 antagonist antibody or antigen-binding fragment thereof, or another checkpoint targeting agent, either in a single pharmaceutical composition, or in separate pharmaceutical compositions administered together or separately.

[00438] In some embodiments, provided herein are methods for treating cancer in a subject comprising administering to the subject an anti-GITR antibody or antigen-binding fragment thereof and an agonist of OX40 and/or an antagonist(s) of LAG-3, TIM-3, PD-1 and/or CTLA-4. In some embodiments, the cancer is selected from glioblastoma multiforme, metastatic melanoma, resistant metastatic melanoma, metastatic ovarian cancer, metastatic renal cell carcinoma, head and neck cancer, gastric cancer, esophageal cancer, non-small cell lung cancer, pediatric brain tumors, low-grade astrocytoma, ependymoma, and meduloblastoma.

[00439] In a specific embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered to a subject in combination with an agent that inhibits (partially or completely) CTLA-4 signal transduction, such as an antibody that specifically binds to human CTLA-4 (*e.g.*, tremelimumab (Pfizer); ipilimumab (Yervoy[®], Bristol-Myers Squibb)) or a

CTLA-4-Ig fusion protein. In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof is used in combination with an antagonist of CTLA-4 (e.g., tremelimumab or ipilimumab) for the treatment of metastatic ovarian cancer. In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof is used in combination with an antagonist of CTLA-4 (e.g., tremelimumab or ipilimumab) for the treatment of metastatic ovarian cancer that is resistant to an antagonist of CTLA-4 (e.g., tremelimumab or ipilimumab). In some embodiments, an anti-GITR antibody or antigen-binding fragment thereof and an antagonist of CTLA-4 (e.g., tremelimumab or ipilimumab) are used for the treatment of glioblastoma multiforme. In some embodiments, the glioblastoma multiforme is recurrent. In some embodiments, the glioblastoma multiforme is newly diagnosed. In some embodiments, the glioblastoma multiforme is in a subject having non -methylated MGMT promoters. In some embodiments, the glioblastoma multiforme is refractory to Bevacizumab therapy. In some embodiments, the glioblastoma multiforme is in a subject that has not received Bevacizumab therapy. Examples of anti-CTLA-4 antibodies that may be used in treatment methods disclosed herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entirety for all purposes: International Publication Nos. WO 00/037504, WO 01/014424 and WO 09/100140; U.S. Patent Nos. 6,207,156 and 7,034,121. Further examples of anti-CTLA-4 antibodies that may be used in accordance with the methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entirety for all purposes, U.S. Patent Nos. 7,465,446, 8,263,073; 8,142,778 and 8,226,946; and U.S. Application Nos. US 2003/086930, US 2005/226875, US 2007/243184, US 2009/123477 and US 2011/044953.

[00440] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that inhibits (partially or completely) LAG-3 signal transduction, such as an antibody that specifically binds to human LAG-3. Examples of anti-LAG-3 antibodies or antibody fragments thereof that may be used in treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entirety for all purposes: U.S. Patent Nos. 6,143,273 and 6,197,524; U.S. Patent Publication Nos. US 2011/0150892, US 2010/0233183 and US 2010/196394.

[00441] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that inhibits (partially or completely) TIM-3 signal transduction, such as an antibody that specifically binds to human TIM-3. Examples of anti-TIM-3 antibodies or antibody fragments thereof that may be used in

treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent Nos. 7,470,428 and 8,101,176; U.S. Publication Nos. US 2013/0022623, US 2010/0100131, US 2010/0100131 and US 2010/061992.

[00442] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that inhibits (partially or completely) PD-1 signal transduction, such as an antibody that specifically binds to human PD-1. In some embodiments, an anti-PD-1 antibody or antibody fragment thereof is administered to a subject as described herein. In some embodiments, the anti-PD-1 antibody is Nivolumab (BMS-936558 or MDX1106) or Lambrolizumab (MK-3475) or Pidilizumab (CT-011). Further non-limiting examples of anti-PD-1 antibodies that may be used in treatment methods disclosed herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent No. 6,808,710; 7,488,802; 8,008,449; 8,114,845 and 8,168,757, U.S. Publication No. US 2013/0202623 and PCT Publication No. WO 2013/033091.

[00443] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that inhibits (partially or completely) PD-L1 activity, such as an antibody that specifically binds to human PD-L1. In some embodiments, the anti-PD-L1 antibody is BMS-936559, MPDL3280A, MEDI4736 or MSB0010718C. Further non-limiting examples of anti-PD-L1 antibodies that may be used in treatment methods disclosed herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent No. 8,168,179 and U.S. Publication Nos. US 2010/0203056 and US 2003/0232323. In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that inhibits (partially or completely) PD-L2 activity, such as an antibody that specifically binds to human PD-L2.

[00444] In another embodiment, an anti-GITR antibody or antigen-binding fragment thereof described herein is administered in combination with an agent that activates or enhances OX-40 signal transduction, such as an antibody that specifically binds to human OX-40. Examples of anti-OX40 antibodies or antibody fragments thereof that may be used in treatment methods described herein are disclosed in the following patents and patent applications, which are incorporated herein by reference in their entireties for all purposes: U.S. Patent No. 7,550,140; 7,807,156; 8,283,450; 8,614,295 and 7,531,170; U.S. Publication No. US 2010/0196359, US 2010/0136030 and US 2013/0183315.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED:

1. An isolated antibody that specifically binds to human glucocorticoid-induced TNFR-related protein (GITR), comprising:

(a) a heavy chain variable region (VH) complementarity determining region (CDR) 1 comprising the amino acid sequence of $X_1YX_2MX_3$ (SEQ ID NO: 1), wherein

X_1 is D, E, G or A;

X_2 is A, V, L, I, P, F, M or Y; and

X_3 is Y, G, N, Q, S, T, C, W, F or H;

(b) a VH CDR2 comprising the amino acid sequence of $X_1IX_2X_3X_4SGX_5X_6X_7YX_8QKFX_9X_{10}$ (SEQ ID NO: 2), wherein

X_1 is V, A, L, I, P, F, M or T;

X_2 is R, K, H, Q or A;

X_3 is T, G, N, Q, S, C, W, Y, V, I or P;

X_4 is Y, G, N, Q, S, T, C, W, F, H, or A;

X_5 is D, E, G or A;

X_6 is V, A, L, I, P, F, M or T;

X_7 is T, G, N, Q, S, C, W, Y, V, I, P or A;

X_8 is N, G, Q, S, T, C, W, Y or A;

X_9 is K, R, H, Q or A; and

X_{10} is D, E, G or A;

(c) a VH CDR3 comprising the amino acid sequence of $SGTVRGX_1X_2X_3$ (SEQ ID NO: 3), wherein

X_1 is F, A, V, L, I, P, M, Y, W, H or S;

X_2 is A, or D; and

X_3 is Y, G, N, Q, S, T, C, W, F, H or V;

(d) a light chain variable region (VL) CDR1 comprising the amino acid sequence of $KSSQSX_1X_2X_3X_4X_5X_6X_7KX_8Y LX_9$ (SEQ ID NO: 4), wherein:

X_1 is L, A, V, I, P, F or M;

X_2 is L, A, V, I, P, F, M or S;

X_3 is N, G, Q, S, T, C, W, Y or A;

X_4 is S, G, N, Q, T, C, W, Y or A;

X_5 is G, N, Q, S, T, C, W, Y or A;

X_6 is N, G, Q, S, T, C, W, Y or A;

X₇ is Q, G, N, S, T, C, W, Y or A;

X₈ is N, G, Q, S, T, C, W, Y or A; and

X₉ is T, G, N, Q, S, C, W, Y, V, I or A;

(e) a VL CDR2 comprising the amino acid sequence of X₁ASTRX₂X₃ (SEQ ID NO: 5), wherein:

X₁ is W, G, N, Q, S, T, C, Y, F, H or A;

X₂ is E, D or A; and

X₃ is S, G, N, Q, T, C, W, Y or A; and

(f) a VL CDR3 comprising the amino acid sequence of QX₁X₂YX₃X₄PYT (SEQ ID NO: 6), wherein:

X₁ is N, G, Q, S, T, C, W or Y;

X₂ is D, E or Y; and

X₃ is S, G, N, Q, T, C, W, Y or A; and

X₄ is Y, G, N, Q, S, T, C, W, F, H, L, or A.

2. An isolated antibody that specifically binds to human GITR, comprising:

(a) a heavy chain variable region (VH) CDR1 comprising the amino acid sequence of X₁YX₂MX₃ (SEQ ID NO: 7), wherein

X₁ is D, E or G;

X₂ is A or V; and

X₃ is Y or H;

(b) a VH CDR2 comprising the amino acid sequence of X₁IX₂TX₃SGX₄X₅X₆YNQKFX₇X₈ (SEQ ID NO: 8), wherein

X₁ is V or L;

X₂ is R, K or Q;

X₃ is Y or F;

X₄ is D, E or G;

X₅ is V or L;

X₆ is T or S;

X₇ is K, R or Q; and

X₈ is D, E or G;

(c) a VH CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO: 9);

(d) a light chain variable region (VL) CDR1 comprising the amino acid sequence of KSSQSLLNSX₁NQKNYLX₂ (SEQ ID NO: 10), wherein

X₁ is G or S; and

X₂ is T or S;

(e) a VL CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 11);
and

(f) a VL CDR3 comprising the amino acid sequence of QNX₁YSX₂PYT (SEQ ID NO: 12), wherein

X₁ is D or E; and

X₂ is Y, F or S.

3. The antibody of claim 1 or 2, wherein the VH CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 13, 19-23, and 117-119.
4. The antibody of claim 1 or 2, wherein the VH CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 35 and SEQ ID NO: 116.
5. The antibody of claim 1 or 2, wherein the VH CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 24-33, and 120-188.
6. The antibody of claim 1 or 2, wherein the VH CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 114, 115, and 194.
7. The antibody of claim 1 or 2, wherein the VH CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 15, 34 and 189.
8. The antibody of claim 1 or 2, wherein the VL CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 16 and 101-104.
9. The antibody of claim 1 or 2, wherein the VL CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 17 and 105.
10. The antibody of claim 1 or 2, wherein the VL CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 18, 106-109, 192, and 193.
11. The antibody of claim 1 or 2, wherein the VH CDR1, VH CDR2, and VH CDR3 each comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antibody in Table 2.
12. The antibody of claim 1 or 2, wherein the VH CDR1, VH CDR2, and VH CDR3 each comprise the amino acid sequence of the VH CDR1, VH CDR2, and VH CDR3 of an antibody in Table 6.
13. The antibody of claim 1 or 2, wherein the VL CDR1, VL CDR2, and VL CDR3 each comprise the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in Table 1.
14. The antibody of claim 1 or 2, wherein the VL CDR1, VL CDR2, and VL CDR3 each

comprise the amino acid sequence of the VL CDR1, VL CDR2, and VL CDR3 of an antibody in Table 5.

15. An isolated antibody that specifically binds to human GTR, comprising:
 - (a) a heavy chain variable region (VH) comprising a VH CDR1 comprising the amino acid sequence of DYAMY (SEQ ID NO: 13),
 - a VH CDR2 comprising the amino acid sequence of VIRTYSGDVTYNQKFKD (SEQ ID NO: 14), and
 - a VH CDR3 comprising the amino acid sequence of SGTVRGFAY (SEQ ID NO: 15); and
 - (b) a light chain variable region (VL) comprising a VL CDR1 comprising the amino acid sequence of KSSQSLLNSGNQKNYLT (SEQ ID NO: 16),
 - a VL CDR2 comprising the amino acid sequence of WASTRES (SEQ ID NO: 17), and
 - a VL CDR3 comprising the amino acid sequence of QNDYSYPYT (SEQ ID NO: 18).
16. An isolated antibody that specifically binds to human GTR, comprising the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2, and VH CDR3 of antibody 22 as set forth in Table 1 and Table 2.
17. The antibody of any one of claims 1-16, wherein the antibody partially inhibits human GTR ligand (GITRL) from binding to human GTR.
18. The antibody of any one of claims 1-16, wherein the antibody at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM of human GITRL from binding to human GTR coupled to beads at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody in a suspension array assay.
19. The antibody of any one of claims 1-16, wherein at least 20% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody in an assay comprising the following steps:
 - (a) coupling human GTR to beads at a concentration of 5pg/ml/bead;
 - (b) incubating the human GTR coupled beads at a concentration of 40 beads/ μ l with or without 1000ng/ml of the antibody in a well;
 - (c) adding labeled human GITRL to the well to obtain a final concentration of 0.5nM of the human GITRL and 20 beads/ μ l of the GTR coupled beads; and
 - (d) detecting the labeled human GITRL bound to the human GTR coupled beads.
20. The antibody of claim 17 or 18, wherein the antibody inhibits 50% to 70% of human GITRL binding to human GTR.

21. The antibody of claim 19, wherein 30% to 50% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody.
22. An isolated antibody that specifically binds to human GTR and partially inhibits human GTR ligand (GITRL) from binding to human GTR.
23. The antibody of claim 22, wherein the antibody at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM of human GITRL from binding to human GTR coupled to beads at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody in a suspension array assay.
24. The antibody of claim 22, wherein at least 20% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody as assessed in an assay comprising the following steps:
 - (a) coupling human GTR to beads at a concentration of 5pg/ml/bead;
 - (b) incubating the human GTR coupled beads at a concentration of 40 beads/ μ l with or without 1000ng/ml of the antibody in a well;
 - (c) adding labeled human GITRL to the well to obtain a final concentration of 0.5nM of the human GITRL and 20 beads/ μ l of the GTR coupled beads; and
 - (d) detecting the labeled human GITRL bound to the human GTR coupled beads.
25. The antibody of claim 22 or 23, wherein the antibody inhibits 50% to 70% of human GITRL binding to human GTR.
26. The antibody of claim 24, wherein 30% to 50% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody.
27. The antibody of any one of claims 1-26, wherein the antibody is agonistic.
28. The antibody of any one of claims 1-21, wherein the antibody further comprises a heavy chain variable region sequence comprising the framework regions of the heavy chain variable region sequence of SEQ ID NO: 203.
29. The antibody of any one of claims 1-15 or 17-28, wherein the antibody comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 203.
30. The antibody of any one of claims 1-27, wherein the antibody comprises a framework region of a heavy chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95% or 100% identical to a framework region of a heavy chain variable region sequence selected from the group consisting of SEQ ID NO: 201, SEQ ID NO: 206, and SEQ ID NOS: 215 to

389.

31. The antibody of any one of claims 1-27, wherein the antibody comprises a heavy chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 201, 206, and SEQ ID NOS: 215 to 389.
32. The antibody of claim 31, wherein the antibody comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 206.
33. The antibody of any one of claims 1-27, wherein the antibody comprises a heavy chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 553, 554 and 567 to 570.
34. The antibody of any one of claim 1-27, wherein the antibody comprises a heavy chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 581 and 582.
35. The antibody of any one of claims 1-27, wherein the antibody comprises a heavy chain variable region having human derived framework regions.
36. The antibody of any one of claims 1-27, wherein the antibody further comprises a heavy chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein said amino acid sequence is selected from the group consisting of IGHV1-2*02 (SEQ ID NO: 601), IGHV1-3*01 (SEQ ID NO: 602), IGHV1-46*01 (SEQ ID NO: 603), IGHV1-18*01 (SEQ ID NO: 604), IGHV1-69*01 (SEQ ID NO: 605), and IGHV7-4-1*02 (SEQ ID NO: 606).
37. The antibody of claim 36, wherein the antibody comprises a heavy chain variable framework region that is derived from amino acid sequence SEQ ID NO: 601 and wherein at least one amino acid in amino acid sequence SEQ ID NO: 601 is substituted with an amino acid in an analogous position in a corresponding non-human heavy chain variable framework region.
38. The antibody of claim 37, wherein the amino acid substitution is at an amino acid position selected from the group consisting of 24, 48, 67, 71, 73, and 94, and wherein the amino acid position of each group member is indicated according to the Kabat numbering.
39. The antibody of claim 38, wherein the amino acid substitution is selected from the group consisting of 24G, 48I, 67A, 71V, 73K, and 94K, and wherein the amino acid position of each group member is indicated according to the Kabat numbering.
40. The antibody of any one of claims 1-39, wherein the antibody further comprises a light chain variable region sequence comprising the framework regions of the light chain variable region sequence of SEQ ID NO: 204 or SEQ ID NO: 205.
41. The antibody of any one of claims 1-15 or 17-39, wherein the antibody comprises a light

chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 204 or SEQ ID NO: 205.

42. The antibody of any one of claims 1-39, wherein the antibody further comprises a framework region of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to a framework region of a light chain variable region sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208, and SEQ ID NOs: 400-518.
43. The antibody of any one of claims 1-39, wherein the antibody further comprises a framework region of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to the framework region of a light chain variable region sequence of SEQ ID NO: 519.
44. The antibody of any one of claims 1-39, wherein the antibody comprises a light chain variable region sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 202, SEQ ID NO: 207, SEQ ID NO: 208 and SEQ ID NOs: 400 to 518.
45. The antibody of claim 42, wherein the antibody comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 519.
46. The antibody of claim 44, wherein the antibody comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 207.
47. The antibody of claim 44, wherein the antibody comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO: 208.
48. The antibody of any one of claims 1-39, wherein the antibody comprises a light chain sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 555, 556 and 571 to 576.
49. The antibody of any one of claims 1-39, wherein the antibody comprises a light chain variable sequence having human derived framework regions.
50. The antibody of any one of claims 1-39, wherein the antibody comprises a light chain variable framework region that is or is derived from an amino acid sequence encoded by a human gene, wherein said amino acid sequence is selected from the group consisting of IGKV4-1*01 (SEQ ID NO: 607) and IGKV3-7*02 (SEQ ID NO: 608).
51. The antibody of claim 50, wherein the antibody comprises a light chain variable framework region that is derived from an amino acid sequence selected from the group consisting of IGKV4-1*01 (SEQ ID NO: 607) and IGKV3-7*02 (SEQ ID NO: 608) and at least one amino acid in amino acid sequence SEQ ID NO: 607 or SEQ ID NO: 608 is substituted with an

amino acid in an analogous position in a corresponding non-human light chain variable framework region.

52. The antibody of claim 51, wherein the amino acid substitution is at amino acid position 87, and wherein the amino acid position is indicated according to the Kabat numbering.
53. The antibody of claim 52, wherein the amino acid substitution is 87H, and wherein the amino acid position is indicated according to the Kabat numbering.
54. The antibody of any one of claims 1-27, wherein the antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of an antibody in the table of Figure 23 or any one of Figures 24A-24C.
55. The antibody of any one of claims 1-27, wherein the antibody comprises a heavy chain variable region and a light chain variable region comprising the amino acid sequences of an antibody in Table 17.
56. An isolated antibody that specifically binds to human GITR, comprising:
 - (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 206; and
 - (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 207.
57. An isolated antibody that specifically binds to human GITR, comprising:
 - (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 206; and
 - (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 208.
58. An isolated antibody that specifically binds to human GITR, comprising a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, a VH CDR3 and framework regions derived from a human immunoglobulin, wherein the VH CDR1 comprises the amino acid sequence of DYAMY (SEQ ID NO: 13), the VH CDR2 comprises the amino acid sequence of VIRTYSGDVTYNQKFKD (SEQ ID NO: 14) and the VH CDR3 comprises the amino acid sequence of SGTVRGFAY (SEQ ID NO: 15).
59. An isolated antibody that specifically binds to human GITR, comprising a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, a VL CDR3 and framework regions derived from a human immunoglobulin, wherein the VL CDR1 comprises the amino acid sequence of KSSQSLLNSGNQKNYLT (SEQ ID NO: 16), the VL CDR2 comprises the amino acid sequence of WASTRES (SEQ ID NO: 17) and the VL CDR3 comprises the amino acid sequence of QNDYSYPYT (SEQ ID NO: 18).
60. An isolated antibody that specifically binds to human GITR, comprising a heavy chain variable region (VH) comprising an amino acid sequence selected from the group consisting

of SEQ ID NO: 201, 203, 206 and 215-389.

61. An isolated antibody that specifically binds to human GTR, comprising a light chain variable region (VL) comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 202, 204, 205, 207, 208 and 400-518.
62. An isolated antibody that specifically binds to human GTR, comprising a light variable region (VL) comprising the amino acid sequence of SEQ ID NO: 519.
63. The antibody of any one of claims 58-62, wherein the antibody partially inhibits human GITRL from binding to human GTR.
64. The antibody of any one of claims 58-62, wherein the antibody at a concentration of 1000ng/ml inhibits less than 80% of 0.5nM of human GITRL from binding to human GTR coupled to beads at a concentration of 5pg/ml/bead relative to the binding of 0.5nM GITRL to the GTR coupled beads at a concentration of 5pg/ml/bead in the absence of the anti-GTR antibody in a suspension array assay.
65. The antibody of any one of claims 58-62, wherein at least 20% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody as assessed in an assay comprising the following steps:
 - (a) coupling human GTR to beads at a concentration of 5pg/ml/bead;
 - (b) incubating the human GTR coupled beads at a concentration of 40 beads/ μ l with or without 1000ng/ml of the antibody in a well;
 - (c) adding labeled human GITRL to the well to obtain a final concentration of 0.5nM of the human GITRL and 20 beads/ μ l of the GTR coupled beads; and
 - (d) detecting the labeled human GITRL bound to the human GTR coupled beads.
66. The antibody of claim 63 or 64, wherein the antibody inhibits 50% to 70% of human GITRL binding to human GTR.
67. The antibody of claim 65, wherein 30% to 50% of the amount of human GITRL that binds to human GTR in the absence of the antibody binds to human GTR in the presence of the antibody.
68. An isolated antibody that specifically binds to human GTR, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL amino acid sequences comprise the amino acid sequence listed in a single row of Figure 23 or any one of Figures 24A-24C.
69. An isolated antibody that specifically binds to human GTR, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL amino acid sequences comprise the amino acid sequence listed in a single row of Table 17.

70. The antibody of any one of claims 1-32, 35-47 or 49-69, further comprising heavy and/or light chain constant regions.
71. The antibody of claim 70, wherein the heavy chain constant region is selected from the group of human immunoglobulins consisting of IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂.
72. The antibody of claim 70 or 71, wherein the light chain constant region is selected from the group of human immunoglobulins consisting of IgG_κ and IgG_λ.
73. The antibody of claim 72, wherein the IgG₁ is non-fucosylated IgG₁.
74. The antibody of claim 72, wherein the amino acid sequence of IgG₁ comprises a N297A mutation.
75. The antibody of claim 72, wherein the amino acid sequence of IgG₁ comprises a N297Q mutation.
76. The antibody of claim 72, wherein the amino acid sequence of IgG₄ comprises a S228P mutation.
77. The antibody of claim 72, wherein the amino acid sequence of IgG₂ comprises a C127S mutation.
78. The antibody of claim 72, wherein the heavy chain constant region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 557-562.
79. The antibody of claim 72, wherein the heavy chain constant region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 583-584.
80. The antibody of any one of claims 1-27, wherein the antibody comprises:
- (a) a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 553, 554, and 567 to 570; and
 - (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576.
81. The antibody of any one of claims 1-27, wherein the antibody comprises:
- (a) a heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 581 and 582; and
 - (b) a light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 555, 556, and 571 to 576.
82. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556.
83. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and

- (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556.
84. The antibody of claim 81, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 581; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556.
85. The antibody of claim 81, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 556.
86. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 553; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555.
87. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 555.
88. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 573.
89. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.
90. The antibody of claim 80, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 554; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.
91. The antibody of claim 81, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 581; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.
92. The antibody of claim 81, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 582; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 576.
93. An isolated antibody that specifically binds to GITR, wherein the antibody comprises:
- (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 567; and
 - (b) a light chain comprising the amino acid sequence of SEQ ID NO: 587.
94. An isolated antibody that binds to the same epitope of human GITR as the antibody of any one of claims 1-93.
95. The antibody of any one of claims 1-94, wherein the antibody binds to human GITR

comprising residues 26-241 of SEQ ID NO: 701, wherein the binding between the antibody and a variant GITR is substantially weakened relative to the binding between the antibody and the human GITR, and wherein the variant GITR comprises residues 26-241 of SEQ ID NO: 701 except for an amino acid substitution selected from the group consisting of D60A and G63A.

96. The antibody of any one of claims 1-94, wherein the antibody binds to an epitope comprising residues 60-63 of SEQ ID NO: 701.
97. The antibody of any one of claims 1-94, wherein the antibody binds to at least one residue within the amino acid sequence set forth by residues 60-63 of SEQ ID NO: 701.
98. The antibody of any one of claims 1-94, wherein the antibody binds an epitope of the human GITR comprising at least one of residues 60 or 63 of SEQ ID NO: 701.
99. The antibody of any one of claims 1-94, wherein the antibody specifically binds to each of i) human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701 and ii) a variant of cynomolgus GITR, the variant comprising residues 26-234 of SEQ ID NO: 699, wherein the antibody does not specifically bind to cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 704.
100. The antibody of any one of claims 1-94, wherein the antibody exhibits, as compared to binding to human GITR, reduced or absent binding to a protein identical to human GITR except for the presence of a D60A or G63A amino acid substitution.
101. An isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, wherein the binding between the antibody and a variant GITR is substantially weakened relative to the binding between the antibody and the human GITR, and wherein the variant GITR comprises residues 26-241 of SEQ ID NO: 701 except for an amino acid substitution selected from the group consisting of D60A and G63A.
102. The antibody of claim 95 or 101, wherein the amino acid substitution is D60A.
103. The antibody of claim 95 or 101, wherein the amino acid substitution is G63A.
104. An isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the antibody binds to an epitope comprising residues 60-63 of SEQ ID NO: 701.
105. An isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the antibody binds to at least one residue within the amino acid sequence set forth by residues 60-63 of SEQ ID NO: 701.
106. The antibody of claim 97 or 105, wherein the antibody binds to at least one residue selected

from the group consisting of residues 60, 62, and 63 of SEQ ID NO: 701.

107. The antibody of claim 97 or 105, wherein the antibody binds to at least one residue selected from the group consisting of residues 62 and 63 of SEQ ID NO: 701.
108. An isolated antibody that specifically binds to human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701, and wherein the antibody binds an epitope of the human GITR comprising at least one of residues 60 or 63 of SEQ ID NO: 701.
109. An isolated antibody that specifically binds to each of i) human GITR, wherein the human GITR comprises residues 26-241 of SEQ ID NO: 701 and ii) a variant of cynomolgus GITR, the variant comprising residues 26-234 of SEQ ID NO: 699, wherein the antibody does not specifically bind to cynomolgus GITR comprising residues 26-234 of SEQ ID NO: 704.
110. An isolated antibody that specifically binds to human GITR, wherein the antibody exhibits, as compared to binding to human GITR, reduced or absent binding to a protein identical to human GITR except for the presence of a D60A or G63A amino acid substitution.
111. The antibody of any one of claims 94-110, wherein the antibody induces, activates, or enhances an activity of human GITR.
112. An isolated antibody that competes with the antibody of any one of claims 1-111 for binding to human GITR to the extent that the antibody of any one of claims 1-111 self-competes for binding to human GITR.
113. An isolated first antibody that competes with the antibody of any one of claims 1-111 for binding to human GITR, wherein the first antibody competes for binding in an assay comprising the following steps:
- (a) incubating GITR-transfected cells with the first antibody in unlabeled form in a container;
 - (b) adding the antibody of any one of claims 1-111 in labeled form to the cells in the container and incubating the cells in the container; and
 - (c) detecting the binding of the antibody of any one of claims 1-111 in labeled form to the cells.
114. An isolated first antibody that competes with the antibody of any one of claims 1-111 for binding to human GITR, wherein the competition is exhibited as reduced binding of the first antibody to human GITR by more than 80%.
115. The antibody of any one of claims 1-114, wherein the antibody induces, activates or enhances an activity of human GITR.
116. The antibody of any one of claims 1-115, wherein the antibody induces, activates or enhances an activity of human GITR in a cell independent of TCR triggering.
117. The antibody of any one of claims 1-116, wherein the antibody induces, activates or

enhances an activity of NF- κ B in a cell independent of TCR triggering.

118. The antibody of claim 116 or 117, wherein the cell is a T cell.
119. The antibody of claim 116 or 117, wherein the cell is not a T cell.
120. The antibody of claim 116 or 117, wherein the cell is selected from the group consisting of a B cell, a plasma cell, a memory cell, a natural killer cell, a granulocyte, a neutrophil, an eosinophil, a basophil, a mast cell, a monocyte, a dendritic cell, a plasmacytoid dendritic cell, an NKT cell, and a macrophage.
121. The antibody of any one of claims 1-120, wherein the antibody increases the percentage of polyfunctional (IFN γ + TNF α +) T cells.
122. The antibody of any one of claims 1-121, wherein the antibody, when bound to activated regulatory T cells, binds to activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64 to a greater extent than the antibody, when bound to activated effector T cells, binds to the activating Fc gamma receptors selected from the group consisting of CD16, CD32A and CD64.
123. The antibody of claim 122, wherein the activating Fc gamma receptor is expressed on a cell selected from the group consisting of myeloid-derived effector cells and lymphocyte-derived effector cells.
124. The antibody of any one of claims 1-123, wherein the antibody increases surface expression of OX40, PD-1, or a combination thereof in activated T cells.
125. The antibody of any one of claims 1-68, wherein the antibody is a humanized antibody, murine antibody or chimeric antibody.
126. The antibody of any one of claims 1-125, wherein the antibody binds to human GITR with a K_D in the range of about 0.5 nM to 5 nM.
127. The antibody of any one of claims 1-126 further comprising a detectable label.
128. An isolated nucleic acid molecule encoding a heavy chain variable region and/or a light chain variable region, or a light chain and/or a heavy chain of the antibody of any one of claims 1-127.
129. The isolated nucleic acid molecule of claim 128, wherein the nucleic acid molecule encodes a heavy chain variable region comprising the nucleic acid sequence of SEQ ID NO: 209.
130. The isolated nucleic acid molecule of claim 128 or 129, wherein the nucleic acid molecule encodes a light chain variable region comprising the nucleic acid sequence of SEQ ID NO: 210 or SEQ ID NO: 211.
131. An isolated vector comprising the nucleic acid molecule of claim 128, 129 or 130.

132. A host cell comprising the isolated nucleic acid molecule of 128, 129, or 130, or the isolated vector of claim 131.
133. The host cell of claim 132, which is selected from the group consisting of *E. coli*, *Pseudomonas*, *Bacillus*, *Streptomyces*, yeast, CHO, YB/20, NS0, PER-C6, HEK-293T, NIH-3T3, HeLa, BHK, Hep G2, SP2/0, R1.1, B-W, L-M, COS 1, COS 7, BSC1, BSC40, BMT10 cell, plant cell, insect cell, and human cell in tissue culture.
134. A method of producing an antibody that binds to human GITR comprising culturing the host cell of claim 132 or 133 so that the nucleic acid molecule is expressed and the antibody is produced.
135. An isolated antibody that specifically binds to human GITR and is encoded by the isolated nucleic acid molecule of any one of claims 128-130.
136. A pharmaceutical composition comprising the antibody of any one of claims 1-127, the nucleic acid molecule of any one of claims 128-130, the vector of claim 131, or the host cell of claim 132 or 133, and a pharmaceutically acceptable carrier or excipient.
137. A pharmaceutical composition comprising the antibody of any one of claims 1-127, and a pharmaceutically carrier or excipient.
138. A method of modulating an immune response in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
139. The method of claim 138, which is a method for enhancing or inducing the immune response of the subject.
140. A method for enhancing the expansion of T cells and T cell effector function in a subject, comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
141. A method for enhancing the expansion of CD8⁺ T cells in a subject, comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
142. A method for activating T cells independent of TCR triggering in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 136 or 137.
143. A method for inducing, activating or enhancing an activity of NF- κ B independent of TCR triggering in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 136 or 137.
144. A method for increasing the percentage of polyfunctional (IFN γ ⁺ TNF α ⁺) T cells in a

subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 136 or 137.

145. A method for increasing surface expression of OX40, PD-1, or a combination thereof, in activated T cells in a subject, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 136 or 137.
146. A method of treating cancer in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
147. The method of claim 146, wherein the cancer is squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's or non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, salivary gland carcinoma, kidney cancer, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, or a type of head or neck cancer.
148. The method of claim 147, wherein the cancer is desmoplastic melanoma, inflammatory breast cancer, thymoma, rectal cancer, anal cancer, or surgically treatable or non-surgically treatable brain stem glioma.
149. The method of claim 146, further comprising administering to the subject an inhibitor of indoleamine-2,3-dioxygenase (IDO).
150. The method of claim 149, wherein the inhibitor is selected from the group consisting of epacadostat, F001287, indoximod, and NLG919.
151. The method of claim 149, wherein the inhibitor is epacadostat.
152. The method of claim 149, wherein the inhibitor is F001287.
153. The method of claim 149, wherein the inhibitor is indoximod.
154. The method of claim 149, wherein the inhibitor is NLG919.
155. A method of treating a viral infection in a subject, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
156. The method of claim 155, wherein the viral infection is a viral infection caused by a human papilloma virus (HPV), a Herpes simplex or other herpes virus, hepatitis B virus (HBV), hepatitis C virus (HCV) or other hepatitis virus, measles virus, HIV or Epstein Barr virus (EBV).
157. A method of treating cancer in a subject, the method comprising: administering to the

subject in need thereof an effective amount of the antibody of any one of claims 1-127 in combination with another therapeutic agent.

158. The method of claim 157, wherein the other therapeutic agent is an inhibitor of indoleamine-2,3-dioxygenase (IDO), wherein the antibody and the inhibitor of IDO are administered in different pharmaceutical compositions and as separate dosage forms.
159. The method of claim 158, wherein the inhibitor is selected from epacadostat, F001287, indoximod and NLG919.
160. The method of claim 157, wherein the other therapeutic agent is a checkpoint targeting agent.
161. The method of claim 160, wherein the checkpoint targeting agent is selected from the group consisting of an antagonist of PD-1, an antagonist of PD-L1, an antagonist of PD-L2, an antagonist of CTLA-4, an antagonist of TIM-3, an antagonist of LAG-3, and an agonist of OX40.
162. The method of claim 160, wherein the checkpoint targeting agent is selected from the group consisting of an antagonist anti-PD-1 antibody, an antagonist anti-PD-L1 antibody, an antagonist anti-PD-L2 antibody, an antagonist anti-CTLA-4 antibody, an antagonist anti-TIM-3 antibody, an antagonist anti-LAG-3 antibody, and an agonist anti-OX40 antibody.
163. The method of claim 161, wherein the other therapeutic agent is an antagonist of PD-1 or an agonist of OX40.
164. The method of claim 161, wherein the antagonist of PD-1 or the agonist of OX40 is administered subsequent to the administration of the anti-GITR antibody.
165. The method of claim 161, wherein the antagonist of PD-1 or the agonist of OX40 is administered simultaneously with the anti-GITR antibody or prior to the administration of the anti-GITR antibody.
166. The method of claim 157, wherein the other therapeutic agent is an anti-CD25 antibody.
167. The method of claim 166, wherein the anti-CD25 antibody is administered subsequent to the administration of the anti-GITR antibody.
168. The method of claim 166, wherein the anti-CD25 antibody is administered simultaneously with the anti-GITR antibody or prior to the administration of the anti-GITR antibody.
169. A method of treating cancer in a subject, the method comprising administering an anti-PD-1 antibody to a subject who has received an anti-GITR antibody, wherein the anti-PD-1 antibody is administered at a time at which the anti-GITR antibody has increased expression of PD-1 in the subject relative to expression of PD-1 in the subject at the time of the administering.

170. A method of treating cancer in a subject, the method comprising administering an anti-OX40 antibody to a subject who has received an anti-GITR antibody, wherein the anti-OX40 antibody is administered at a time at which the anti-GITR antibody has increased expression of OX40 in the subject relative to expression of OX40 in the subject at the time of the administering.
171. A method of treating cancer in a subject comprising administering an anti-GITR antibody to a subject in need thereof, wherein the anti-GITR antibody increases expression of PD-1 in the subject relative to expression of PD-1 in the subject at the time of the administering, and administering an anti-PD-1 antibody to the subject when expression of PD-1 is increased.
172. A method of treating cancer in a subject comprising administering an anti-GITR antibody to a subject in need thereof, wherein the anti-GITR antibody increases expression of OX40 in the subject relative to expression of OX40 in the subject at the time of the administering, and administering an anti-OX40 antibody to the subject when expression of OX40 is increased.
173. The method of any one of claims 169-172, wherein the anti-GITR antibody induces, activates or enhances an activity of GITR.
174. A method of treating cancer or a viral infection in a first subject, the method comprising the steps of:
- (a) incubating T cells *ex vivo* with the antibody of any one of claims 1-127; and
 - (b) infusing the T cells into the first subject.
175. The method of claim 174 further comprising prior to step (a) isolating the T cells from a second subject, wherein the T cells are autologous or allogenic to the first subject.
176. The method of claim 174 further comprising, prior to step (a):
- (1) assaying the T cells for cell surface expression of GITR; and
 - (2) if step (1) does not result in detection of GITR above a threshold value, inducing expression of GITR on the surface of the T cells by incubating the T cells with a T cell receptor (TCR) complex stimulating agent.
177. The method of claim 174, further comprising, prior to, simultaneously with or subsequent to step (a) incubating the T cells with a TCR complex stimulating agent.
178. The method of claim 174, 175, 176, or 177 further comprising administering to the first subject an anti-cancer agent.
179. The method of claim 178, wherein the anti-cancer agent is a vaccine.
180. The method of claim 179, wherein the vaccine comprises a heat shock protein peptide complex (HSPPC) comprising a heat shock protein complexed with an antigenic peptide.
181. The method of claim 180, wherein the heat shock protein is gp96 protein and is

complexed with a tumor-associated antigenic peptide, wherein the HSPPC is derived from a tumor obtained from a subject.

182. An *ex vivo* method for enhancing the expansion of T cells and T cell effector function, comprising incubating *ex vivo* T cells with the antibody of any one of claims 1-127.
183. The method of claim 182, wherein the T cells have been isolated from a first subject.
184. The method of claim 182 or 183, further comprising, prior to, simultaneously with or subsequent to incubating the T cells with the antibody, incubating the T cells with a TCR complex stimulating agent.
185. The method of claim 182, 183, or 184, further comprising infusing the T cells which were incubated with the antibody into a second subject, wherein the T cells are autologous or allogenic to the second subject.
186. A method for enhancing the stimulation of T cells, comprising incubating *ex vivo* T cells, which have been stimulated with a TCR complex stimulating agent, with the antibody of any one of claims 1-127.
187. A method for activating T cells, comprising incubating *ex vivo* T cells with a TCR complex stimulating agent and the antibody of any one of claims 1-127.
188. The method of claim 186 or 187, wherein the T cells were isolated from a first subject.
189. The method of claim 186, 187, or 188, further comprising infusing the T cells which were incubated with the antibody into a second subject, wherein the T cells are autologous or allogenic to the second subject.
190. The method of any one of claims 138-173, wherein the subject is human.
191. The method of claim 174, 176, 177, 183, 184 or 188, wherein the first subject is human.
192. The method of claim 175, 178, 179, 180, 181, 185 or 189, wherein the first and second subject are human.
193. A method for preferential expansion of effector T-cells over the expansion of T-regulatory cells in a subject, comprising administering to the subject an effective amount of the antibody of any one of claims 1-127 or the pharmaceutical composition of claim 136 or 137.
194. The method of claim 193, wherein the subject is human.
195. A method of identifying an anti-GITR antibody that is capable of inducing, activating, or enhancing an activity of GITR in the absence of a TCR agonist comprising contacting a cell expressing GITR with an anti-GITR antibody in the absence of a TCR agonist and measuring GITR activity, wherein increased GITR activity compared to GITR activity in the absence of the anti-GITR antibody indicates the anti-GITR antibody is capable of inducing,

activating, or enhancing an activity of GITR in the absence of a TCR agonist.

196. The method of claim 195, wherein the GITR activity is assessed by measuring NF- κ B activity.
197. The method of claim 195, wherein the GITR activity is assessed by measuring activation of canonical and non-canonical NF- κ B pathways.
198. The method of claim 195, wherein the GITR activity is assessed by measuring activation of TRAF adapter mediated signaling pathways, wherein the TRAF adapter is selected from the group consisting of TRAF1, TRAF2, TRAF3, TRAF4, and TRAF5.
199. The method of claim 195, wherein the GITR activity is assessed by measuring activation of MAPK/ERK pathway.
200. The method of any one of claims 195-199, wherein the anti-GITR antibody increases the GITR activity at least two-fold compared to the GITR activity in the absence of the anti-GITR antibody.
201. The method of any one of claims 195-200, wherein the cell is a T cell.
202. The method of any one of claims 195-200, wherein the cell is not a T cell.
203. An isolated antibody that specifically binds to human GITR, wherein said antibody is capable of inducing, activating, or enhancing an activity of GITR in a cell in the absence of TCR triggering.
204. An isolated antibody that specifically binds to human GITR, wherein said antibody is capable of inducing, activating, or enhancing an activity of NF- κ B in a cell in the absence of TCR triggering.
205. A method of treating cancer in a subject comprising administering to the subject an effective amount of the antibody of claim 203 or 204.

FIGURE 1

Specificity of 231-32-15 Western Blot
Non-reducing condition

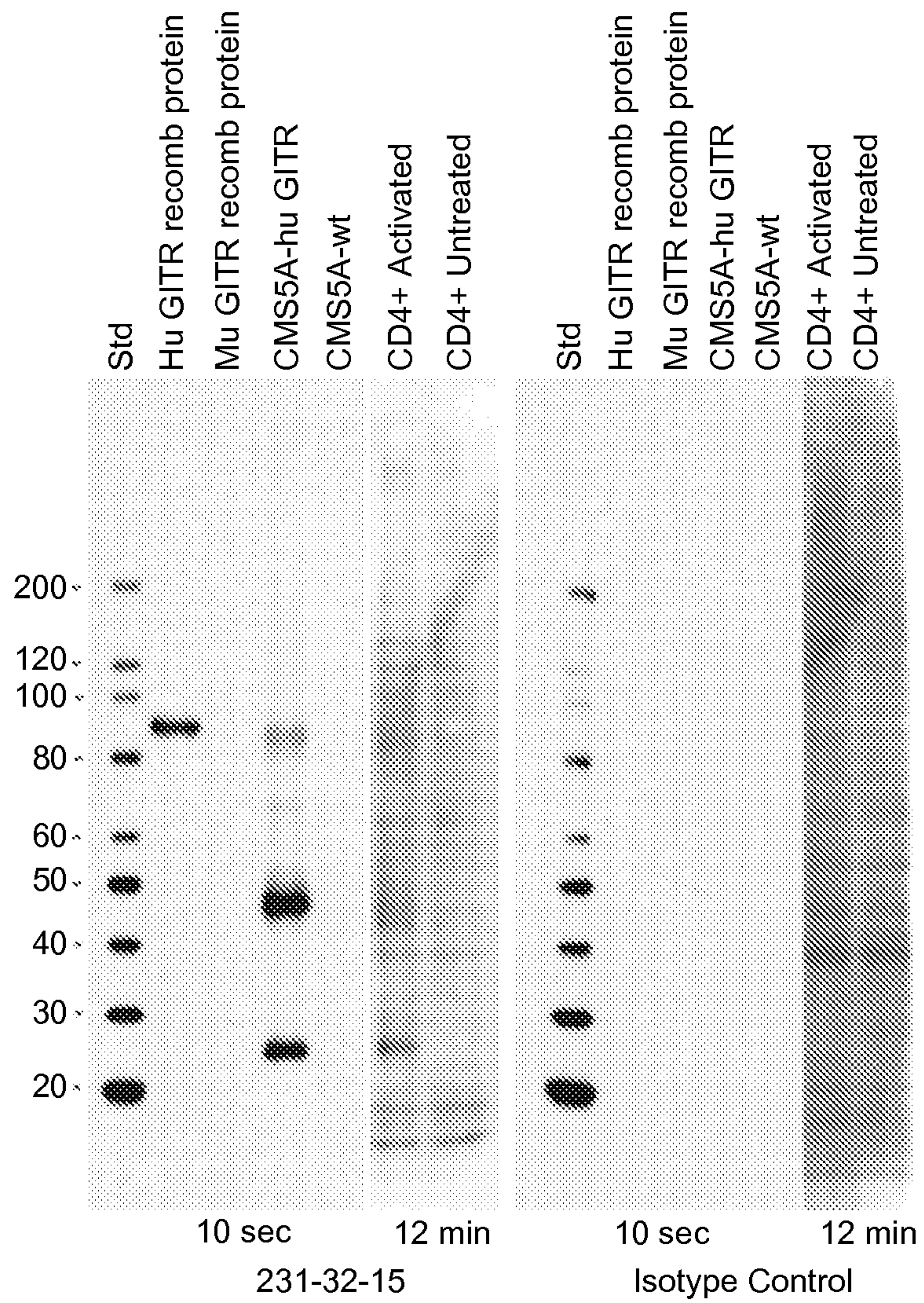


FIGURE 2A

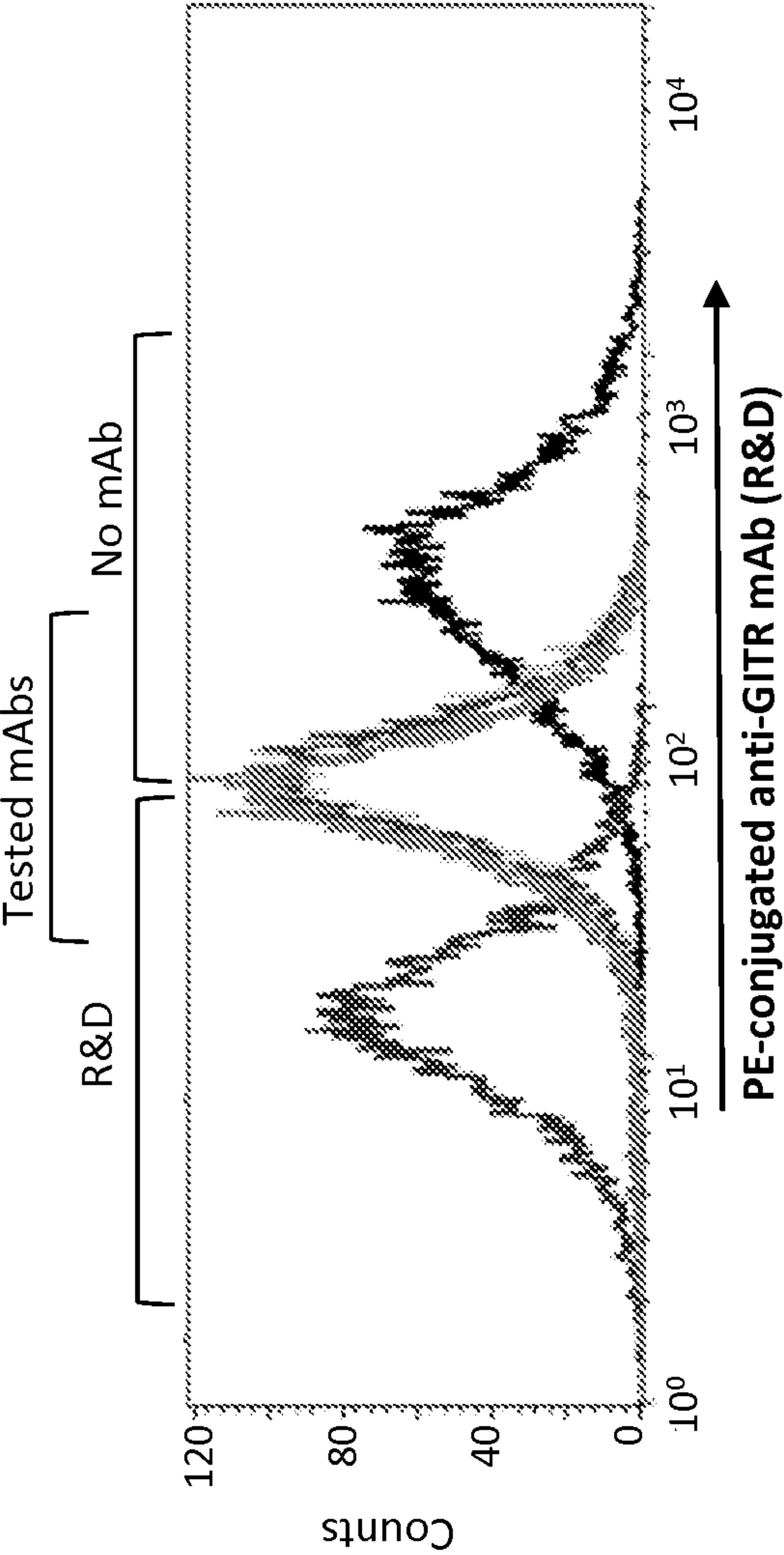


FIGURE 2B

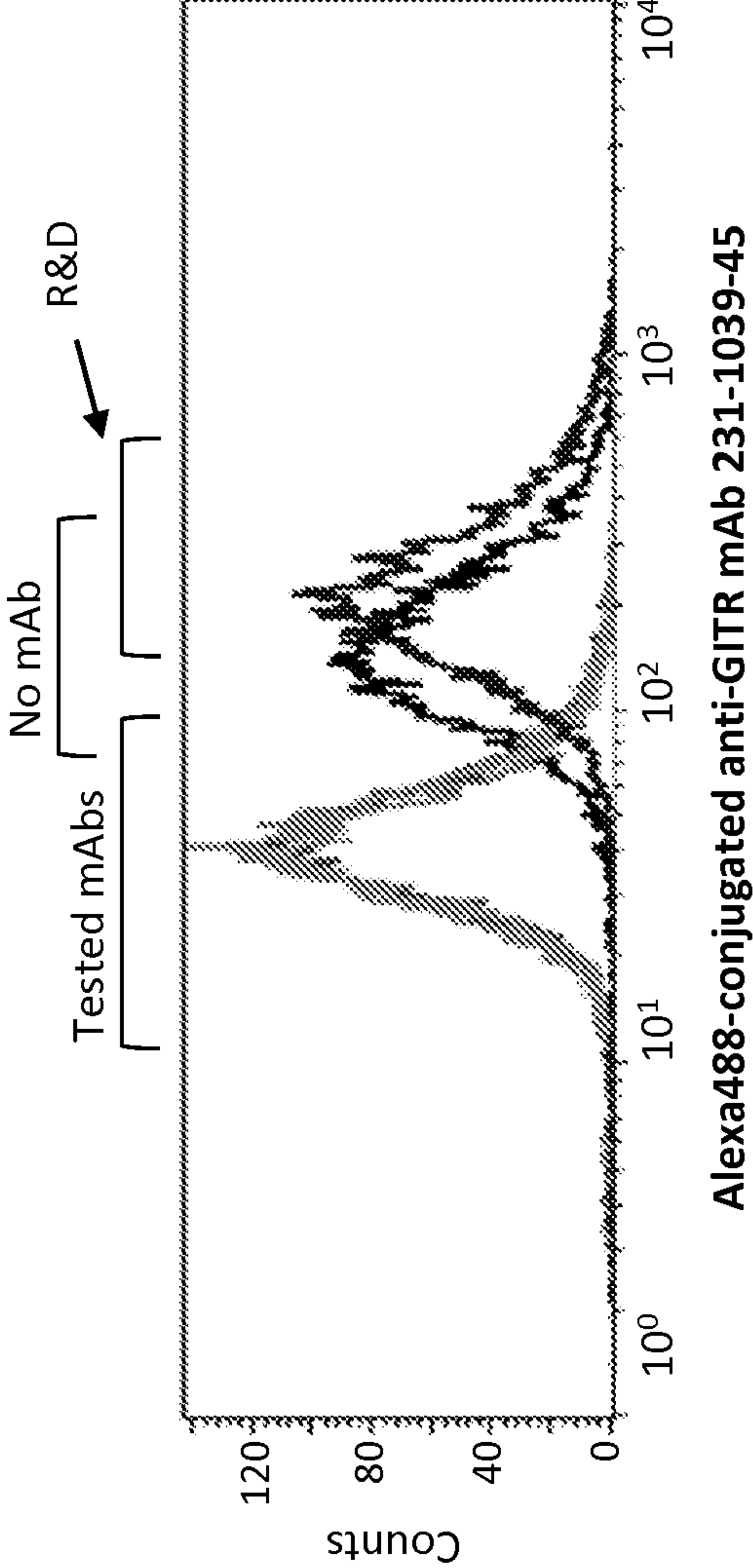


FIGURE 3A

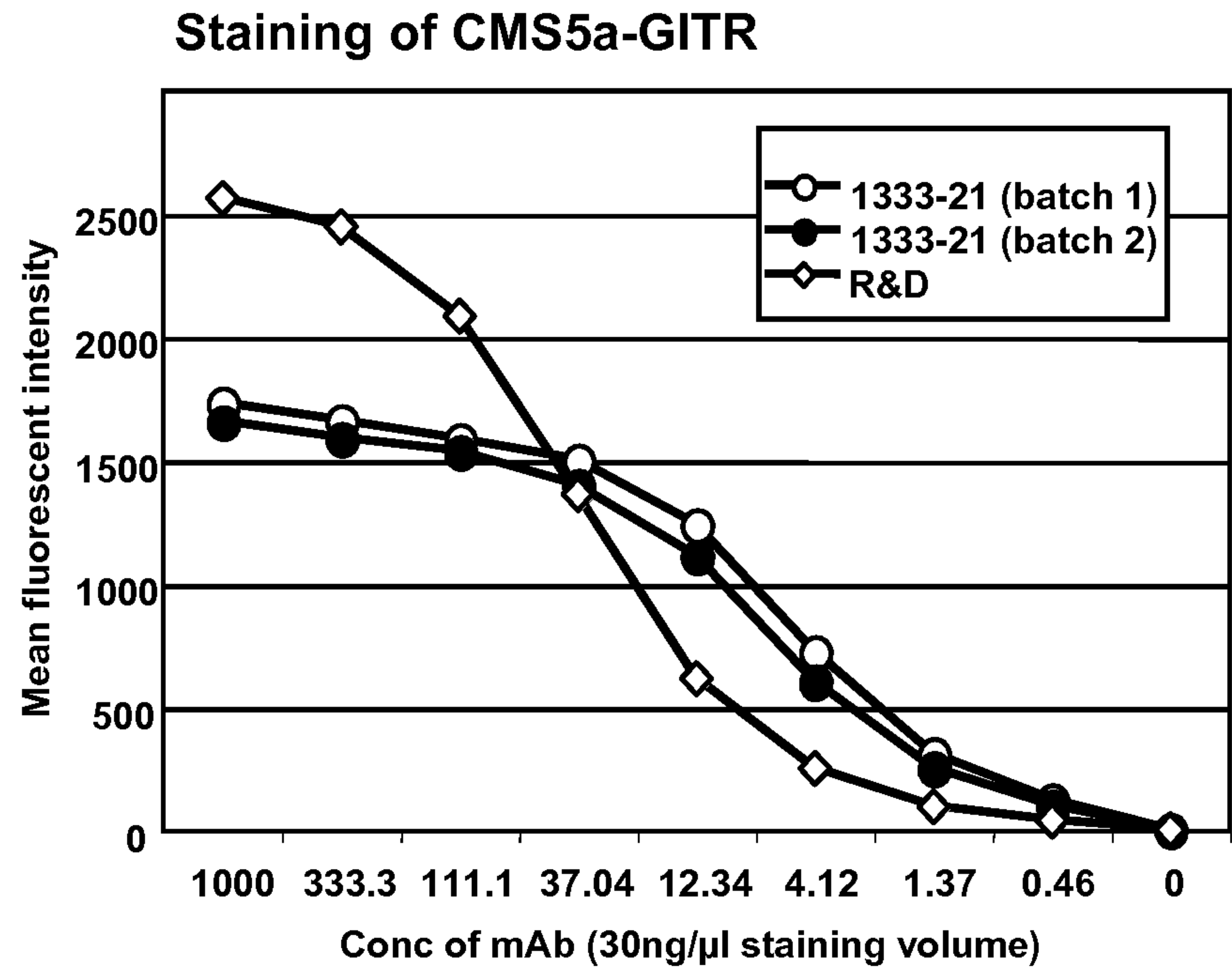


FIGURE 3B

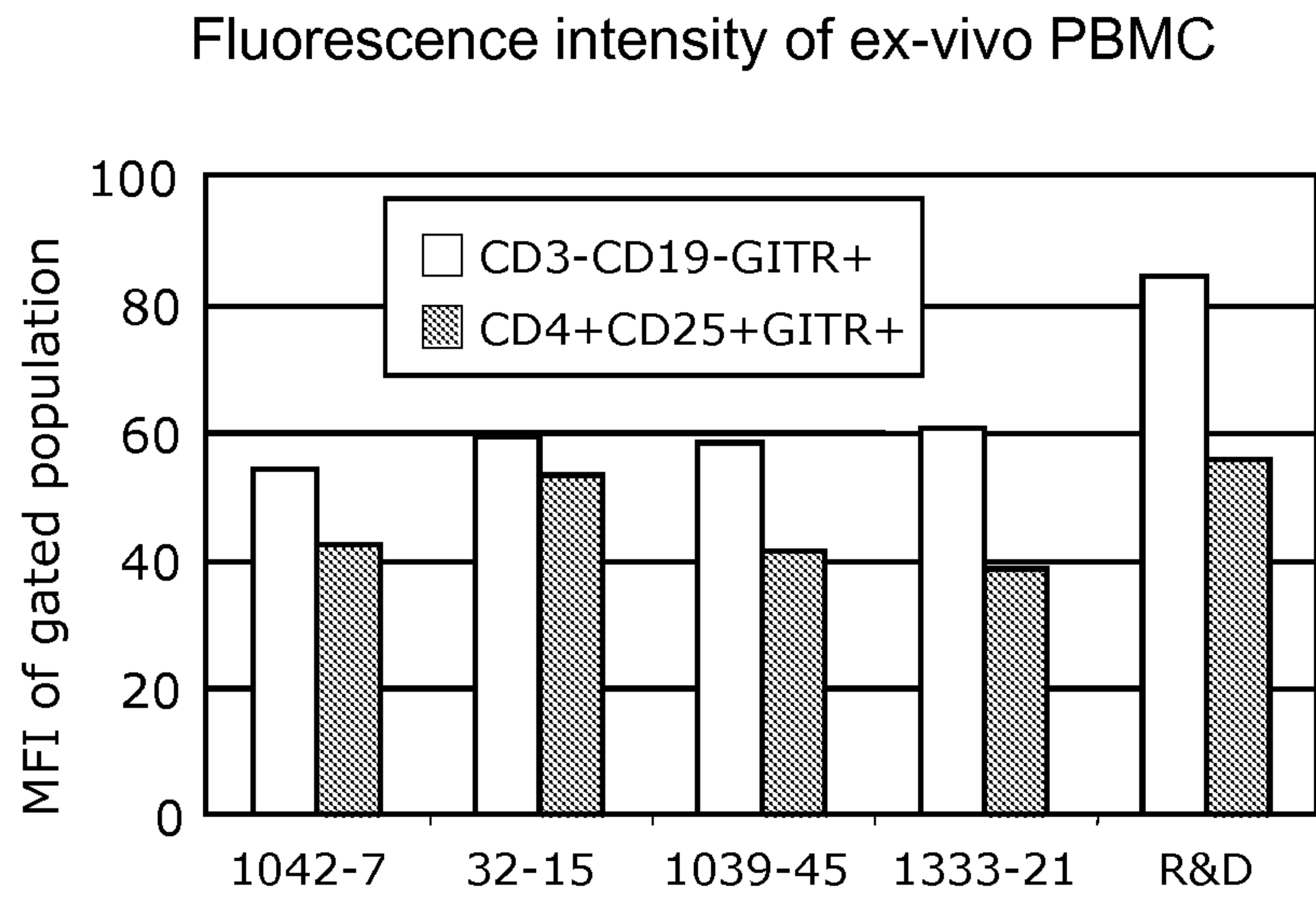


FIGURE 3C

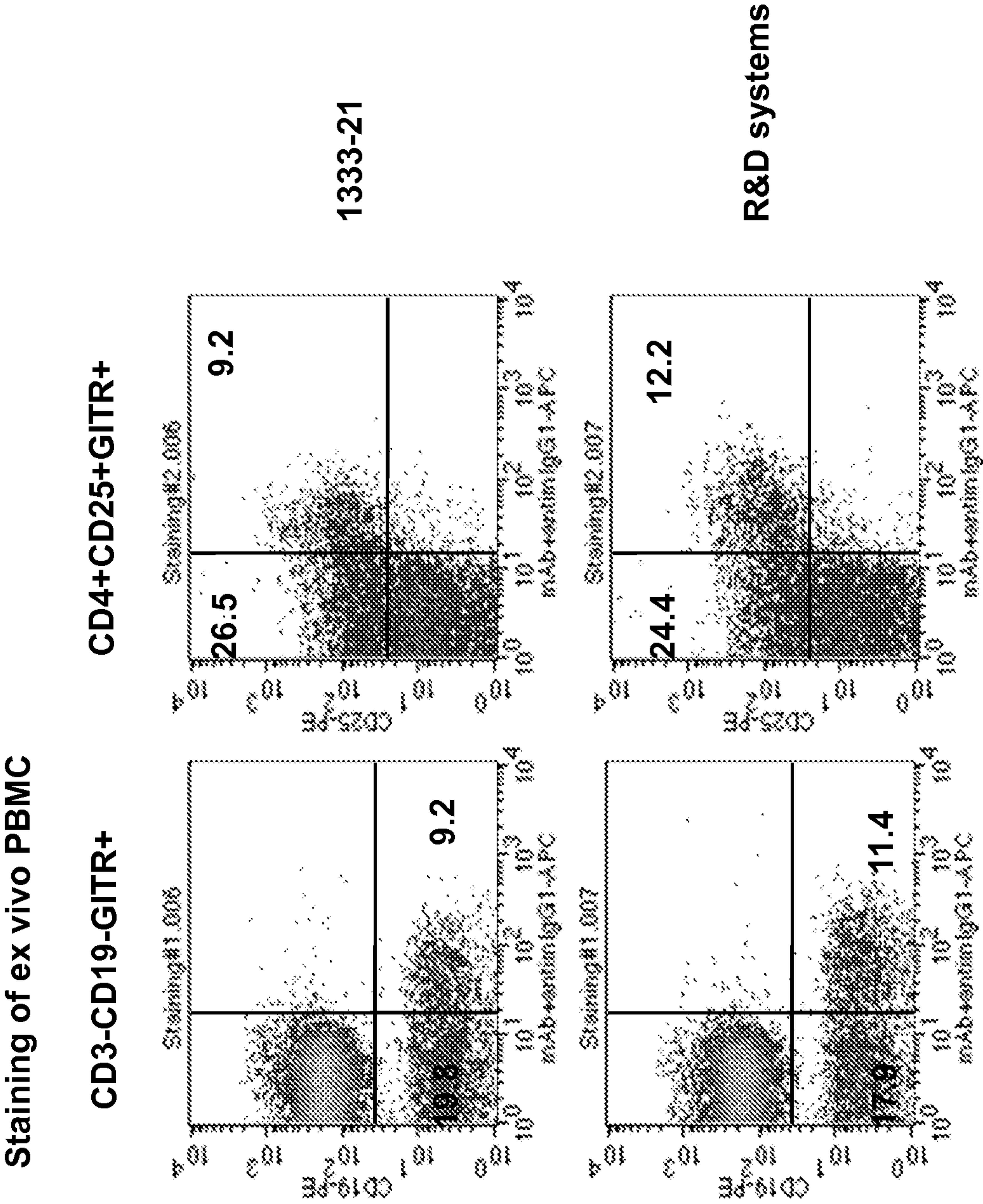


FIGURE 4

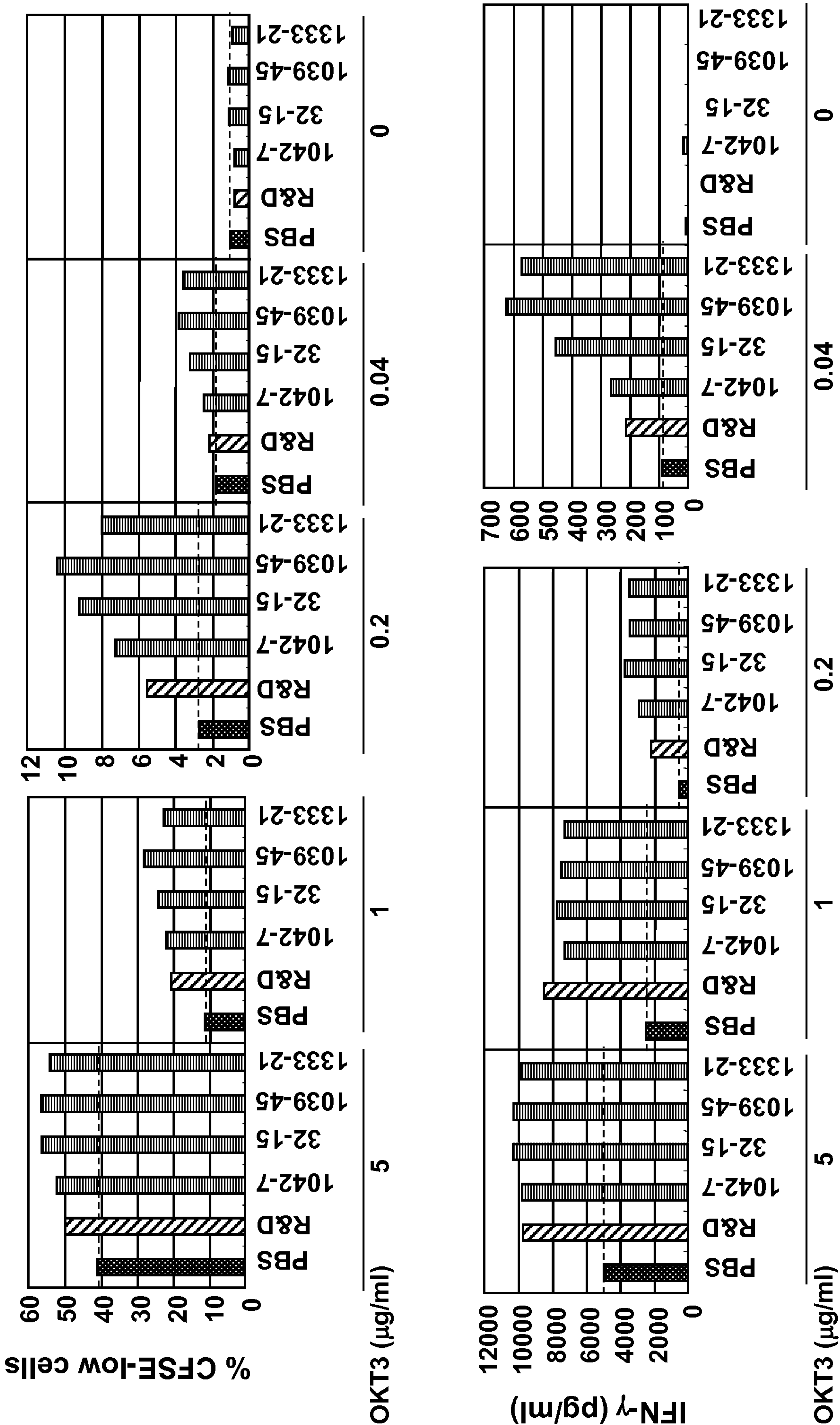


FIGURE 5

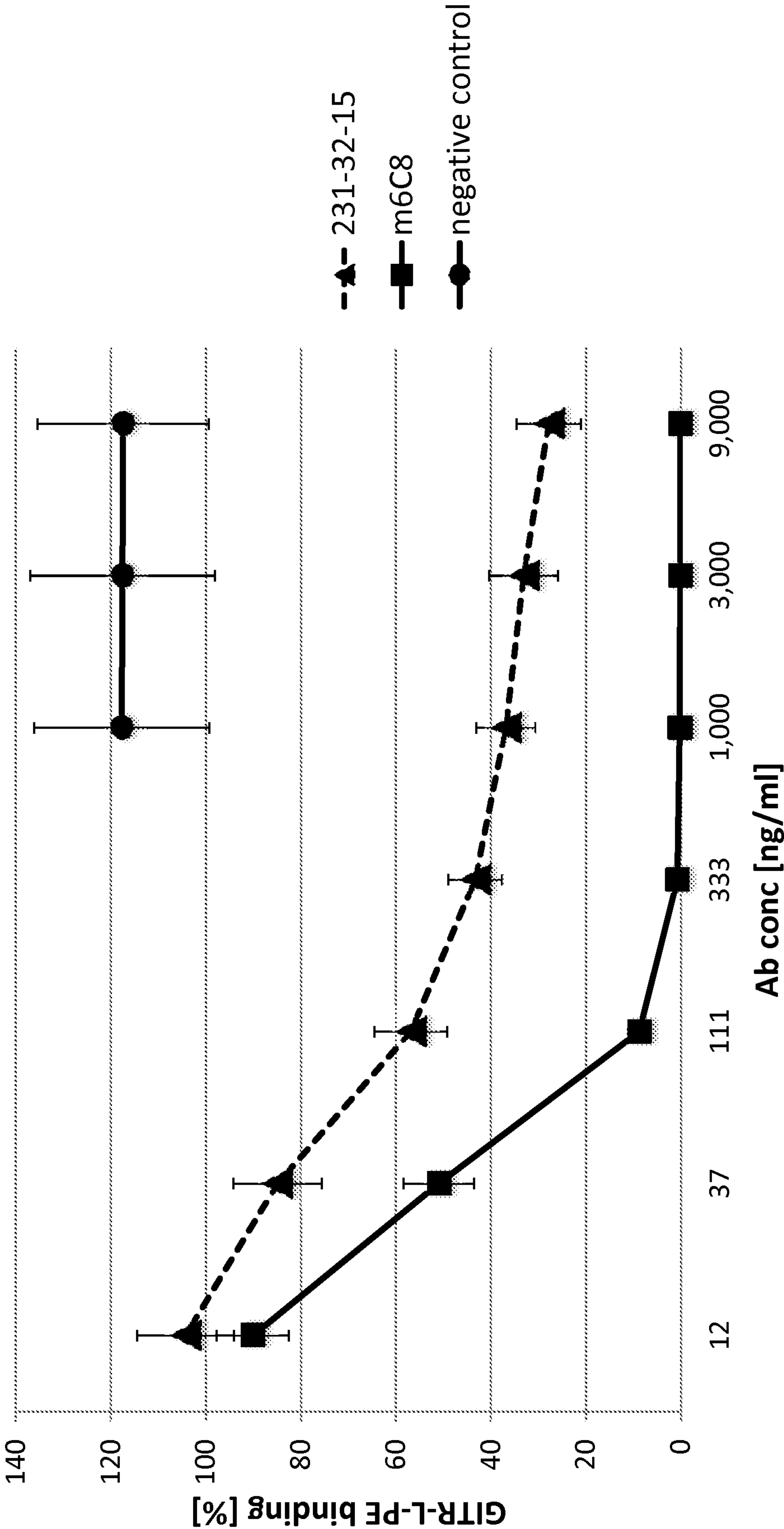


FIGURE 6

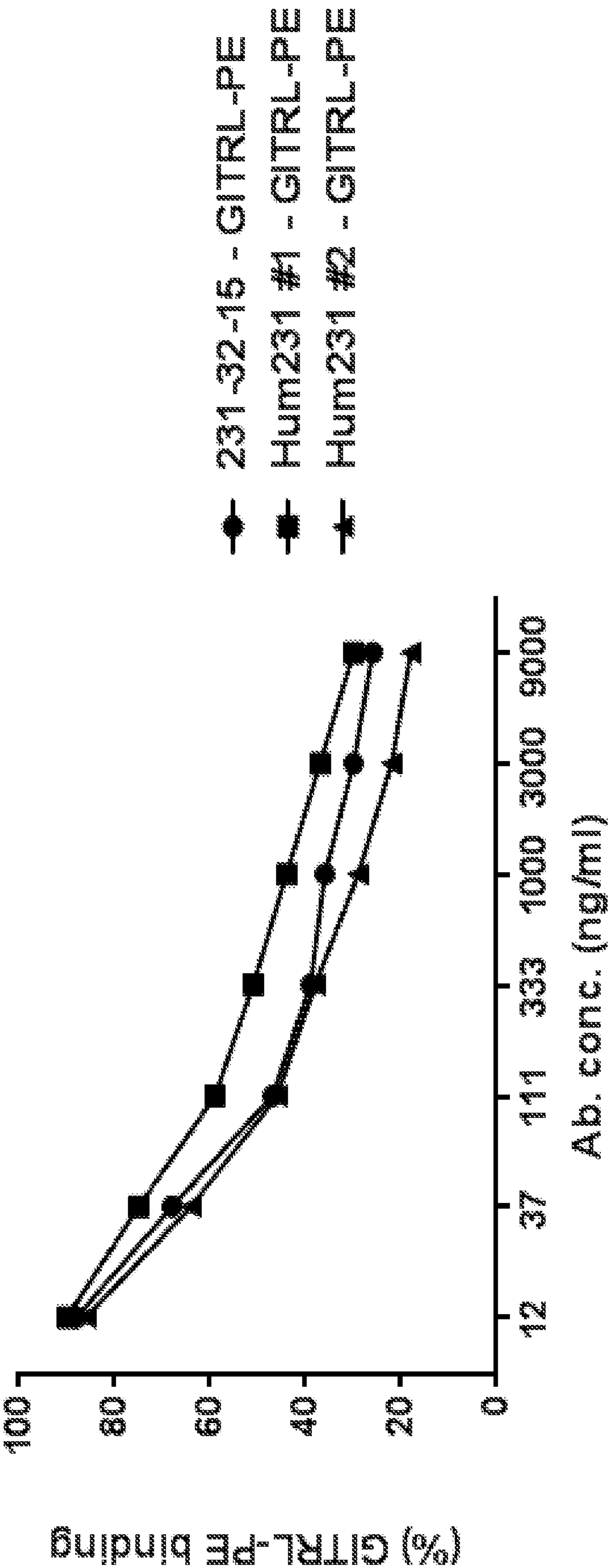
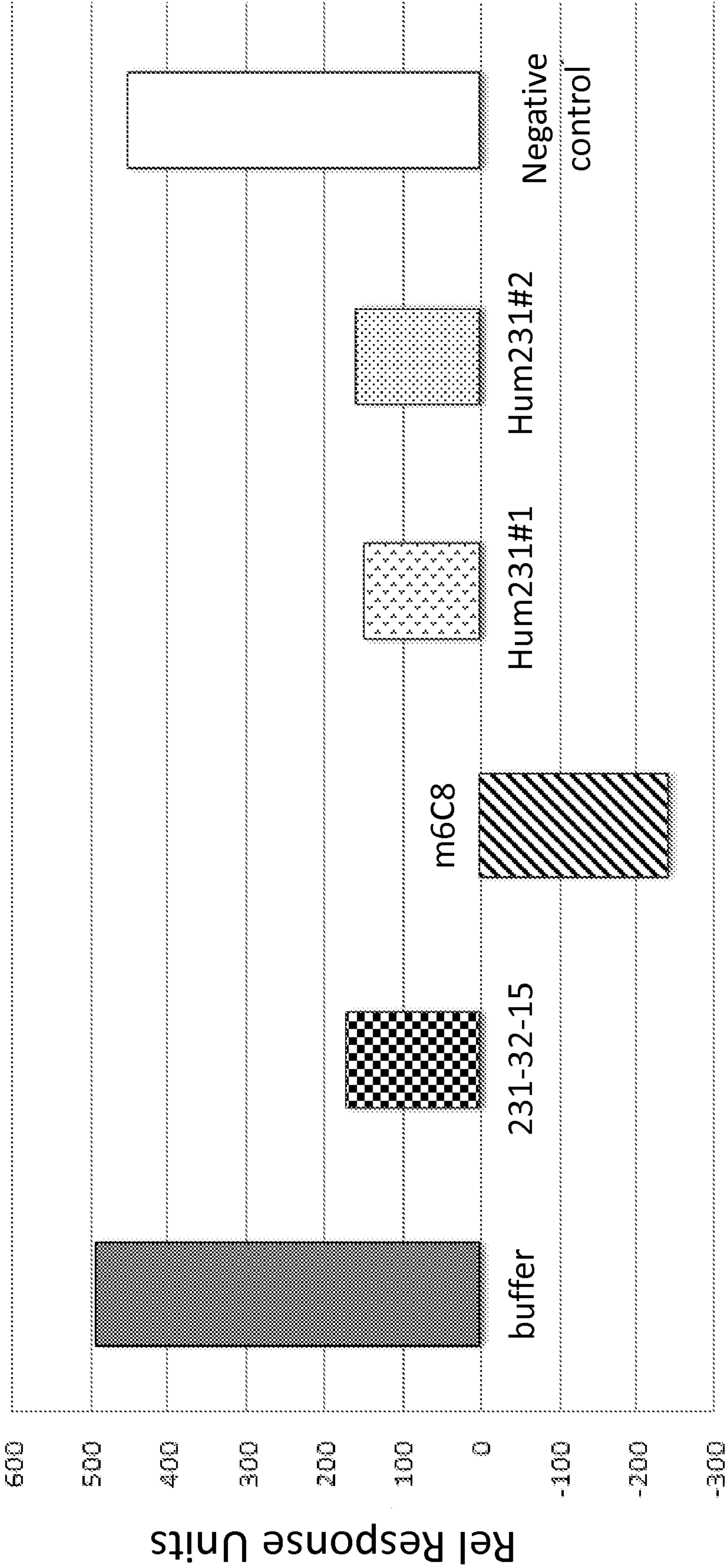
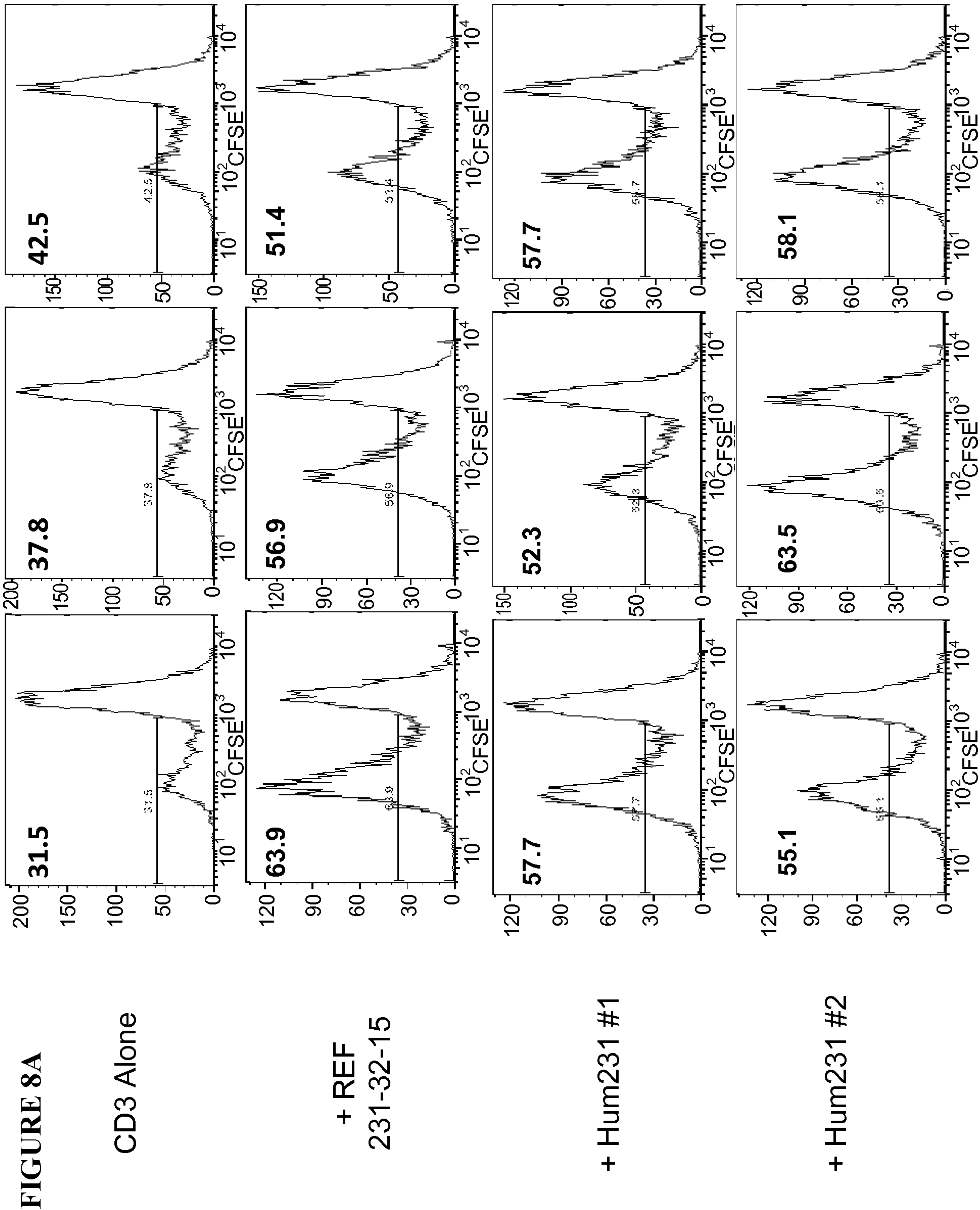


FIGURE 7
GTR ligand binding in the presence of mAbs





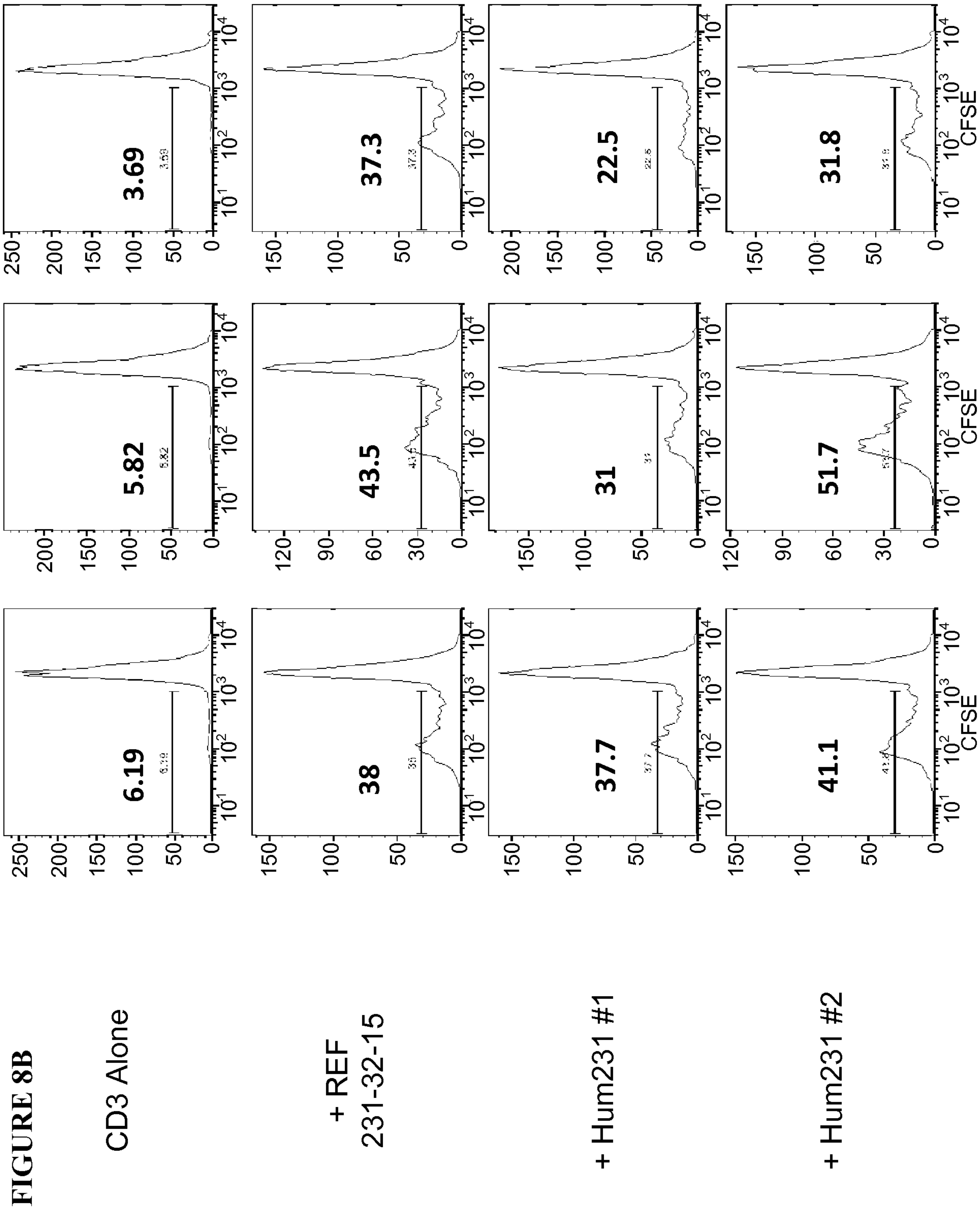


FIGURE 9A

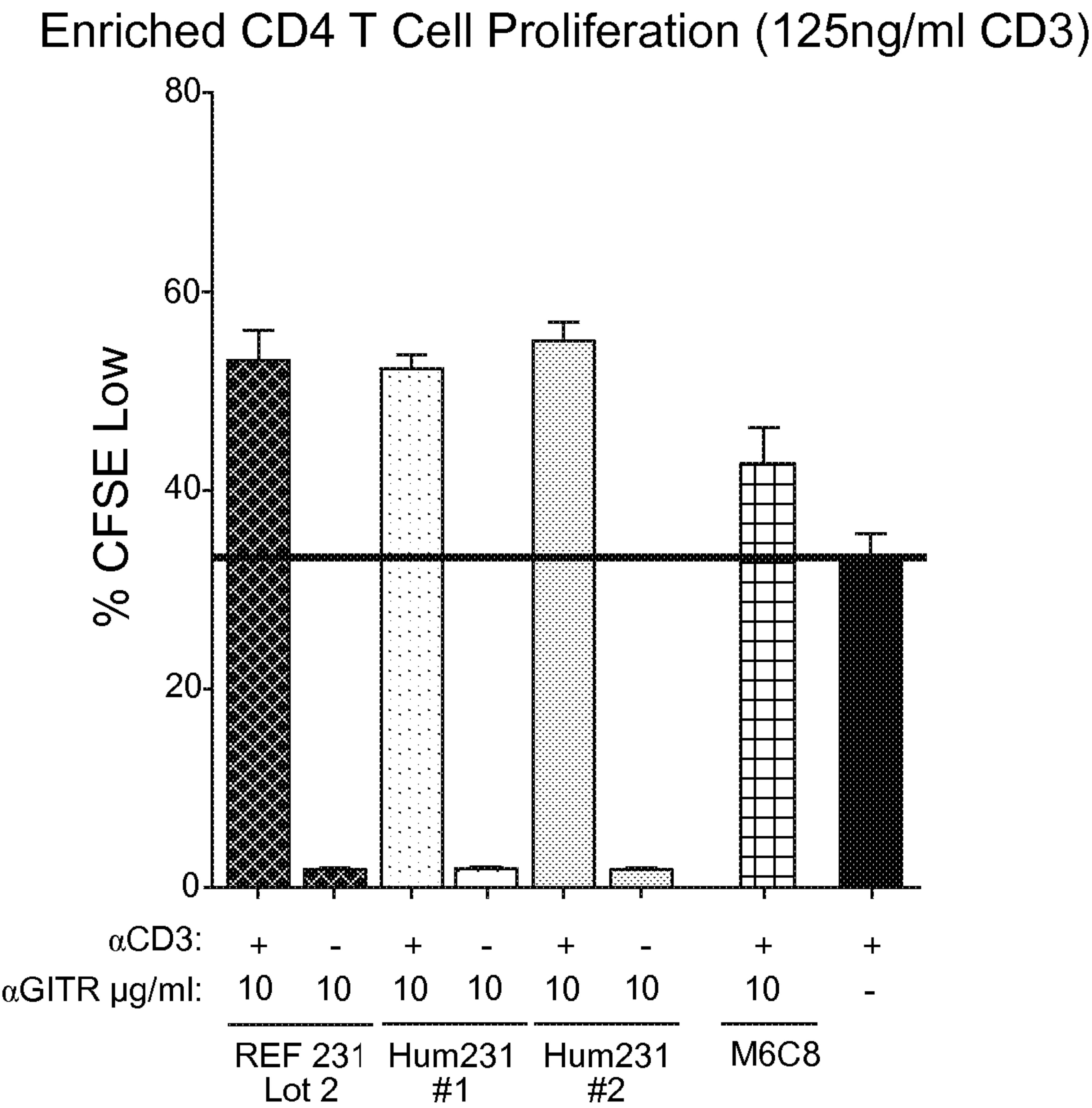


FIGURE 9B

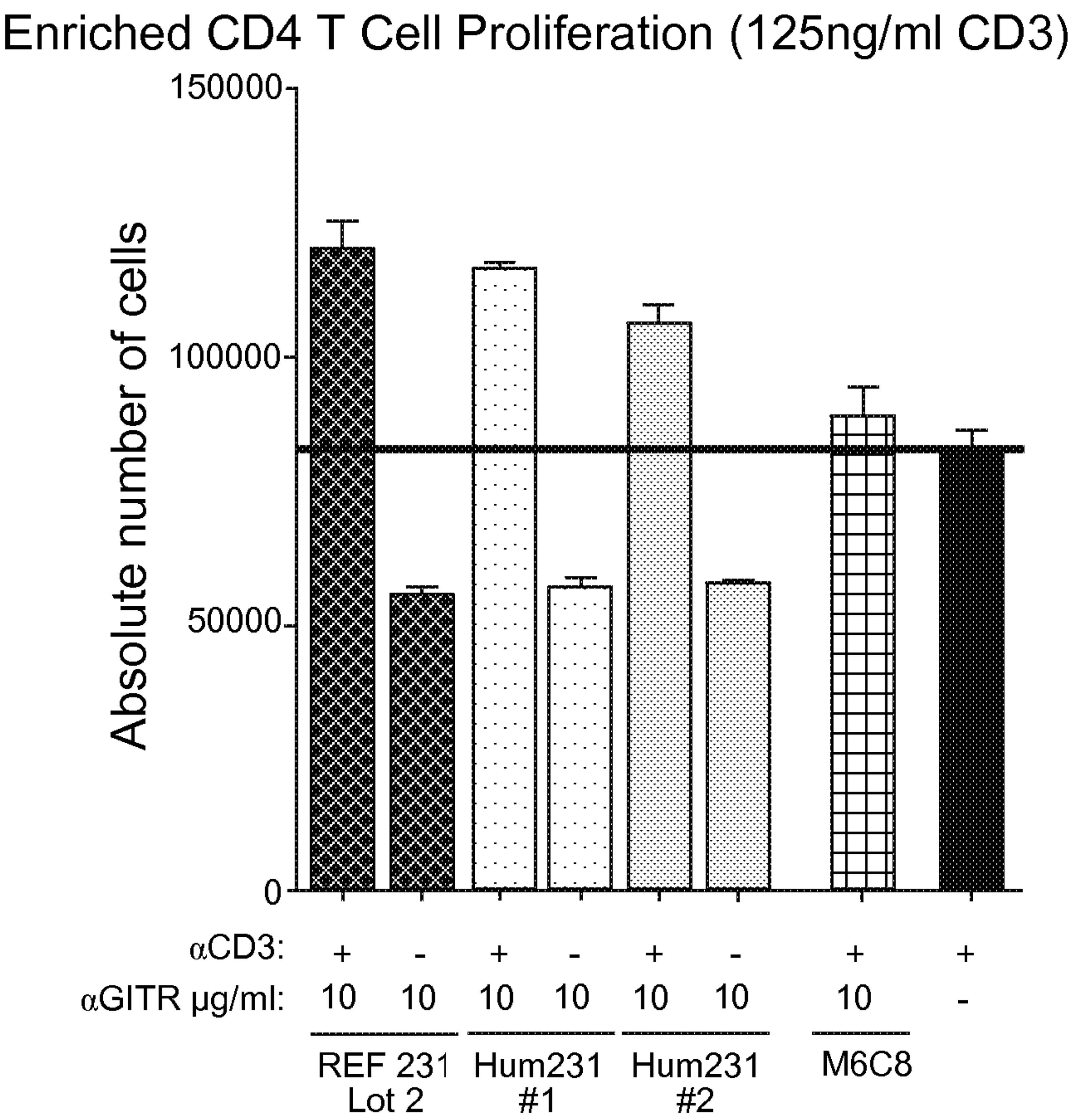


FIGURE 10A

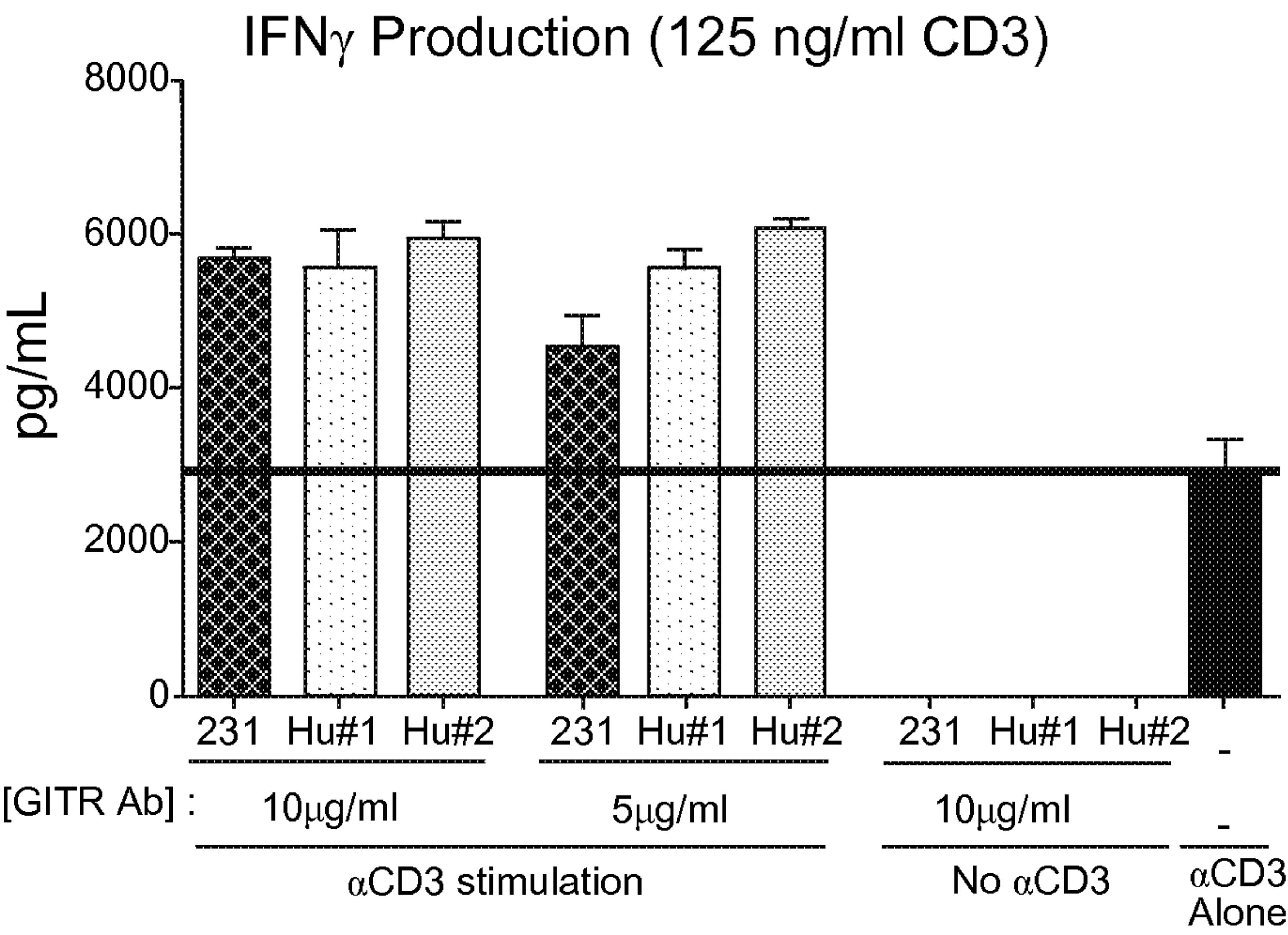


FIGURE 10B

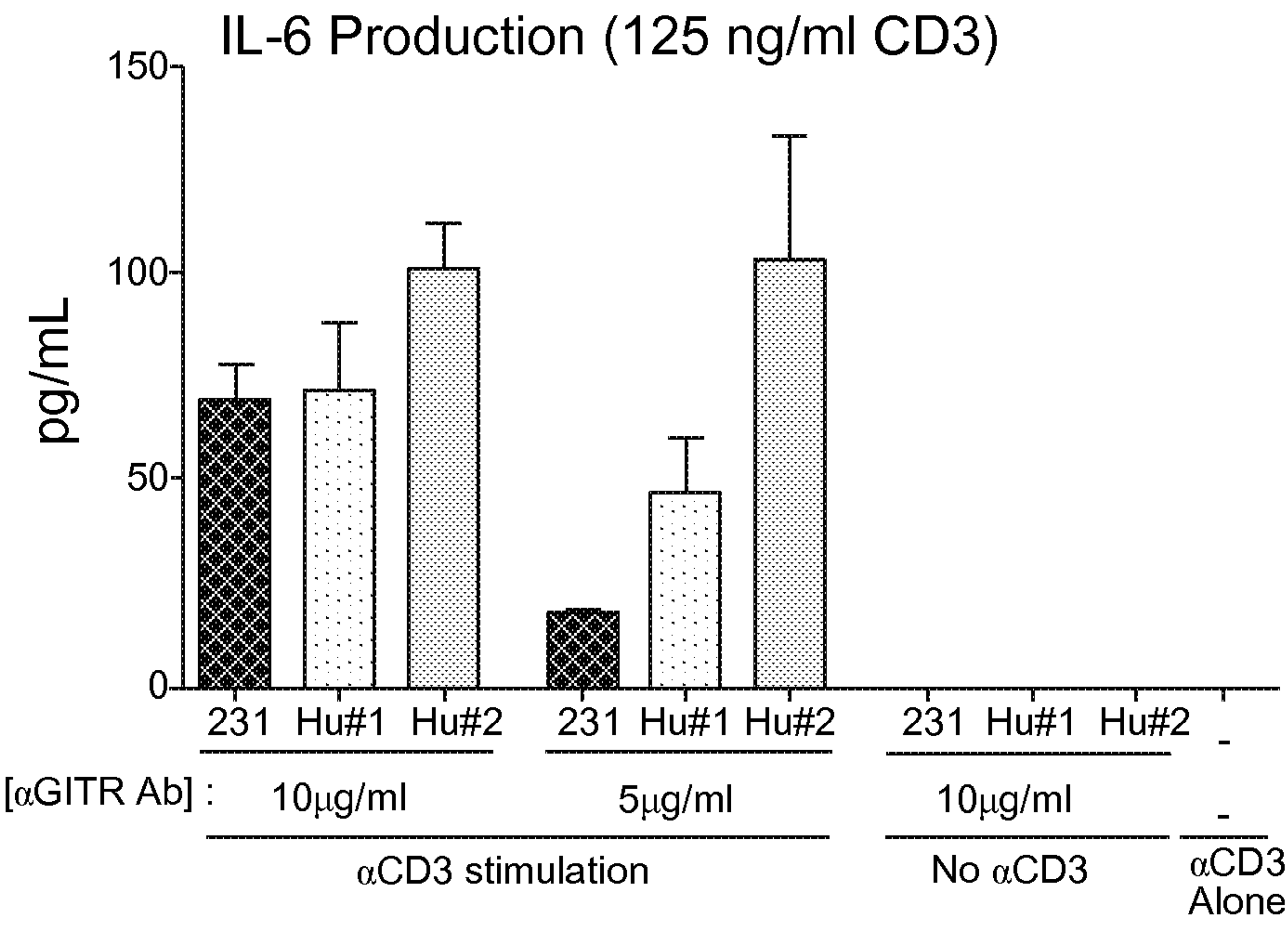


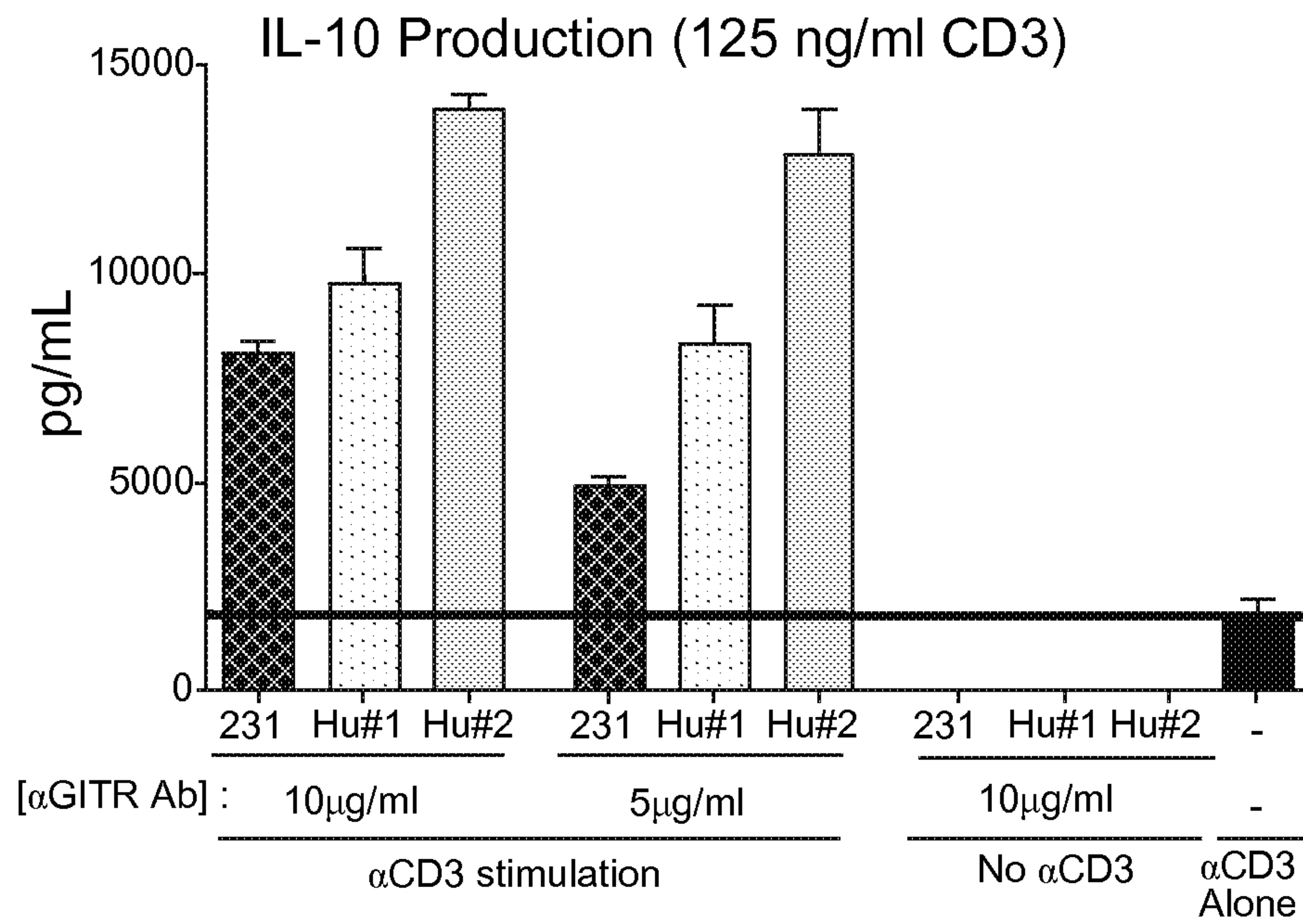
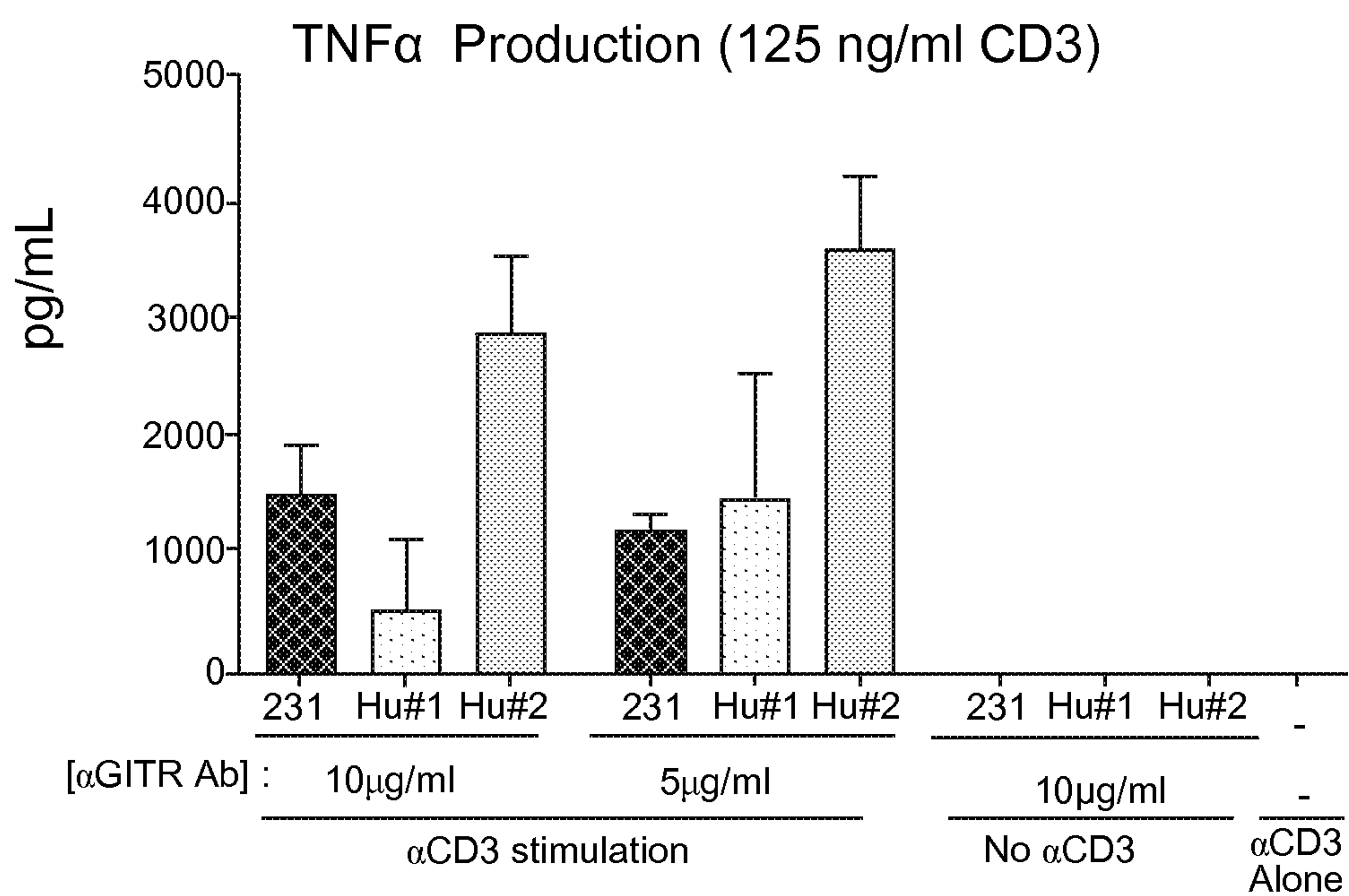
FIGURE 10C**FIGURE 10D**

FIGURE 11

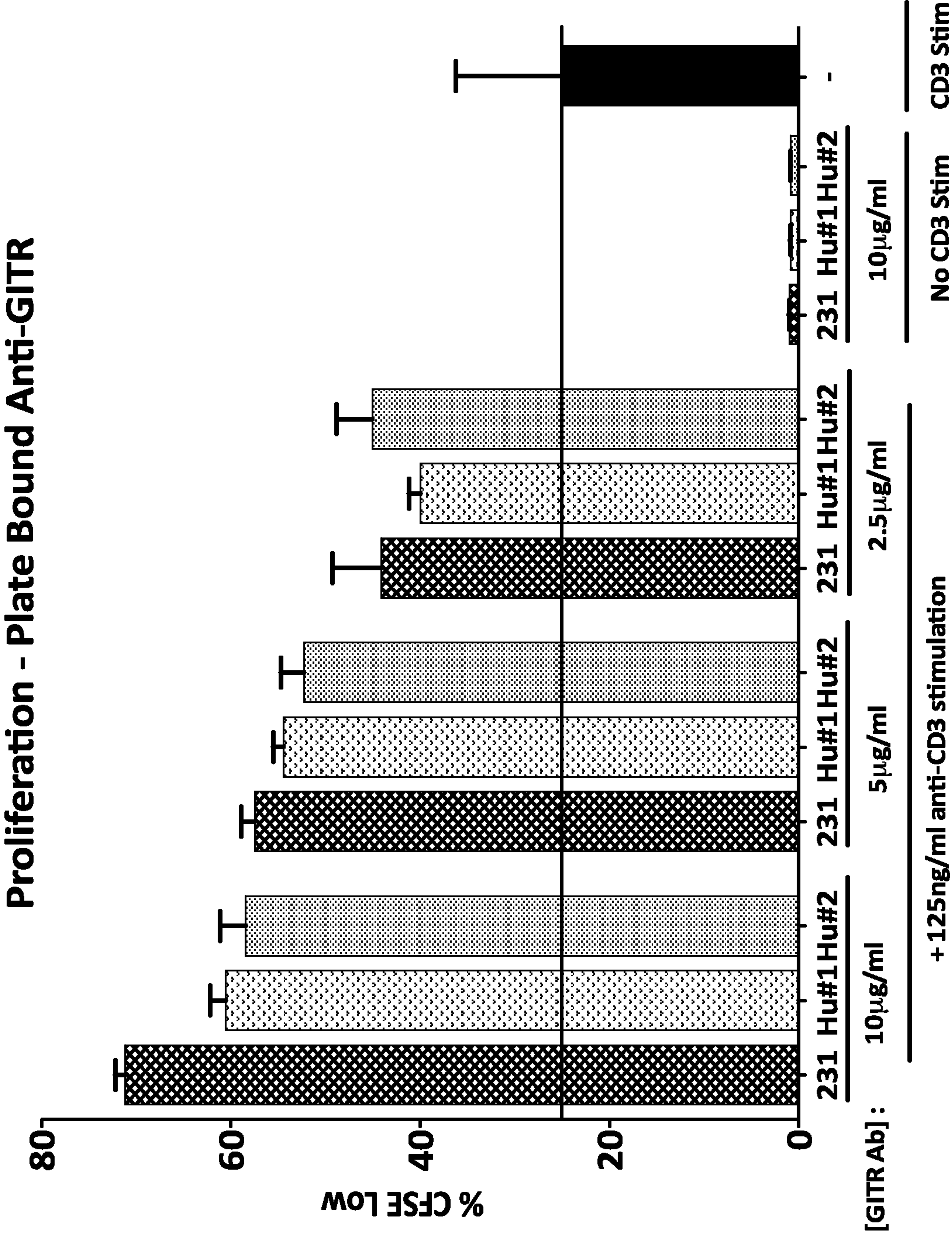


FIGURE 12A

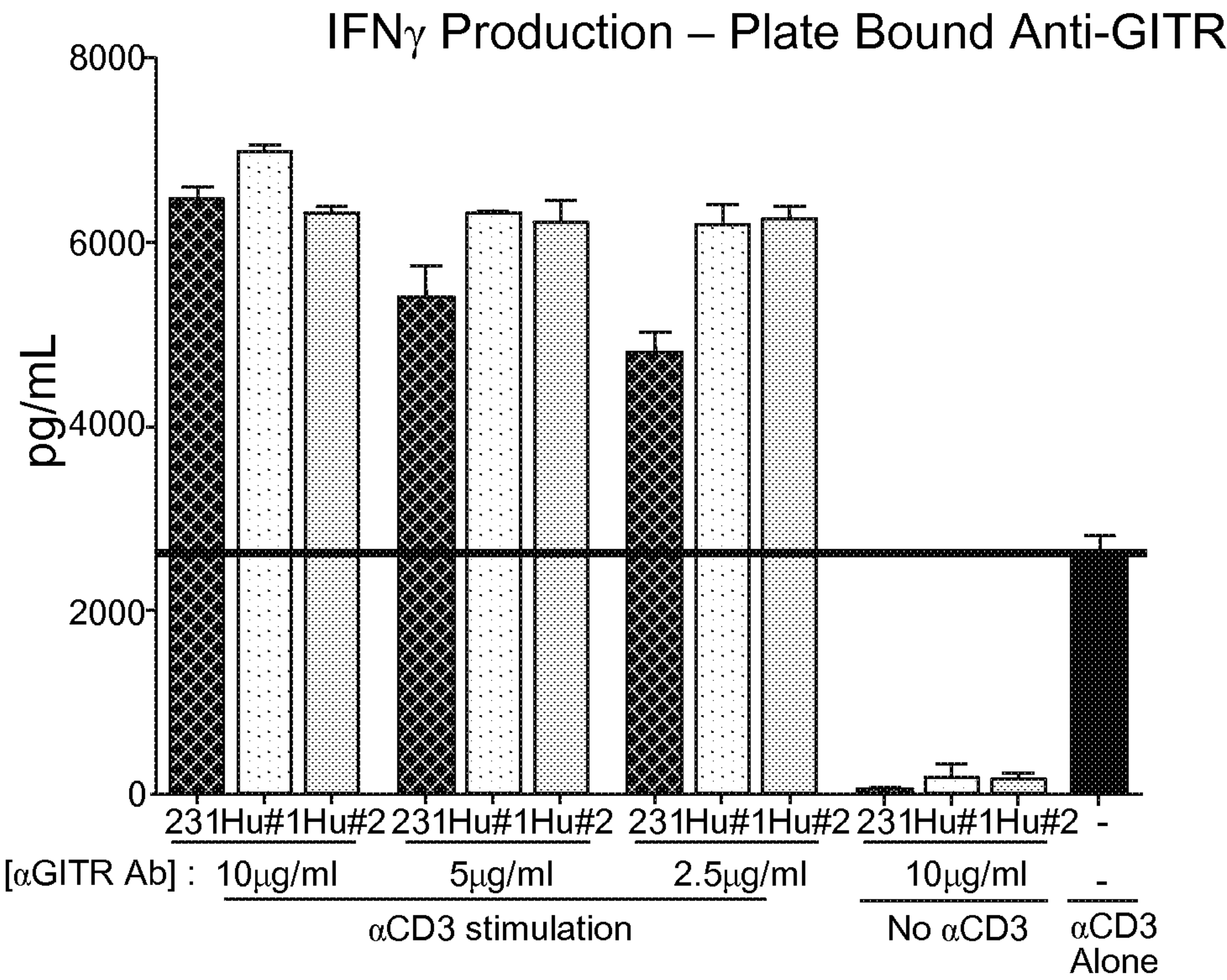


FIGURE 12B

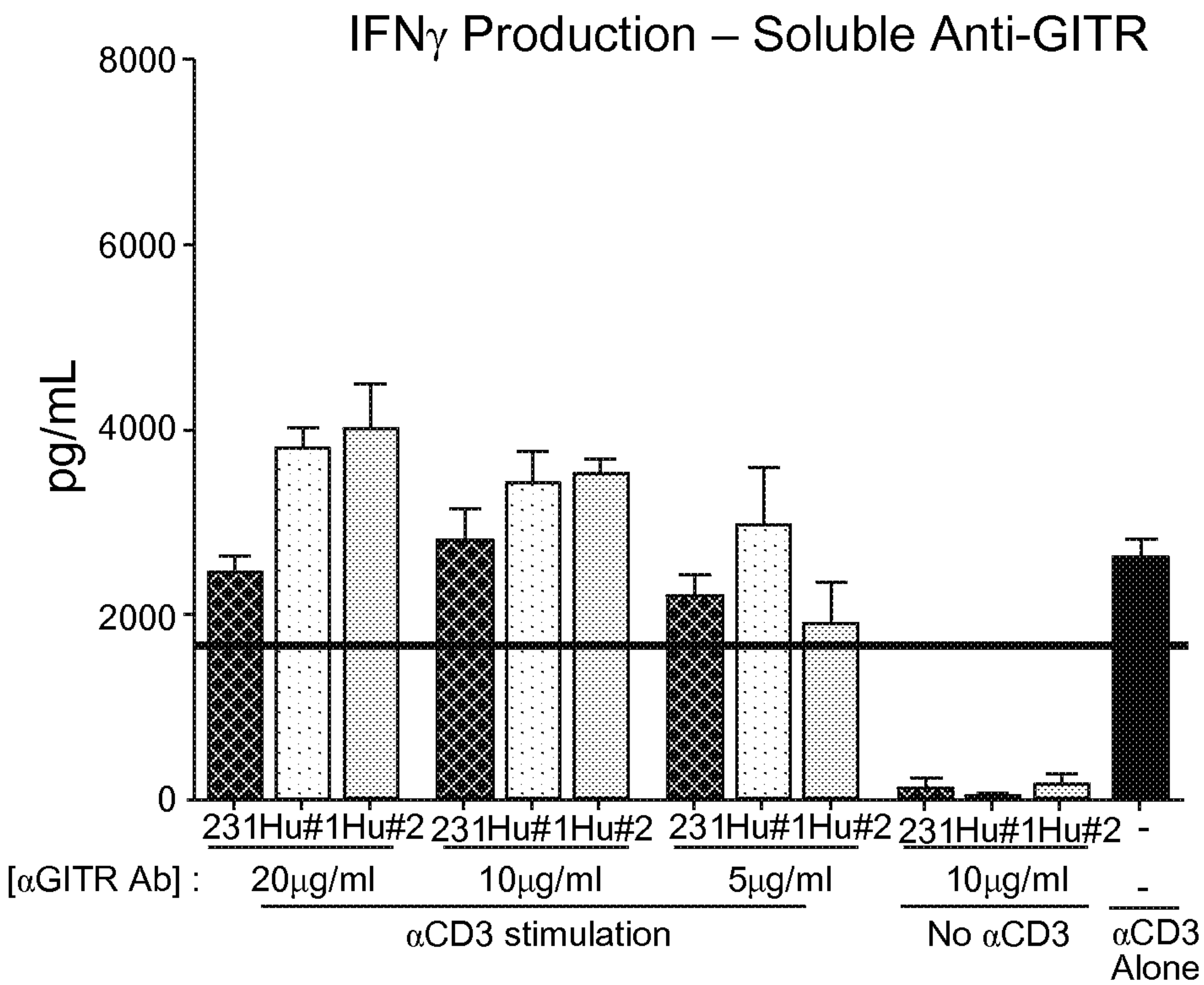
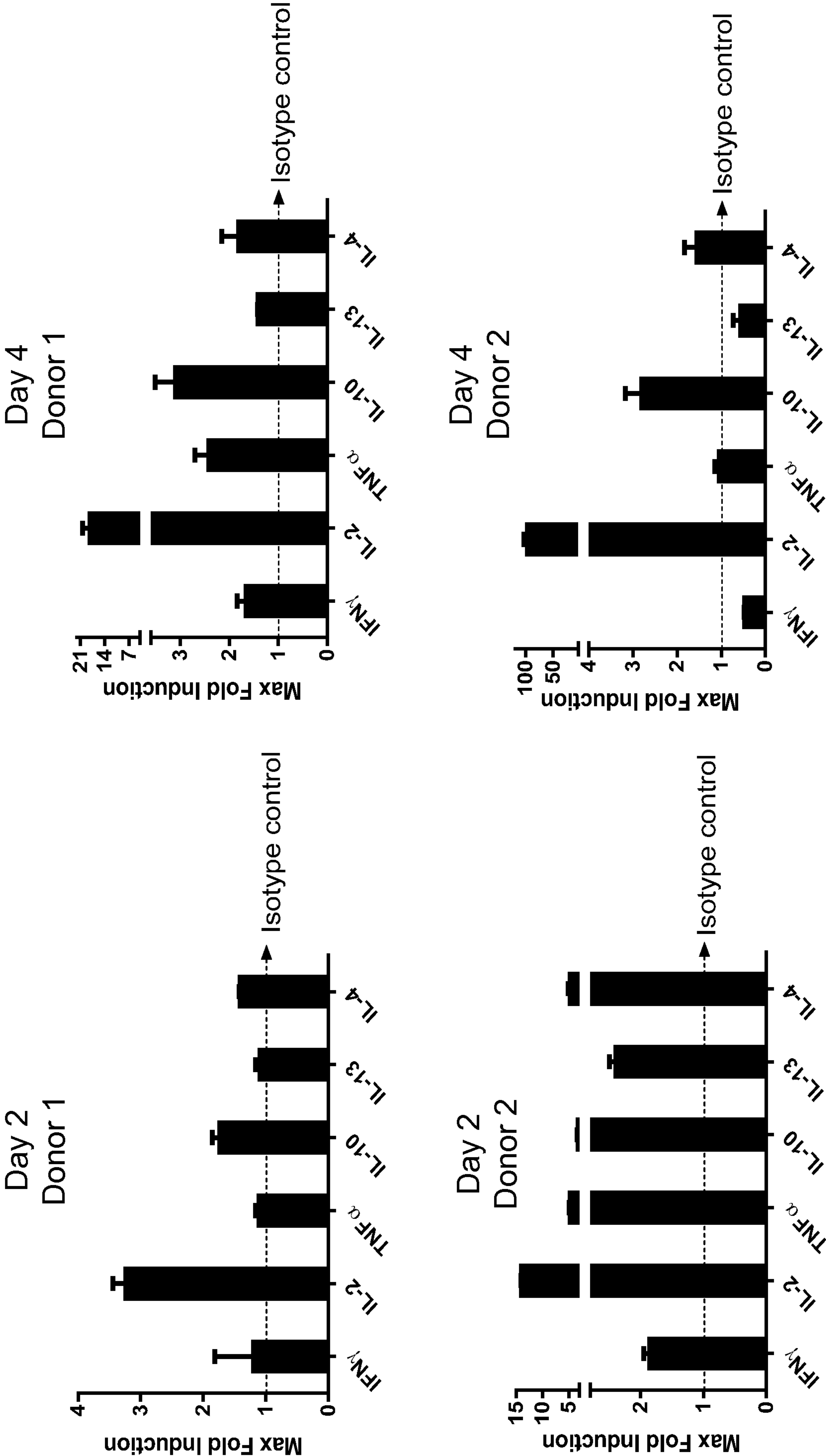
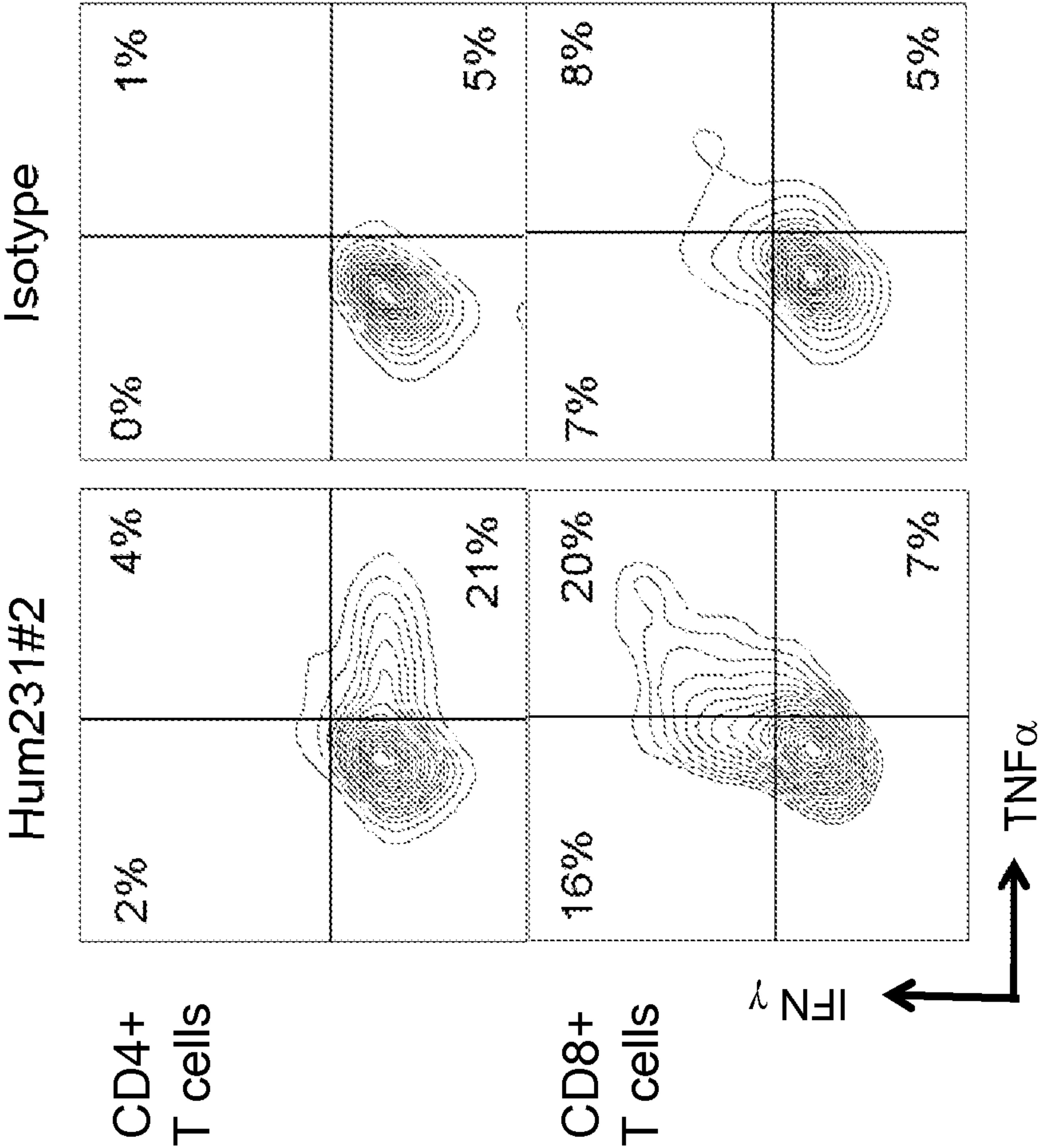


FIGURE 13



■ Hum231#2

FIGURE 14A



● Hum231#2
▨ Isotype

FIGURE 14B

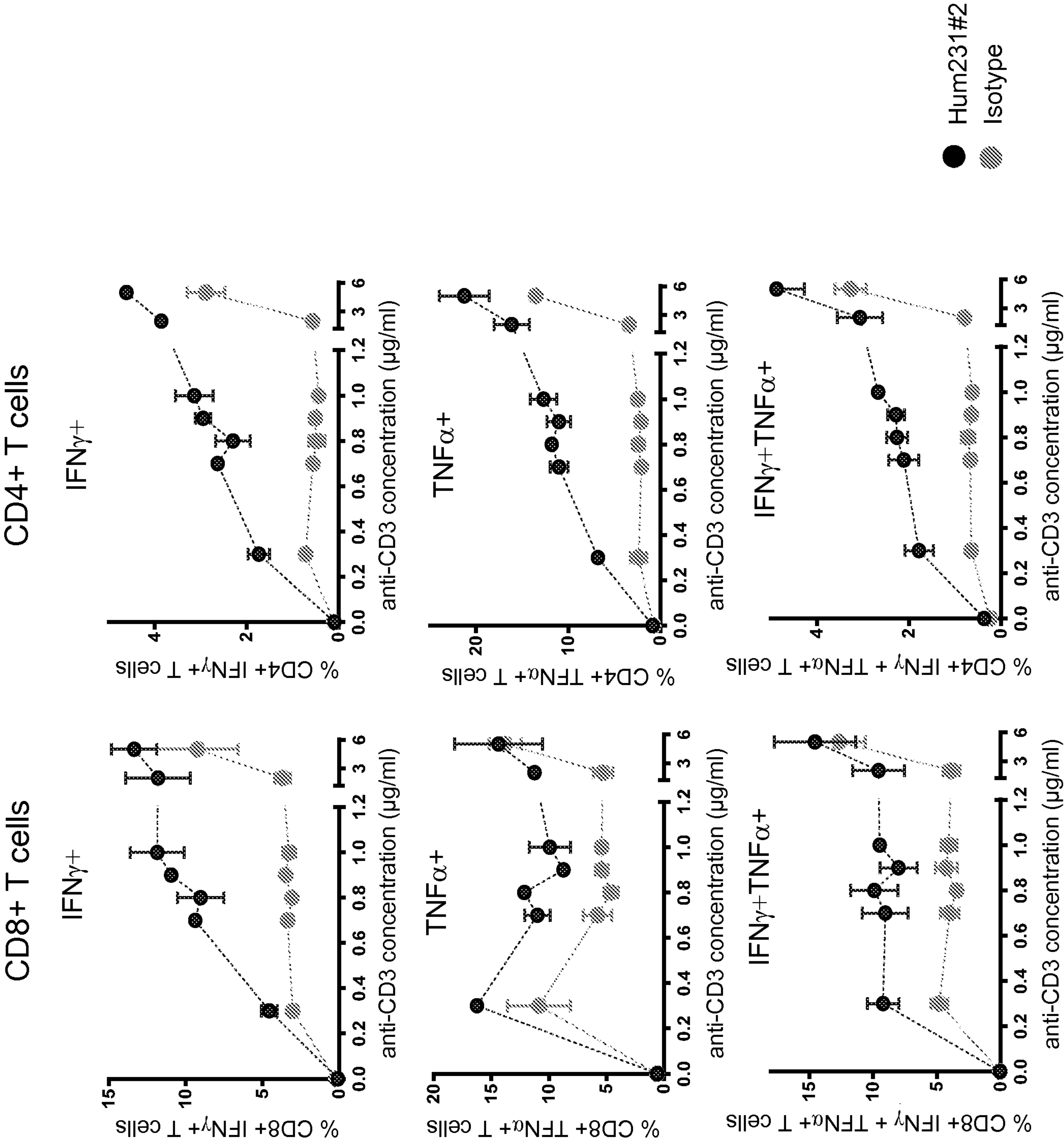


FIGURE 14C

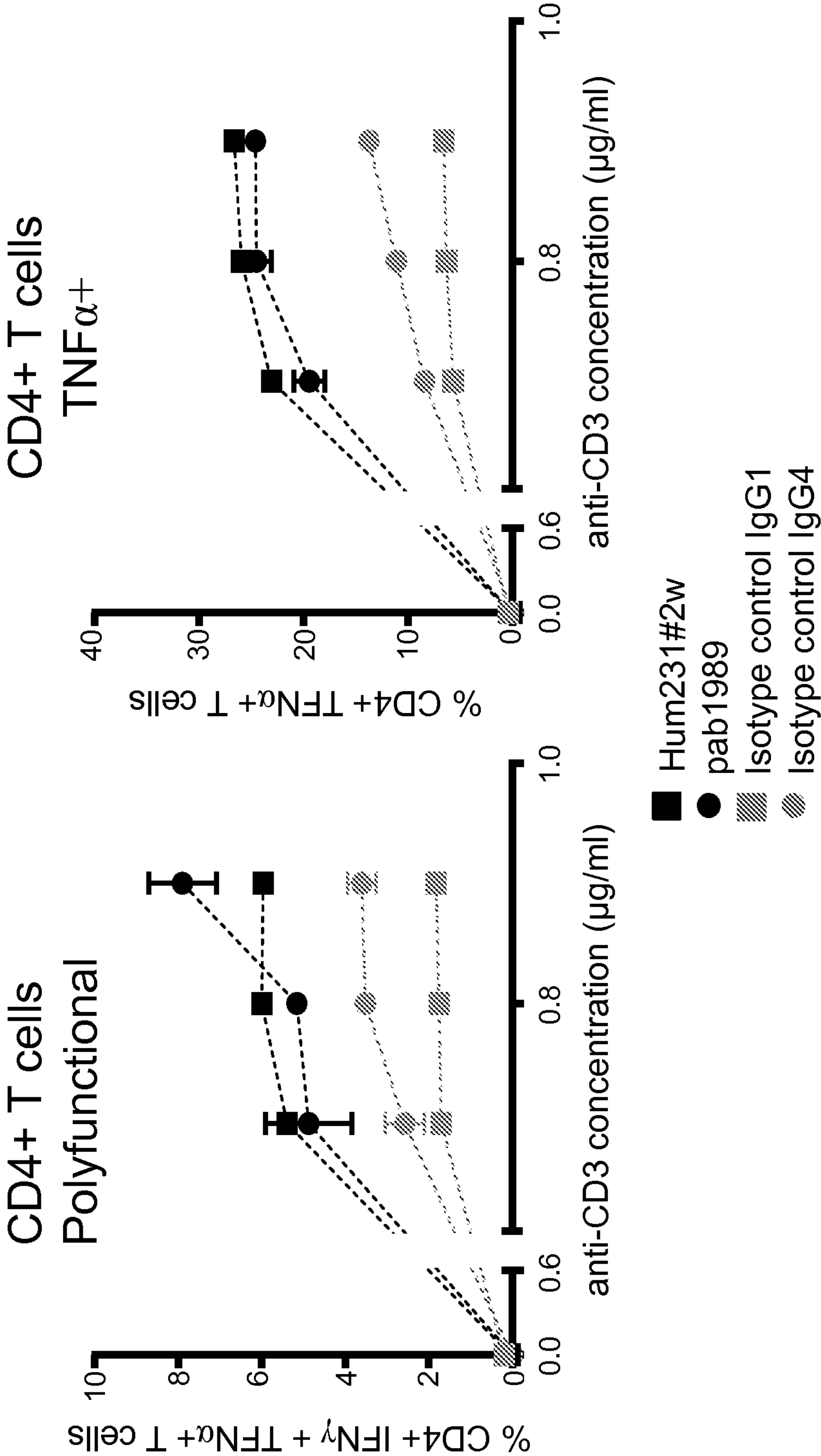


FIGURE 15B

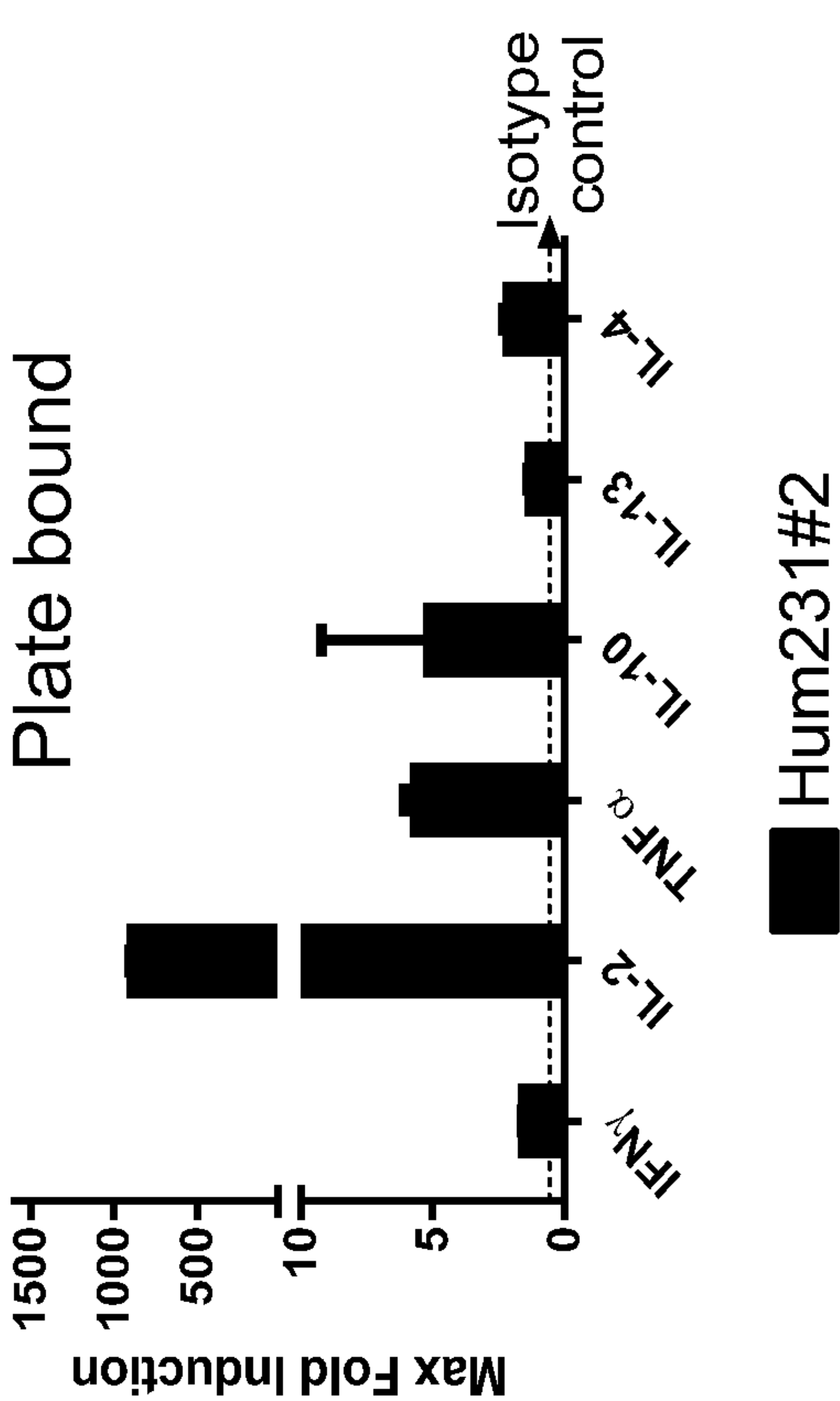


FIGURE 15C

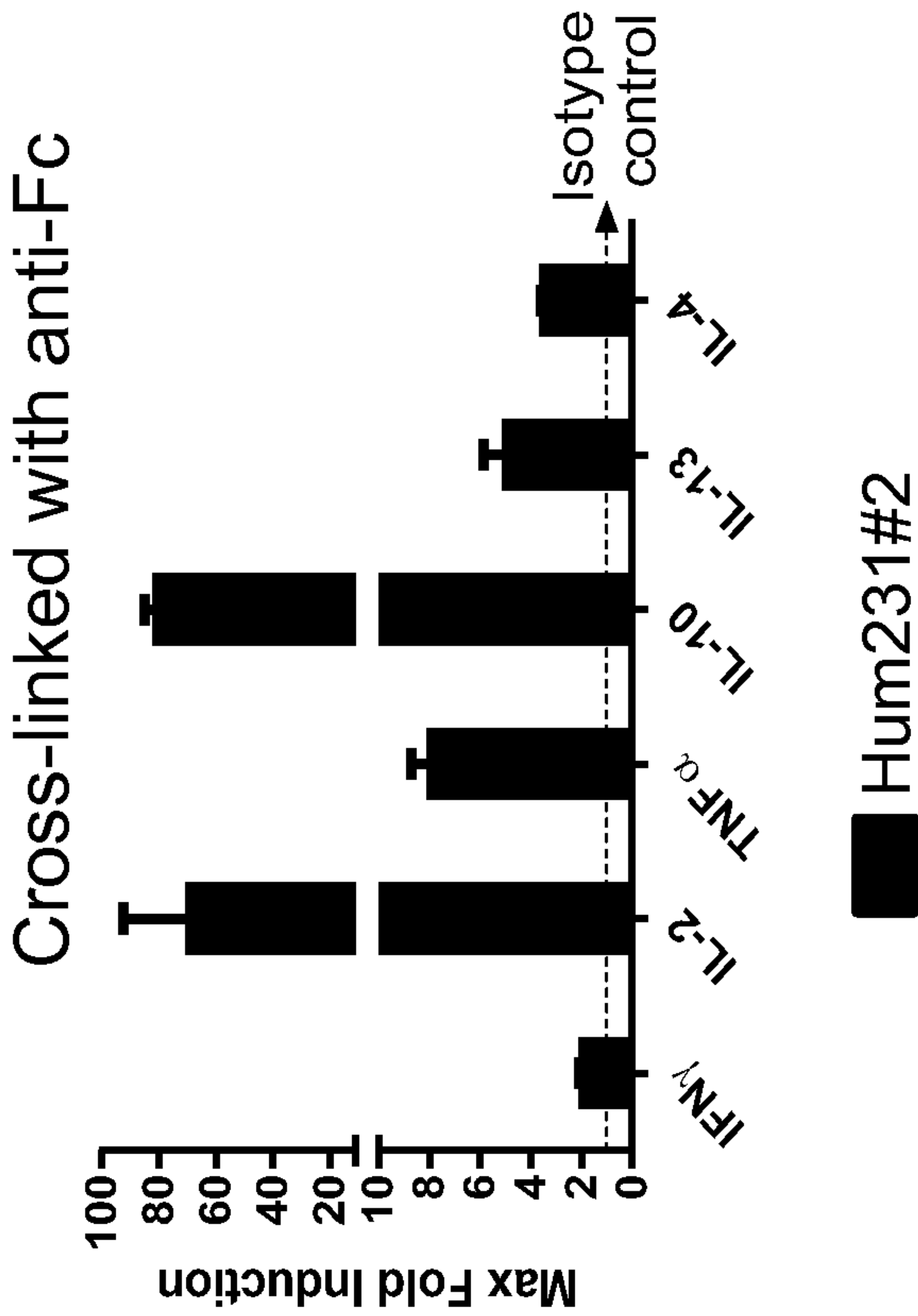


FIGURE 15A

CD8+ T cells
Polyfunctional

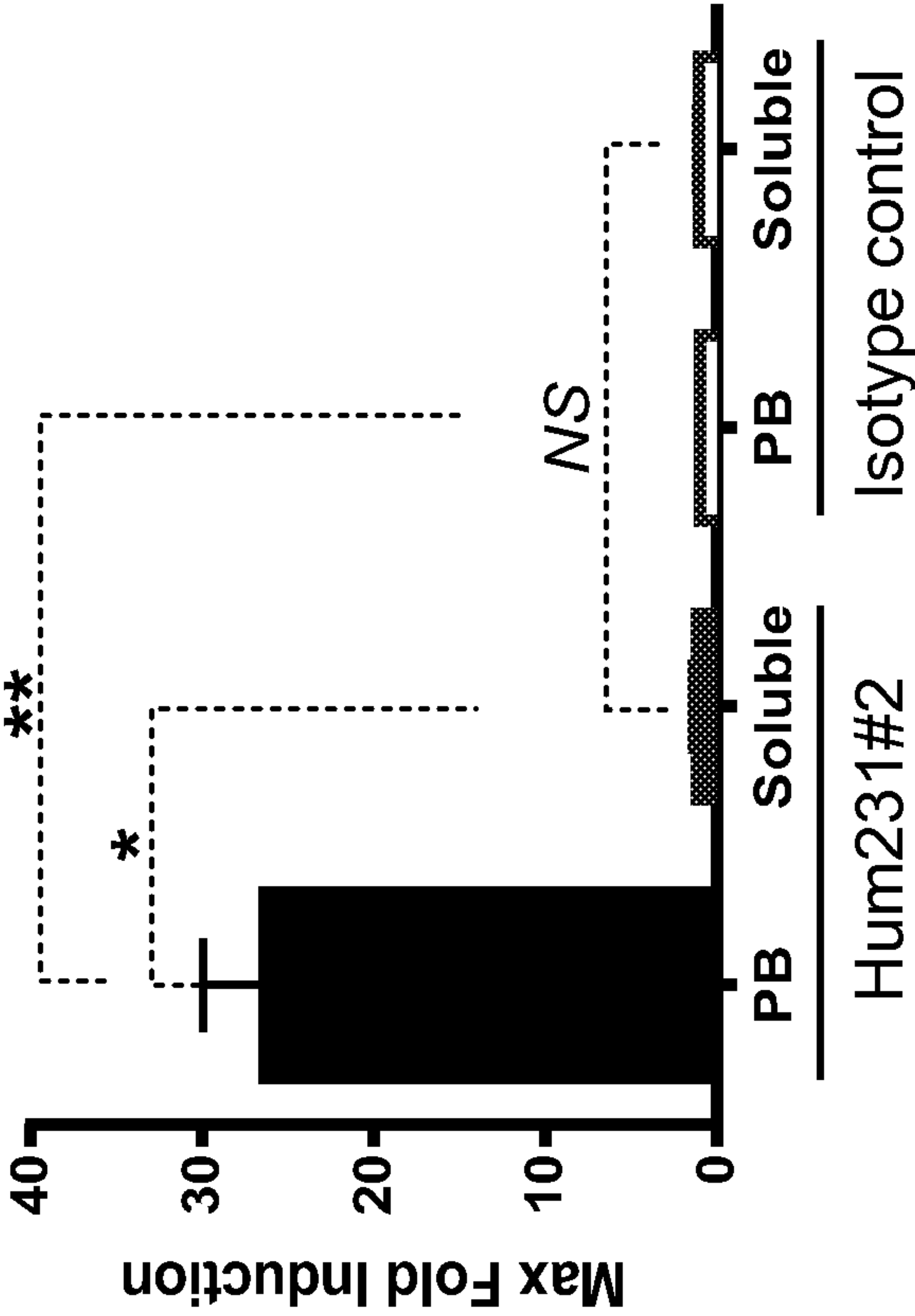


FIGURE 16A

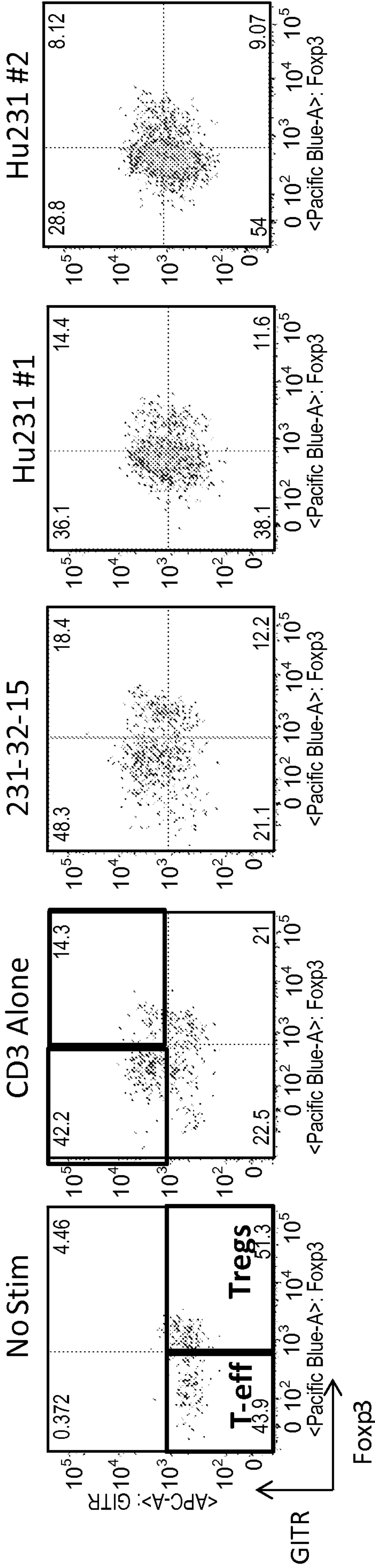


FIGURE 16B

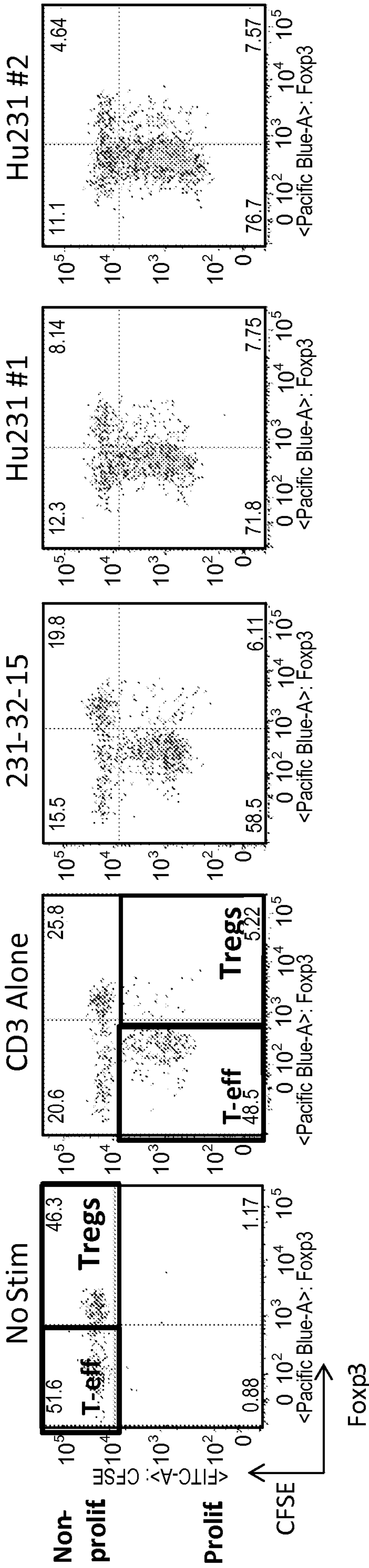


FIGURE 17A

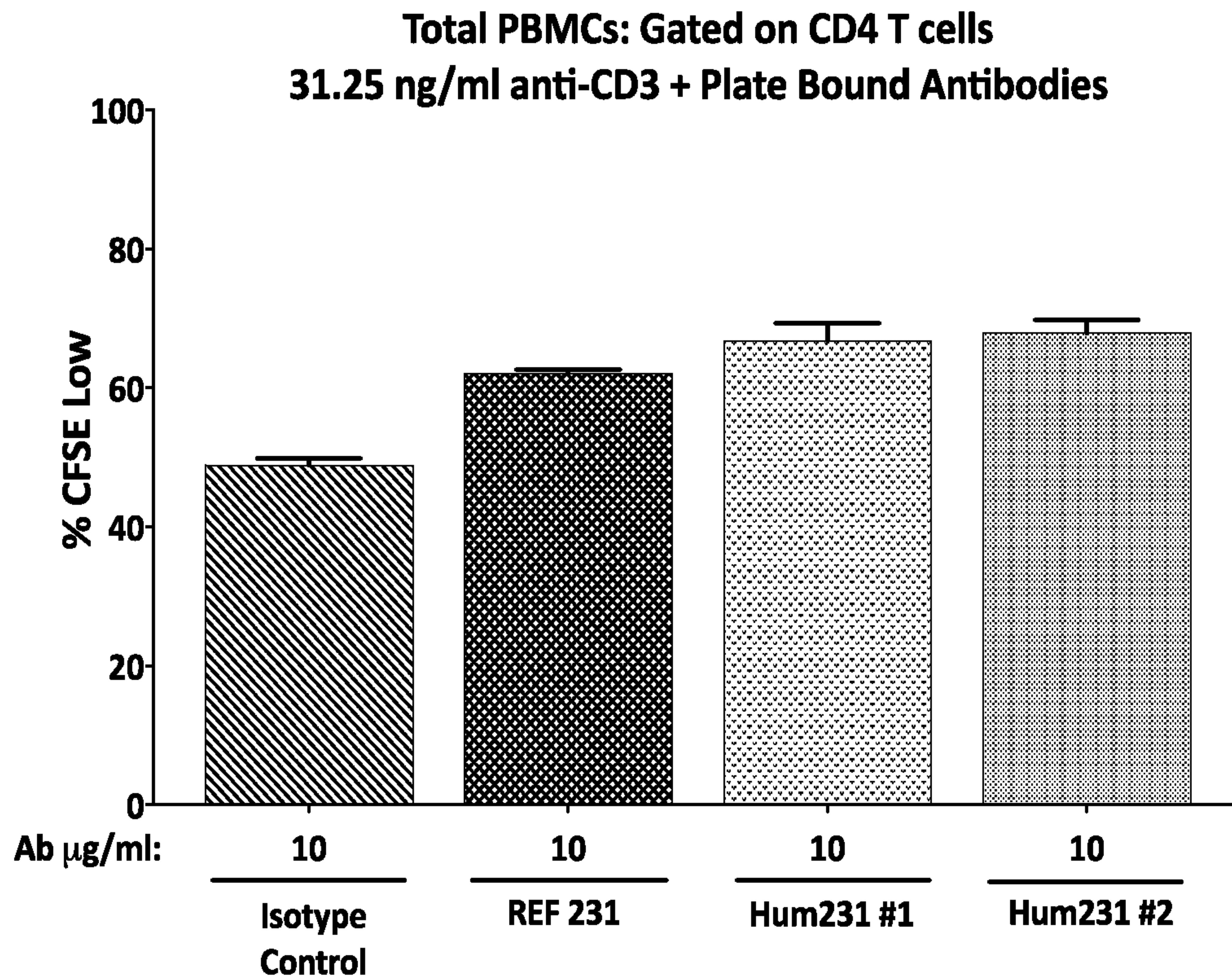
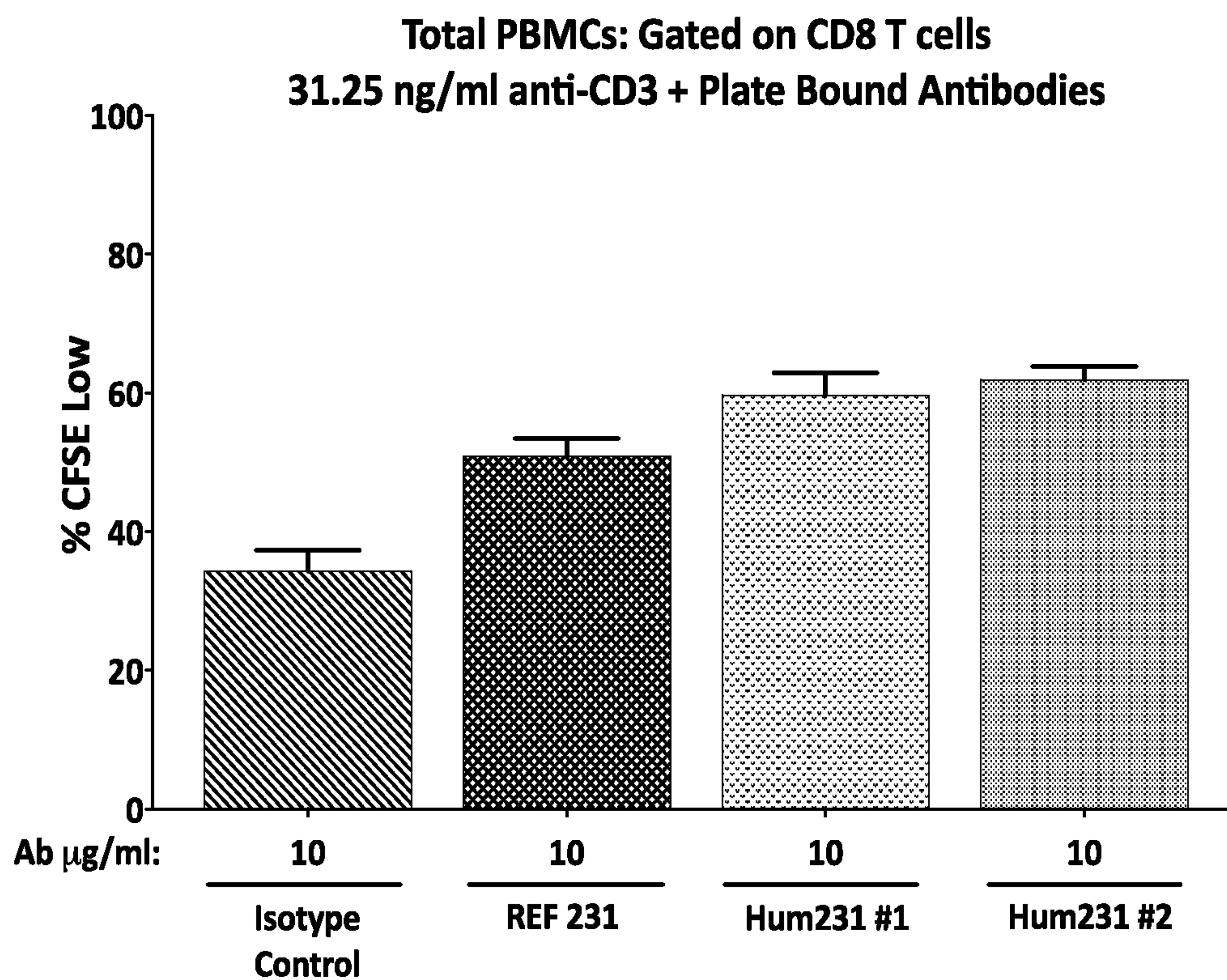


FIGURE 17B



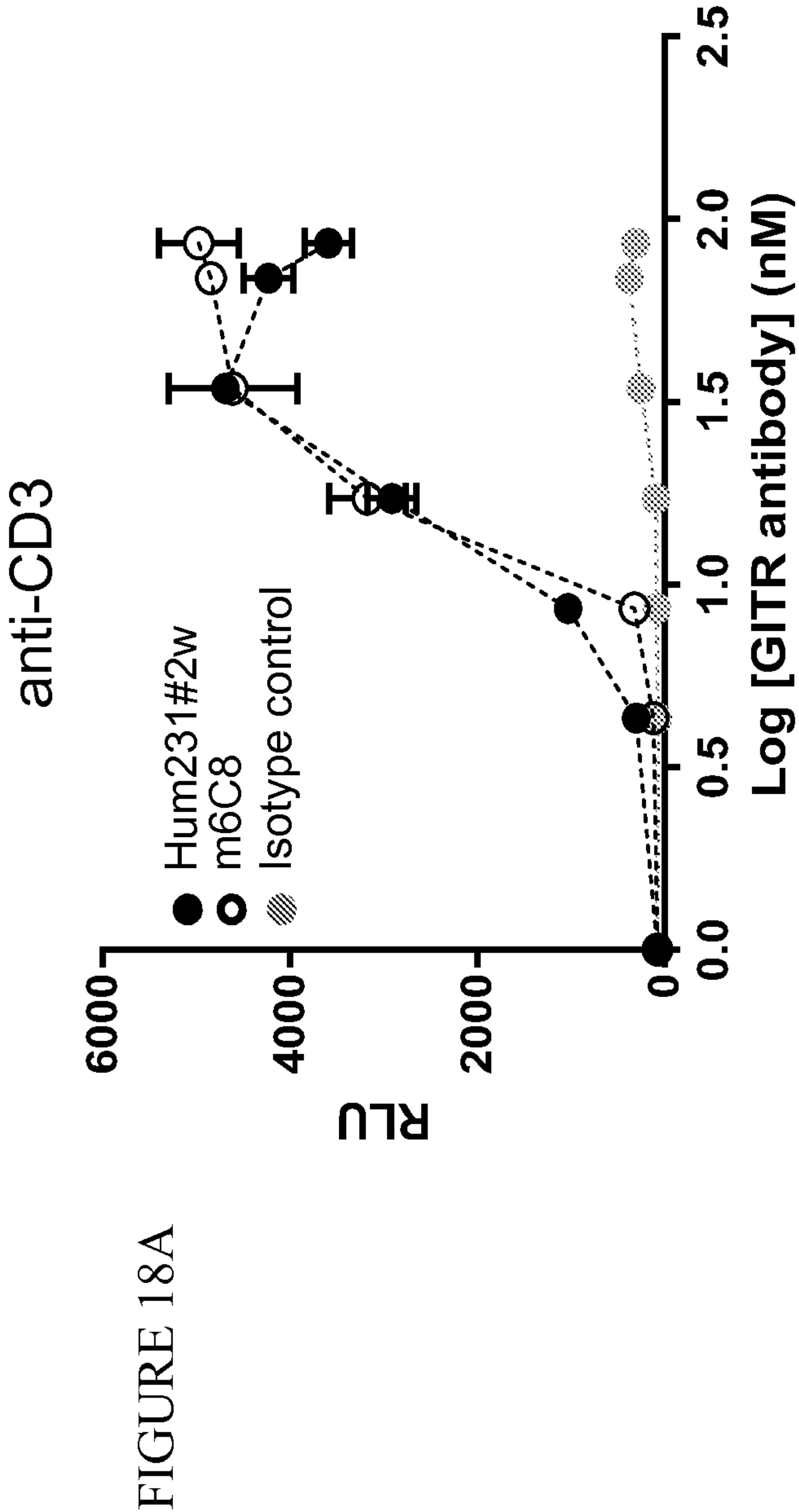


FIGURE 18B

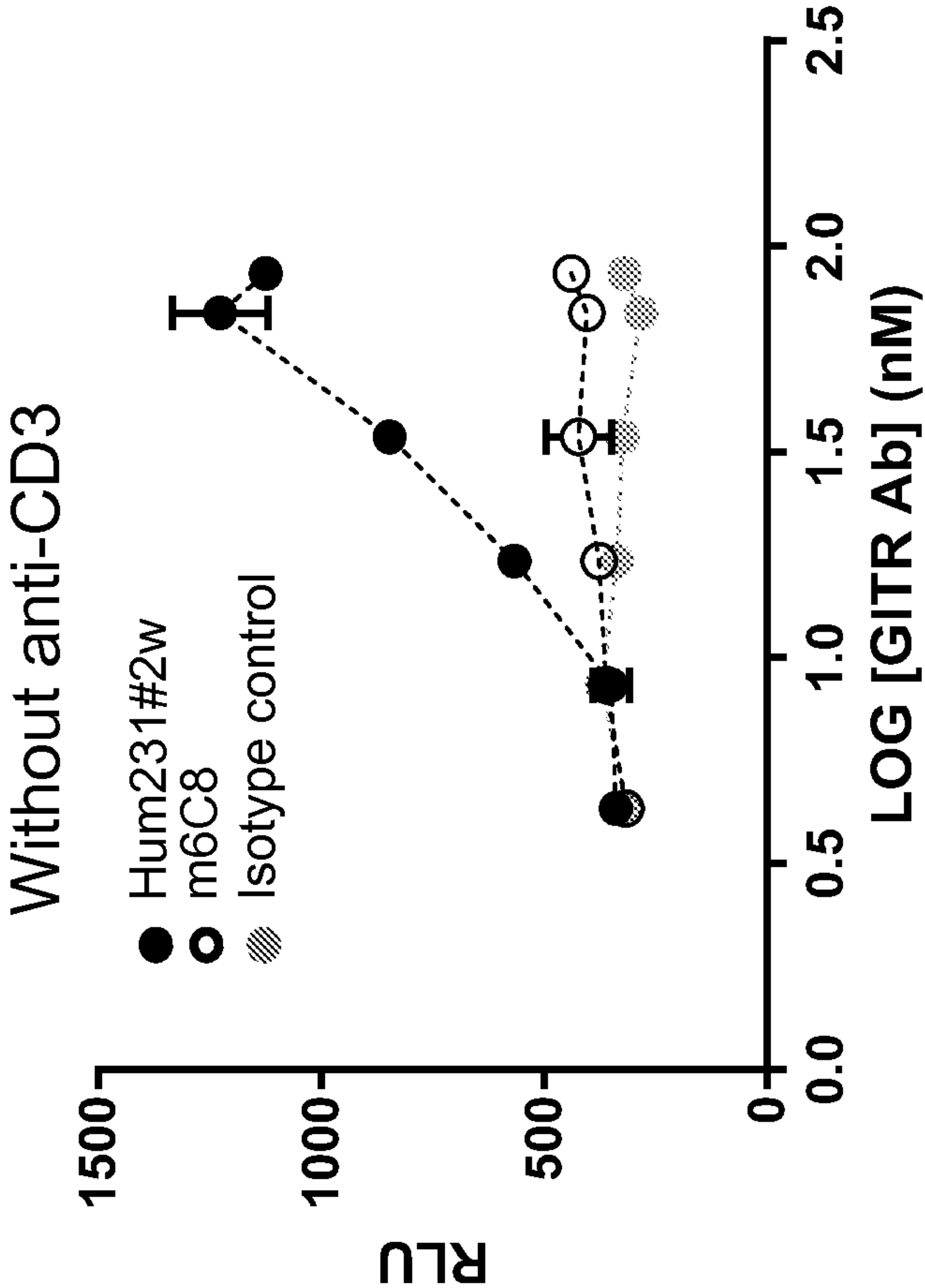


FIGURE 18C

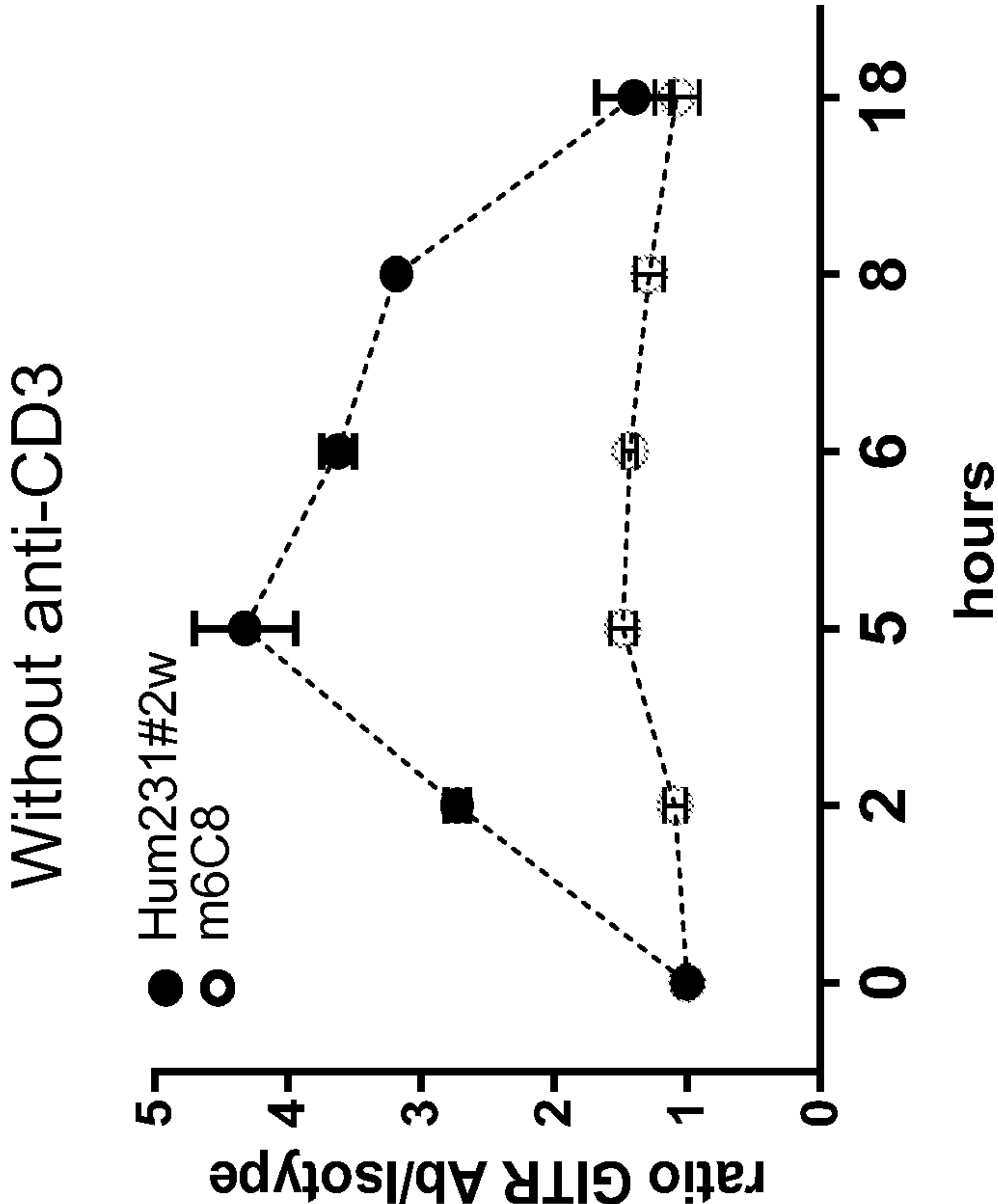


FIGURE 19A

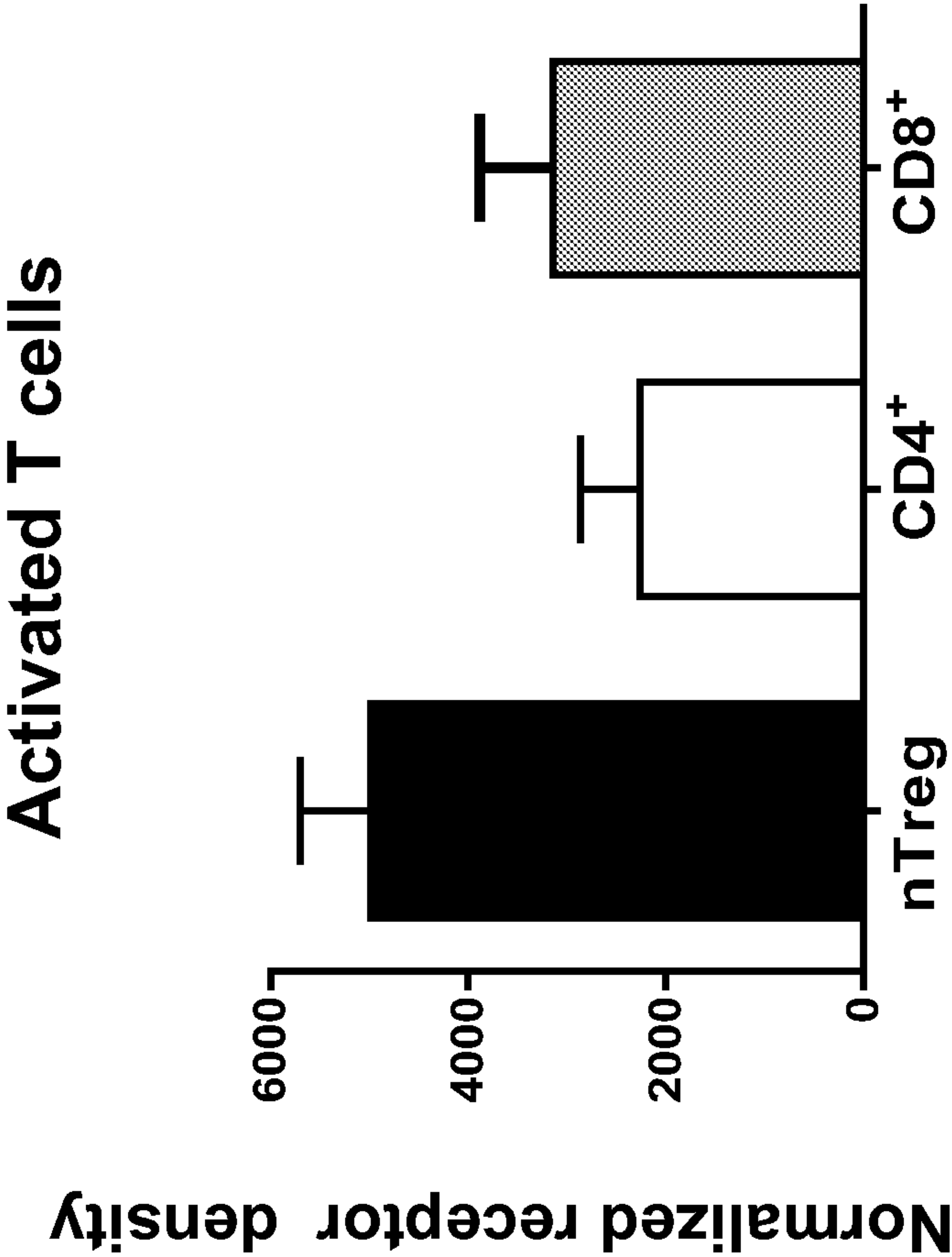


FIGURE 19B

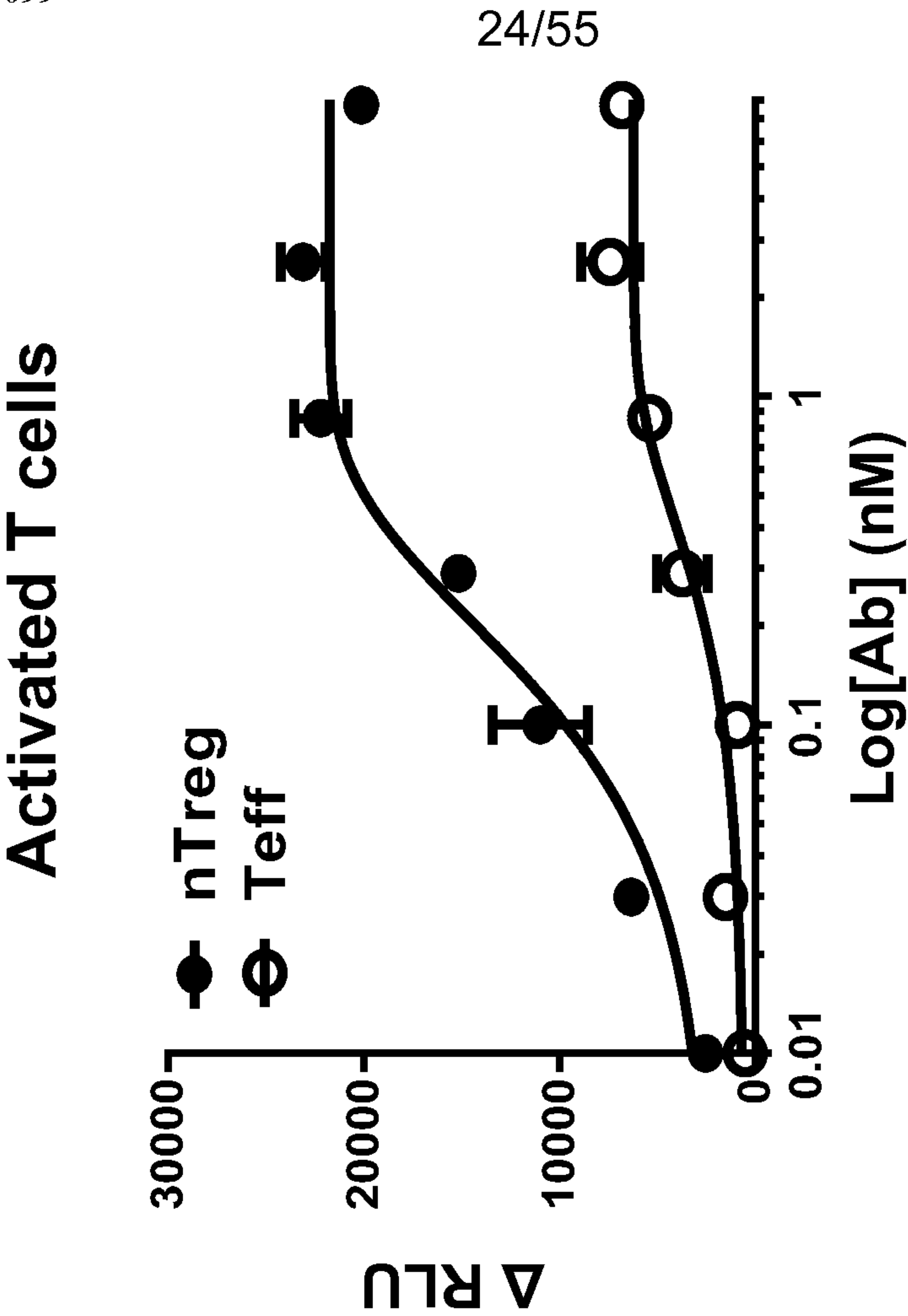


FIGURE 19C

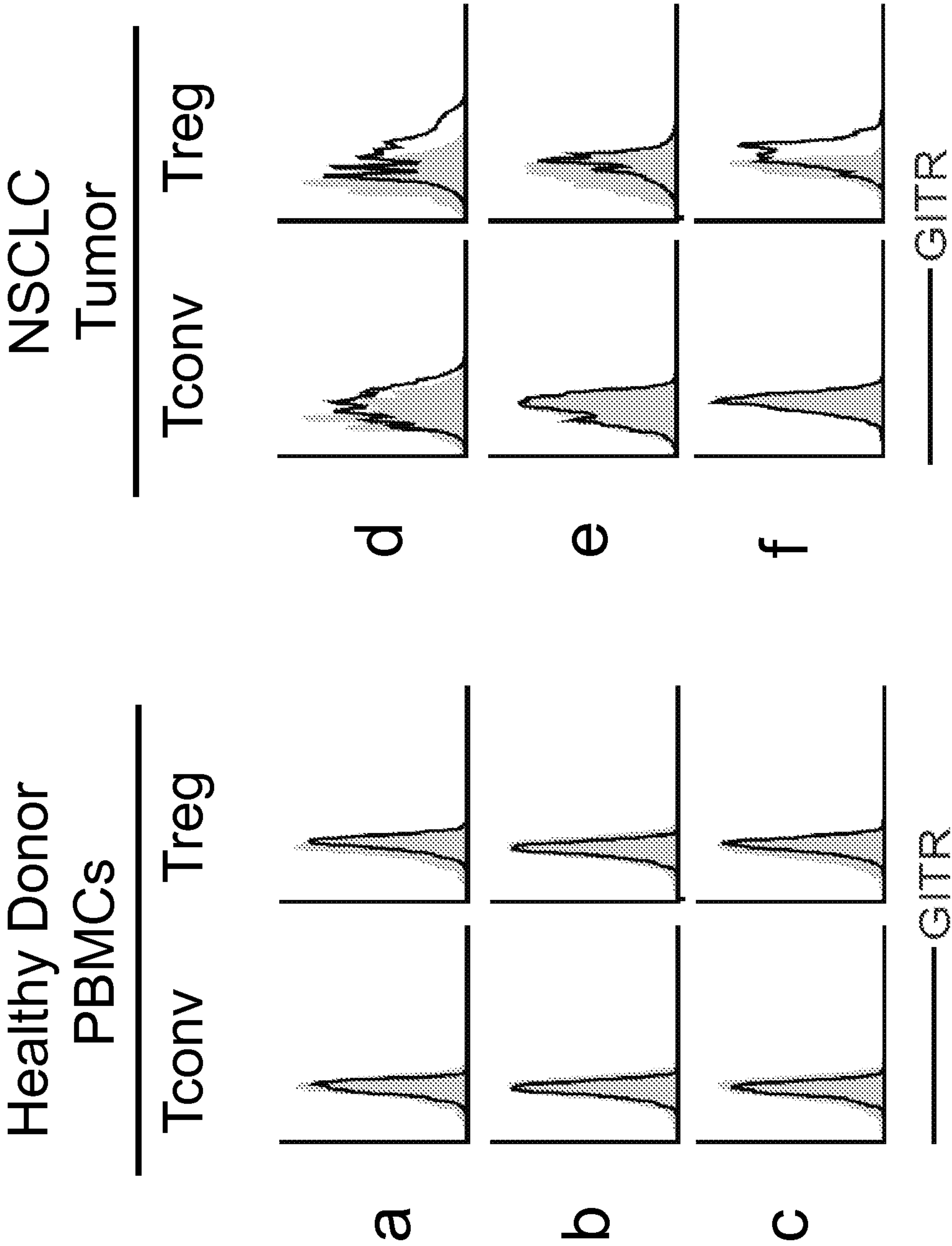


FIGURE 20A

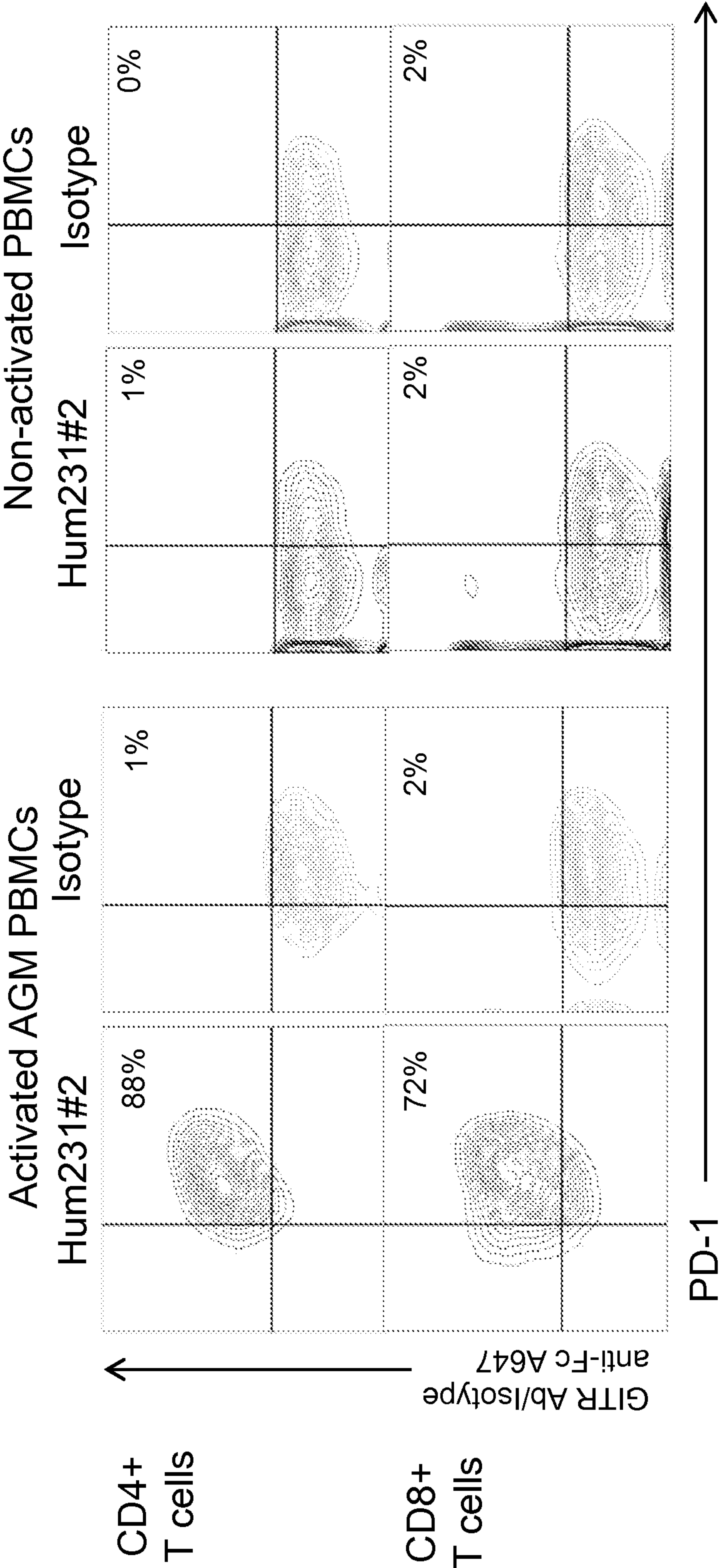


FIGURE 20B

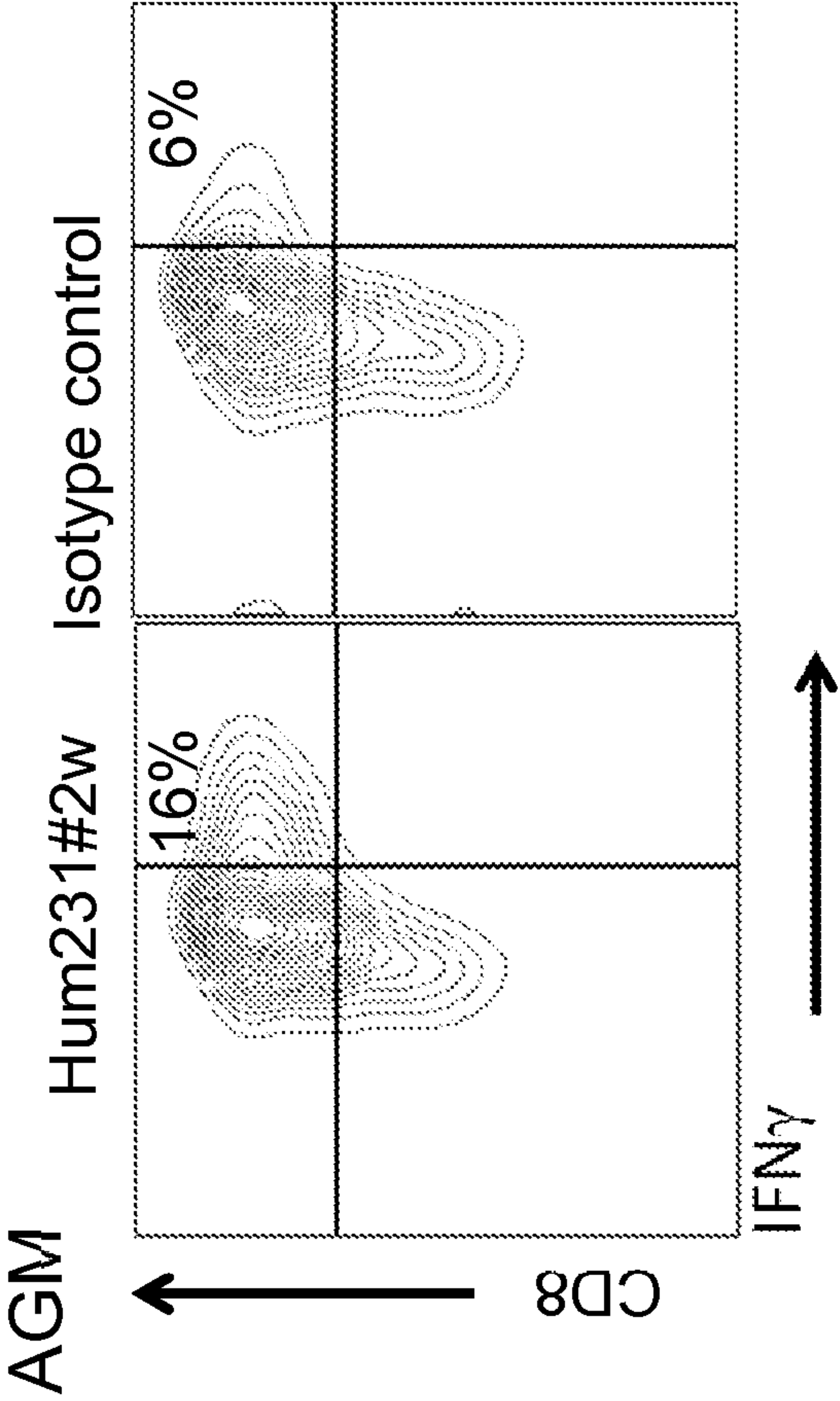


FIGURE 20C

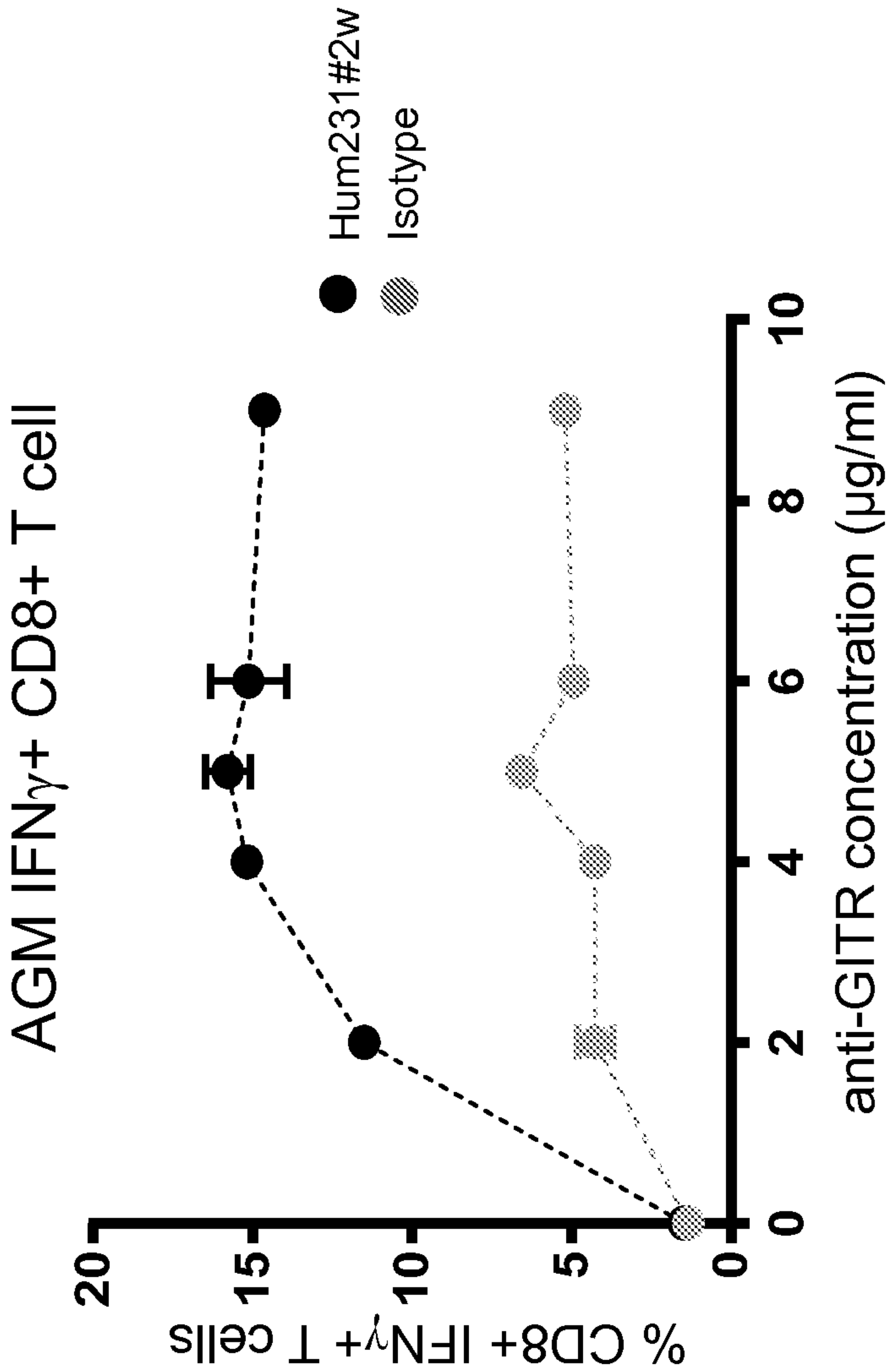


FIGURE 21A

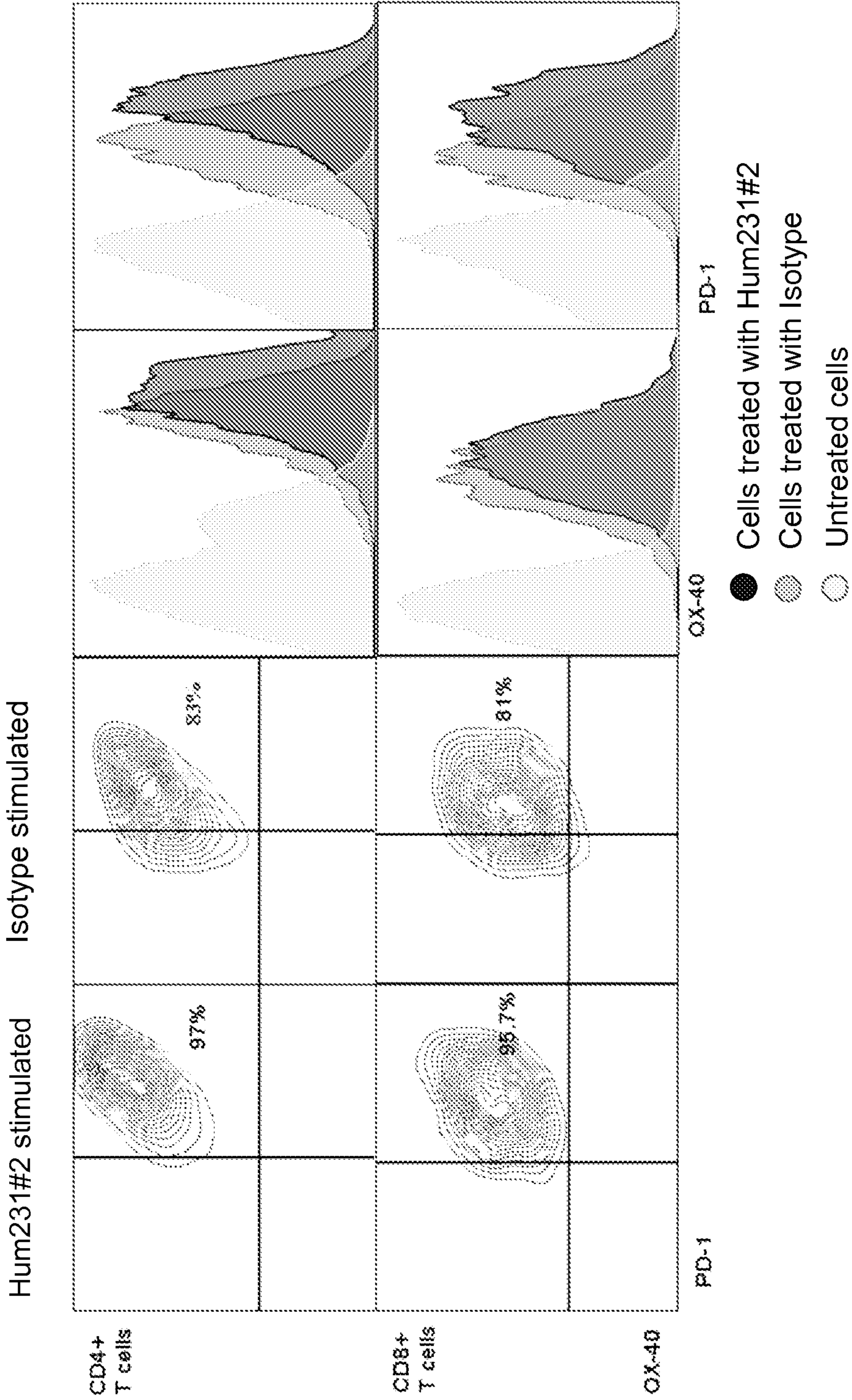


FIGURE 21B

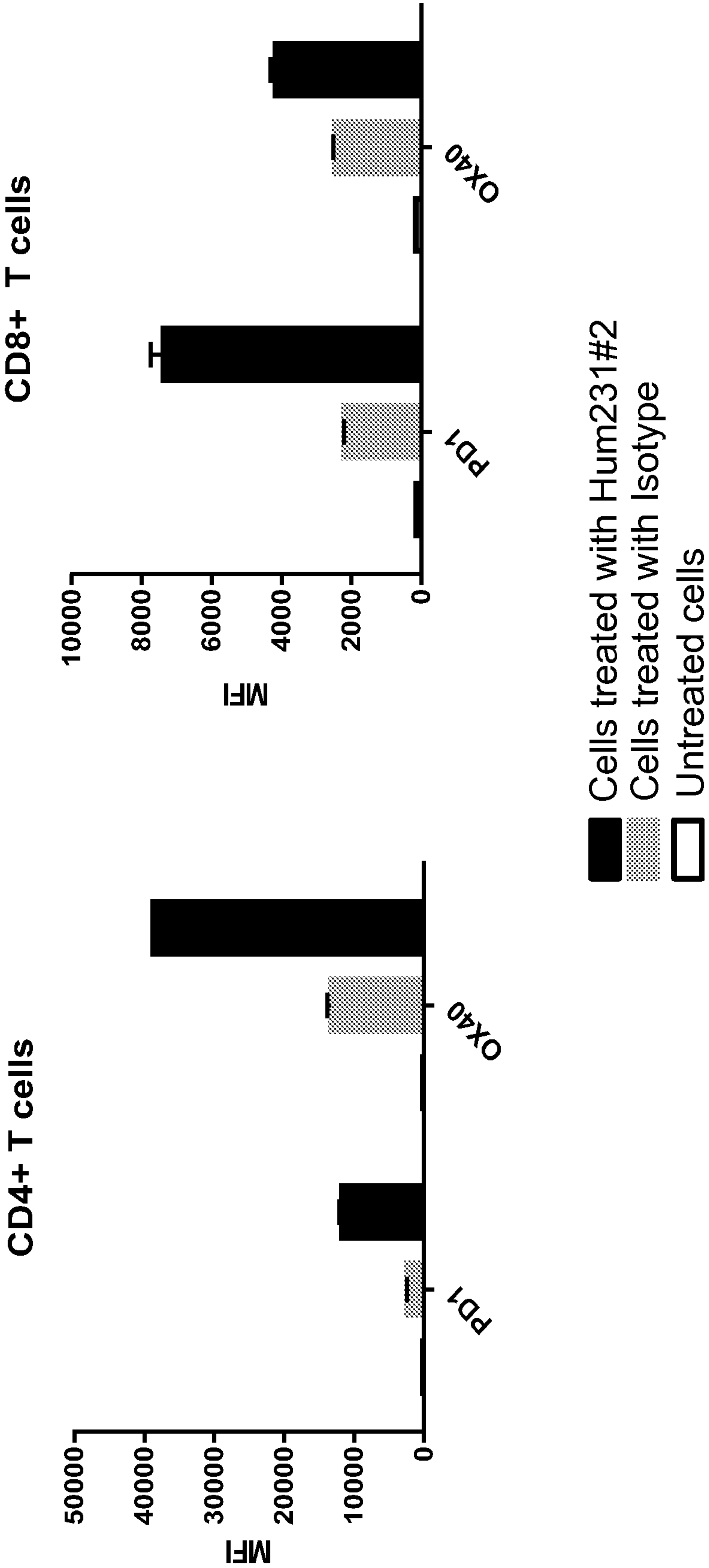


FIGURE 22A

		FR1				CDR1				FR2				CDR2																FR3				SEQ ID NO:					
IMGT			9		25		32	33	34	39	40		50		53		55	56	57	58	59	60	61	62	63	66	67	68	69	70	71	72	74		76		82		
Numbering Scheme					H2		H3	H3	H3	H3	H3		H4		H4		H5	H5		H	H5	H5		H	H		H5	H6	H6	H6		H	H		H				
Kabat			H9		4		1	2	3	4	5		5		8		0	1	H52	52A	3	4	H55	56	57	58	9	0	1	2	H63	64	65		67		73		
hum231-32-15VH			A		G		D	Y	A	M	Y		L		I		V	I	R	T	Y	S	G	D	V	T	Y	N	Q	K	F	K	D		A		K		
		X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	X15	X16	X17																					
Design of ML38			A		G		D	Y	A	M	Y		L		I		V	I	R	T	Y	S	G	D	V	T	Y	N	Q	K	F	K	D		A		K		
			T		A		E		V		H		M				L		K		F			E	L	S					R	E		V		T			
							G												Q				G								Q	G							
Variant		D03	A		A		G	Y	A	M	Y		M		I		L	I	R	T	Y	S	G	G	V	T	Y	N	Q	K	F	Q	G		V		T	39	
		D05	A		G		G	Y	A	M	Y		M		I		V	I	R	T	F	S	G	D	V	T	Y	N	Q	K	F	R	G		V		T	40	
		D07	T		G		E	Y	A	M	Y		M		I		L	I	R	T	F	S	G	E	V	T	Y	N	Q	K	F	K	D		V		T	41	
		D08	T		G		G	Y	A	M	Y		L		I		V	I	K	T	Y	S	G	G	V	T	Y	N	Q	K	F	R	G		V		K	42	
		D09	A		G		G	Y	A	M	H		L		M		L	I	R	T	Y	S	G	G	V	S	Y	N	Q	K	F	R	E		A		T	43	
		E01	T		A		D	Y	A	M	Y		L		I		V	I	R	T	F	S	G	D	L	T	Y	N	Q	K	F	Q	D		V		T	44	
		F09	A		A		E	Y	A	M	H		L		M		L	I	R	T	Y	S	G	G	V	S	Y	N	Q	K	F	Q	G		A		T	45	
		F10	T		A		D	Y	A	M	Y		L		I		L	I	R	T	Y	S	G	G	V	T	Y	N	Q	K	F	Q	G		V		T	46	
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		D11	T		A		E	Y	A	M	Y		M		M		V	I	R	T	F	S	G	G	V	T	Y	N	Q	K	F	Q	E		V		K	52	
		F08	A		A		E	Y	A	M	H		L		M		V	I	R	T	Y	S	G	G	V	S	Y	N	Q	K	F	Q	E		V		T	53	

FIGURE 22B

		CDR1												FR2				CDR2								FR3				CDR3								SEQ ID NO:																
IMGT		24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	52	56	57	58	66	67	68	69	77	78	94	95	103	105	106	107	108	109	110	111													
		L		L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L35	L37	L38	L46	L50	L51	L52	L53	L54	L55	L56	L63	L64	L78	L79	L87	L89	L90	L91	L92	L93	L94	L95	L96	L97											
Numbering Scheme Kabat		24	L25	26	27	A	B	C	D	27E	27F	28	29	30	31	32	L33	34	L35	L37	L38	L46	L50	L51	L52	L53	L54	L55	L56	L63	L64	L78	L79	L87	L89	L90	L91	L92	L93	L94	L95	L96	L97											
hum231-32-15VK		K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	G	L	L	Q	H	Q	N	D	Y	S	Y	P	Y	T	54									
		X1												X2		X3		X4														X5		X6		X7		X8								X9								
Design of ML39		K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	G	L	L	Q	H	Q	N	D	Y	S	Y	P	Y	T										
											S							S		H		M									T		V	Y		E		F		S														
Variant		D03	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	S	W	H	Q	L	W	A	S	T	R	E	S	S	G	V	Q	H	Q	N	E	Y	S	Y	P	Y	T	56									
		D05	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	T	W	H	Q	L	W	A	S	T	R	E	S	S	T	G	V	Q	Y	Q	N	D	Y	S	Y	P	Y	T	57								
		D07	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	T	G	L	Q	H	Q	N	E	Y	S	Y	P	Y	T	58								
		D08	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	S	G	L	Q	Y	Q	N	D	Y	S	Y	P	Y	T	59								
		D09	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	T	G	V	Q	H	Q	N	E	Y	S	F	P	Y	T	60								
		E01	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	S	W	Q	Q	L	W	A	S	T	R	E	S	S	S	G	L	Q	Y	Q	N	D	Y	S	Y	P	Y	T	61								
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		G05	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	S	W	H	Q	L	W	A	S	T	R	E	S	S	S	G	V	Q	H	Q	N	D	Y	S	Y	P	Y	T	64								
		n.a.	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	T	G	V	Q	H	Q	N	D	Y	S	Y	P	Y	T	65								
		G09	K	S	S	Q	S	L	L	N	S	G	N	Q	K	N	Y	L	S	W	H	Q	L	W	A	S	T	R	E	S	S	T	G	V	Q	H	Q	N	D	Y	S	Y	P	Y	T	66								
		C11	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	S	W	Q	Q	L	W	A	S	T	R	E	S	S	S	G	L	Q	H	Q	N	D	Y	S	Y	P	Y	T	67								
		F02	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	T	G	L	Q	Y	Q	N	D	Y	S	Y	P	Y	T	68								
		F03	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	T	W	Q	Q	M	W	A	S	T	R	E	S	S	S	G	L	Q	Y	Q	N	D	Y	S	Y	P	Y	T	69								
		D07.2	K	S	S	Q	S	L	L	N	S	S	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	T	G	L	Q	Y	Q	N	D	Y	S	F	P	Y	T	70								
F05	K	S	S	Q	S	L	L	N	S	S	G	N	Q	K	N	Y	L	T	W	Q	Q	L	W	A	S	T	R	E	S	S	S	G	L	Q	H	Q	N	D	Y	S	F	P	Y	T	71									

FIGURE 23

Antibody ID	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:	Number of extra germline amino acids	Mean relative affinity vs. 231-32-15 (%)
pab1964	BADD427-2616	249	BADD427-2631	435	4	95
pab1965	BADD427-2617	251	BADD427-2632	437	0	93
pab1966	BADD427-2619	254	BADD427-2634	440	4	91
pab1967	BADD427-2620	255	BADD427-2635	441	4	90
pab1968	BADD427-2621	259	BADD427-2636	444	4	84
pab1969	BADD427-2622	276	BADD427-2637	458	6	79
pab1970	BADD427-2623	277	BADD427-2638	459	4	77
pab1971	BADD427-2624	280	BADD427-2639	453	3	73
pab1972	BADD427-2625	284	BADD427-2640	463	3	72
pab1973	BADD427-2626	304	BADD427-2641	519	3	72
pab1975	BADD427-2622	276	BADD427-2634	440	8	68
pab1976	BADD427-2622	276	BADD427-2636	444	8	67
pab1977	BADD427-2622	276	BADD427-2644	453	8	66
pab1979	BADD427-2630	345	BADD427-2634	440	8	63
pab1980	BADD427-2630	345	BADD427-2636	444	8	62
pab1981	BADD427-2630	345	BADD427-2644	453	8	58
pab1983	BADD427-2616	249	BADD427-2634	440	7	16

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FIGURE 24A

Antibody ID	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
1	H1916A01	215	K1916A01	400
2	H1916A03	217	K1916A03	401
3	H1916A04	218	K1916A04	402
4	H1916A05	219	K1916A05	403
5	H1916A06	220	K1916A06	404
6	H1916A07	221	K1916A07	405
7	H1916A08	222	K1916A08	406
8	H1916A09	223	K1916A09	407
9	H1916A10	224	K1916A10	408
10	H1916A11	225	K1916A11	409
11	H1916A12	226	K1916A12	410
12	H1916B01	227	K1916B01	411
13	H1916B03	228	K1916B03	413
14	H1916B04	229	K1916B04	414
15	H1916B05	230	K1916B05	415
16	H1916B06	231	K1916B06	416
17	H1916B08	232	K1916B08	418
18	H1916B09	233	K1916B09	419
19	H1916B10	234	K1916B10	420
20	H1916B12	236	K1916B12	421
21	H1916C03	237	K1916C03	423
22	H1916C04	238	K1916C04	424
23	H1916C05	239	K1916C05	425
24	H1916C06	240	K1916C06	426
25	H1916C07	241	K1916C07	427
26	H1916C08	242	K1916C08	428
27	H1916C09	243	K1916C09	429
28	H1916C10	244	K1916C10	430
29	H1916C11	245	K1916C11	431
30	H1916C12	246	K1916C12	432
31	H1916D01	247	K1916D01	433
32	H1916D02	248	K1916D02	434
33	H1916D03	249	K1916D03	435
34	H1916D04	250	K1916D04	436
35	H1916D05	251	K1916D05	437
36	H1916D06	252	K1916D06	438
37	H1916D07	253	K1916D07	439
38	H1916D08	254	K1916D08	440
39	H1916D09	255	K1916D09	441
40	H1916D10	256	K1916D10	442

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FIGURE 24B

Antibody ID	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
41	H1916D12	258	K1916D12	443
42	H1916E01	259	K1916E01	444
43	H1916E03	261	K1916E03	445
44	H1916E04	262	K1916E04	446
45	H1916E05	263	K1916E05	447
46	H1916E06	264	K1916E06	448
47	H1916E08	265	K1916E08	450
48	H1916E10	267	K1916E10	451
49	H1916E11	268	K1916E11	452
50	H1916F03	270	K1916F03	454
51	H1916F04	271	K1916F04	455
52	H1916F05	272	K1916F05	456
53	H1916F06	273	K1916F06	457
54	H1916F09	276	K1916F09	458
55	H1916F10	277	K1916F10	459
56	H1916G01	280	K1916G01	460
57	H1916G02	281	K1916G02	461
58	H1916G04	283	K1916G04	462
59	H1916G05	284	K1916G05	463
60	H1916G06	285	K1916G06	464
61	H1917A02	287	K1917A02	467
62	H1917A03	288	K1917A03	468
63	H1917A05	290	K1917A05	469
64	H1917A06	291	K1917A06	470
65	H1917A09	294	K1917A09	471
66	H1917A11	296	K1917A11	472
67	H1917A12	297	K1917A12	473
68	H1917B01	298	K1917B01	474
69	H1917B02	299	K1917B02	475
70	H1917B04	301	K1917B04	476
71	H1917B07	304	K1917B07	477
72	H1917B12	305	K1917B12	481
73	H1917C01	306	K1917C01	482
74	H1917C03	308	K1917C03	483
75	H1917C09	313	K1917C09	484
76	H1917C10	314	K1917C10	485
77	H1917C11	315	K1917C11	486
78	H1917D01	316	K1917D01	488
79	H1917D04	319	K1917D04	489
80	H1917D07	320	K1917D07	490

FIGURE 24C

Antibody ID	Heavy chain variable region	SEQ ID NO:	Light chain variable region	SEQ ID NO:
81	H1917D09	322	K1917D09	491
82	H1917D10	323	K1917D10	492
83	H1917D11	324	K1917D11	493
84	H1917D12	325	K1917D12	494
85	H1917E02	327	K1917E02	495
86	H1917E03	328	K1917E03	496
87	H1917E08	333	K1917E08	497
88	H1917E11	336	K1917E11	498
89	H1917F01	338	K1917F01	499
90	H1917F02	339	K1917F02	500
91	H1917F03	340	K1917F03	501
92	H1917F05	342	K1917F05	502
93	H1917F06	343	K1917F06	503
94	H1917G01	350	K1917G01	504
95	H1917G05	354	K1917G05	505
96	H1917G06	355	K1917G06	506
97	H1917G07	356	K1917G07	507
98	H1917G09	358	K1917G09	508
99	H1917G10	359	K1917G10	509
100	H1917G11	360	K1917G11	510
101	H1917H01	362	K1917H01	511
102	H1917H02	363	K1917H02	512
103	H1917H04	364	K1917H04	513
104	H1917H06	365	K1917H06	515
105	H1917H07	366	K1917H07	516
106	H1917H08	367	K1917H08	517
107	H1917H09	368	K1917H09	518

FIGURE 25A

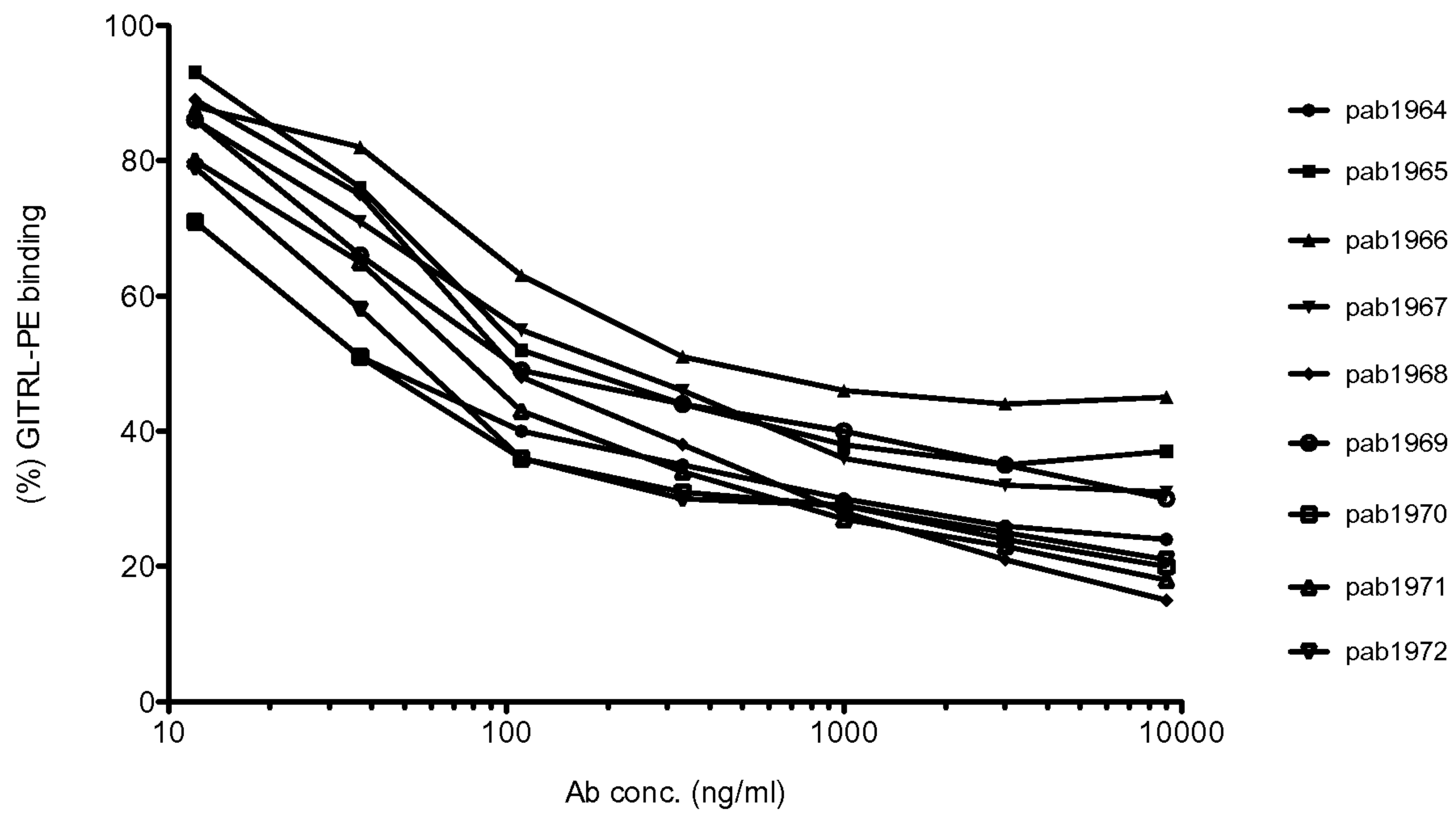


FIGURE 25B

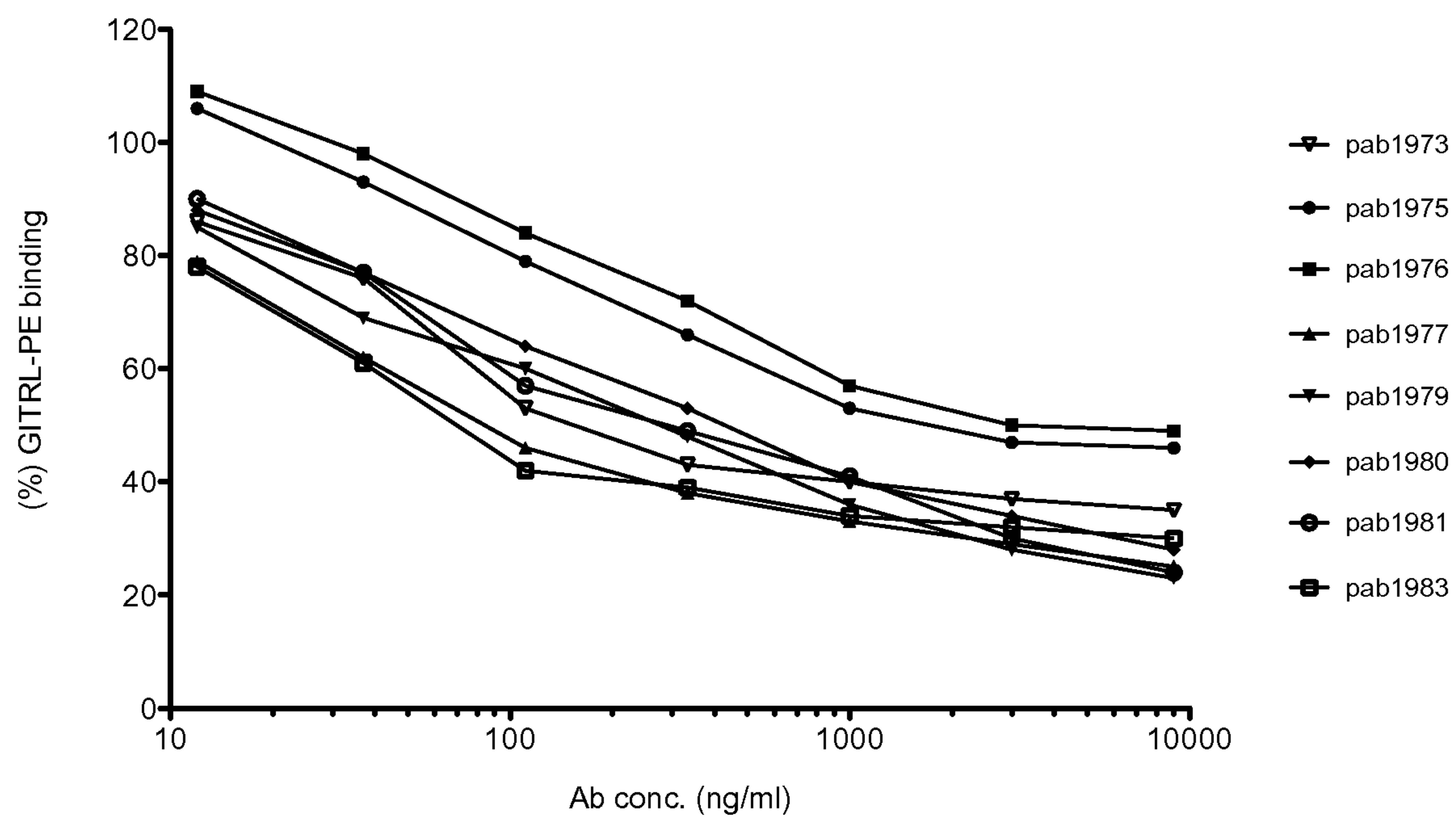


FIGURE 26A

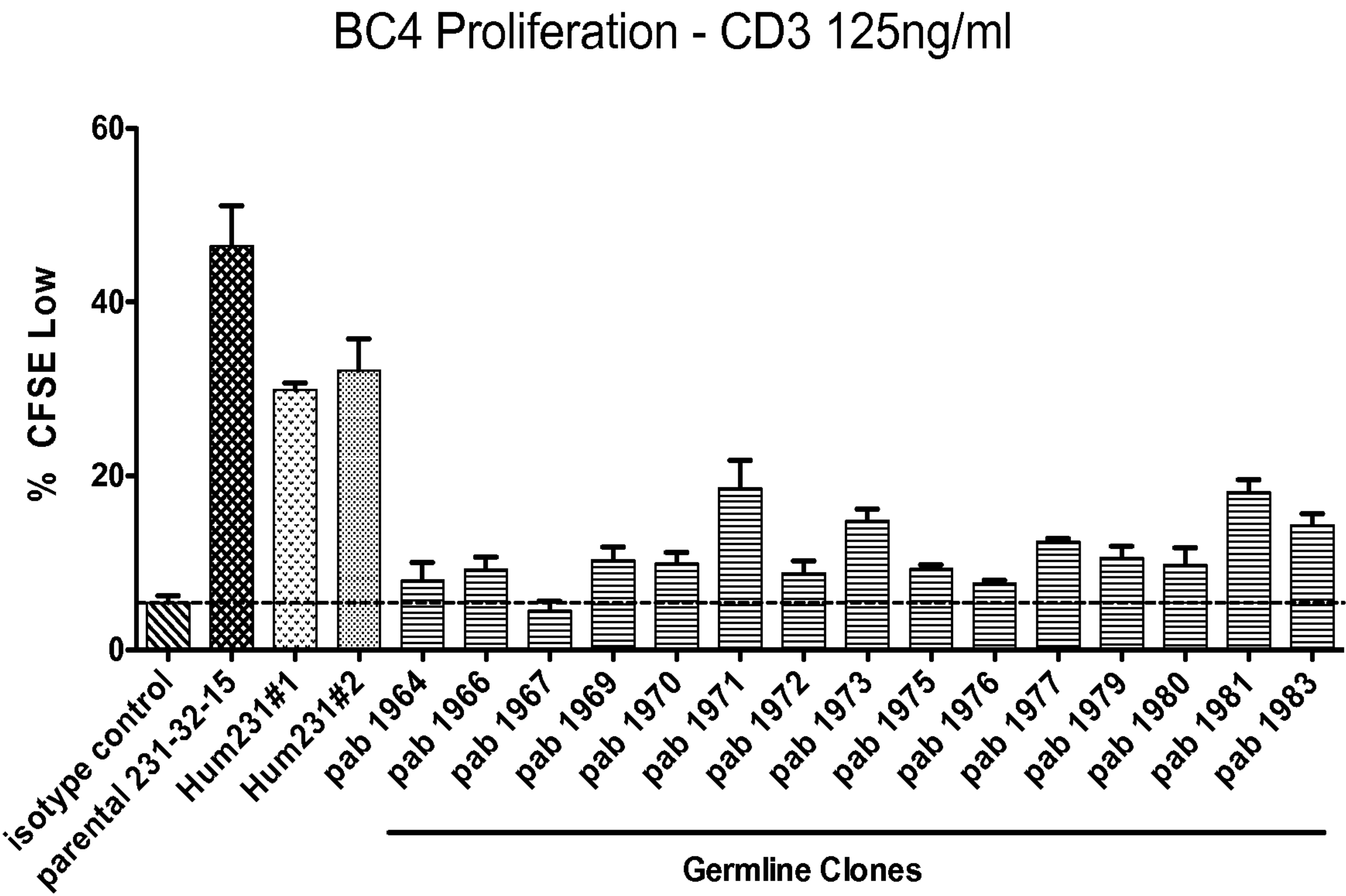


FIGURE 26B

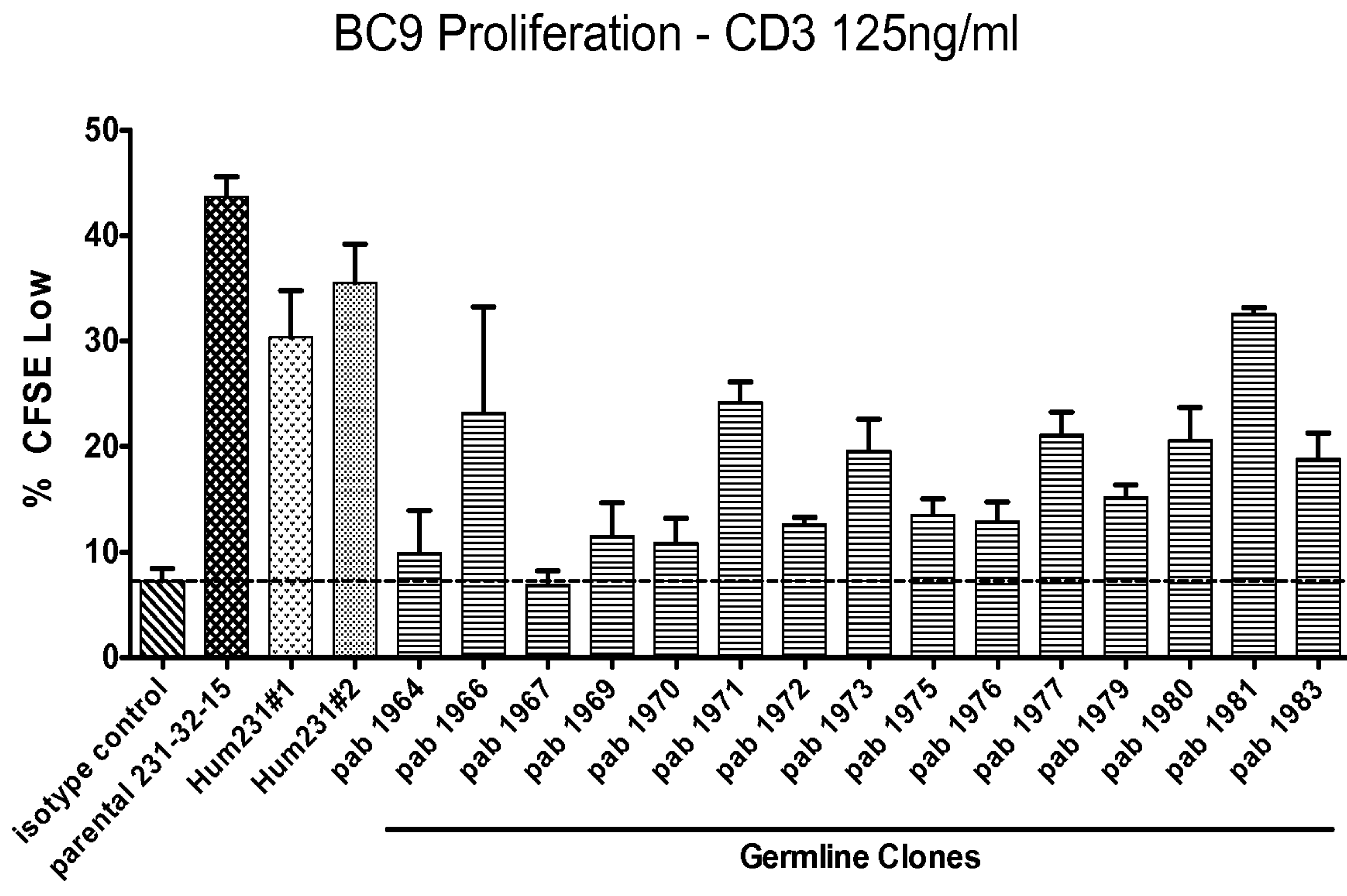


FIGURE 27A

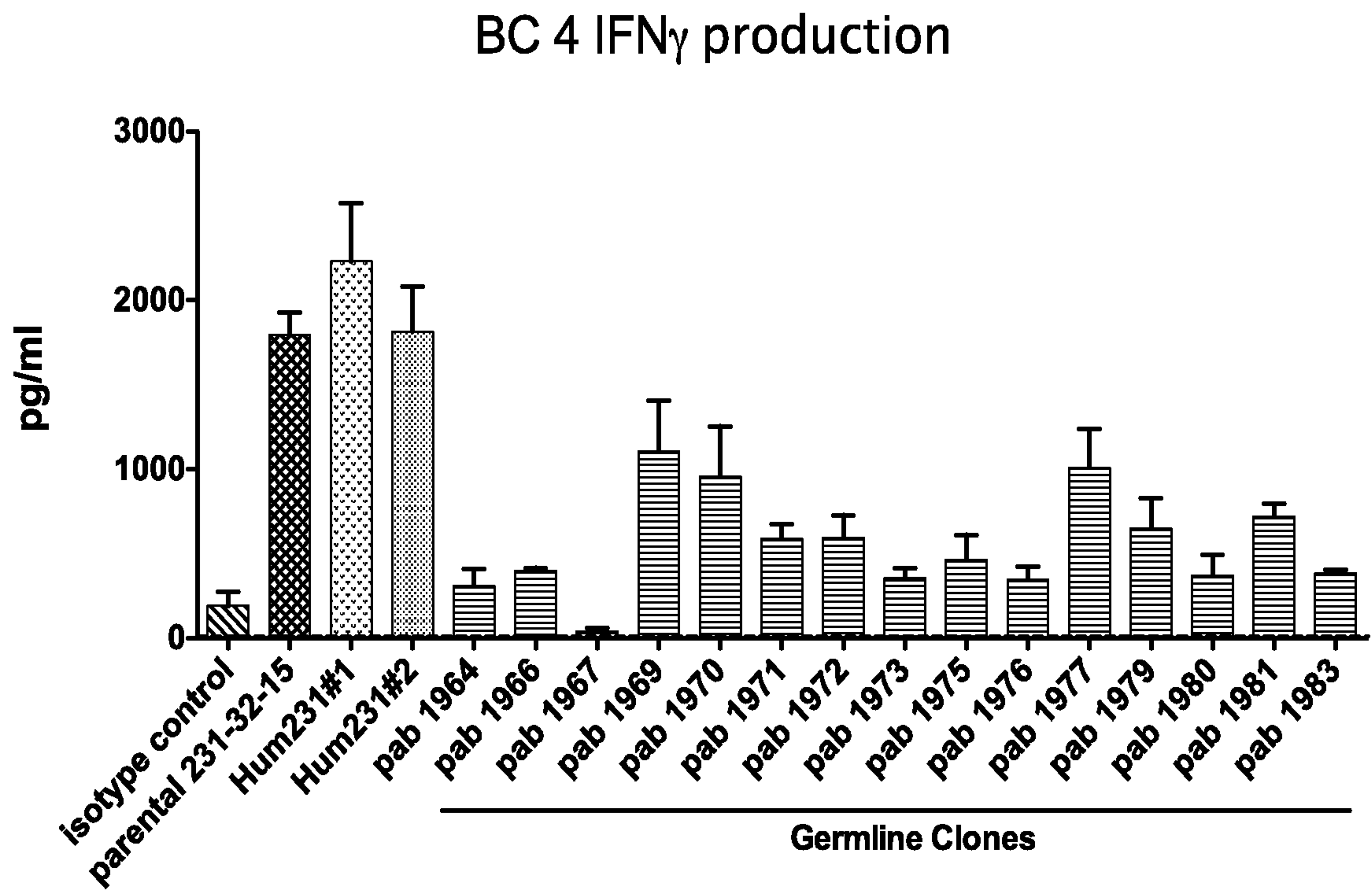


FIGURE 27B

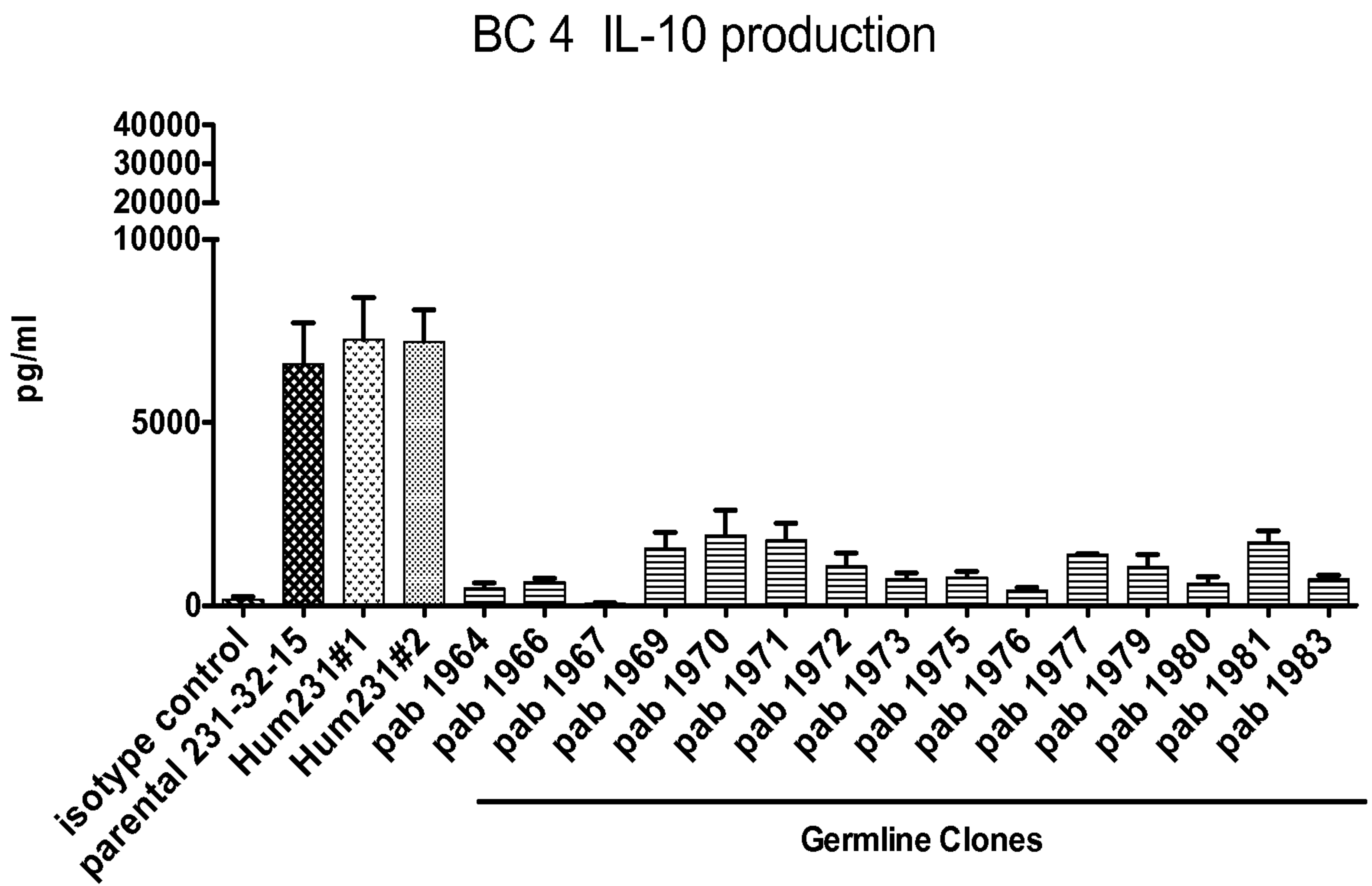


FIGURE 28A

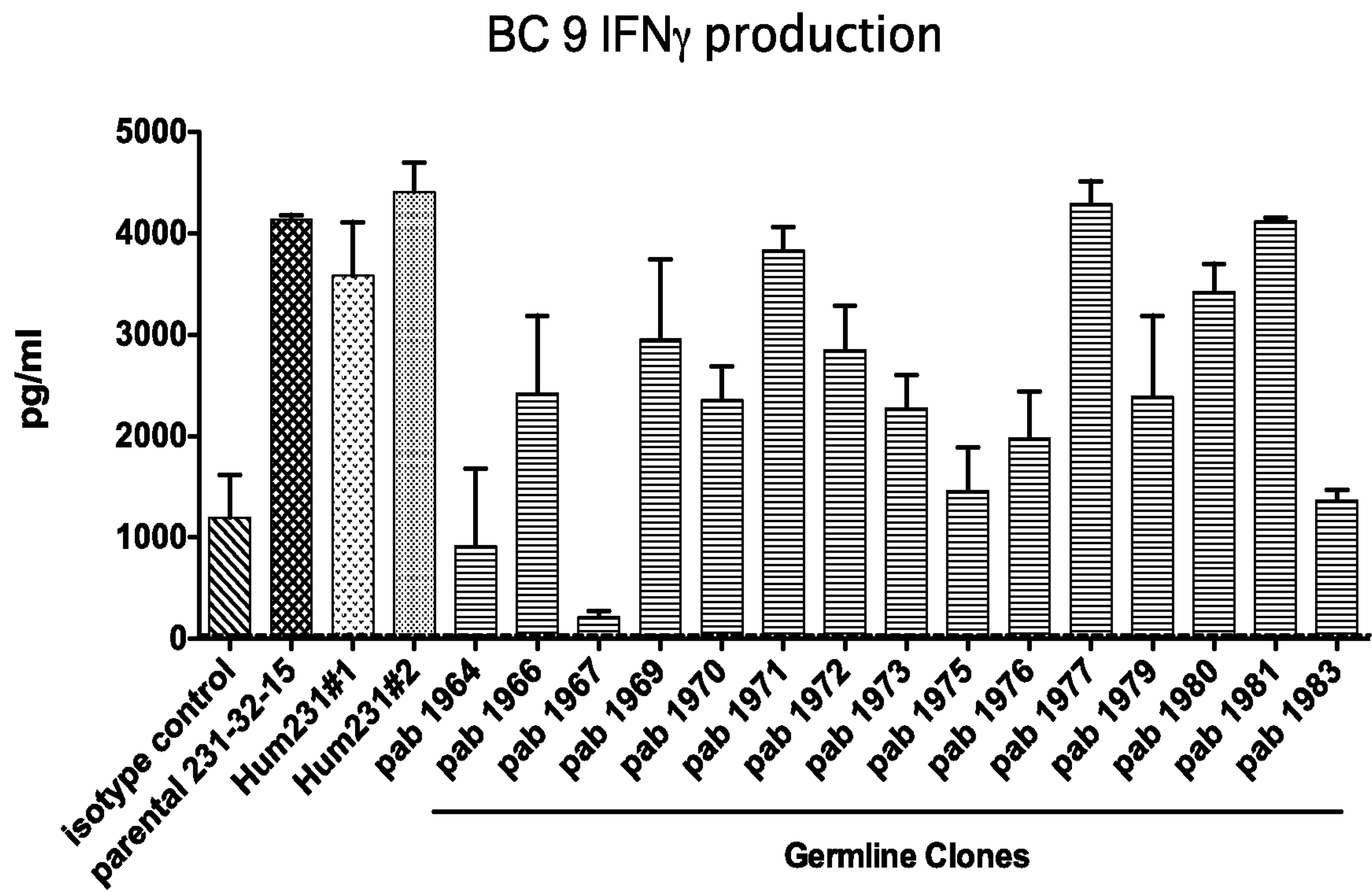


FIGURE 28B

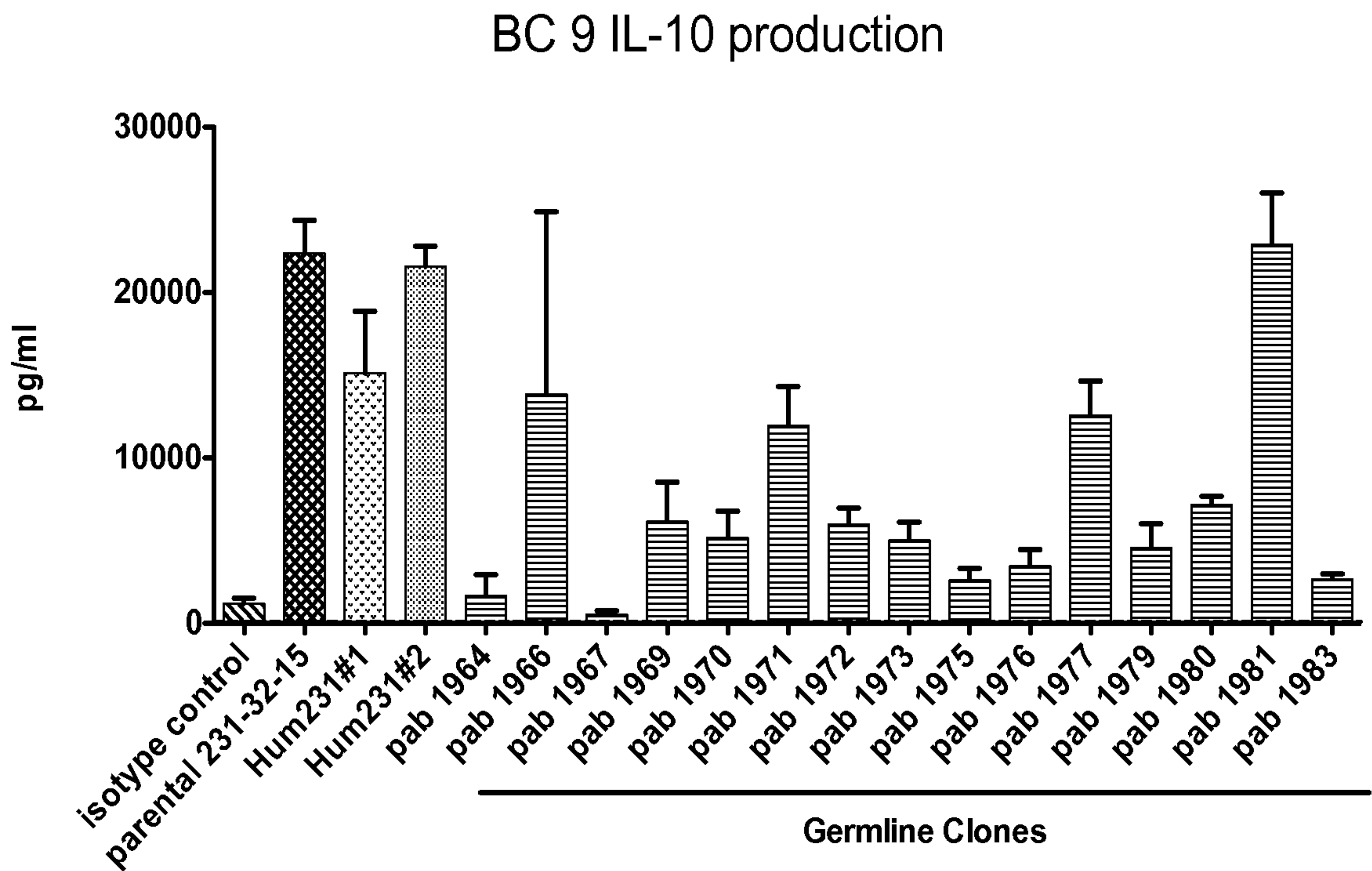


FIGURE 29A

BC 13 IFN γ production

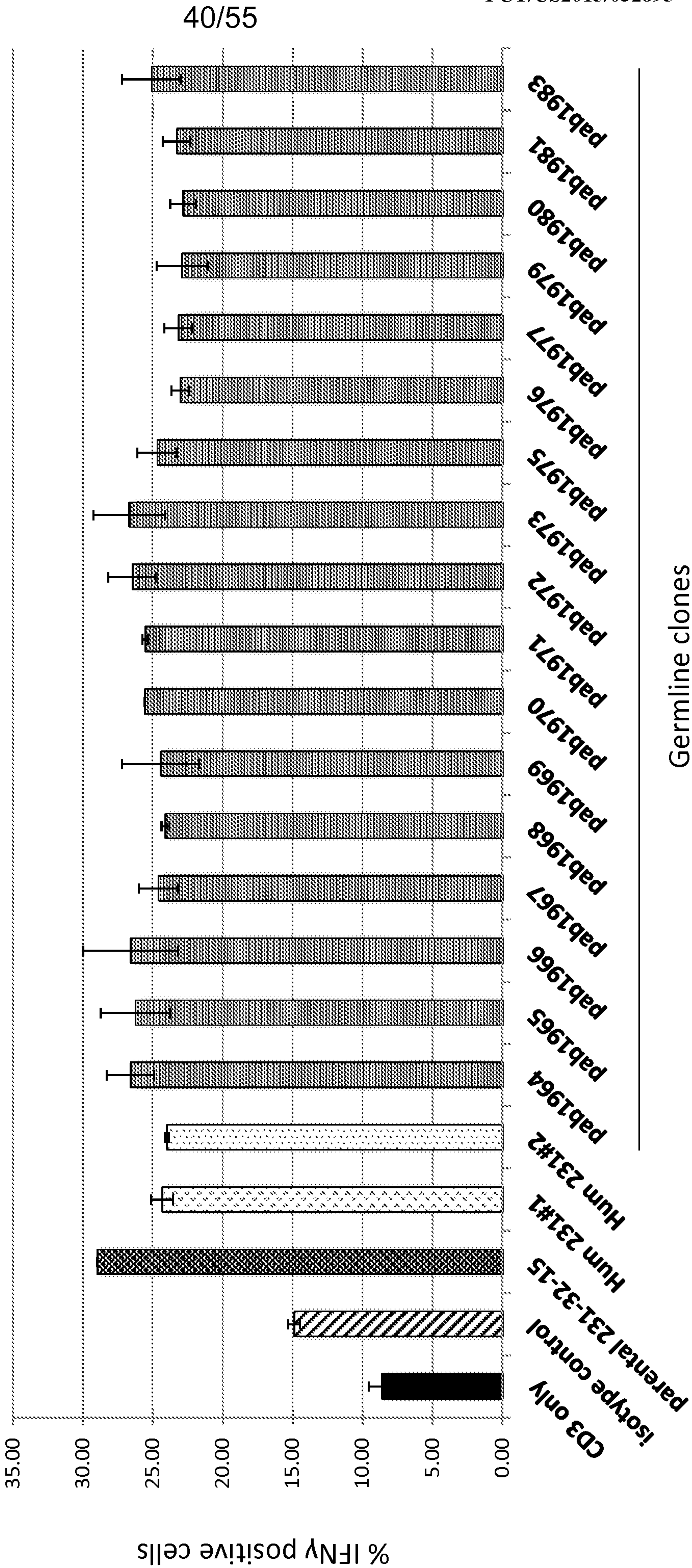


FIGURE 29B

BC 18 IFN γ production

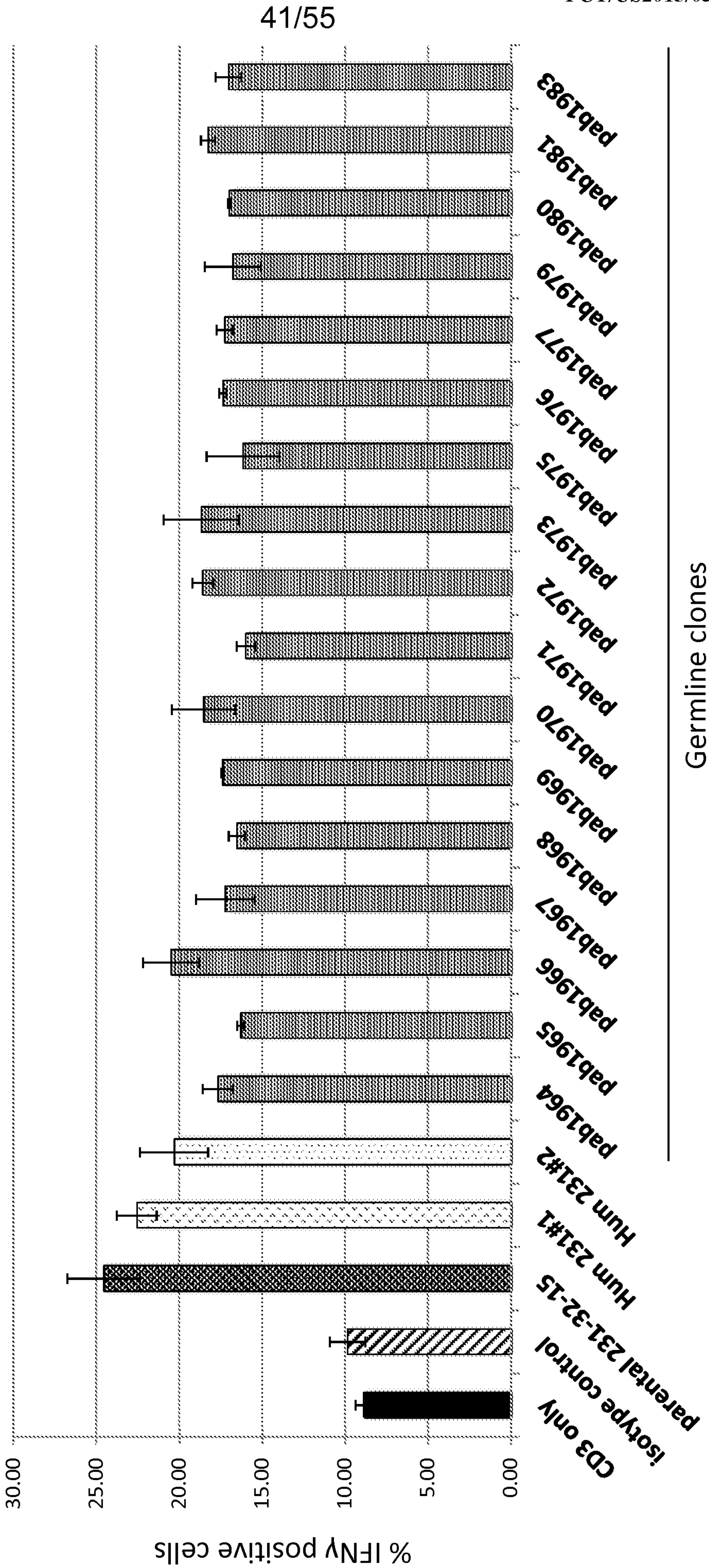


FIGURE 30A

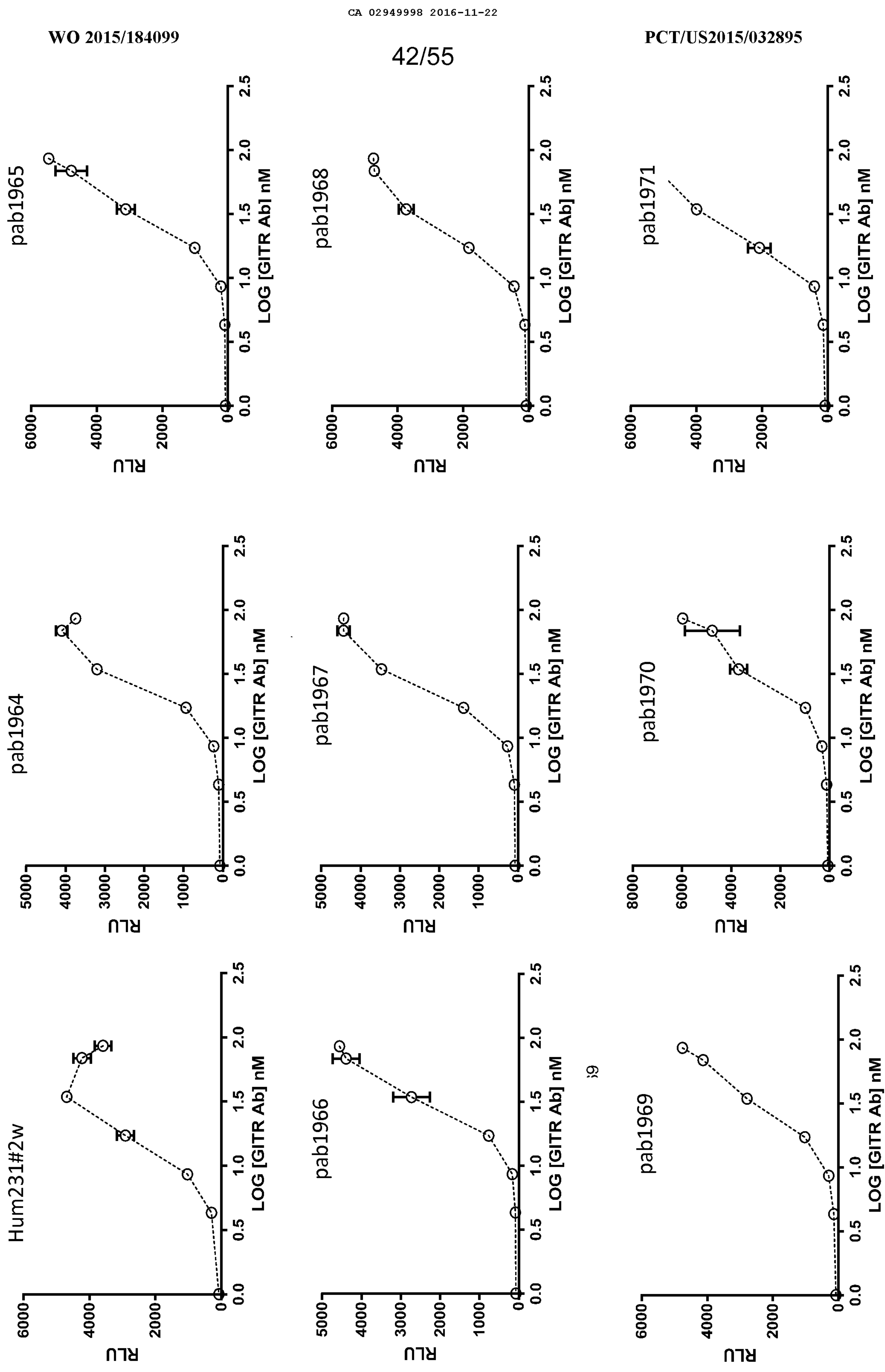


FIGURE 30B

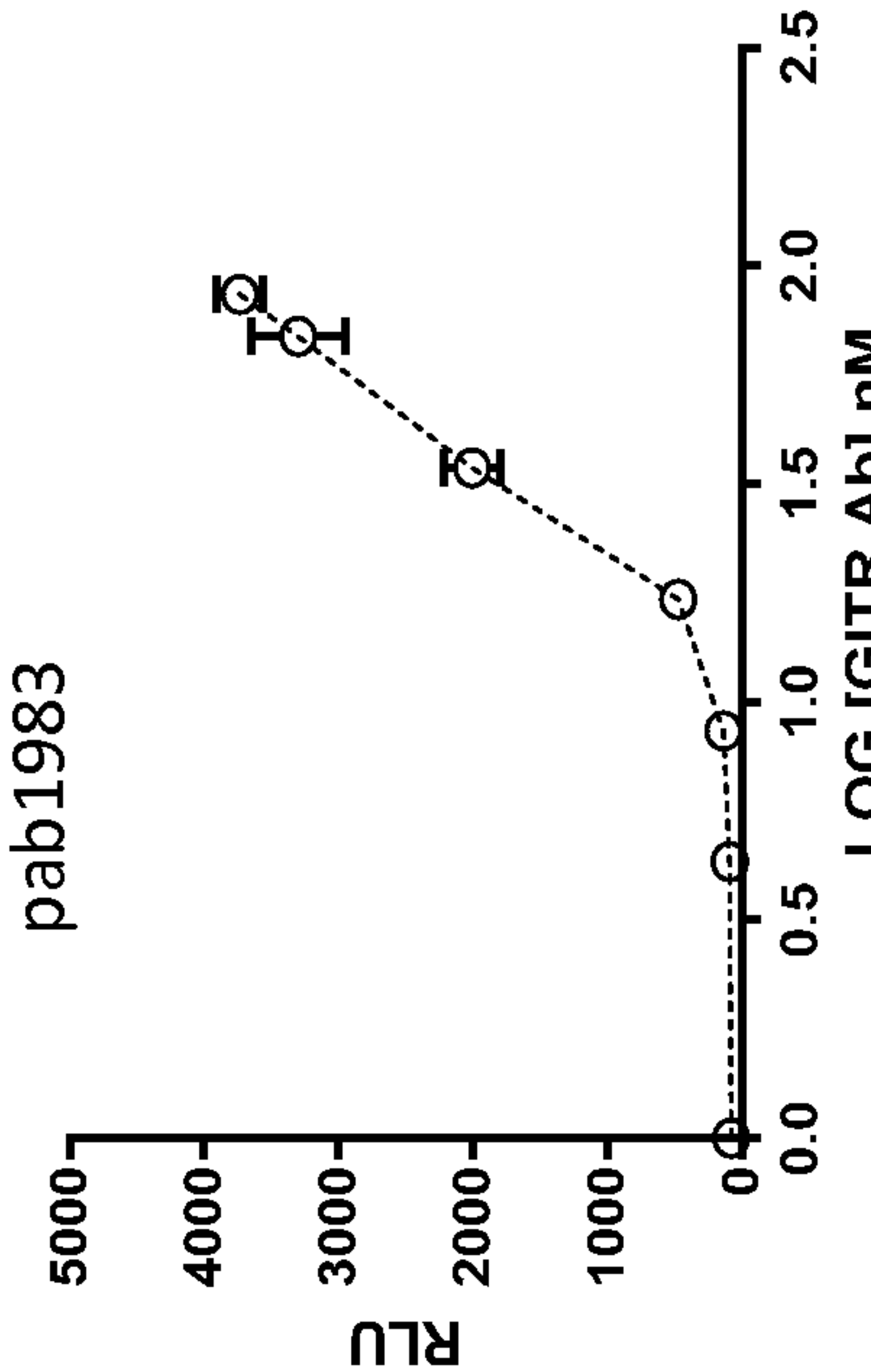
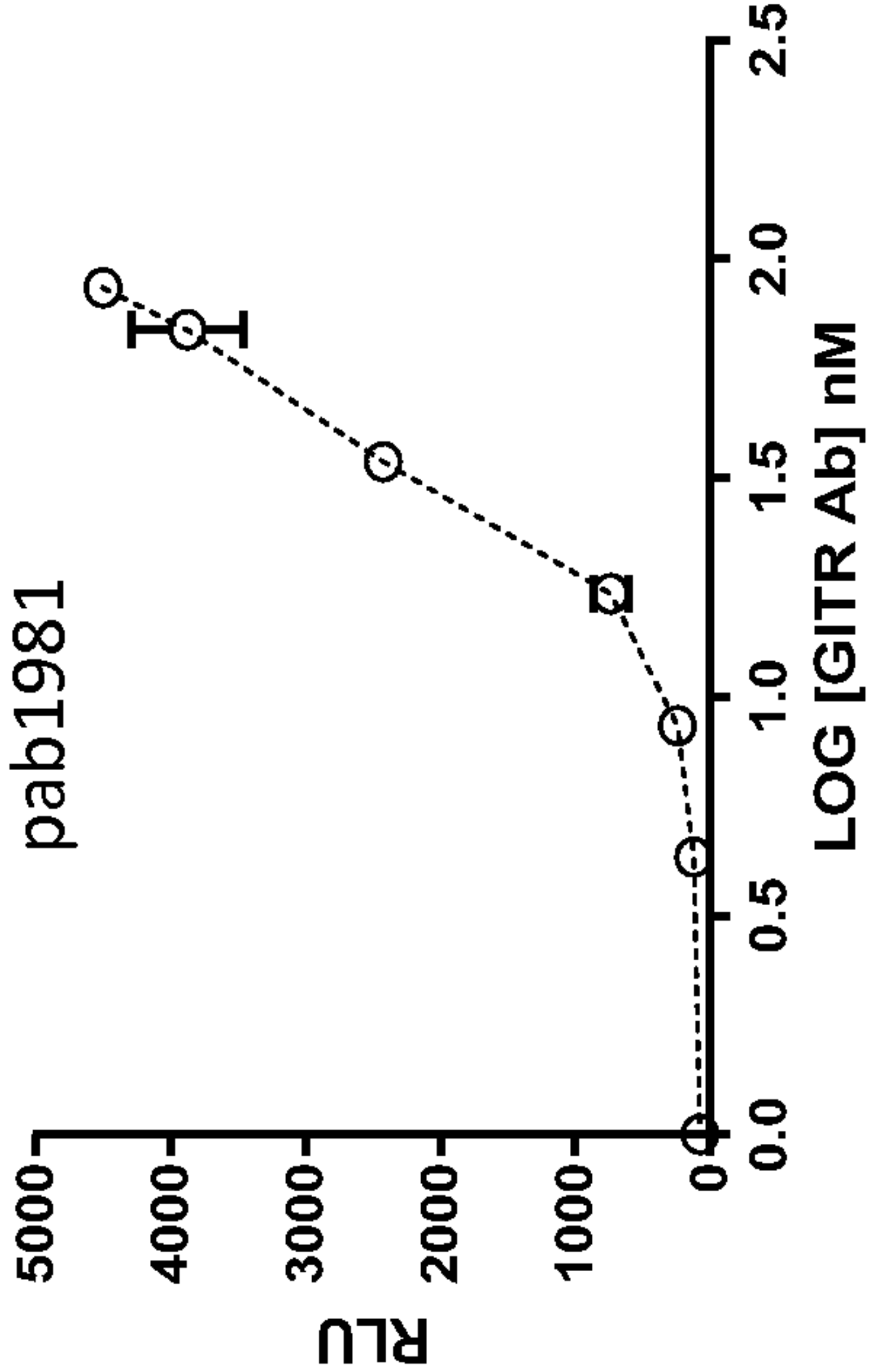
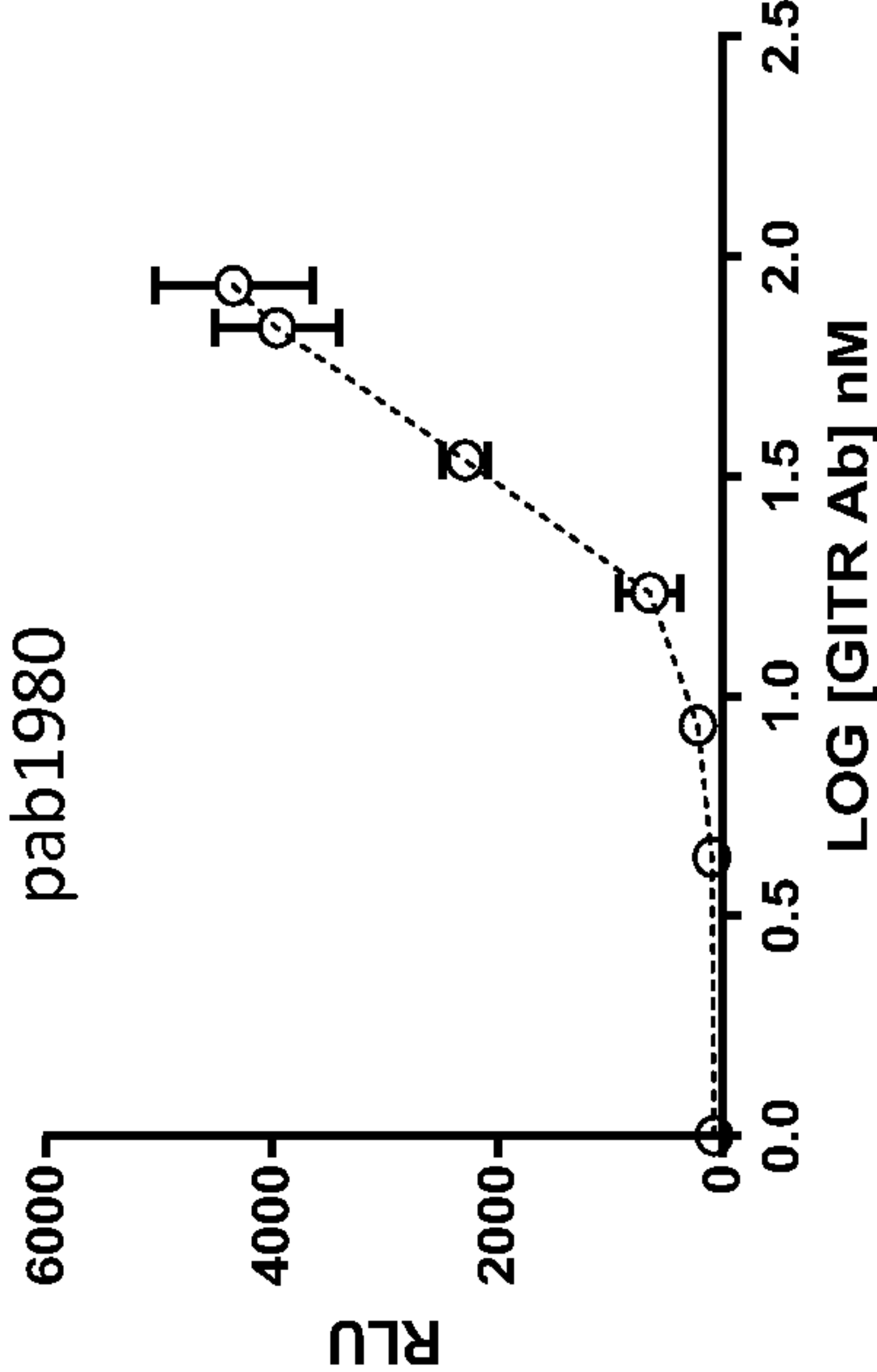
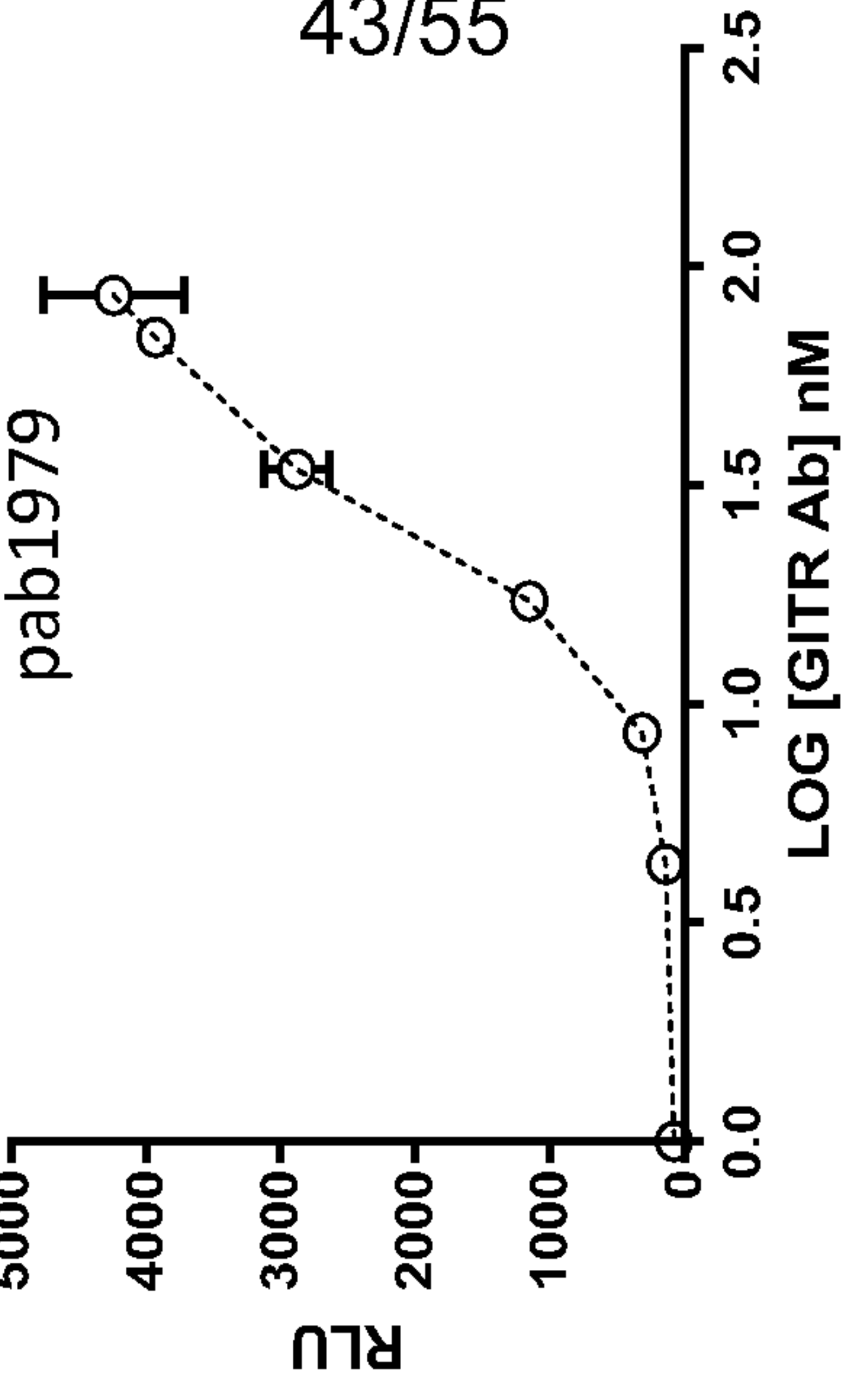
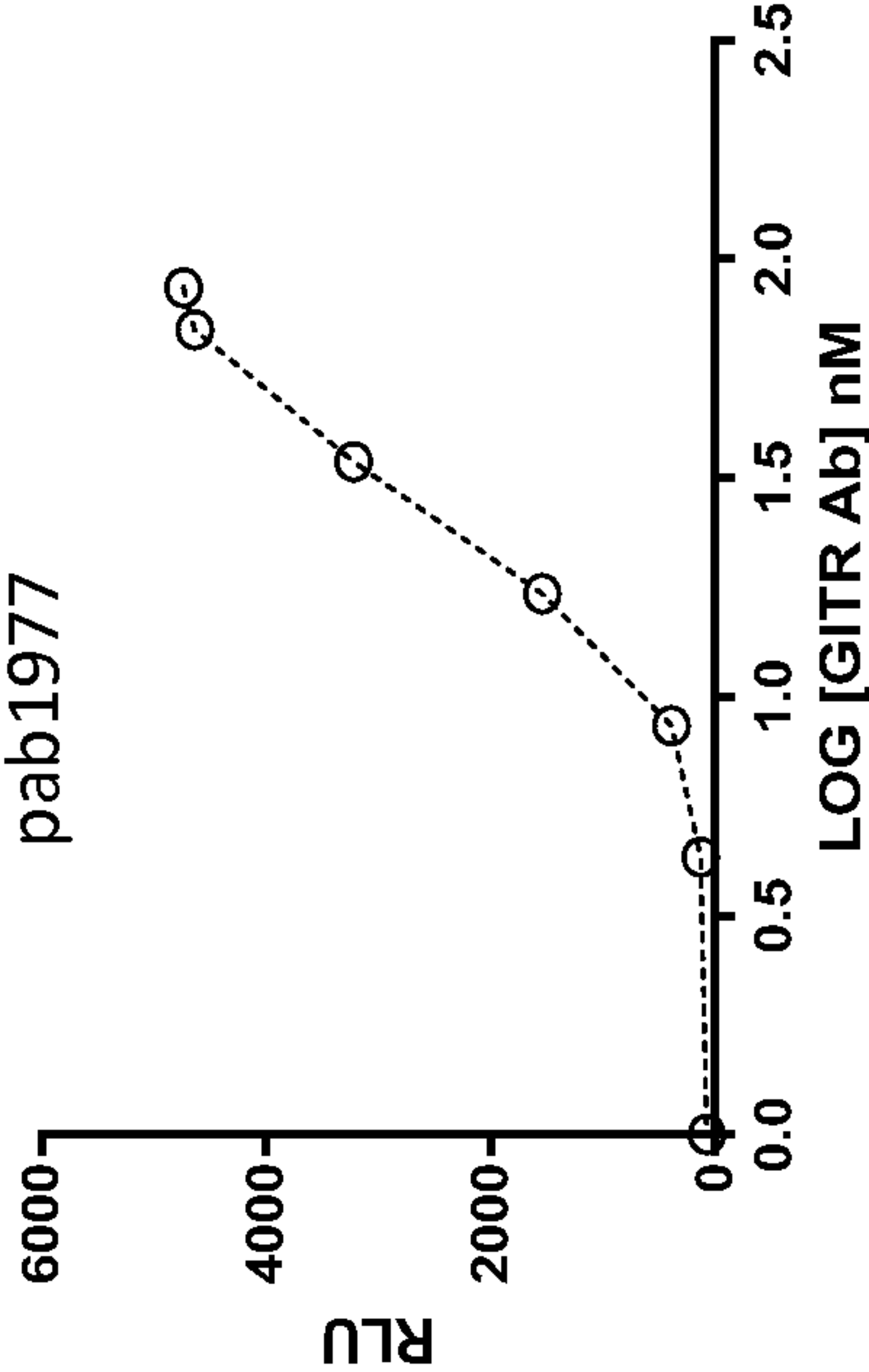
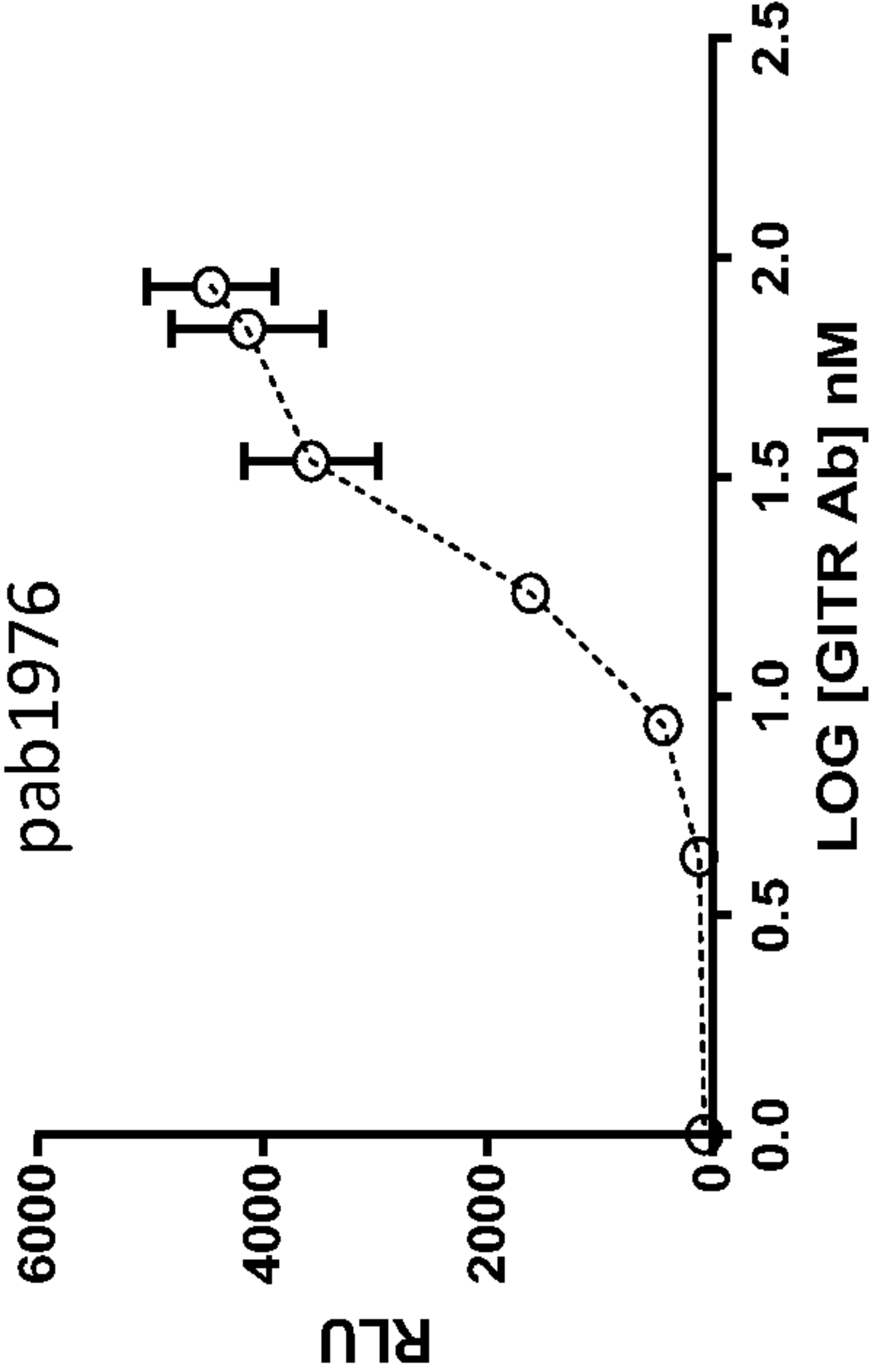
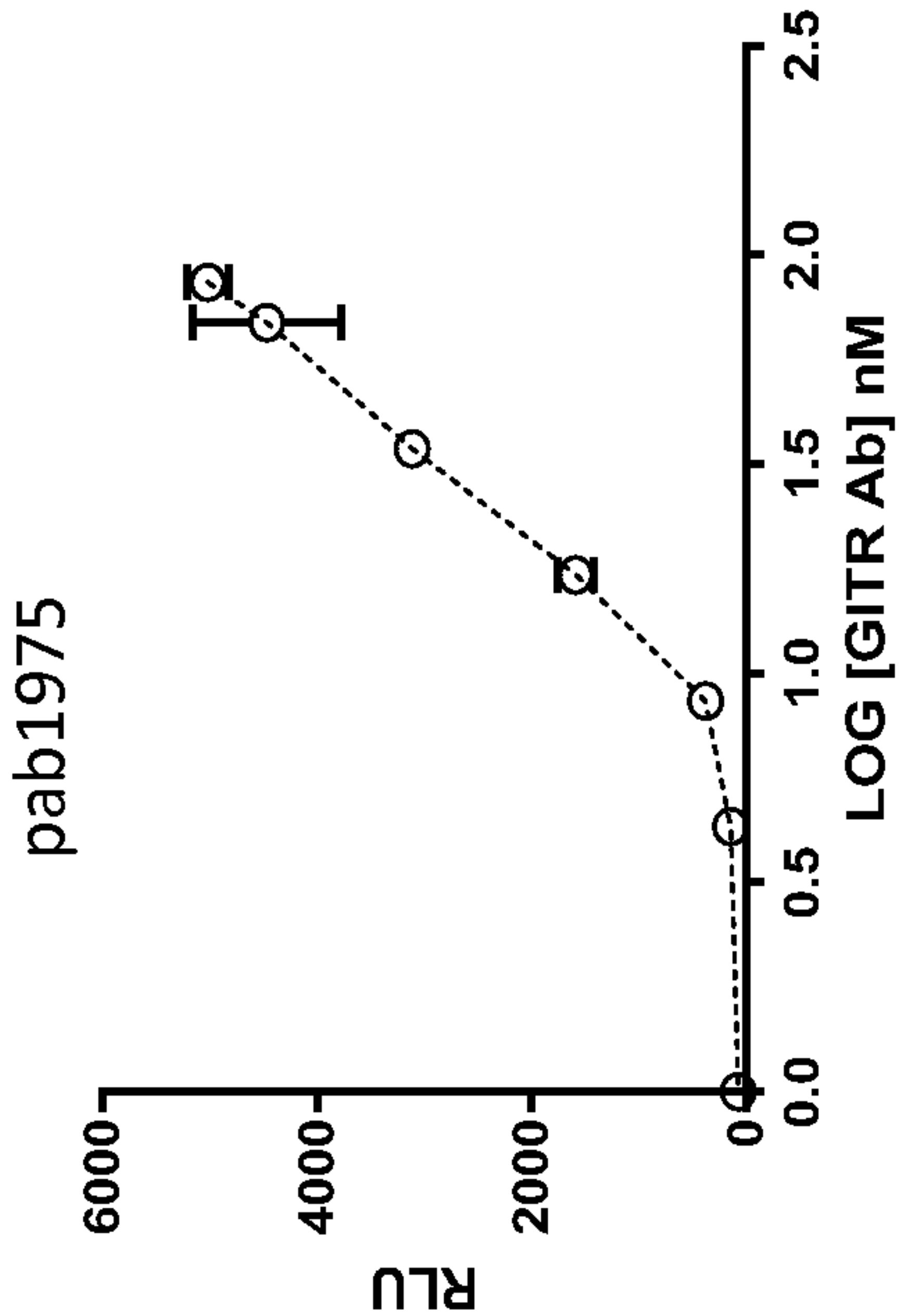
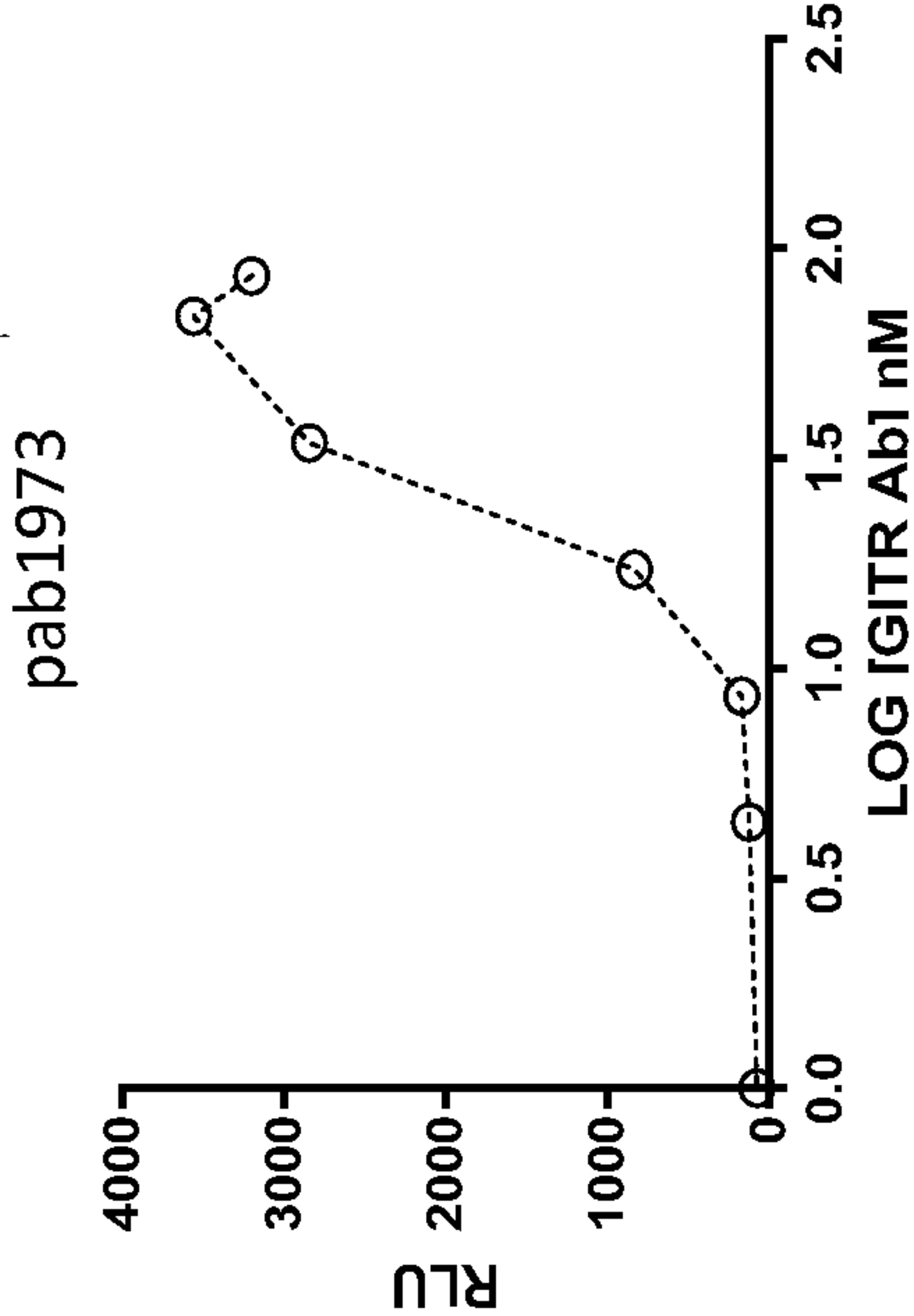
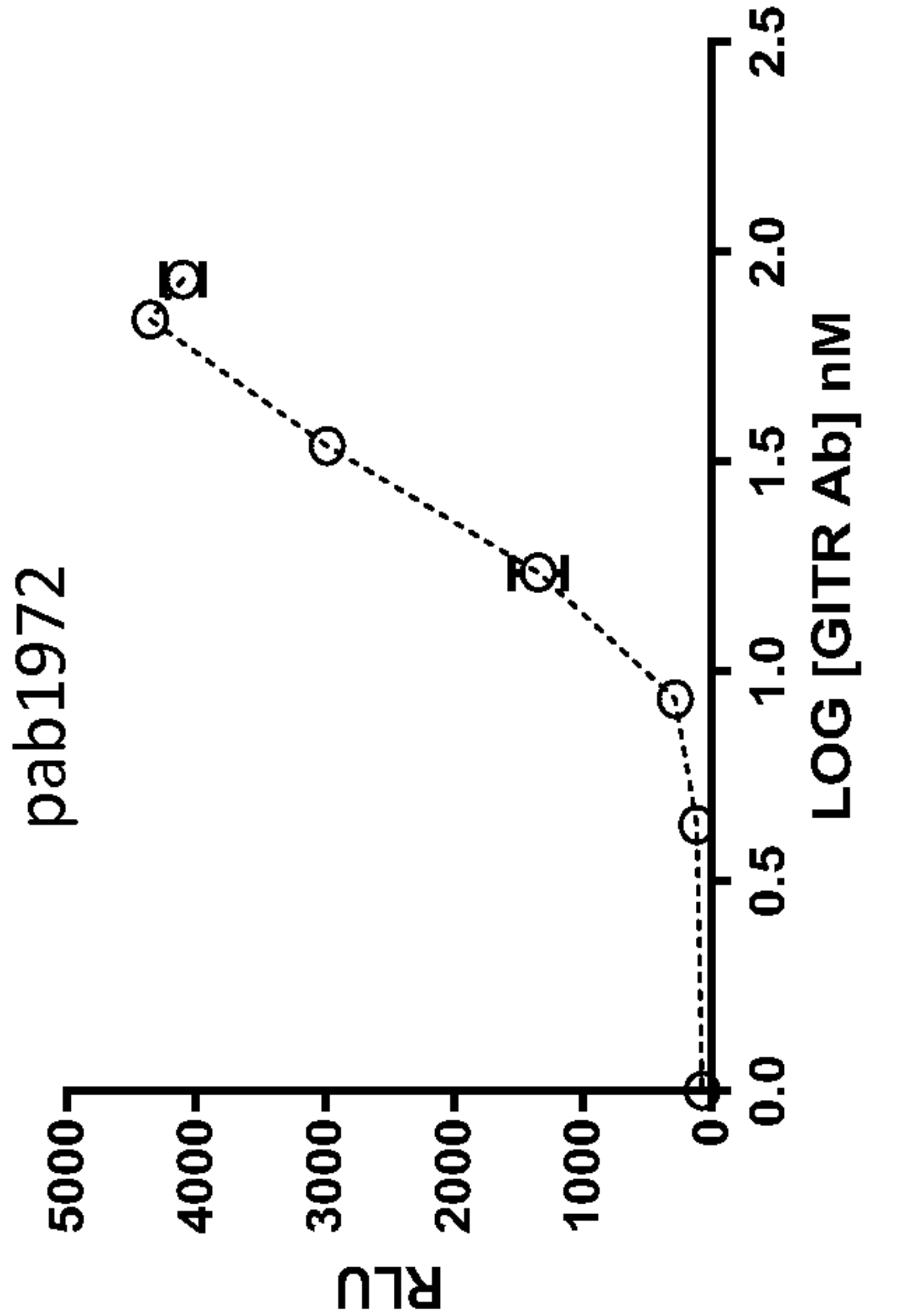


FIGURE 30C

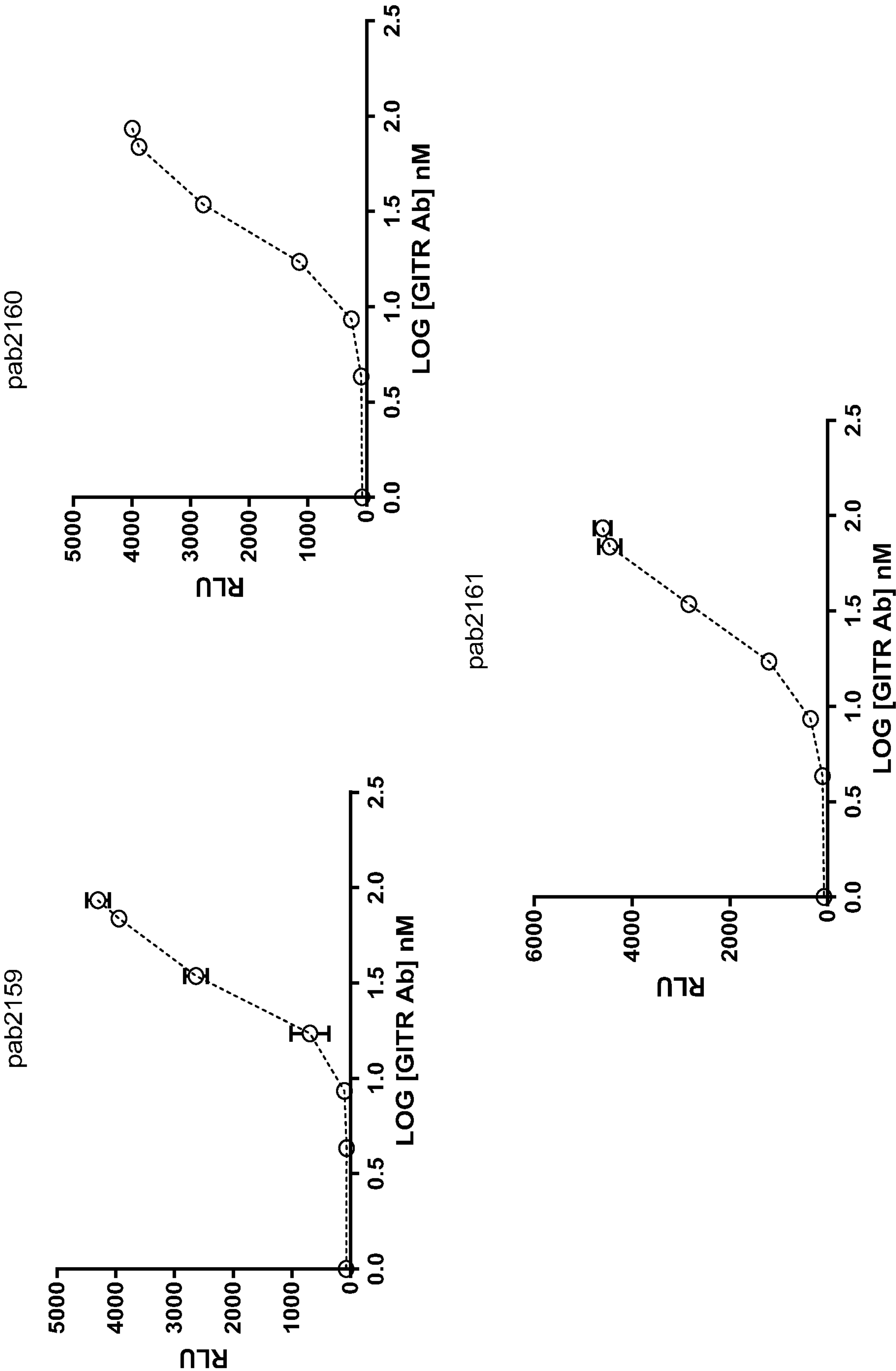


FIGURE 30D

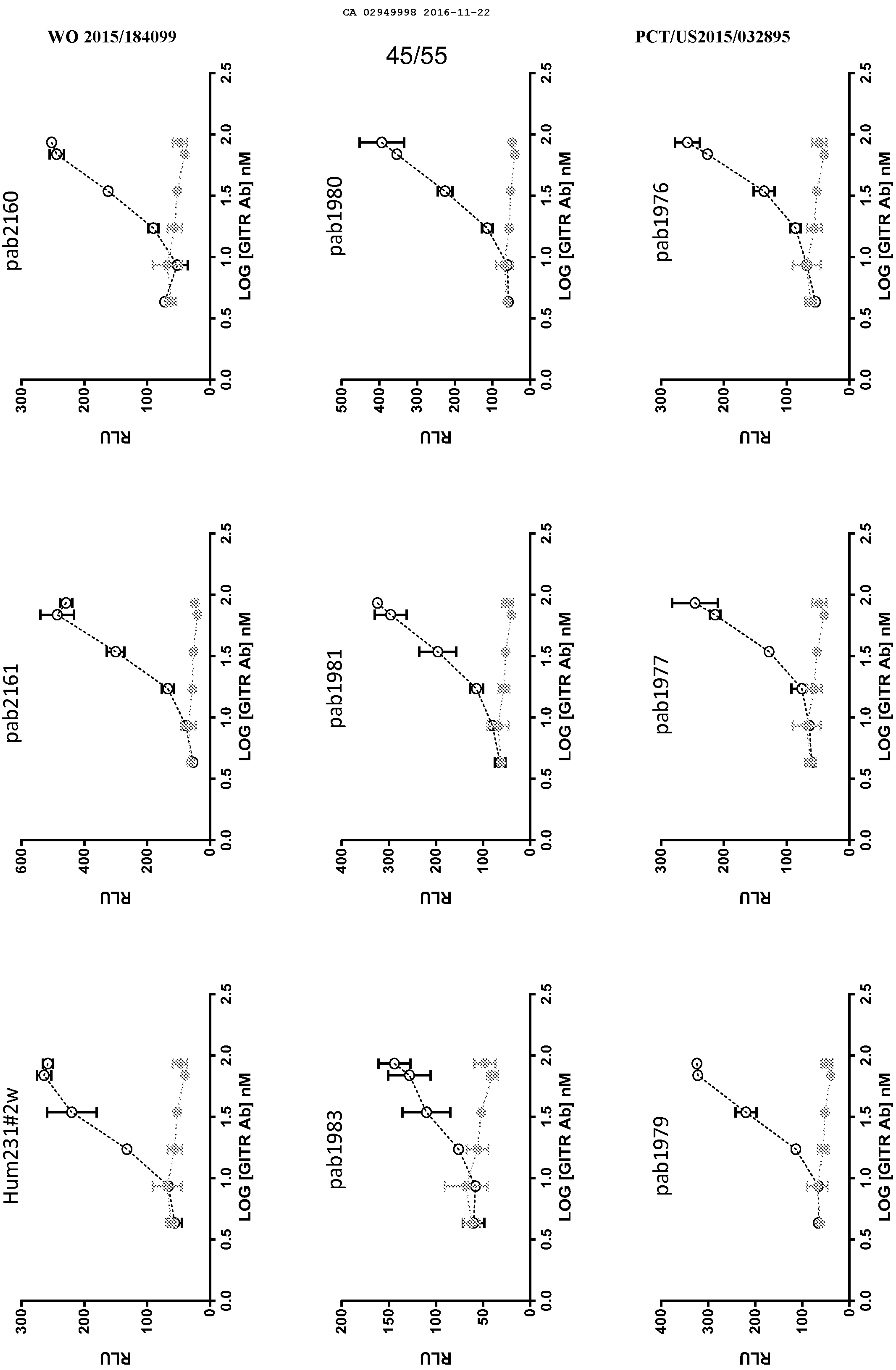
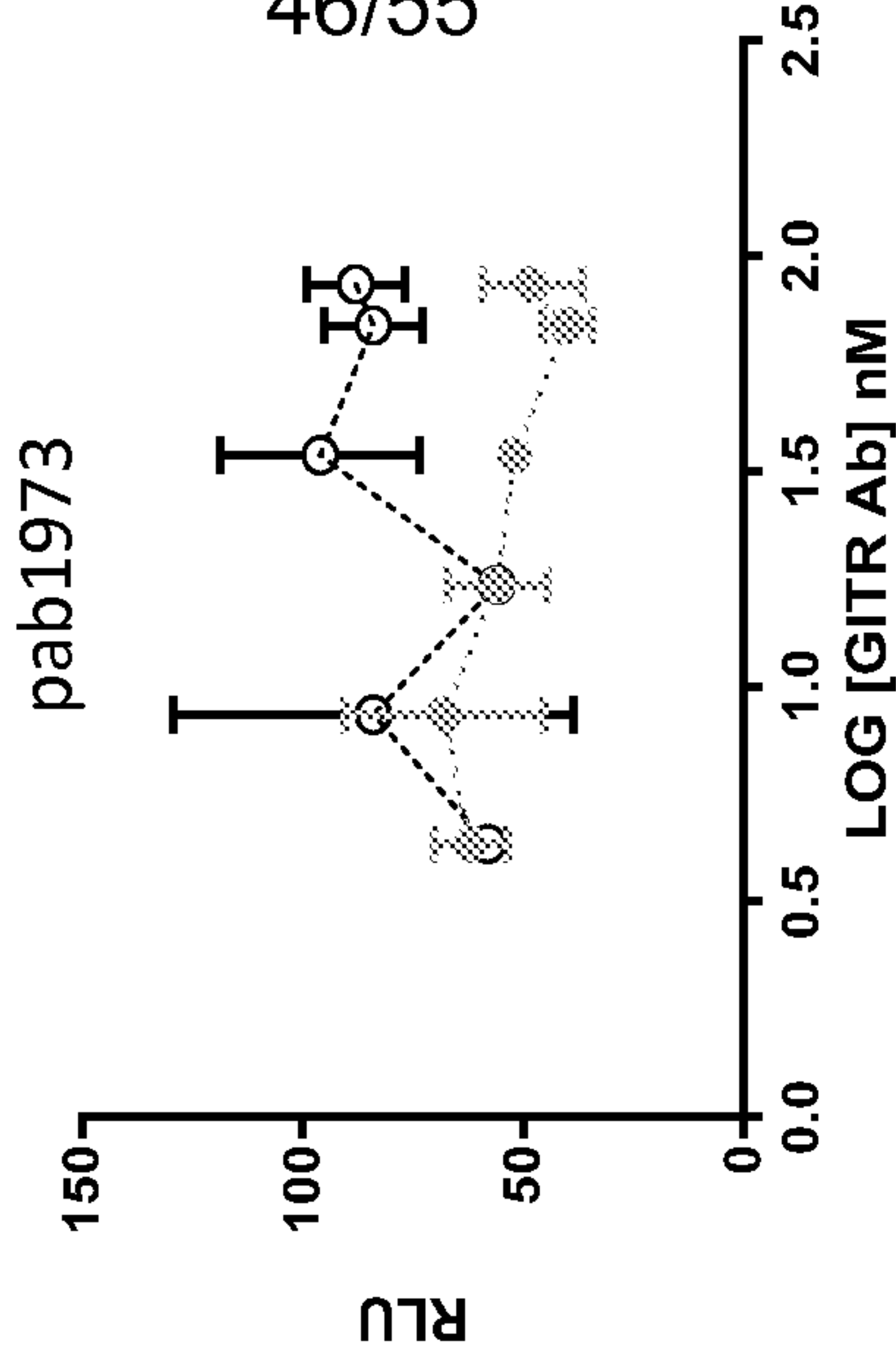
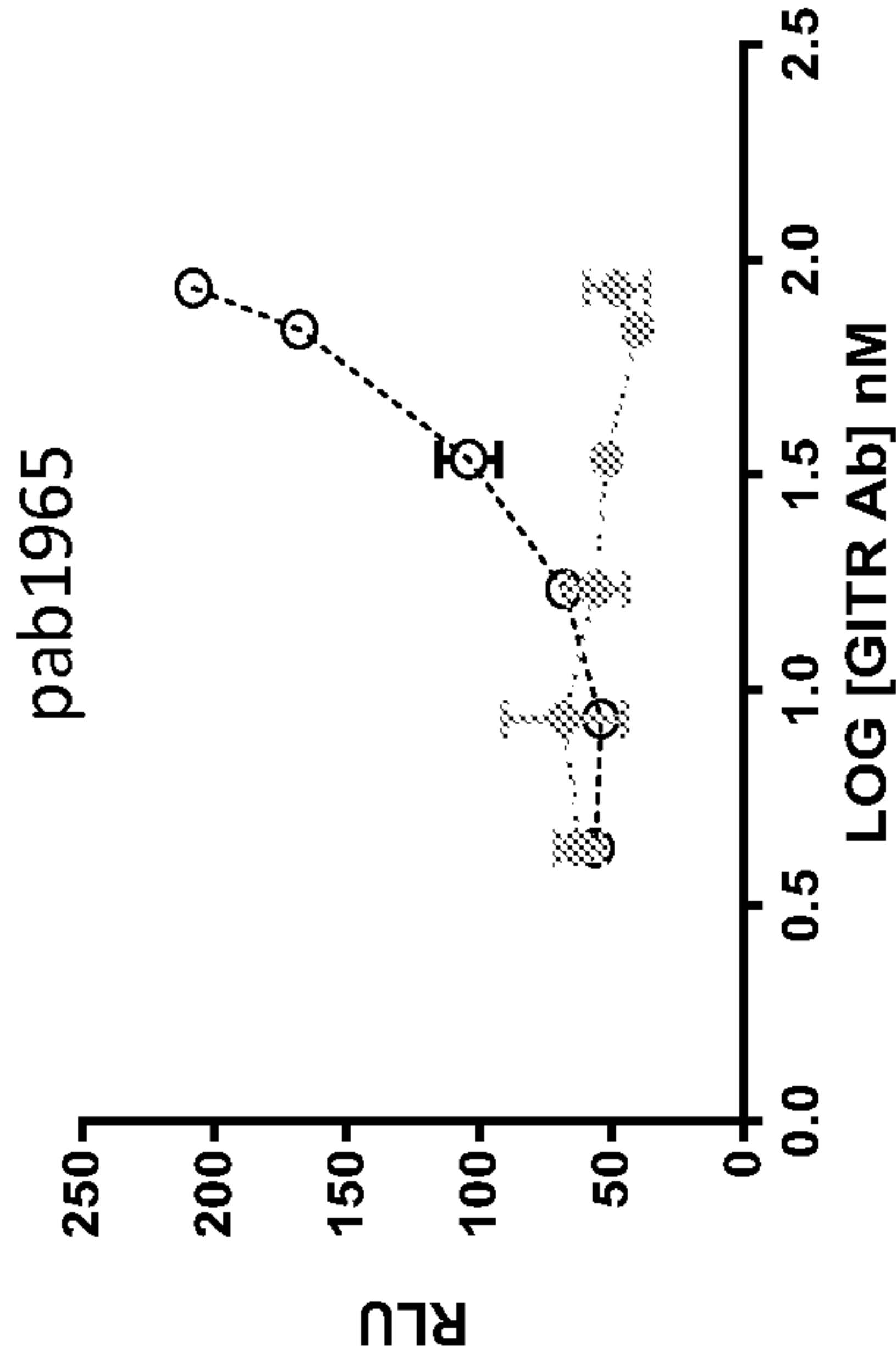
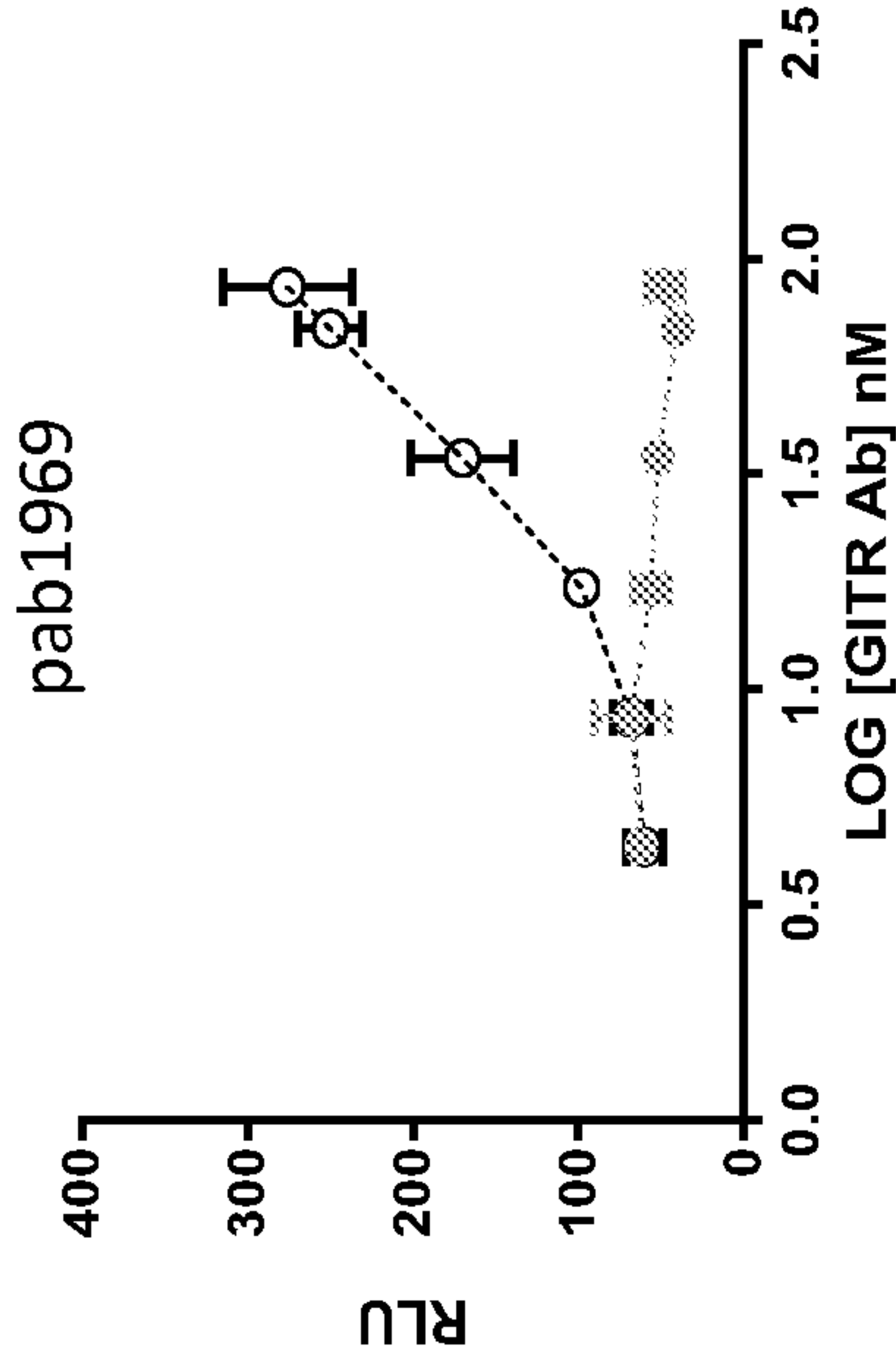
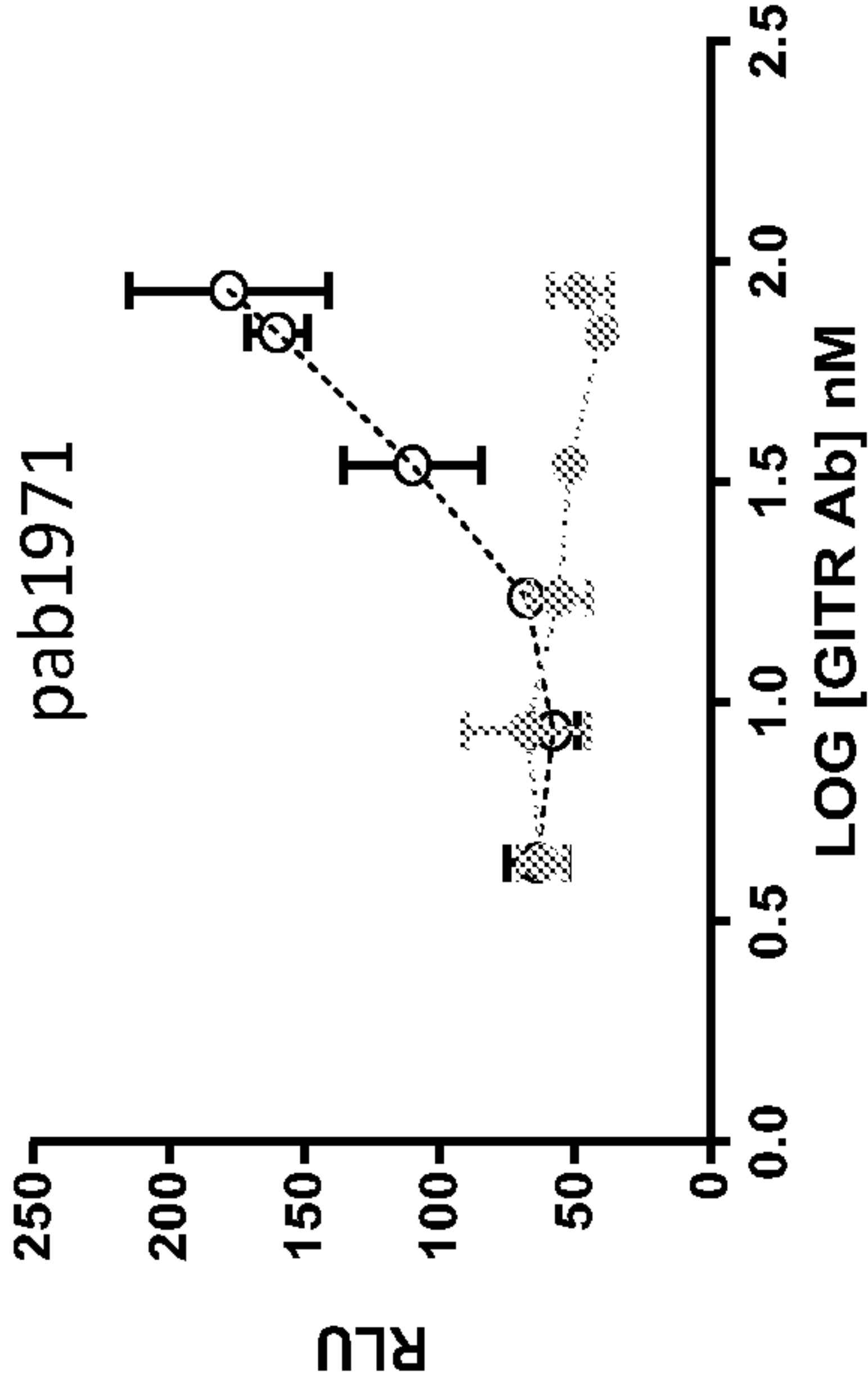
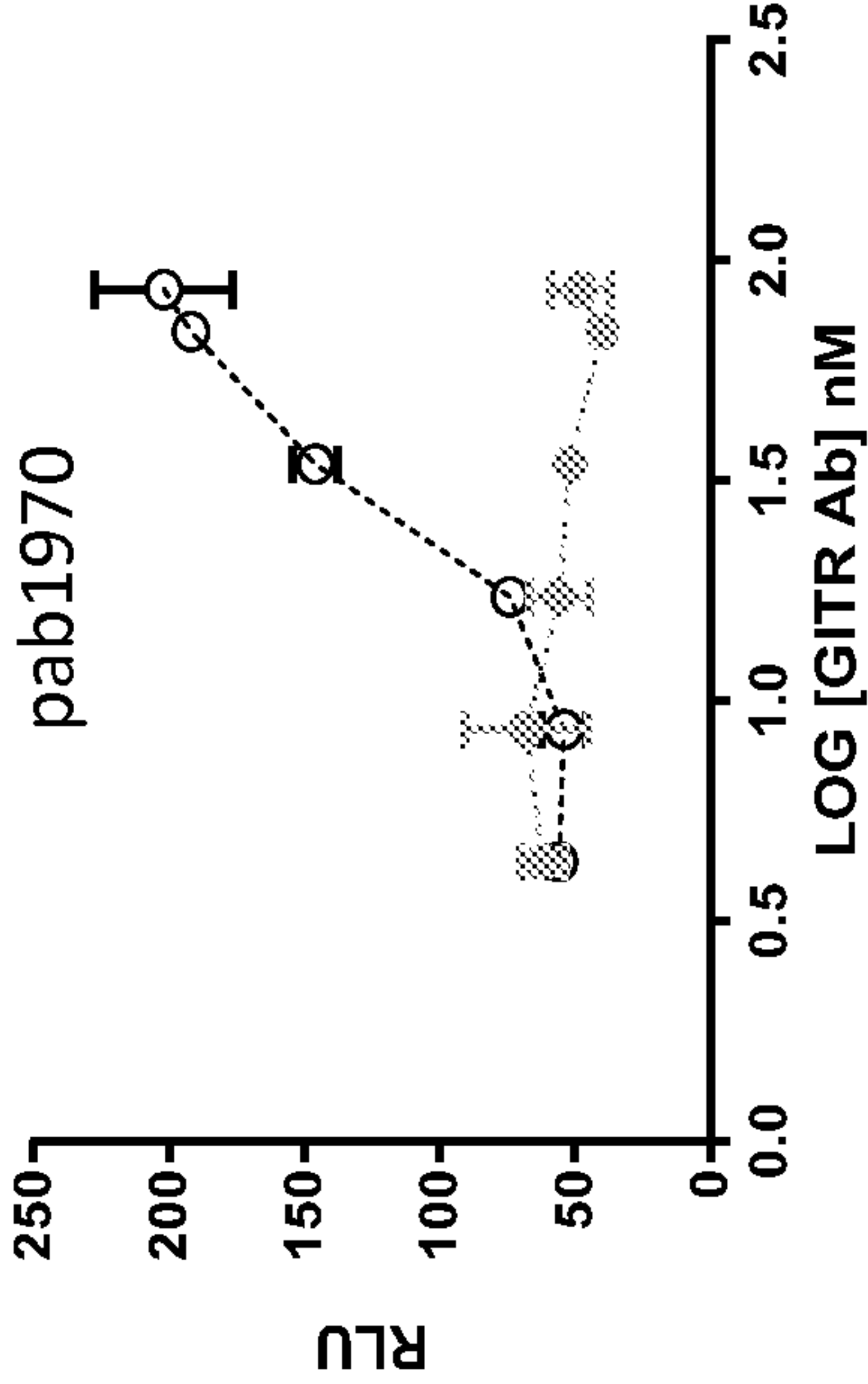
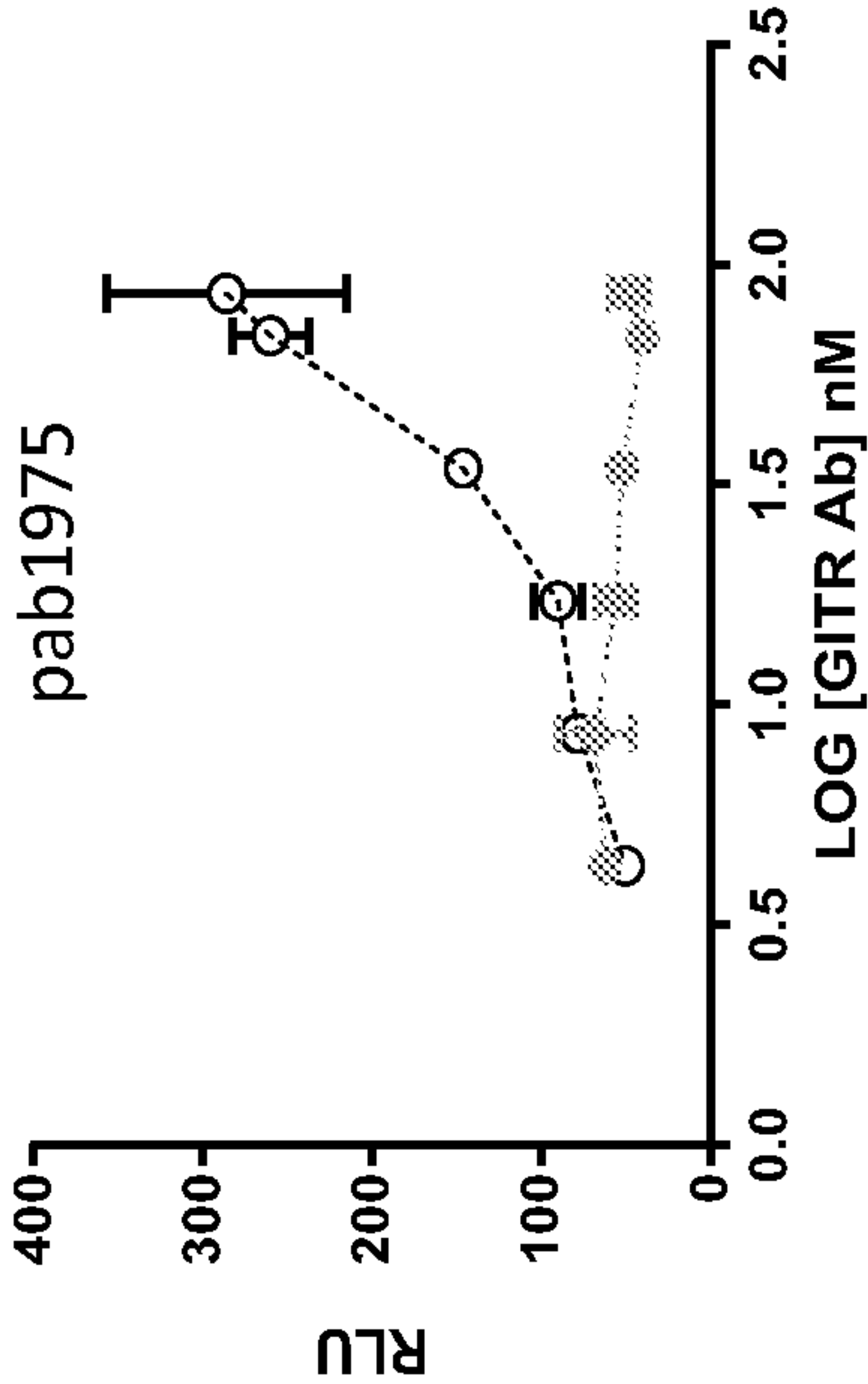
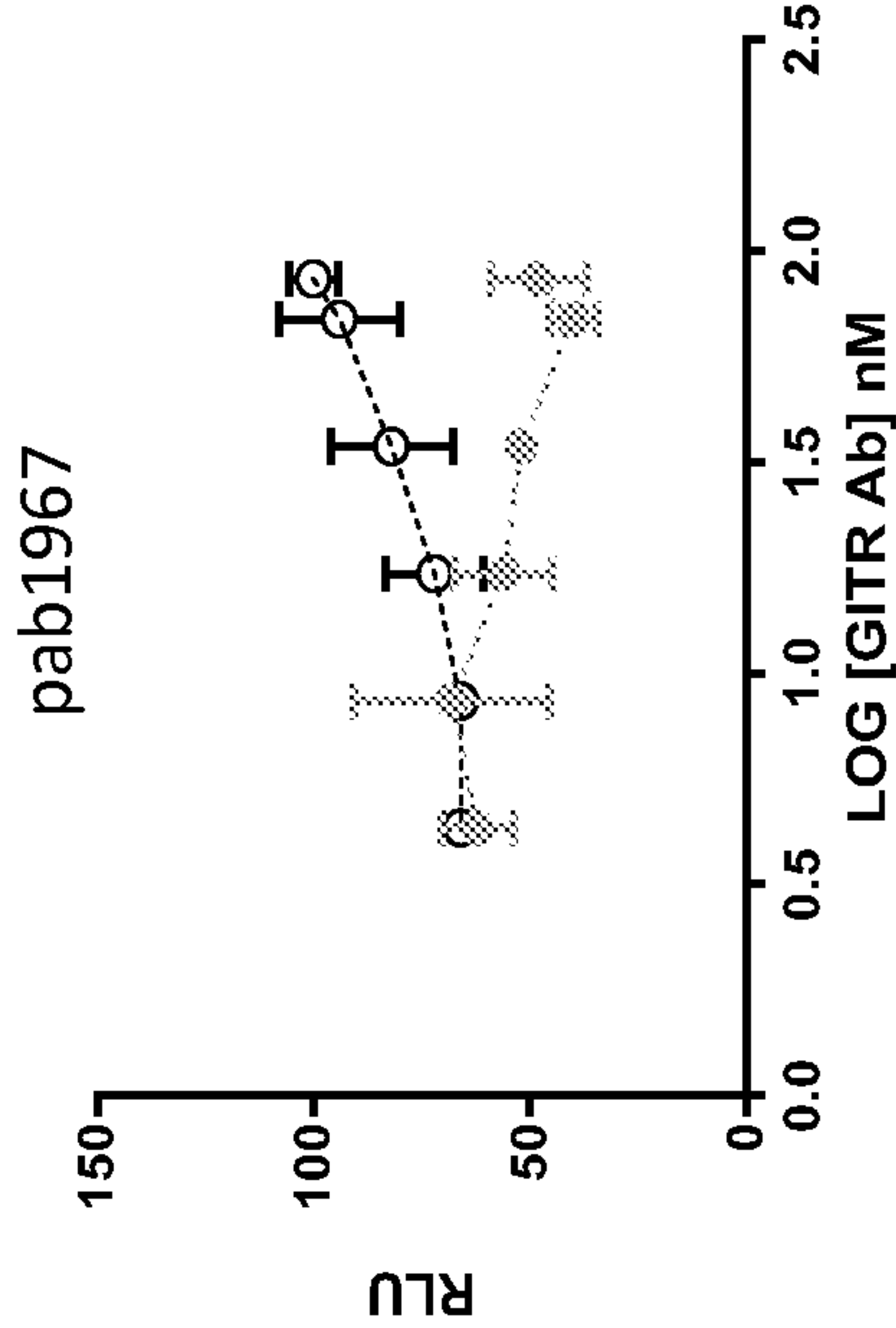
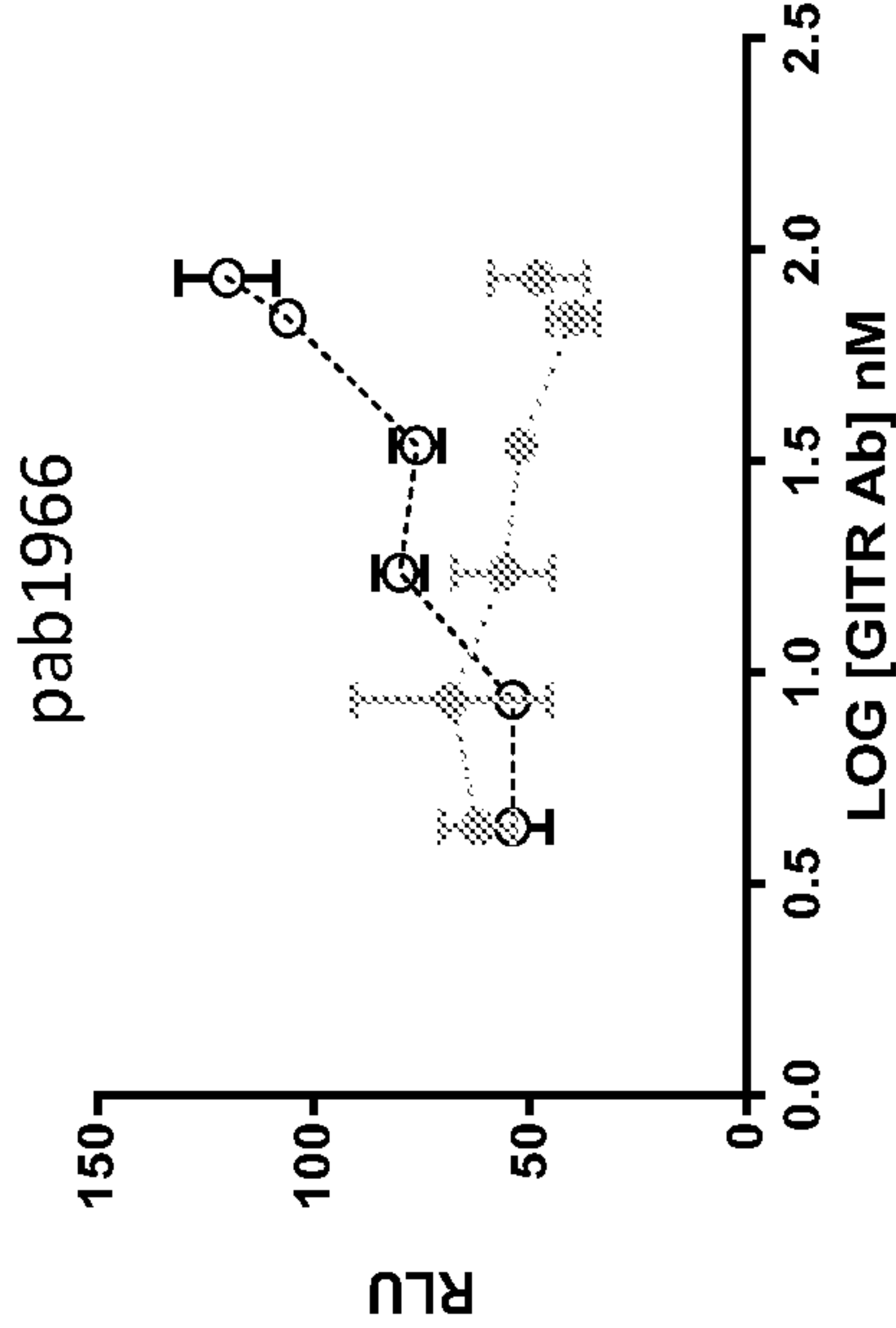
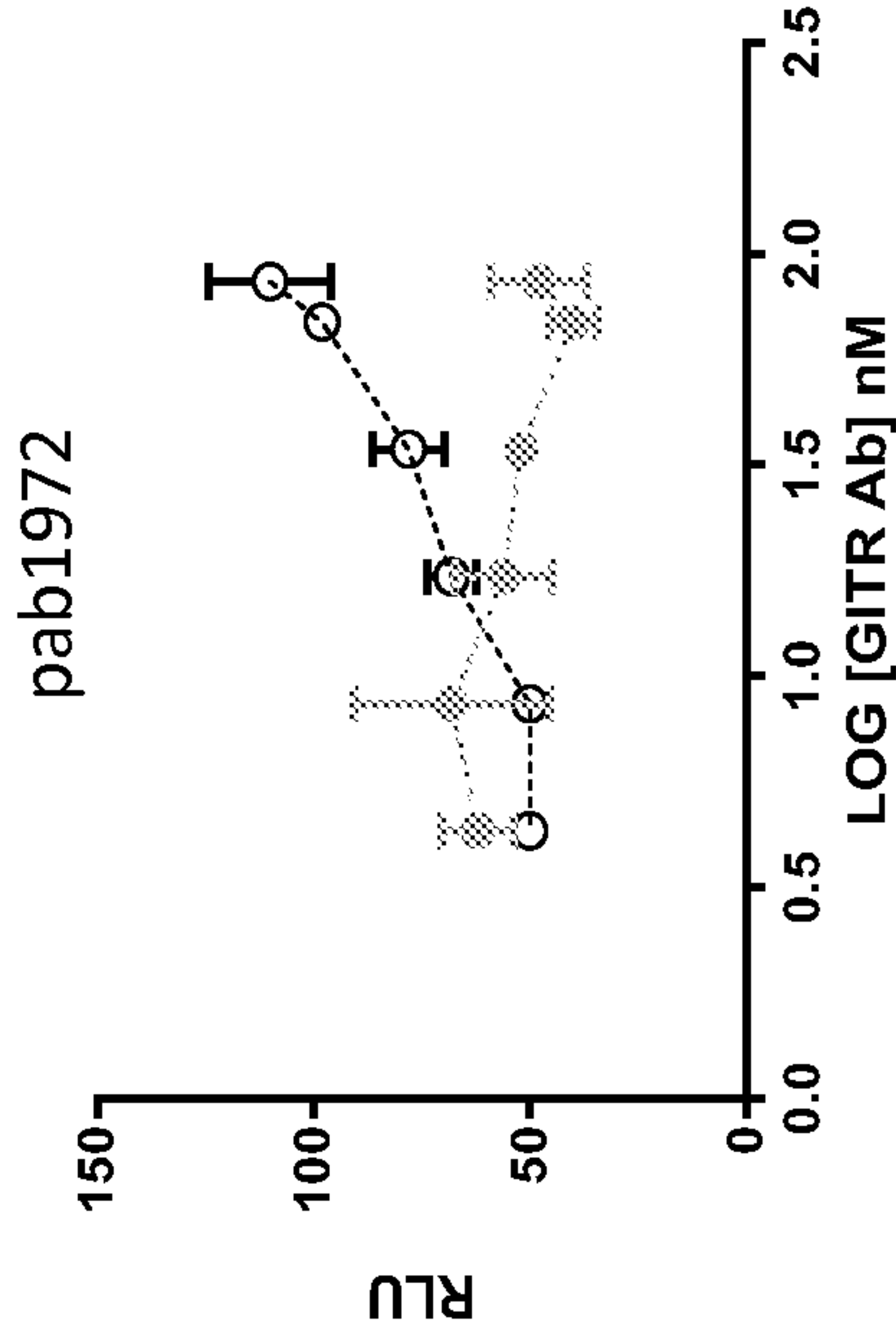


FIGURE 30E



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FIGURE 30F

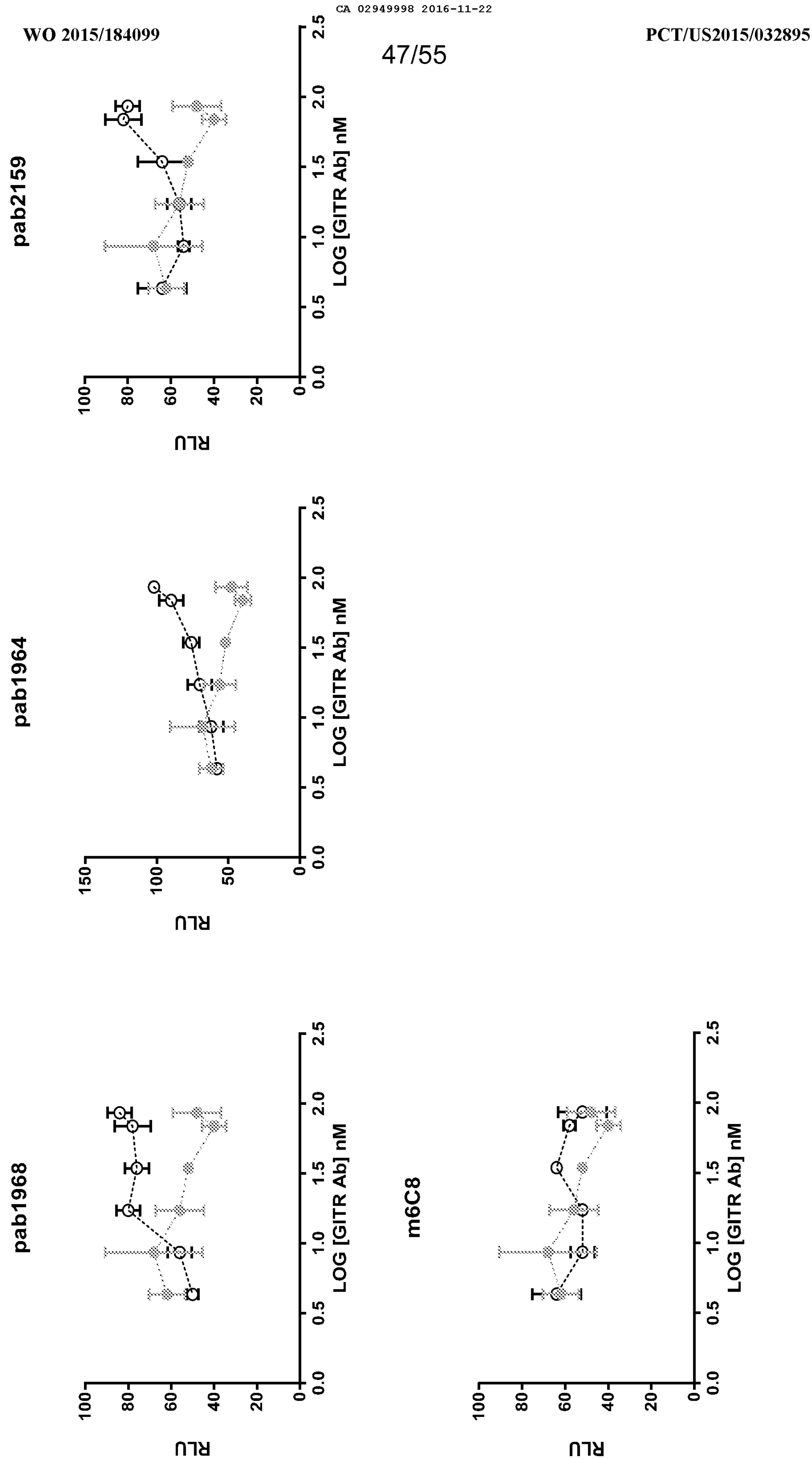


FIGURE 31

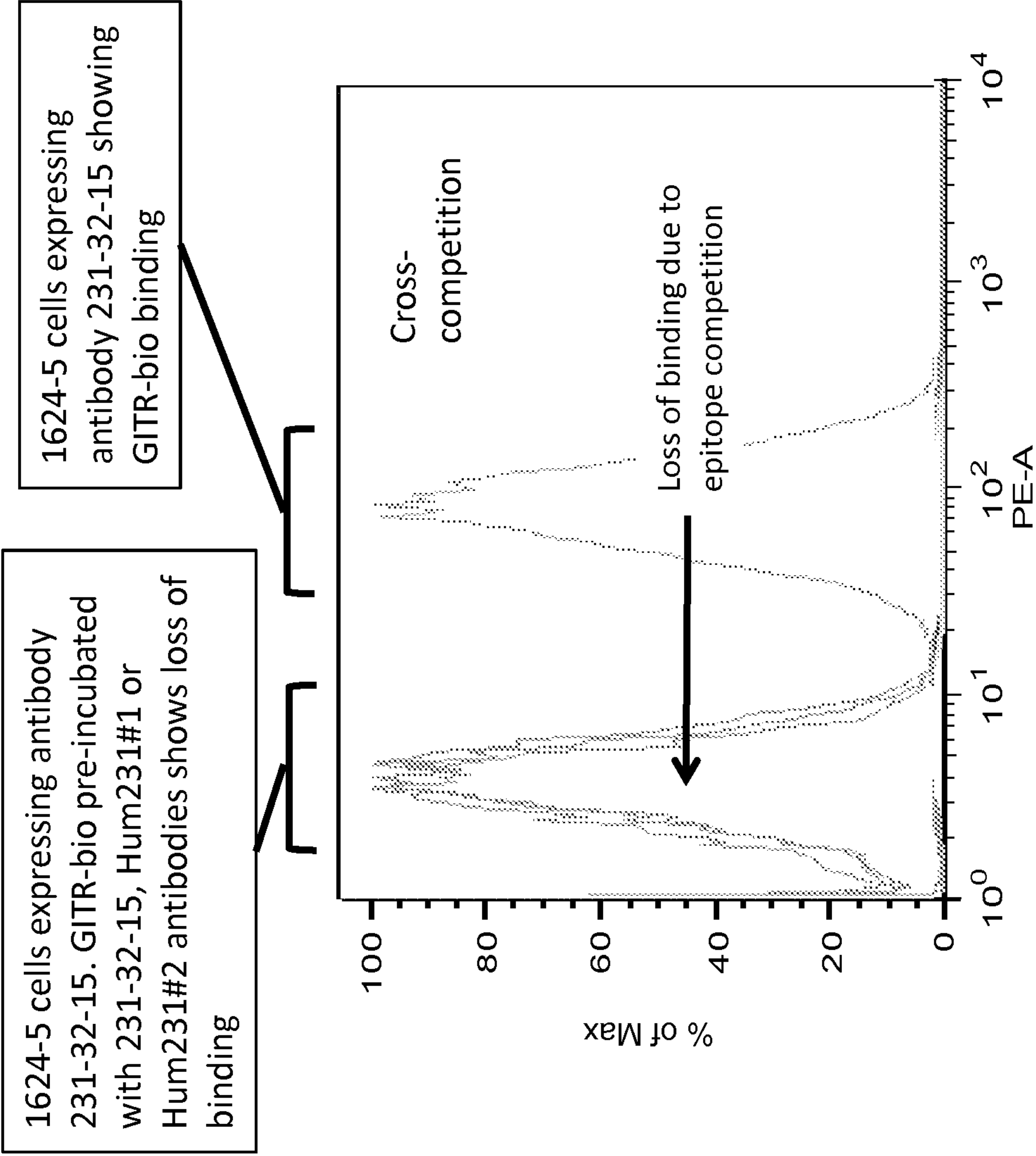
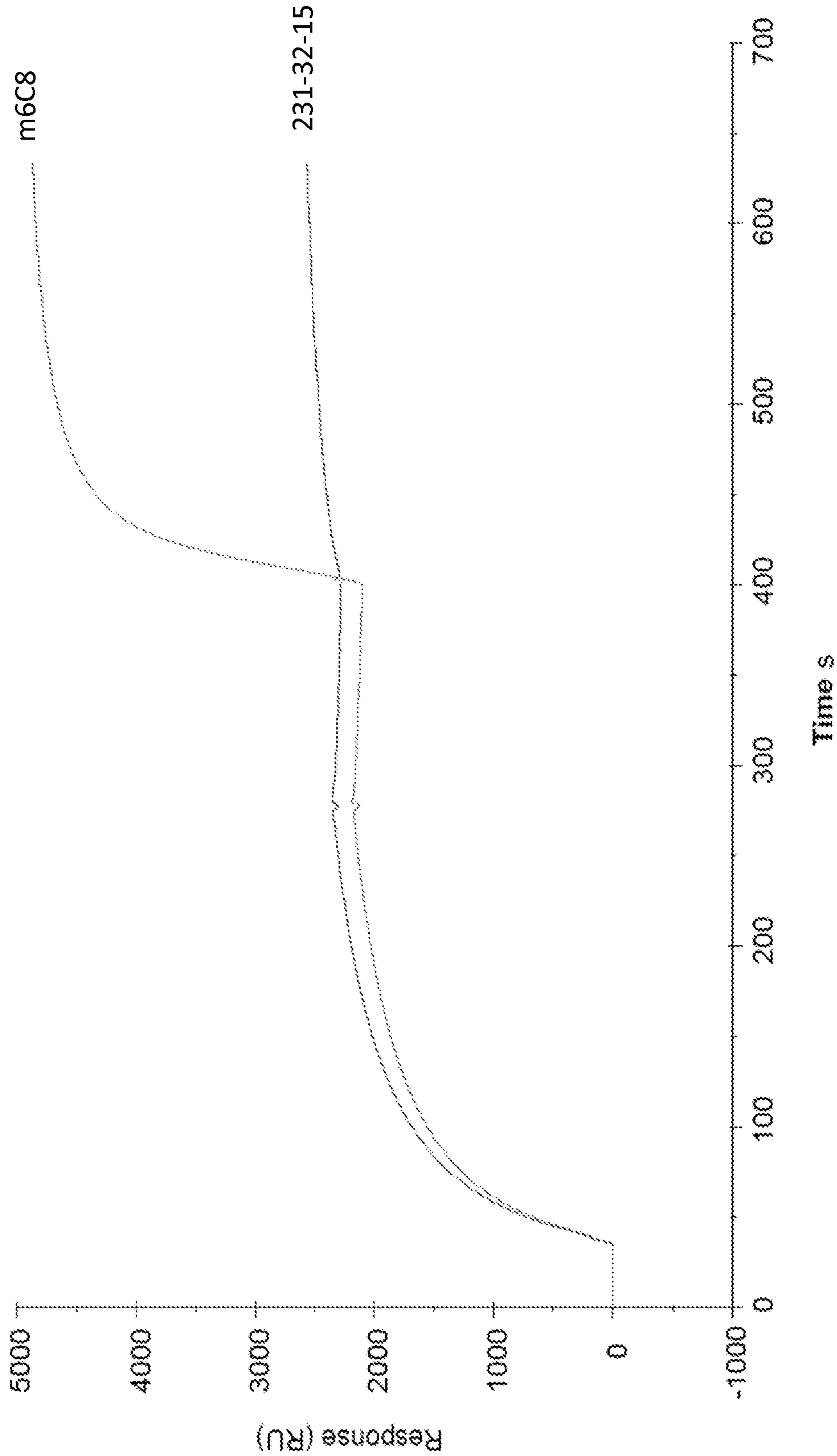


FIGURE 32



MAQHGMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLTGTDAARCCRVHHTTRCCRDYDPDEECCSEWDOMCVQPEFFHCG									
10	20	30	40	50	60	70	80		
MAQHGMGAFRALCGLALLCALSLGQRPTGGPGCGPGRLLLTGTDAARCCRVHHTTRCCRDYDPDEECCSEWDOMCVQPEFFHCG									
2124B07_1155-Je	curated.seq								
2124C01_1155-Je	curated.seq								
2124C02_1155-Je	curated.seq								
2124D03_1155-Je	curated.seq								
2124A01_1155-Je	curated.seq								
2124A03_1155-Je	curated.seq								
2124A05_1155-Je	curated.seq								
2124A11_1155-Je	curated.seq								
2124A12_1155-Je	curated.seq								
2124B01_1155-Je	curated.seq								
2124B04_1155-Je	curated.seq								
2124B12_1155-Je	curated.seq								
2124C03_1155-Je	curated.seq								
2124C08_1155-Je	curated.seq								
2124C12_1155-Je	curated.seq								
2124A02_1155-Je	curated.seq								
2124A09_1155-Je	curated.seq								
2124A10_1155-Je	curated.seq								
2124B08_1155-Je	curated.seq								
2124A04_1155-Je	curated.seq								
2124A07_1155-Je	curated.seq								
2124B05_1155-Je	curated.seq								
2124B06_1155-Je	curated.seq								
2124B09_1155-Je	curated.seq								
2124D04_1155-Je	curated.seq								
2124C10_1155-Je	curated.seq								
2124A08_1155-Je	curated.seq								
2124B02_1155-Je	curated.seq								
2124B03_1155-Je	curated.seq								
2124A06_1155-Je	curated.seq								
2124C04_1155-Je	curated.seq								
2124C09_1155-Je	curated.seq								

[illegible]

FIGURE 34A

Mutant	construct number	Hum231#2	pab1967	pab1975	pab1979	m6C8
T54A	4526	+	+	+	+	+
T55A	4527	+	+	+	+	+
R56A	4528	+	+	+	+	+
C57A	4529	+	+	+	+	+
C58A	4530	+/-	+/-	+/-	+/-	+/-
R59A	4531	+	+	+	+	+
D60A	4532	-	+/-	+/-	+/-	+
Y61A	4533	+	+	+	+	+
P62A	4534	+	+	+	+	+
G63A	4535	+/-	+/-	+/-	+/-	+
E64A	4536	+	+	+	+	+
E65A	4537	+	+	+	+	+
C66A	4538	+	+	+	+	+
C67A	4539	+	+	+	+	+
S68A	4540	+	+	+	+	+
E69A	4541	+	+	+	+	+
W70A	4542	+	+	+	+	+
D71A	4543	+	+	+	+	+
C72A	4544	+	+	+	+	+
M73A	4545	+	+	+	+	+
C74A	4546					
V75A	4547	+	+	+	+	+
Q76A	4548	+	+	+	+	+
P28A	4595	+	+	+	+	+
T29A	4596	+	+	+	+	+
G30A	4597	+	+	+	+	+
G31A	4598	+	+	+	+	+
P32A	4599	+	+	+	+	+

FIGURE 34B

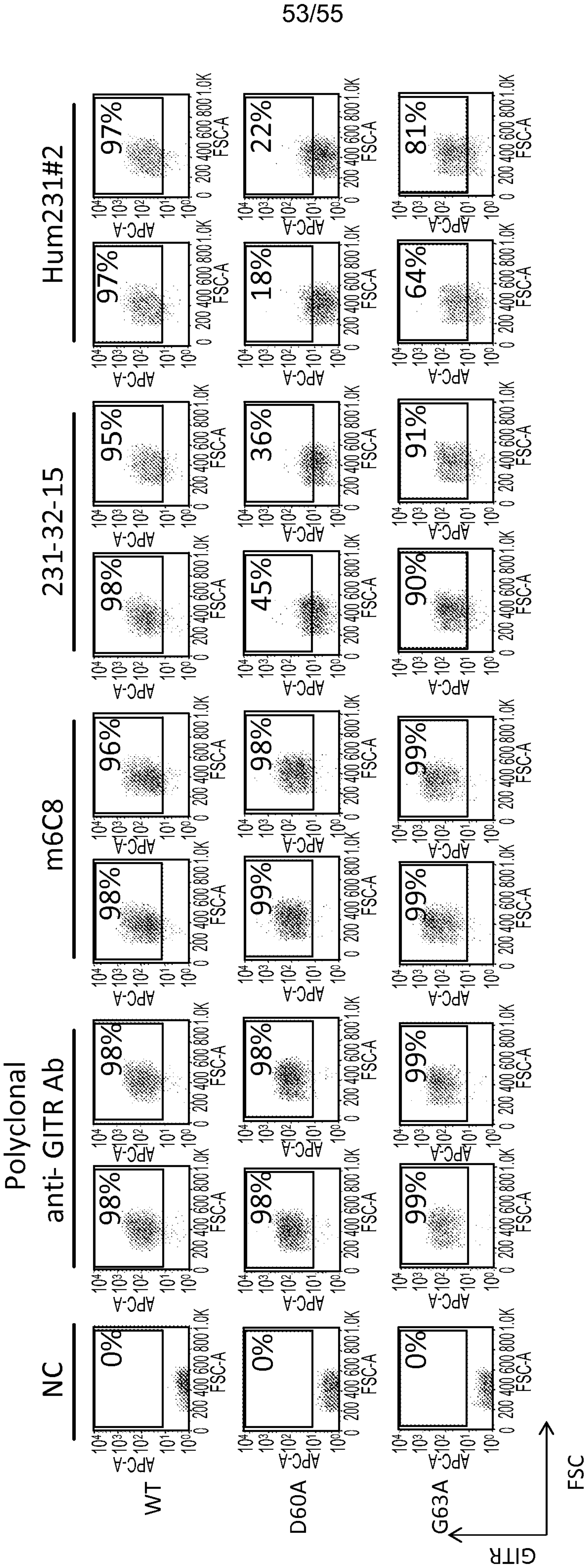


FIGURE 35A

human G1TR
V1M/Q62P/S63G cyno G1TR
V1M cyno G1TR

MARHGAMCAGTLCCLALLCAASLGQRPTGGPGCGPGRLLLTGTGDARCCRVHPTRCRDYPGEECCSEWDCVCVQPEFH	10	20	30	40	50	60	70	80
MAQHGMGAFFALCGLALLCALSLGQRPTGGPGCGPGRLLLTGTGDARCCRVHTTRCCRDYPGEECCSEWDCMCVQPEFH	80							
.R...C.CGT..C...A...K...P...V...V...V...	80							
.R...C.CGT..C...A...K...P...Q...S...*	80							

human G1TR
V1M/Q62P/S63G cyno G1TR
V1M cyno G1TR

CGNPCCCTTCQHHPCPSEGQGVQPQGFSEFGRFCVDCALGTFSRGHGHCCKPWTDCIQFGFLTVFPGNKTHNAVCPGSPPA	90	100	110	120	130	140	150	160
CGDPCCCTTCRHHPCPPGQGVQSQGKFSGFQCIDCASGTFSGGHEGHCKPWTDCIQFGFLTVFPGNKTHNAVCPGSPPA	160							
.N...Q...S...P...R.V...L...R..D...	160							
.N...Q...S...P...R.V...L...R..D...	160							

human G1TR
V1M/Q62P/S63G cyno G1TR
V1M cyno G1TR

EPPGWLTIVLLAVAACVLLLTSAQLGLHIWQLG-----KTQLLLEVPSTEDASSQFPPEERGERLAEEKGRLGDLW	170	180	190	200	210	220	230	240
EPLGWLTVVLLAVAACVLLLTSAQLGLHIWQLRSQCMWPRETQLLLEVPSTEDARSCQFPPEERGERSAEEKGRLGDLW	240							
.P...I...G-----K...S...L...	233							
.P...I...G-----K...S...L...	233							

human G1TR
V1M/Q62P/S63G cyno G1TR
V1M cyno G1TR

V-	242
V.	235
.	234

