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Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3049445 A1 2018/10/11

(21) 3 049 445

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/01/17
(87) Date publication PCT/PCT Publication Date: 2018/10/11
(85) Entrée phase nationale/National Entry: 2019/07/04
(86) N° demande PCT/PCT Application No.: US 2018/014008
(87) N° publication PCT/PCT Publication No.: 2018/186924
(30) Priorité/Priority: 2017/01/17 (US62/447,199)

(51) Cl.Int./Int.Cl. *A61K 39/395* (2006.01), *C07K 16/28* (2006.01), *C12N 5/0783* (2010.01)

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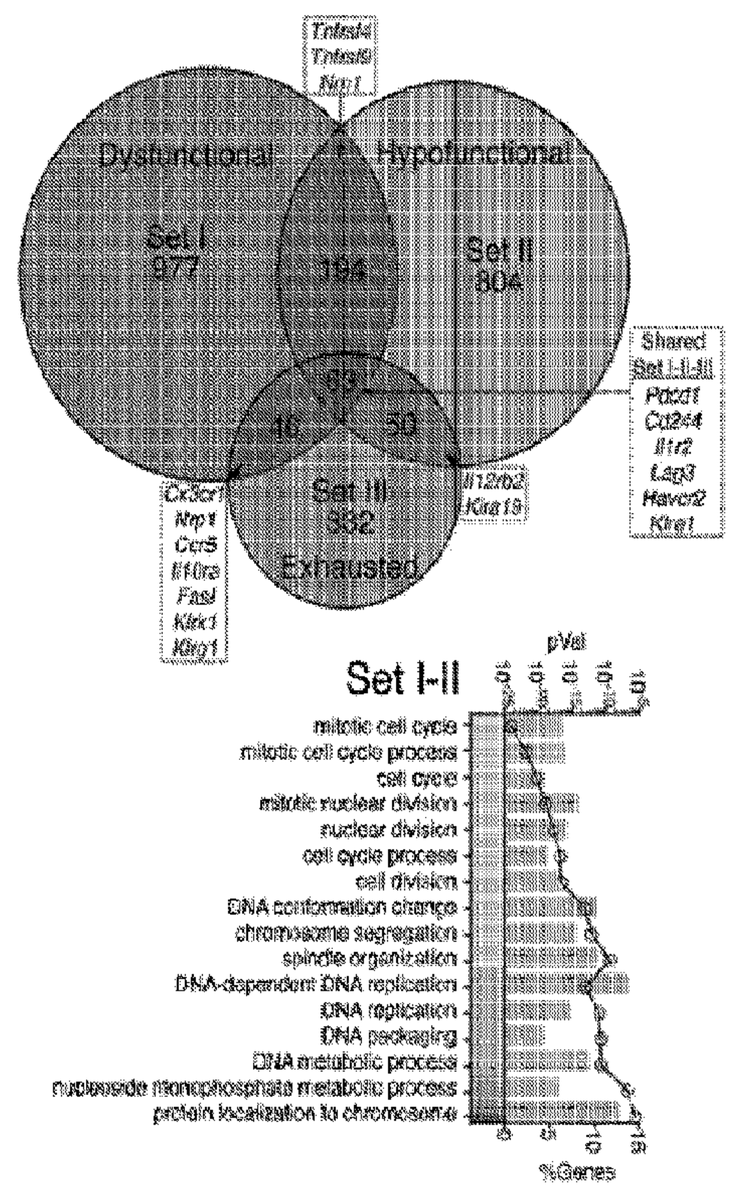
(54) Titre : CELLULES T CD8$^+$ SPECIFIQUES D'UN ANTIGENE DYSFONCTIONNELLES DANS LE MICROENVIRONNEMENT TUMORAL

(54) Title: DYSFUNCTIONAL ANTIGEN-SPECIFIC CD8$^+$ T CELLS IN THE TUMOR MICROENVIRONMENT

FIG. 6A



(57) Abrégé/Abstract:
Provided herein are compositions and methods for detecting and/or targeting dysfunctional tumor antigen-specific CD8$^+$ T cells in the tumor microenvironment for diagnostic, therapeutic and/or research applications. In particular, dysfunctional tumor antigen-specific CD8$^+$ T cellsare detected and/ortargeted via their expression of cell suface receptors described herein, such as 4-1BB, LAG-3, or additional markers that correlate with 4-1BB and LAG-3 expression, such as markers differentially expressed on the surface of the T cells.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 October 2018 (11.10.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/186924 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/28* (2006.01)
C12N 5/0783 (2010.01)

(21) International Application Number:
PCT/US2018/014008

(22) International Filing Date:
17 January 2018 (17.01.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/447,199 17 January 2017 (17.01.2017) 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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*

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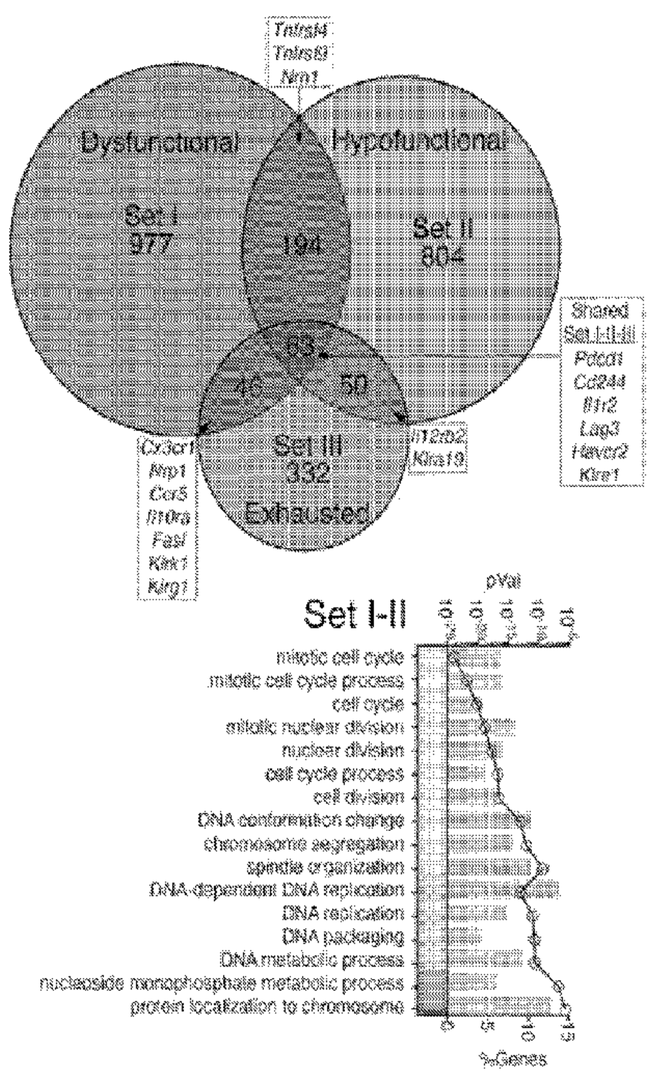
FIG. 6A



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DYSFUNCTIONAL ANTIGEN-SPECIFIC CD8$^+$ T CELLS IN THE TUMOR MICROENVIRONMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Patent Application Serial Number 62/447,199, filed January 17, 2017, which is incorporated by reference in its entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under Grant No. R01 CA161005 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD

Provided herein are compositions and methods for detecting and/or targeting dysfunctional tumor antigen-specific CD8$^+$ T cells in the tumor microenvironment for diagnostic, therapeutic and/or research applications. In particular, dysfunctional tumor antigen-specific CD8$^+$ T cells are detected and/or targeted via their expression of cell surface receptors described herein, such as 4-1BB, LAG-3, or additional markers that correlate with 4-1BB and LAG-3 expression, such as markers differentially expressed on the surface of the T cells.

BACKGROUND

The immune system plays a critical role in protecting the host from cancer (Vesely et al., 2011; incorporated by reference in its entirety). Innate sensing of tumors leads to an adaptive T cell response through the presentation of tumor-associated antigens (TAAs) derived from mutations and epigenetic changes that contribute to carcinogenesis (Gajewski et al., 2013; incorporated by reference in its entirety). Spontaneously-primed CD8+ T cells home to tumor sites in mouse tumor models (Harlin et al., 2009; Fuertes et al., 2011; incorporated by reference in their entireties) and in a subset of patients with advanced cancer (Harlin et al., 2006; incorporated by reference in its entirety). These tumor-infiltrating lymphocytes (TIL) have the ability to recognize tumor antigens and are believed to contribute to tumor control in cancer patients, based on the correlation between activated CD8+ T cell

infiltration with improved prognosis and response to immunotherapy (Fridman et al., 2012; Tumeh et al., 2014; incorporated by reference in their entireties). However, without additional manipulation, this endogenous anti-tumor response is usually not sufficient to mediate complete rejection of an established tumor (Gajewski, 2007b; Pardoll, 2012; Baitsch et al., 2011; Gajewski et al., 2006; Larkin et al., 2015). Data accumulated over the past several years have indicated that tumors with spontaneous anti-tumor T cell responses have high expression of immune-inhibitory pathways that subvert the effector phase of the response. These include PD-L1/PD-1 interactions (Pardoll, 2012; incorporated by reference in its entirety), recruitment of CD4+Foxp3+ regulatory T (Treg) cells (Gajewski, 2007a; incorporated by reference in its entirety), and metabolic dysregulation by indoleamine-2,3-dioxygenase (IDO) (Spranger et al., 2013; incorporated by reference in its entirety). However, even when CD8+ T cells specific for tumor antigens are isolated from tumors, away from these extrinsic immune inhibitory factors, they still show altered functional properties ex vivo (Harlin et al., 2006; Baitsch et al., 2011; incorporated by reference in their entireties).

Expression of PD-1 has been described to identify tumor-specific exhausted T cells (Ahmadzadeh et al., 2009; Fourcade et al., 2012; Wu et al., 2014; Gros et al., 2014; incorporated by reference in their entireties). However, T cells expressing PD-1 in the context of chronic infection can still retain effector function (Wherry and Kurachi, 2015; incorporated by reference in its entirety), and PD-1 is not required for the induction of T cell exhaustion (Odorizzi et al., 2015; incorporated by reference in its entirety). In addition to PD-1, several additional co-inhibitory receptors, including CD223 (LAG-3), CD244 (2B4), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), hepatitis A virus cellular receptor 2 (TIM-3), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are also be expressed on dysfunctional T cells and expression of a greater number of inhibitory receptors has been correlated with diminished cytokine secretion (in particular IFN-g and TNF-a) as well as proliferative capacity (Blackburn et al., 2009; incorporated by reference in its entirety). Expression of these receptors has been observed in both viral and cancer models, however, a complete analysis of both co-inhibitory and co-stimulatory receptors on the same population is lacking in the tumor setting.

SUMMARY

Provided herein are compositions and methods for detecting and/or targeting dysfunctional tumor antigen-specific $CD8^+$ T cells in the tumor microenvironment for

diagnostic, therapeutic and/or research applications. In particular, dysfunctional tumor antigen-specific $CD8^+$ T cells are detected and/or targeted via their expression of cell surface receptors described herein, such as 4-1BB, LAG-3, or additional markers that correlate with 4-1BB and LAG-3 expression, such as markers differentially expressed on the surface of the T cells (e.g., PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM and Sema7a).

In some embodiments, provided herein are methods of treating a subject with cancer comprising administering an agent that specifically targets dysfunctional tumor antigen-specific $CD8^+$ T cells. In some embodiments, the subject suffers from a solid tumor cancer. In some embodiments, the tumor allows T cell infiltration, but is resistant to immunotherapies. In some embodiments, the tumor environment comprises dysfunctional tumor antigen-specific $CD8^+$ T cells. In some embodiments, contacting the dysfunctional tumor antigen-specific $CD8^+$ T cells with an anti-4-1BB and/or anti-LAG3 agent. In some embodiments, the anti-4-1BB and/or anti-LAG3 agent is an antibody, antibody fragment, or antibody mimetic molecule. In some embodiments, methods further comprise co-administration of an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic or an immunotherapeutic agent. In some embodiments, the additional therapeutic agent is an immunotherapeutic agent selected from the list consisting of cell-based therapies, monoclonal antibody (mAb) therapy, cytokine therapy, and adjuvant treatment. In some embodiments, the immunotherapeutic agent is a mAb therapy selected from the list consisting of anti-CTLA-4 monoclonal antibodies and/or anti-PD-L1 monoclonal antibodies. In some embodiments, the immunotherapeutic agent is a cell-based therapy selected from the list consisting of dendritic-cell therapy and T-cell therapy. In some embodiments, the additional therapeutic agent targets one of the markers/receptors listed in Table 2. In some embodiments, the additional therapeutic targets a marker/receptor expressed on the surface of the T cells. In some embodiments, the additional therapeutic targets PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM or Sema7a. In some embodiments, the additional therapeutic agent targets Nrn1, Sema7a, or CRTAM.

In some embodiments, provided herein are methods of treating a subject with cancer comprising administering a therapeutic agent that specifically targets dysfunctional tumor antigen-specific $CD8^+$ T cells, wherein the agent targets one of the receptors listed in Table 2. In some embodiments, the therapeutic targets a marker/receptor expressed on the surface of

the T cells. In some embodiments, the therapeutic targets PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM or Sema7a. In some embodiments, the therapeutic agent targets Nrn1, Sema7a, or CRTAM. In some embodiments, the therapeutic agent is an antibody, antibody fragment, or antibody mimetic molecule that binds the target marker/receptor. In some embodiments, the therapeutic agent is an anti-Nrn antibody, antibody fragment, or antibody mimetic molecule. In some embodiments, the therapeutic agent is an anti-Sema7a antibody, antibody fragment, or antibody mimetic molecule. In some embodiments, the therapeutic agent is an anti-CRTAM antibody, antibody fragment, or antibody mimetic molecule.

In some embodiments, provided herein are compositions comprising: (a) one or more of an anti-4-1BB agent, an anti-LAG-3 agent, an anti-Nrn1 agent, an anti-Sema7a agent, and an anti-CRTAM agent; and (b) an immunotherapeutic agent, said composition formulated for therapeutic delivery to a subject. In some embodiments, the anti-4-1BB agent, anti-LAG-3 agent, anti-Nrn1 agent, anti-Sema7a agent, and/or anti-CRTAM agent is an antibody, antibody fragment, or antibody mimetic molecule.

In some embodiments, provided herein are compositions comprising: (a) an agent that targets and/or binds one of PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A; and (b) an immunotherapeutic agent, said composition formulated for therapeutic delivery to a subject.

In some embodiments, provided herein are methods comprising: (a) testing $CD8^+$ T cells from a cell population to determine whether the CD8+ T Cells co-express LAG-3 and 4-1BB; and (b) administering one or more agents that target and/or bind one of PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A. In some embodiments, the agent is an anti-Nrn1 agent, an anti-Sema7a agent, and an anti-CRTAM agent. In some embodiments, the anti-Nrn1 agent, anti-Sema7a agent, and/or anti-CRTAM agent is an antibody, antibody fragment, or antibody mimetic molecule. In some embodiments, testing is performed *in vitro*.

In some embodiments, provided herein are methods of identifying dysfunctional T cells by testing said cells for co-expression of 4-1BB and LAG-3. In some embodiments, provided herein are methods of identifying dysfunctional T cells by testing said cells for expression of one or more of the markers/receptors of Table 2 (e.g., a T-cell surface marker/receptor (e.g., PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, TMEM126A).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-J. Co-expression of 4-1BB and LAG-3 identifies a significant fraction of the $CD8^+$ TIL compartment found in progressing tumors. (A) Representative analysis of 4-1BB and LAG-3 expression on $CD8^+$ T cells from B16.SIY tumors and the spleen and TdLN from tumor bearing mice on day 7, 14 and 21 after s.c. tumor inoculation. (B-D) Longitudinal summary of the composition, n=5; four to five independent experiments per time point, (C) absolute cell number, n=5; seven to nine independent experiments per time point, and (D) cellular density of the $CD8^+$ 4-1BB/LAG-3 TIL subpopulations, n=5; two to five independent experiments per time point. Absolute cell numbers were determined by acquiring the complete tumor sample by flow cytometery. (E) Day 14 summary of the proportion of the $CD8^+$ 4-1BB/LAG-3 TIL subpopulations that are $Ki67^+$. n=3-5; two independent experiments. (F) Summary of BrdU uptake on day 13 in the $CD8^+$ 4-1BB/LAG-3 TIL subpopulations after a 24 hour BrdU pulse. n=5; three independent experiments. (G-I) Representative flow plots (G and H) and summary (I) of the 4-1BB/LAG-3 populations in other tumor models. Mice were inoculated with $2x10^6$ C1498.SIY, MC38.SIY, EL4.SIY, B16 Parental, MC57.SIY or 1969.SIY subcutaneously and analyzed for 4-1BB and LAG-3 expression on day 14 after tumor inoculation. n=3-5; two to 5 independent experiments for each time point. (J) Mice were inoculated on both flanks with $2x10^6$ MC57.SIY or B16.SIY, at indicated time points tumors from each mouse were pooled and analyzed for co-expression of 4-1BB and LAG-3 in the $CD8^+$ TIL compartment. n=3-5; two independent experiments for each time point. All error bars indicate ± SEM. *:$P < 0.05$, **:$P<0.01$, ***:$P<0.001$. A two-way ANOVA with Bonferroni post-*hoc* test was used for (B, C, D, H) longitudinal studies and Kruskal-Wallis (non-parametric) test was used for (E and F) analysis at one time-point.

Figure 2A-G. Egr2 and a component of the Egr2-transcriptional network are enriched in 4-$1BB^+$LAG-3^+ $CD8^+$ TILs. (A) Representative flow plot and summary of $Egr2^{EGFP}$ expression. $Egr2^{EGFP}$ mice were inoculated with $2x10^6$ B16.SIY tumors s.c. $CD8^+$ T cells from the tumor, TdLN and spleen were analyzed for $Egr2^{EGFP}$ expression on day 7 and day 14. n=4-5; two-independent experiments. (B) Expression of Egr2 target genes (Zheng et al., 2013). $CD8^+$ TILs from day 14 tumor bearing mice were sorted based on high or low expression of $Egr2^{EGFP}$ and analyzed directly for expression of Egr2 targets by qRT-PCR. Two tumors on opposite flanks pooled per mouse. n=3; two independent experiments. (C) Representative flow plots and summary of the 4-1BB/LAG-3 subpopulations in $CD8^+$ $Egr2GFP^{hi}$ and $Egr2GFP^{lo}$ TILs on day 7 and 14. n=4-5. Two-independent experiments per

time point. (D) Expression of Egr2 targets in the 4-1BB$^+$LAG-3$^+$ and 4-1BB$^-$LAG-3$^-$ subpopulations. The subpopulations were sorted and analyzed directly for the expression of targets by qRT-PCR. Two tumors on opposite flanks pooled per mouse. n=4; two-independent experiments. (E) Egr2$^{flox/flox}$ x pLCKCreERT2 x YFP-Rosa26 mice given 5 doses of tamoxifen by gavage and inoculated 3 days later with 2x10^6 B16.SIY cells. YFP$^+$ or YFP$^-$ CD8$^+$ TILs were sorted and analyzed for *Egr2* transcript directly and after *in vitro* stimulation. Two tumors on opposite flanks pooled per mouse. n=3; two independent experiments. (F) Representative flow plots and summary of 4-1BB/LAG-3 co-expression in YFP$^+$ or YFP$^-$ CD8$^+$ TILs on day 7 and 14. n=3; two independent experiments. (G) Expression of *Egr3* and *Hif1α* in Egr2GFP^{hi} and Egr2GFP^{lo} from day 7 CD8$^+$ TILs isolated from Egr2GFP mice. n=5; two-independent experiments. Error bars indicate ± SEM. *:P < 0.05, **:P<0.01, ***:P<0.001. A two-way ANOVA with Bonferroni post-*hoc* test was used for longitudinal studies (A and C) and a Mann-Whitney test was used to compute significance in (B, D, E, F and G).

Figure 3A-H. Co-expression of 4-1BB and LAG-3 identifies tumor antigen-specific TILs in progressing tumors. (A) Representative CDR3β distributions from the different 4-1BB/LAG-3 subpopulations and CD8$^+$ T cells isolated from the spleen. Boxed regions represent dominant peaks in the 4-1BB$^+$LAG-3$^+$ CD8$^+$ TIL subpopulation. (B) As a measure of skewness, the Hamming Distance (HD) for each Vβ spectratype was calculated between each TIL subpopulation and CD8$^+$ T cell spleen population within the same mouse. As a control the HDs from CD8$^+$ splenocyte populations between mice (grey bar) were calculated. n=3; one independent experiment. (C-D) Representative flow analysis of the 4-1BB/LAG-3 subpopulation in H-2K^b/SIY$^+$ and H-2K^b/SIY$^-$ CD8$^+$ TILs on day 14 after B16.SIY and MC38.SIY or (D) MC57.SIY and 1969.SIY tumor inoculation. n=3-4; three to five independent experiments. (E) Summary of the composition of H-2K^b/SIY$^+$ and H-2K^b/SIY$^-$ CD8$^+$ TILs co-expressing 4-1BB and LAG-3 comparing B16.SIY, MC38.SIY, MC57.SIY and 1969.SIY tumors on day 14 after tumor inoculation. n=5; three to four independent experiments. (F-H) On day 7 after tumor inoculation 1x10^6 P14/CD45.2 and 2C/CD45.1/2 Tg T cells were adoptively transferred, via tail vein, into CD45.1 congenic tumor bearing hosts and analyzed for the (F) total number of recovered cells in the tumor, (G and H) profile of 4-1BB and LAG-3 expression in 2C, P14 and host CD8$^+$ TILs. n=5; two-independent experiments. All error bars indicate ± SEM. *:P < 0.05, **:P<0.01, ***:P<0.001. A Kruskal-Wallis (non-parameteric) test was used for (B) spectratype analysis and (E and F) H-2K^b/SIY

analysis. A two-way ANOVA with Bonferroni post-*hoc* test was used for (H) 2C, Host and P14 composition analysis.

Figure 4A-G. Co-expression of 4-1BB and LAG-3 but not PD-1 define dysfunctional $CD8^+$ TILs with diminished IL-2. (A and B) Sorted cells from day 14 B16.SIY tumor bearing mice were stimulated *in vitro* with anti-CD3ε and anti-CD28 for 12 hours and analyzed for (A) *Il-2* transcript by qRT-PCR and (B) IL-2 protein by ELISA. Two tumors on opposite flanks pooled per mouse. n=4-5; three independent experiments. (C) $Egr2GFP^{hi}$ and $Egr2GFP^{lo}$ TILs were sorted from day 14 B16.SIY tumor bearing $Egr2^{GFP}$ mice and stimulated *in vitro* for 12 hours and analyzed *for Il-2* transcript by qRT-PCR. Two tumors on opposite flanks pooled per mouse. n=5; two independent experiments. (D) On day 7 after tumor inoculation $1x10^6$ 2C/CD45.1/2 Tg T cells were transferred into mice, 7 days later host $4\text{-}1BB^+LAG\text{-}3^+$ T cells sorted from the tumor and 2C T cells sorted from the tumor or TdLN were stimulated *in vitro* and analyzed for expression of *Il-2* transcript by qRT-PCR. Two tumors on opposite flanks pooled per mouse. n=3; two independent experiments. (E and F) Representative flow analysis of PD-1 expression on 4-1BB/LAG-3 $CD8^+$ TIL subpopulations and (F) summary of the composition of the $4\text{-}1BB^-LAG\text{-}3^-PD\text{-}1^+$ subpopulation in the $CD8^+$ TIL compartment on day 14 and 21. n=5; three independent experiments. (G) $4\text{-}1BB^-LAG\text{-}3^-PD\text{-}1^+$ and $LAG\text{-}3^+4\text{-}1BB^+$ $CD8^+$ TILs were sorted from day 14 tumor bearing mice, stimulated *in vitro* and analyzed for *Il-2* transcript by qRT-PCR. Two tumors on opposite flanks pooled per mouse. n=3; two independent experiments. All error bars indicate ± SEM. *:$P < 0.05$, **:$P<0.01$, ***:$P<0.001$ ****:$P<0.0001$. A Kruskal-Wallis (non-parametric) test was used for analysis of multiple comparisons (A, B, and D) and a Mann-Whitney test was used for pair-wise comparisons (C and G).

Figure 5A-E. Dysfunctional $CD8^+$ TILs retain IFN-γ production, cytolytic capacity and produce Treg-recruiting chemokines. (A) Longitudinal analysis $CD8^+$ TIL subpopulation cytokine production capacity. $CD8^+$ TIL subpopulations were sorted and stimulated with anti-CD3ε and anti-CD28 for 10-12 hours and the concentration of IL-2, IFN-γ and TNF-α was measured. Concentration was normalized to cell number. Two tumors on opposite flanks pooled for day 7 and 14. n=4-5; two-independent experiments. (B) *Ifn-γ Tnf-α* and *Gzmb* transcript levels in the 4-1BB/LAG-3 subpopulations analyzed directly *ex vivo*. Two tumors on opposite flanks pooled per mouse. n=3-5; three-independent experiments. (C) Representative flow plot and summary of IFN-γ production analyzed directly *ex vivo*. Briefly, 100 μl of PBS containing 2 mg/mL GolgiPlug was injected intratumorally on day 14 after tumor inoculation. 8 hours later TILs were isolated. All steps were performed on ice

with media containing 1 mg/mL GolgiStop until fixation. n=5; two independent experiments. (D) $CD8^+$ TIL subpopulations at indicated time points were sorted and plated with 50,000 P815 target cells and 1 μg/mL anti-CD3ε. Lysed target cells were measured by positive staining for propidium iodide and/or live/dead fixable viability dye. P815 target cells plated without CTLs were used as a negative control (black bar). Primed OTI cells were used as a positive control. Tumors from 10 mice with 2 tumors on opposite flank were pooled to obtain sufficient quantities of $CD8^+$ TILs. Data are representative of three independent experiments. (E) *Ccl1* and *Ccl22* transcript levels in the 4-1BB/LAG-3 subpopulations analyzed directly *ex vivo* by qRT-PCR. n=4; two independent experiments. *:$P < 0.05$, **:$P<0.01$, ***:$P<0.001$, ****:$P<0.0001$. A Kruskal-Wallis (non-parametric) test was used for (A-C, E) cytokine/chemokine analysis and a two-way ANOVA with Bonferroni post-*hoc* test was used for (D) cytolytic assay.

Figure 6A-D. Dysfunctional $CD8^+$ TILs express a wide range of co-inhibitory and co-stimulatory receptors. (B) Gene expression profile of cell surface receptors in the 4-1BB/LAG-3 $CD8^+$ TIL subsets. Probe sets that revealed a 1.5-fold increase in the 4-$1BB^+LAG\text{-}3^+$ population relative to the $4\text{-}1BB^-LAG\text{-}3^-PD\text{-}1^-$ population are displayed. Columns show the $\log_2$-transformed signal intensity. (C) Longitudinal study of selected up-regulated cell surface receptors. Flow plots are representative of the $CD8^+$ TIL subsets on day 14. n=5; two to five independent experiments for each time point. (D) Representative flow plot and summary of KLRG-1 and IL-7Rα expression among the 4-1BB/LAG-3 subpopulations on day 14 after tumor inoculation. n=5; two independent experiments. *:$P < 0.05$, **:$P<0.01$, ***:$P<0.001$, ****:$P<0.0001$. A two-way ANOVA with Bonferroni post-*hoc* test was used for all analyses.

Figure 7A-G. Anti-4-1BB and anti-LAG-3 acts synergistically to control tumor outgrowth and restore TIL function. (A) Tumor outgrowth measured in mm^2. Arrows indicate on which days mice received antibody therapy. Statistical significance at indicate time points is in comparison to anti-4-1BB + anti-LAG-3 treatment. n=5; two independent experiments. (B) Composition of $H\text{-}2K^b/SIY^+$ $CD8^+$ TILs on day 14. Mice received antibody doses (100 μg each) on days 7,10, 13 and 16. n=5; two independent experiments. (C-F) Representative flow plot and summary of NRP1/2B4 (C and E) and KLRG-1/IL-7Rα (D and F) expression in $H\text{-}2K^b/SIY^+$ $CD8^+$ TILs without FTY720 (C and D) and with FTY720 (E and F) on day 14 after tumor inoculation. Mice received antibody treatment as in (A and B) and FTY720 was administered at a dose of 25 μg/mouse by gavage starting one day before treatment and continuing one dose per day until analysis (day 6 to day 13). n=5; two-independent

experiments. (G) IL-2 production after treatment. Sorted cells from treated or untreated day 14 B16.SIY tumor bearing mice were stimulated *in vitro* for 12 hours and analyzed for *Il-2* transcript by qRT-PCR. Protein concentration was determined by the bead-based LEGENDplex immunoassay and normalized to cell number. Two tumors on opposite flanks pooled per mouse. n=2-3; two independent experiments. A two-way ANOVA with Bonferroni post-*hoc* test was used for all analyses. *:P < 0.05, **:P<0.01, ***:P<0.001.

Figure 8. Spectratype graphs used in the analysis in Figure 3B.

Figure 9. CD3+ T cells on day 14 after FTY720 administration.

Figure 10A-B. Statistical analysis of the cross-study comparison of gene expression profiles. (A) Rank-Rank Hypergeometric plots of each pair-wise comparison. (B) Pair-wise correlation of expression values between each data set. Rho (ρ) is the spearman rank correlation coefficient.

Figure 11A-E. Nrn1, CRTAM and Sema7a are regulators of anti-tumor immunity. (A) Tumor growth measured in mm2. $Nrn1^{-/-}$ or $Sema7a^{-/-}$ and littermate control mice were engrafted with 2 x 106 B16.SIY cells subcutaneously. (B) Gene expression analysis of *Nrn1* in T cell subsets of the spleen, TdLN and Tumor. (C) Representative flow plot and summary of IFN-g production of WT, $Nrn1^{-/-}$ or (D) $CRTAM^{-/-}$ 2C T cells on day 7. Briefly, on the same day as tumor inoculation, $1x10^6$ Cell Trace Violet-labeled 2C T cells were transferred into mice by tail vein injection. On day 7, whole TdLN suspensions were restimulated with SIY peptide for 12 hours and analyzed for cell trace dilution and IFN-g production. (E) Mice that received $1x10^6$ $Nrn1^{-/-}$ 2C T cells are more likely to exhibit complete tumor control compared to mice that received the same number of WT 2C T cells. Adoptive transfer of T cells was performed the same way as in (C).

Figure 12. Exemplary experimental protocol and data.

DEFINITIONS

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments described herein, some preferred methods, compositions, devices, and materials are described herein. However, before the present materials and methods are described, it is to be understood that this invention is not limited to the particular molecules, compositions, methodologies or protocols herein described, as these may vary in accordance with routine experimentation and optimization. It is also to be understood that the terminology used in the description is for the purpose of

describing the particular versions or embodiments only, and is not intended to limit the scope of the embodiments described herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. However, in case of conflict, the present specification, including definitions, will control. Accordingly, in the context of the embodiments described herein, the following definitions apply.

As used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to “an antibody” is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

As used herein, the term “comprise” and linguistic variations thereof denote the presence of recited feature(s), element(s), method step(s), etc. without the exclusion of the presence of additional feature(s), element(s), method step(s), etc. Conversely, the term “consisting of” and linguistic variations thereof, denotes the presence of recited feature(s), element(s), method step(s), etc. and excludes any unrecited feature(s), element(s), method step(s), etc., except for ordinarily-associated impurities. The phrase “consisting essentially of” denotes the recited feature(s), element(s), method step(s), etc. and any additional feature(s), element(s), method step(s), etc. that do not materially affect the basic nature of the composition, system, or method. Many embodiments herein are described using open “comprising” language. Such embodiments encompass multiple closed “consisting of” and/or “consisting essentially of” embodiments, which may alternatively be claimed or described using such language.

As used herein, the term “subject” broadly refers to any animal, including but not limited to, human and non-human animals (e.g., dogs, cats, cows, horses, sheep, poultry, fish, crustaceans, etc.). As used herein, the term “patient” typically refers to a subject that is being treated for a disease or condition (e.g., cancer, solid tumor cancer, etc.).

As used herein, an “immune response” refers to the action of a cell of the immune system (e.g., T lymphocytes, B lymphocytes, natural killer (NK) cells, macrophages, eosinophils, mast cells, dendritic cells, neutrophils, etc.) and soluble macromolecules produced by any of these cells or the liver (including antibodies, cytokines, and complement) that results in selective targeting, binding to, damage to, destruction of, and/or elimination from a subject of invading pathogens, cells or tissues infected with pathogens, or cancerous or other abnormal cells.

As used herein, the term "immunoregulator" refers to a substance, an agent, a signaling pathway or a component thereof that regulates an immune response. "Regulating," "modifying" or "modulating" an immune response refers to any alteration in a cell of the immune system or in the activity of such cell. Such regulation includes stimulation or suppression of the immune system which may be manifested by an increase or decrease in the number of various cell types, an increase or decrease in the activity of these cells, or any other changes which can occur within the immune system. Both inhibitory and stimulatory immunoregulators have been identified, some of which may have enhanced function in the cancer microenvironment.

As used herein, the term "immunotherapy" refers to the treatment or prevention of a disease or condition by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response.

As used herein, "potentiating an endogenous immune response" means increasing the effectiveness or potency of an existing immune response in a subject. This increase in effectiveness and potency may be achieved, for example, by overcoming mechanisms that suppress the endogenous host immune response or by stimulating mechanisms that enhance the endogenous host immune response.

As used herein, the term "antibody" refers to a whole antibody molecule or a fragment thereof (e.g., fragments such as Fab, Fab', and $F(ab')_2$), unless otherwise specified (e.g., "whole antibody," "antibody fragment"). An antibody may be a polyclonal or monoclonal antibody, a chimeric antibody, a humanized antibody, a human antibody, etc.

A native antibody typically has a tetrameric structure. A tetramer typically comprises two identical pairs of polypeptide chains, each pair having one light chain (in certain embodiments, about 25 kDa) and one heavy chain (in certain embodiments, about 50-70 kDa). In a native antibody, a heavy chain comprises a variable region, V_H, and three constant regions, C_{H1}, C_{H2}, and C_{H3}. The V_H domain is at the amino-terminus of the heavy chain, and the C_{H3} domain is at the carboxy-terminus. In a native antibody, a light chain comprises a variable region, V_L, and a constant region, C_L. The variable region of the light chain is at the amino-terminus of the light chain. In a native antibody, the variable regions of each light/heavy chain pair typically form the antigen binding site. The constant regions are typically responsible for effector function.

In a native antibody, the variable regions typically exhibit the same general structure in which relatively conserved framework regions (FRs) are joined by three hypervariable regions, also called complementarity determining regions (CDRs). The CDRs from the two

chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From N-terminus to C-terminus, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The CDRs on the heavy chain are referred to as H1, H2, and H3, while the CDRs on the light chain are referred to as L1, L2, and L3. Typically, CDR3 is the greatest source of molecular diversity within the antigen-binding site. H3, for example, in certain instances, can be as short as two amino acid residues or greater than 26. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat et al. (1991) Sequences of Proteins of Immunological Interest (National Institutes of Health, Publication No. 91-3242, vols. 1-3, Bethesda, Md.); Chothia, C., and Lesk, A. M. (1987) J. Mol. Biol. 196:901-917; or Chothia, C. et al. Nature 342:878-883 (1989). In the present application, the term "CDR" refers to a CDR from either the light or heavy chain, unless otherwise specified.

As used herein, the term "heavy chain" refers to a polypeptide comprising sufficient heavy chain variable region sequence to confer antigen specificity either alone or in combination with a light chain.

As used herein, the term "light chain" refers to a polypeptide comprising sufficient light chain variable region sequence to confer antigen specificity either alone or in combination with a heavy chain.

As used herein, when an antibody or other entity "specifically recognizes" or "specifically binds" an antigen or epitope, it preferentially recognizes the antigen in a complex mixture of proteins and/or macromolecules, and binds the antigen or epitope with affinity which is substantially higher than to other entities not displaying the antigen or epitope. In this regard, "affinity which is substantially higher" means affinity that is high enough to enable detection of an antigen or epitope which is distinguished from entities using a desired assay or measurement apparatus. Typically, it means binding affinity having a binding constant (K_a) of at least 10^7 M^{-1} (e.g., $>10^7$ M^{-1}, $>10^8$ M^{-1}, $>10^9$ M^{-1}, $>10^{10}$ M^{-1}, $>10^{11}$ M^{-1}, $>10^{12}$ M^{-1}, $>10^{13}$ M^{-1}, etc.). In certain such embodiments, an antibody is capable of binding different antigens so long as the different antigens comprise that particular epitope. In certain instances, for example, homologous proteins from different species may comprise the same epitope.

As used herein, the term "anti-4-1BB antibody" or "4-1BB antibody" refers to an antibody which specifically recognizes an antigen and/or epitope presented by 4-1BB. Similarly, the terms "anti-LAG-3 antibody" and "LAG-3 antibody" refer to an antibody which specifically recognizes an antigen and/or epitope presented by LAG-3, the terms "anti-

Nrn1 antibody" and "Nrn1 antibody" refer to an antibody which specifically recognizes an antigen and/or epitope presented by Nrn1, the terms "anti-CRTAM antibody" and "CRTAM antibody" refer to an antibody which specifically recognizes an antigen and/or epitope presented by CRTAM, and the terms "anti-Sema7a antibody" and "Sema7a antibody" refer to an antibody which specifically recognizes an antigen and/or epitope presented by Sema7a. Antibodies that recognize epitopes on other molecular entities may be referred to according to a similar scheme (e.g., anti-CTLA-4, anti-PD-L1, etc.).

As used herein, the term "monoclonal antibody" refers to an antibody which is a member of a substantially homogeneous population of antibodies that specifically bind to the same epitope. In certain embodiments, a monoclonal antibody is secreted by a hybridoma. In certain such embodiments, a hybridoma is produced according to certain methods known to those skilled in the art. See, e.g., Kohler and Milstein (1975) Nature 256: 495-499; herein incorporated by reference in its entirety. In certain embodiments, a monoclonal antibody is produced using recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). In certain embodiments, a monoclonal antibody refers to an antibody fragment isolated from a phage display library. See, e.g., Clackson et al. (1991) Nature 352: 624-628; and Marks et al. (1991) J. Mol. Biol. 222: 581-597; herein incorporated by reference in their entireties. The modifying word "monoclonal" indicates properties of antibodies obtained from a substantially-homogeneous population of antibodies, and does not limit a method of producing antibodies to a specific method. For various other monoclonal antibody production techniques, see, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.); herein incorporated by reference in its entirety.

As used herein, the term "antibody fragment" refers to a portion of a full-length antibody, including at least a portion antigen binding region or a variable region. Antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, Fv, scFv, Fd, diabodies, and other antibody fragments that retain at least a portion of the variable region of an intact antibody. See, e.g., Hudson et al. (2003) Nat. Med. 9:129-134; herein incorporated by reference in its entirety. In certain embodiments, antibody fragments are produced by enzymatic or chemical cleavage of intact antibodies (e.g., papain digestion and pepsin digestion of antibody) produced by recombinant DNA techniques, or chemical polypeptide synthesis.

For example, a "Fab" fragment comprises one light chain and the C_{H1} and variable region of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A "Fab'" fragment comprises one light chain and one

heavy chain that comprises additional constant region, extending between the C_{H1} and C_{H2} domains. An interchain disulfide bond can be formed between two heavy chains of a Fab' fragment to form a "$F(ab')_2$" molecule.

An "Fv" fragment comprises the variable regions from both the heavy and light chains, but lacks the constant regions. A single-chain Fv (scFv) fragment comprises heavy and light chain variable regions connected by a flexible linker to form a single polypeptide chain with an antigen-binding region. Exemplary single chain antibodies are discussed in detail in WO 88/01649 and U.S. Pat. Nos. 4,946,778 and 5,260,203; herein incorporated by reference in their entireties. In certain instances, a single variable region (e.g., a heavy chain variable region or a light chain variable region) may have the ability to recognize and bind antigen.

Other antibody fragments will be understood by skilled artisans.

As used herein, the term "chimeric antibody" refers to an antibody made up of components from at least two different sources. In certain embodiments, a chimeric antibody comprises a portion of an antibody derived from a first species fused to another molecule, e.g., a portion of an antibody derived from a second species. In certain such embodiments, a chimeric antibody comprises a portion of an antibody derived from a non-human animal fused to a portion of an antibody derived from a human. In certain such embodiments, a chimeric antibody comprises all or a portion of a variable region of an antibody derived from a non-human animal fused to a constant region of an antibody derived from a human.

A "humanized" antibody refers to a non-human antibody that has been modified so that it more closely matches (in amino acid sequence) a human antibody. A humanized antibody is thus a type of chimeric antibody. In certain embodiments, amino acid residues outside of the antigen binding residues of the variable region of the non-human antibody are modified. In certain embodiments, a humanized antibody is constructed by replacing all or a portion of a complementarity determining region (CDR) of a human antibody with all or a portion of a CDR from another antibody, such as a non-human antibody, having the desired antigen binding specificity. In certain embodiments, a humanized antibody comprises variable regions in which all or substantially all of the CDRs correspond to CDRs of a non-human antibody and all or substantially all of the framework regions (FRs) correspond to FRs of a human antibody. In certain such embodiments, a humanized antibody further comprises a constant region (Fc) of a human antibody.

The term "human antibody" refers to a monoclonal antibody that contains human antibody sequences and does not contain antibody sequences from a non-human animal. In

certain embodiments, a human antibody may contain synthetic sequences not found in native antibodies. The term is not limited by the manner in which the antibodies are made. For example, in various embodiments, a human antibody may be made in a transgenic mouse, by phage display, by human B-lymphocytes, or by recombinant methods.

As used herein, the term “natural antibody” refers to an antibody in which the heavy and light chains of the antibody have been made and paired by the immune system of a multicellular organism. For example, the antibodies produced by the antibody-producing cells isolated from a first animal immunized with an antigen are natural antibodies. Natural antibodies contain naturally-paired heavy and light chains. The term “natural human antibody” refers to an antibody in which the heavy and light chains of the antibody have been made and paired by the immune system of a human subject.

Native human light chains are typically classified as kappa and lambda light chains. Native human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM1 and IgM2. IgA has subclasses including, but not limited to, IgA1 and IgA2. Within native human light and heavy chains, the variable and constant regions are typically joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See, e.g., Fundamental Immunology (1989) Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y.); herein incorporated by reference in its entirety.

The term “neutralizing antibody” or “antibody that neutralizes” refers to an antibody that reduces at least one activity of a polypeptide comprising the epitope to which the antibody specifically binds. In certain embodiments, a neutralizing antibody reduces an activity *in vitro* and/or *In vivo*. In some embodiments, by neutralizing the polypeptide comprising the epitope, the neutralizing antibody inhibits the capacity of the cell displaying the epitope.

As used herein, the term "glycoengineered", as used herein, includes any manipulation of the glycosylation pattern of a naturally occurring or recombinant protein, polypeptide or a fragment thereof.

The term “antigen-binding site” refers to a portion of an antibody capable of specifically binding an antigen. In certain embodiments, an antigen-binding site is provided by one or more antibody variable regions.

The term “epitope” refers to any polypeptide determinant capable of specifically binding to an immunoglobulin or a T-cell or B-cell receptor. In certain embodiments, an epitope is a region of an antigen that is specifically bound by an antibody. In certain embodiments, an epitope may include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl, or sulfonyl groups. In certain embodiments, an epitope may have specific three dimensional structural characteristics (e.g., a "conformational" epitope) and/or specific charge characteristics.

An epitope is defined as “the same” as another epitope if a particular antibody specifically binds to both epitopes. In certain embodiments, polypeptides having different primary amino acid sequences may comprise epitopes that are the same. In certain embodiments, epitopes that are the same may have different primary amino acid sequences. Different antibodies are said to bind to the same epitope if they compete for specific binding to that epitope.

A “conservative” amino acid substitution refers to the substitution of an amino acid in a polypeptide with another amino acid having similar properties, such as size or charge. In certain embodiments, a polypeptide comprising a conservative amino acid substitution maintains at least one activity of the unsubstituted polypeptide. A conservative amino acid substitution may encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include, but are not limited to, peptidomimetics and other reversed or inverted forms of amino acid moieties. Naturally occurring residues may be divided into classes based on common side chain properties, for example: hydrophobic: norleucine, Met, Ala, Val, Leu, and Ile; neutral hydrophilic: Cys, Ser, Thr, Asn, and Gln; acidic: Asp and Glu; basic: His, Lys, and Arg; residues that influence chain orientation: Gly and Pro; and aromatic: Trp, Tyr, and Phe. Non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class; whereas conservative substitutions may involve the exchange of a member of one of these classes for another member of that same class.

As used herein, the term “sequence identity” refers to the degree to which two polymer sequences (e.g., peptide, polypeptide, nucleic acid, etc.) have the same sequential composition of monomer subunits. The term “sequence similarity” refers to the degree with which two polymer sequences (e.g., peptide, polypeptide, nucleic acid, etc.) have similar polymer sequences. For example, similar amino acids are those that share the same biophysical characteristics and can be grouped into the families (see above). The “percent

sequence identity" (or "percent sequence similarity") is calculated by: (1) comparing two optimally aligned sequences over a window of comparison (e.g., the length of the longer sequence, the length of the shorter sequence, a specified window, etc.), (2) determining the number of positions containing identical (or similar) monomers (e.g., same amino acids occurs in both sequences, similar amino acid occurs in both sequences) to yield the number of matched positions, (3) dividing the number of matched positions by the total number of positions in the comparison window (e.g., the length of the longer sequence, the length of the shorter sequence, a specified window), and (4) multiplying the result by 100 to yield the percent sequence identity or percent sequence similarity. For example, if peptides A and B are both 20 amino acids in length and have identical amino acids at all but 1 position, then peptide A and peptide B have 95% sequence identity. If the amino acids at the non-identical position shared the same biophysical characteristics (e.g., both were acidic), then peptide A and peptide B would have 100% sequence similarity. As another example, if peptide C is 20 amino acids in length and peptide D is 15 amino acids in length, and 14 out of 15 amino acids in peptide D are identical to those of a portion of peptide C, then peptides C and D have 70% sequence identity, but peptide D has 93.3% sequence identity to an optimal comparison window of peptide C. For the purpose of calculating "percent sequence identity" (or "percent sequence similarity") herein, any gaps in aligned sequences are treated as mismatches at that position.

The term "effective dose" or "effective amount" refers to an amount of an agent, e.g., an antibody, that results in the reduction of symptoms in a patient or results in a desired biological outcome. In certain embodiments, an effective dose or effective amount is sufficient to treat or reduce symptoms of a disease or condition.

As used herein, the terms "administration" and "administering" refer to the act of giving a drug, prodrug, or other agent, or therapeutic to a subject or *in vivo*, *in vitro*, or *ex vivo* cells, tissues, and organs. Exemplary routes of administration to the human body can be through space under the arachnoid membrane of the brain or spinal cord (intrathecal), the eyes (ophthalmic), mouth (oral), skin (topical or transdermal), nose (nasal), lungs (inhalant), oral mucosa (buccal), ear, rectal, vaginal, by injection (e.g., intravenously, subcutaneously, intratumorally, intraperitoneally, etc.) and the like.

The term "treatment" encompasses both therapeutic and prophylactic/preventative measures unless otherwise indicated. Those in need of treatment include, but are not limited to, individuals already having a particular condition as well as individuals who are at risk of acquiring a particular condition or disorder (e.g., those having a genetic or epigenetic

predisposition; based on age, gender, lifestyle, etc.). The term "treating" refers to administering an agent to a subject for therapeutic and/or prophylactic/preventative purposes.

A “therapeutic agent” refers to an agent that may be administered *In vivo* to bring about a therapeutic and/or prophylactic/preventative effect.

A "therapeutic antibody" refers to an antibody that may be administered *In vivo* to bring about a therapeutic and/or prophylactic/preventative effect.

As used herein, the terms “co-administration” and “co-administering” refer to the administration of at least two agent(s) or therapies to a subject. In some embodiments, the co-administration of two or more agents or therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents or therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents or therapies are co-administered, the respective agents or therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents or therapies lowers the requisite dosage of a potentially harmful (e.g., toxic) agent(s), and/or when co-administration of two or more agents results in sensitization of a subject to beneficial effects of one of the agents via co-administration of the other agent.

As used herein, the term pharmaceutical composition” refers to the combination of an active agent (e.g., binding agent) with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vitro*, *in vivo* or *ex vivo*.

The terms “pharmaceutically acceptable” or “pharmacologically acceptable,” as used herein, refer to compositions that do not substantially produce adverse reactions, e.g., toxic, allergic, or immunological reactions, when administered to a subject.

As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers including, but not limited to, phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents, any and all solvents, dispersion media, coatings, sodium lauryl sulfate, isotonic and absorption delaying agents, disintigrants (e.g., potato starch or sodium starch glycolate), and the like. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see, e.g., Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. (1975), incorporated herein by reference in its entirety.

As used herein, a "diagnostic" or "diagnostic test" includes the detection, identification, or characterization of a disease state or condition of a subject. For example, a disease or condition may be characterized to determine the likelihood that a subject with a disease or condition will respond to a particular therapy, determine the prognosis of a subject with a disease or condition (or its likely progression or regression), determine the effect of a treatment on a subject with a disease or condition, or determine a future treatment course of action.

DETAILED DESCRIPTION

Provided herein are compositions and methods for detecting and/or targeting dysfunctional tumor antigen-specific $CD8^+$ T cells in the tumor microenvironment for diagnostic, therapeutic and/or research applications. In particular, dysfunctional tumor antigen-specific $CD8^+$ T cells are detected and/or targeted via their expression of cell surface receptors described herein, such as 4-1BB,LAG-3, or additional markers that correlate with 4-1BB and LAG-3 expression, such as markers differentially expressed on the surface of the T cells (e.g., PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM and Sema7a).

Experiments conducted during development of embodiments herein identified markers/receptors that correlate and/or are responsible for tumor antigen-specific $CD8^+$ T cell dysfunction. In some embodiments, the markers/receptors are overexpressed in dysfunctional tumor antigen-specific $CD8^+$ T cells. In such embodiments, detecting the level (e.g., above a threshold) of such markers provides a diagnostic for detecting tumor antigen-specific $CD8^+$ T cell dysfunction. Further, in such embodiments, targeting (e.g., inhibiting (e.g., expression and/or activity of)) such markers/receptors provides a therapeutic. In other embodiments, the markers/receptors are underexpressed in dysfunctional tumor antigen-specific $CD8^+$ T cells. In such embodiments, detecting the level (e.g., below a threshold) of such markers provides a diagnostic for detecting tumor antigen-specific $CD8^+$ T cell dysfunction. Further, in such embodiments, targeting (e.g., enhancing (e.g., expression and/or activity of)) such markers/receptors provides a therapeutic.

Transcription factor Egr2 is a critical regulator of the anergic state in $CD4^+$ T cell clones manipulated in vitro (Zheng et al., 2013; 2012; incorporated by reference in their entireties). Egr2 has also been shown to be involved in negative regulation of T cell activation in several in vivo model systems (Sumitomo et al., 2013; incorporated by reference

in its entirety). Egr2 contributes to upregulation of DGKa and -z which act to blunt TCR-mediated Ras pathway activation (Zha et al., 2006; incorporated by reference in its entirety). By comparing gene expression profiling of anergized cells along with Egr2 ChIP-Seq analysis multiple additional Egr2-driven gene targets were identified (Zheng et al., 2013; incorporated by reference in its entirety). These gene targets include 4-1BB (Tnfrsf9 or CD137), Lag3, Nrn1, Sema7a, Crtam, and Rankl, which encode cell surface proteins.

4-1BB is a co-stimulatory molecule transiently expressed after TCR engagement. Lag3 (lymphocyte-activation gene 3 or CD223) is a CD4 homologue and functions as an inhibitory receptor. Expression of 4-1BB and Lag3 is regulated following TCR engagement and continues throughout differentiation. In humans, 4-1BB and LAG-3 are expressed on CD8+ TILs from human melanoma tumors (Gros et al., 2014; Baitsch et al., 2012; incorporated by reference in their entireties). In both mice and humans, either molecule alone are expressed on populations of activated T cells. However, co-expression is more limited and is rarely observed in circulating T cells. The function of CD8+ TILs co-expressing these markers is unknown.

Experiments were conducted during development of embodiments herein to investigate the detailed characteristics of CD8+ TILs expressing 4-1BB and LAG-3 using mouse tumor models. It was found that the co-expression of 4-1BB and LAG-3 was sufficient to identify tumor antigen-specific dysfunctional CD8+ TILs enriched in the expression of Egr2 target genes. These CD8+ TILs failed to make IL-2 following in vitro stimulation, yet still produced IFN-g and Treg-recruiting chemokines and lysed target cells ex vivo, indicating they are not completely functionally inert. Combinatorial treatment with anti-LAG-3/anti-4-1BB restored the function of this population and promoted in situ acquisition of KLRG-1hi effector cells. Additional gene expression profiling provided a complete phenotyping of this T cell subset, which revealed expression of a broad panel of both inhibitory receptors and co-stimulatory receptors (e.g., receptors of Table 2 (e.g. Nrn1, Sema7a, CRTAM, etc.)). Inhibitory receptors and co-stimulatory receptors idientified in this profiling that are displayed on the surface of T cells include PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A. These approaches have thus enabled the characterization of the population of tumor antigen-specific CD8+ T cells that arise specifically within the tumor microenvironment having altered functional properties. In some embodiments, this population is a target for immunotherapeutic approaches to restore desired functionality and promote tumor regression. In some embodiments, the receptors/markers identified herein

(e.g., 4-1BB, LAG-3, receptors/markers of Table 2 (e.g., surface markers/receptors (e.g. Nrn1, Sema7a, CRTAM, etc.), etc.) etc.) are targeted (e.g., via immunotherapeutic approaches) to restore desired immunoresponsiveness, to promote tumor regression, and/or for the treatment of cancer.

Experiments conducted during development of embodiments herein applied knowledge of Egr2 targets to evaluate applicability of these markers toward understanding dysfunctional T cells within tumors in vivo. The data indeed confirm that co-expression of LAG-3 and 4-1BB is sufficient to identify the majority of tumor antigen-specific $CD8^+$ T cells within the tumor microenvironment. Co-expression of these markers was not observed within peripheral lymphoid organs in tumor-bearing mice, indicating that a property unique to the tumor context drives 4-1BB and LAG-3 expression. In addition, acquisition of LAG-3 and 4-1BB expression was not observed within tumors that were undergoing successful rejection, indicating that the acquisition of this phenotype occurs under conditions of incomplete antigen clearance.

In some embodiments, cancer treatment methods described herein comprise administration (or co-administration with one or more additional therapies/therapeutics) of one or more anti-4-1BB and/or anti-LAG-3 agents (e.g., antibodies, antibody fragments, antibody mimetic molecules (e.g., DARPins, affibodies, aptamers, nanobodies, etc.), etc.). In some embodiments, an anti-4-1BB and/or anti-LAG-3 agents is administered to render cancer cells, tumor(s), and/or the tumor microenvironment accessible or susceptible to treatment with additional therapies/therapeutics (e.g., immunotherapeutics). Anti-4-1BB and/or anti-LAG-3 agents that find use in embodiments described herein are not limited by their mechanism of action. Agents may be small molecules, peptide, polypeptides, proteins, nucleic acids (e.g., antisense, RNAi, etc.), antibodies, antibody fragments, etc.

In some embodiments, cancer treatment methods described herein comprise enhancing the activity or expression of a marker/receptor identified herein that negatively correlates with tumor antigen-specific $CD8^+$ T cell dysfunction.

Experiments conducted during development of embodiments herein identified receptors/markers that are differentially expressed in dysfunctional CD8+ TILs (See Table 2). Testing of targets of interest identified in that screen demonstrate that at least neuritin 1 (Nrn1), cytotoxic and regulatory t-cell molecule (CRTAM), and Semaphorin 7A (Sema7a) are regulators of anti-tumor immunity, with Nrn1 and CRTAM blockade correlating with increased tumor area, and Sema7a blockade correlating with decreased tumor area.

In some embodiments, cancer treatment methods described herein comprise administration (or co-administration with one or more additional therapies/therapeutics) of agents (e.g., antibodies, antibody fragments, antibody mimetic molecules (e.g., DARPins, affibodies, aptamers, nanobodies, etc.), etc.) that target one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, Nrn1, CRTAM, Sema7a, etc.). In some embodiments, an agent is administered to render cancer cells, tumor(s), and/or the tumor microenvironment accessible or susceptible to treatment with additional therapies/therapeutics (e.g., immunotherapeutics). Agents targeting one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, Nrn1, CRTAM, Sema7a, etc.) that find use in embodiments described herein are not limited by their mechanism of action. Agents may be small molecules, peptide, polypeptides, proteins, nucleic acids (e.g., antisense, RNAi, etc.), antibodies, antibody fragments, etc. In some embodiments, an antagonist of Nrn1 is administered. In some embodiments, an antagonist of CRTAM is administered. In some embodiments, an agonist of Sema7a is administered.

In some embodiments, antibodies, antibody fragments, antibody mimetic molecules (e.g., DARPins, affibodies, aptamers, nanobodies, etc.) targeting 4-1BB, LAG-3 and/or one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM, Sema7a, etc.), or fragments thereof, are provided. Such agents may be naked, deriving their effect by target binding (e.g., neutralizing the target), or may be conjugated to a functional moiety (e.g., drug, toxin, effector moiety, etc.).

In some embodiments, a subject is treated with (i) one or more agents (e.g., antibodies, antibody fragments, antibody mimetic molecules (e.g., DARPins, affibodies, aptamers, nanobodies, etc.), etc.) that target 4-1BB, LAG-3 and/or one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM, Sema7a, etc.), as well as (ii) one or more additional cancer therapies. Such therapies include chemotherapy, immunotherapy, radiation, surgery, etc. In some embodiments, agents targeting the receptors/markers described herein are co-administered with one or more additional agents for the treatment of cancer.

In some embodiments, exemplary anticancer agents suitable for use in compositions and methods described herein include, but are not limited to: 1) alkaloids, including

microtubule inhibitors (e.g., vincristine, vinblastine, and vindesine, etc.), microtubule stabilizers (e.g., paclitaxel (Taxol), and docetaxel, etc.), and chromatin function inhibitors, including topoisomerase inhibitors, such as epipodophyllotoxins (e.g., etoposide (VP-16), and teniposide (VM-26), etc.), and agents that target topoisomerase I (e.g., camptothecin and isirinotecan (CPT-11), etc.); 2) covalent DNA-binding agents (alkylating agents), including nitrogen mustards (e.g., mechlorethamine, chlorambucil, cyclophosphamide, ifosphamide, and busulfan (MYLERAN), etc.), nitrosoureas (e.g., carmustine, lomustine, and semustine, etc.), and other alkylating agents (e.g., dacarbazine, hydroxymethylmelamine, thiotepa, and mitomycin, etc.); 3) noncovalent DNA-binding agents (antitumor antibiotics), including nucleic acid inhibitors (e.g., dactinomycin (actinomycin D), etc.), anthracyclines (e.g., daunorubicin (daunomycin, and cerubidine), doxorubicin (adriamycin), and idarubicin (idamycin), etc.), anthracenediones (e.g., anthracycline analogues, such as mitoxantrone, etc.), bleomycins (BLENOXANE), etc., and plicamycin (mithramycin), etc.; 4) antimetabolites, including antifolates (e.g., methotrexate, FOLEX, and MEXATE, etc.), purine antimetabolites (e.g., 6-mercaptopurine (6-MP, PURINETHOL), 6-thioguanine (6-TG), azathioprine, acyclovir, ganciclovir, chlorodeoxyadenosine, 2-chlorodeoxyadenosine (CdA), and 2'-deoxycoformycin (pentostatin), etc.), pyrimidine antagonists (e.g., fluoropyrimidines (e.g., 5-fluorouracil (ADRUCIL), 5-fluorodeoxyuridine (FdUrd) (floxuridine)) etc.), and cytosine arabinosides (e.g., CYTOSAR (ara-C) and fludarabine, etc.); 5) enzymes, including L-asparaginase, and hydroxyurea, etc.; 6) hormones, including glucocorticoids, antiestrogens (e.g., tamoxifen, etc.), nonsteroidal antiandrogens (e.g., flutamide, etc.), and aromatase inhibitors (e.g., anastrozole (ARIMIDEX), etc.); 7) platinum compounds (e.g., cisplatin and carboplatin, etc.); 8) monoclonal antibodies (e.g., conjugated with anticancer drugs, toxins, and/or radionuclides, etc.; neutralizing antibodies; etc.); 9) biological response modifiers (e.g., interferons (e.g., IFN-.alpha., etc.) and interleukins (e.g., IL-2, etc.), etc.); 10) adoptive immunotherapy; 11) hematopoietic growth factors; 12) agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid, etc.); 13) gene therapy techniques; 14) antisense therapy techniques; 15) tumor vaccines; 16) therapies directed against tumor metastases (e.g., batimastat, etc.); 17) angiogenesis inhibitors; 18) proteosome inhibitors (e.g., VELCADE); 19) inhibitors of acetylation and/or methylation (e.g., HDAC inhibitors); 20) modulators of NF kappa B; 21) inhibitors of cell cycle regulation (e.g., CDK inhibitors); and 22) modulators of p53 protein function.

In some embodiments, agents targeting 4-1BB, LAG-3 and/or one or more receptors/markers of Table 2 (e.g. Nrn1, Sema7a, CRTAM, etc.) are administered to

overcome immune invasion of the cancer cells, tumor, tumor microenvironment, etc. In some embodiments, one or more additional cancer immunotherapies are employed (e.g., concurrently or serially) to make use of the immune-responsiveness of the treated cells/tumor. Suitable immunotherapies may include, but are not limited to: cell-based therapies (e.g., dendritic cell or T cell therapy, etc.), monoclonal antibody (mAb) therapy (e.g., naked mAbs, conjugated mAbs), cytokine therapy (e.g., interferons, interleukins, etc.), adjuvant treatment (e.g., polysaccharide-K), etc.

In some embodiments, agents targeting 4-1BB, LAG-3 and/or one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM, Sema7a, etc.) are co-administered with agents (e.g., small molecules, peptides, antibodies, antibody fragments, etc.) that target one or more cancer cell or tumor) markers or components. In some embodiments, such co-administration renders the cancer cells, tumor, and/or tumor microenvironment susceptible and/or accessible to the treatment with the additional agent.

In some embodiments, agents for use in the methods and compositions described herein target and/or binds a cancer or tumor cell marker or component, selected from the group including but not limited to, epidermal growth factor receptor (EGFR, EGFR1, ErbB-1, HER1). ErbB-2 (HER2/neu), ErbB-3/HER3, ErbB-4/HER4, EGFR ligand family; insulin-like growth factor receptor (IGFR) family, IGF-binding proteins (IGFBPs), IGFR ligand family (IGF-1R); platelet derived growth factor receptor (PDGFR) family, PDGFR ligand family; fibroblast growth factor receptor (FGFR) family, FGFR ligand family, vascular endothelial growth factor receptor (VEGFR) family, VEGF family; HGF receptor family: TRK receptor family; ephrin (EPH) receptor family: AXL receptor family; leukocyte tyrosine kinase (LTK) receptor family; TIE receptor family, angiopoietin 1, 2; receptor tyrosine kinase-like orphan receptor (ROR) receptor family; discoidin domain receptor (DDR) family; RET receptor family; KLG receptor family; RYK receptor family; MuSK receptor family; Transforming growth factor alpha (TGF-α), TGF-α receptor; Transforming growth factor-beta (TGF-β), TGF-β receptor; Interleukin β receptor alpha2 chain (IL13Ralpha2), Interleukin-6 (IL-6), 1L-6 receptor, interleukin-4, IL-4 receptor, Cytokine receptors, Class I (hematopoietin family) and Class II (interferon/1L-10 family) receptors, tumor necrosis factor (TNF) family, TNF-α, tumor necrosis factor (TNF) receptor superfamily (TNTRSF), death receptor family, TRAIL-receptor; cancer-testis (CT) antigens, lineage-specific antigens, differentiation antigens, alpha-actinin-4, ARTC1, breakpoint cluster region-Abelson (Bcr-abl) fusion products, B-

RAF, caspase-5 (CASP-5), caspase-8 (CASP-8), beta-catenin (CTNNB1), cell division cycle 27 (CDC27), cyclin-dependent kinase 4 (CDK4), CDKN2A, COA-1, dek-can fusion protein, EFTUD-2, Elongation factor 2 (ELF2), Ets variant gene 6/acute myeloid leukemia 1 gene ETS (ETC6-AML1) fusion protein, fibronectin (FN), GPNMB, low density lipid receptor/GDP-L fucose: beta-Dgalactose 2-alpha-Lfucosyltraosferase (LDLR/FUT) fusion protein, HLA-A2, MLA-A11, heat shock protein 70-2 mutated (HSP70-2M), KIAA0205, MART2, melanoma ubiquitous mutated 1, 2, 3 (MUM-1, 2, 3), prostatic acid phosphatase (PAP), neo-PAP, Myosin class 1, NFYC, OGT, OS-9, pml-RARalpha fusion protein, PRDX5, PTPRK, K-ras (KRAS2), N-ras (NRAS), HRAS, RBAF600, SIRT12, SNRPD1, SYT-SSX1 or -SSX2 fusion protein, Triosephosphate Isomerase, BAGE, BAGE-1, BAGE-2, 3, 4, 5, GAGE-1, 2, 3, 4, 5, 6, 7, 8, GnT-V (aberrant N-acetyl glucosaminyl transferase V, MGAT5), HERV-K MEL, KK-LC, KM-HN-1, LAGE, LAGE-1, CTL-recognized antigen on melanoma (CAMEL), MAGE-A1 (MAGE-1). MAGE-A2, MAGE-A3, MAGE-A4, MAGE-AS, MAGE-A6, MAGE-A8, MAGE-A9, MAGE-A10. MAGE-All, MAGE-A12, MAGE-3, MAGE-B1, MAGE-B2, MAGE-B5. MAGE-B6, MAGE-C1, MAGE-C2, mucin 1 (MUC1), MART-1/Melan-A (MLANA), gp100, gp100/Pme117 (S1LV), tyrosinase (TYR), TRP-1, HAGE, NA-88, NY-ESO-1, NY-ESO-1/LAGE-2, SAGE, Sp17. SSX-1, 2, 3, 4, TRP2-1NT2, carcino-embryonic antigen (CEA), Kallikrein 4, mammaglobin-A, OA1, prostate specific antigen (PSA), prostate specific membrane antigen, TRP-1/, 75. TRP-2 adipophilin, interferon inducible protein absent in melanorna 2 (AIM-2). BING-4, CPSF, cyclin D1, epithelial cell adhesion molecule (Ep-CAM), EpbA3, fibroblast growth factor-5 (FGF-5), glycoprotein 250 (gp250intestinal carboxyl esterase (iCE), alpha-feto protein (AFP), M-CSF, mdm-2, MUCI, p53 (TP53), PBF, PRAME, PSMA, RAGE-1, RNF43, RU2AS, SOX10, STEAP1, survivin (BIRCS), human telomerase reverse transcriptase (hTERT), telomerase, Wilms' tumor gene (WT1), SYCP1, BRDT, SPANX, XAGE, ADAM2, PAGE-5, LIP1, CTAGE-1, CSAGE, MMA1, CAGE, BORIS, HOM-TES-85, AF15q14, HCA66I, LDHC, MORC, SGY-1, SPO11, TPX1, NY-SAR-35, FTHLI7, NXF2 TDRD1, TEX 15, FATE, TPTE, immunoglobulin idiotypes, Bence-Jones protein, estrogen receptors (ER), androgen receptors (AR), CD40, CD30, CD20, CD19, CD33, CD4, CD25, CD3, cancer antigen 72-4 (CA 72-4), cancer antigen 15-3 (CA 15-3), cancer antigen 27-29 (CA 27-29), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), beta-human chorionic gonadotropin, 1-2 microglobulin, squamous cell carcinoma antigen, neuron-specific enolase, heat shock protein gp96. GM2, sargramostim, CTLA-4, 707 alanine proline (707-AP), adenocarcinoma antigen recognized by T cells 4 (ART-4), carcinoembryogenic antigen peptide-1 (CAP-1), calcium-

activated chloride channel-2 (CLCA2), cyclophilin B (Cyp-B), human signet ring tumor-2 (HST-2), etc.

Examples of antibodies which can be incorporated into compositions and methods disclosed herein include, but are not limited, to antibodies such as trastuzumab (anti-HER2/neu antibody); Pertuzumab (anti-HER2 mAb); cetuximab (chimeric monoclonal antibody to epidermal growth factor receptor EGFR); panitumumab (anti-EGFR antibody); nimotuzumab (anti-EGFR antibody); Zalutumumab (anti-EGFR mAb); Necitumumab (anti-EGFR mAb); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-210 (humanized anti-HER-2 bispecific antibody); MDX-447 (humanized anti-EGF receptor bispecific antibody); Rituximab (chimeric murine/human anti-CD20 mAb); Obinutuzumab (anti-CD20 mAb); Ofatumumab (anti-CD20 mAb); Tositumumab-1131 (anti-CD20 mAb); Ibritumomab tiuxetan (anti-CD20 mAb); Bevacizumab (anti-VEGF mAb); Ramucirumab (anti-VEGFR2 mAb); Ranibizumab (anti-VEGF mAb); Aflibercept (extracellular domains of VEGFR1 and VEGFR2 fused to IgG1 Fc); AMG386 (angiopoietin-1 and -2 binding peptide fused to IgG1 Fc); Dalotuzumab (anti-IGF-1R mAb); Gemtuzumab ozogamicin (anti-CD33 mAb); Alemtuzumab (anti-Campath-1/CD52 mAb); Brentuximab vedotin (anti-CD30 mAb): Catumaxomab (bispecific mAb that targets epithelial cell adhesion molecule and CD3); Naptumomab (anti-5T4 mAb); Girentuximab (anti-Carbonic anhydrase ix); or Farletuzumab (anti-folate receptor). Other examples include antibodies such as Panorex™ (17-1A) (murine monoclonal antibody); Panorex (@(17-1A)) (chimeric murine monoclonal antibody); BEC2 (ami-idiotypic mAb, mimics the GD epitope) (with BCG); Oncolym (Lym-1 monoclonal antibody); SMART M195 Ab, humanized 13′ 1 LYM-1 (Oncolym). Ovarex (B43.13, anti-idiotypic mouse mAb); 3622W94 mAb that binds to EGP40 (17-1A) pancarcinoma antigen on adenocarcinomas; Zenapax (SMART Anti-Tac (IL-2 receptor); SMART M195 Ab, humanized Ab, humanized); NovoMAb-G2 (pancarcinoma specific Ab); TNT (chimeric mAb to histone antigens); TNT (chimeric mAb to histone antigens); Gliomab-H (Monoclonals—Humanized Abs); GNI-250 Mab; EMD-72000 (chimeric-EGF antagonist); LymphoCide (humanized IL.L.2 antibody); and MDX-260 bispecific, targets GD-2, ANA Ab, SMART IDIO Ab, SMART ABL 364 Ab, or ImmuRAIT-CEA.

In some embodiments, an agent that finds use in embodiments herein specifically binds a component of a regulatory T cell, myeloid suppressor cell, or dendritic cell. In another aspect, the targeting moiety specifically binds one of the following molecules: CD4; CD25 (IL-2α receptor; IL-2αR); cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152); Interleukin-10 (IL-10); Transforming growth factor-beta receptor (TGF-βR); Transforming

growth factor-beta (TGF-β); Programmed Death-1 (PD-1); Programmed death-1 ligand (PD-L1 or PD-L2); Receptor activator of nuclear factor-κB (RANK); Receptor activator of nuclear factor-κB (RANK) ligand (RANKL); LAG-3; glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR; TNFRSF18); or Interleukin-4 receptor (IL-4R). In some embodiments, the agent is an agonist that increases the function of the targeted molecule. In other embodiments, the agent is an antagonist that inhibits the function of the targeted molecule.

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

In some embodiments, agents (e.g., immunotherapeutics) targeting 4-1BB, LAG-3 and/or one or more receptors/markers of Table 2 (e.g. PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM, Sema7a, etc.) are co-administered (e.g., serially or sequentially) with one or more adjuvants. Suitable adjuvants include, but are not limited to, one or more of: oil emulsions (e.g., Freund's adjuvant); saponin formulations; virosomes and viral-like particles; bacterial and microbial derivatives; immunostimulatory oligonucleotides; ADP-ribosylating toxins and detoxified derivatives; alum; BCG; mineral-containing compositions (e.g., mineral salts, such as aluminium salts and calcium salts, hydroxides, phosphates, sulfates, etc.); bioadhesives and/or mucoadhesives; microparticles; liposomes; polyoxyethylene ether and polyoxyethylene ester formulations; polyphosphazene; muramyl peptides; imidazoquinolone compounds; and surface active substances (e.g. lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol).

Adjuvants may also include immunomodulators such as cytokines, interleukins (e.g., IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, etc.), interferons (e.g., interferon-.gamma.), macrophage colony stimulating factor, and tumor necrosis factor. In addition to variant B7-DC polypeptides, other co-stimulatory molecules, including other polypeptides of the B7 family, may be administered. Proteinaceous adjuvants may be provided as the full-length polypeptide or an active fragment thereof, or in the form of DNA, such as plasmid DNA.

Pharmaceutical and immunotherapeutic compositions described herein may be delivered by any suitable route of administration (e.g., oral delivery, parenteral delivery, mucous membrane delivery, pulmonary delivery, intravenous delivery, etc.). Appropriate formulations for such delivery routes are understood in the field.

Non-limiting examples of cancers that may be treated with the compositions and methods described herein include, but are not limited to: melanoma (e.g., metastatic malignant melanoma), renal cancer (e.g. clear cell carcinoma), prostate cancer (e.g. hormone refractory prostate adenocarcinoma), pancreatic cancer (e.g., adenocarcinoma), breast cancer, colon cancer, lung cancer (e.g. non-small cell lung cancer), esophageal cancer, squamous cell carcinoma of the head and neck, liver cancer, ovarian cancer, cervical cancer, thyroid cancer, glioblastoma, glioma, leukemia, lymphoma, and other neoplastic malignancies. In some embodiments, the cancer is a solid tumor cancer.

Some embodiments described herein are particularly useful for the treatment of tumors that do not otherwise respond to immunotherapeutic approaches. In some embodiments, provided herein is the treatment of cancers that are non-responsive (or have a reduced response) to T cells or antigen presenting cells (e.g., dendritic cells (e.g., $CD103^+$DCs, etc.), etc.). In some embodiments, provided herein is the treatment of cancers that are non-responsive to treatments, despite T cell infiltration. In some embodiments, compositions and methods described herein find use in the treatment of cancers in which T cells are not appropriately primed against tumor-associated antigens. In some embodiments, compositions and methods described herein find use in the treatment of cancers comprising tumors or cells that are defective in recruitment of dendritic cells (e.g., $CD103^+$ DCs, etc.). In some embodiments, compositions and methods described herein find use in the treatment of cancers comprising tumors or cells that are defective in production of the chemokine CCL4.

In some embodiments, the therapeutic compositions and methods herein find use with those described in, for example WO 2016/141312; incorporated by reference in its entirety.

In some embodiments, methods are provided for testing sample (e.g., cell, tissue, population of cells, tumor, blood, urine, saliva, etc.) from a subject for one or more

biomarkers (e.g., biomarkers of dysfunctional tumor antigen-specific $CD8^+$ T cells). Such biomarkers may comprise nucleic acids, small molecules, proteins, peptides, etc., and may be detected using any suitable assay of technique. In some embodiments, provided herein are DNA-, RNA-, small molecule, and/or protein-based diagnostic methods that either directly or indirectly detect the biomarkers of the evasion of immune response or immunotherapy by cancer cells or tumors. The present invention also provides compositions, reagents, and kits for such diagnostic purposes.

In some embodiments, biomarkers are detected at the nucleic acid (e.g., RNA) level. For example, the presence or amount of biomarker nucleic acid (e.g.,mRNA) in a sample is determined (e.g., to determine the presence or level of biomarker expression). Biomarker nucleic acid (e.g., RNA, amplified cDNA, etc.) may be detected/quantified using a variety of nucleic acid techniques known to those of ordinary skill in the art, including but not limited to nucleic acid sequencing, nucleic acid hybridization, nucleic acid amplification (e.g., by PCR, RT-PCR, qPCR, etc.), micorarray, Southern and Northern blotting, sequencing, etc. Non-amplified or amplified nucleic acids can be detected by any conventional means. For example, in some embodiments, nucleic acids are detected by hybridization with a detectably labeled probe and measurement of the resulting hybrids. Nucleic acid detection reagents may be labeled (e.g., fluorescently) or unlabeled, and may by free in solution or immobilized (e.g., on a bead, well, surface, chip, etc.).

In some embodiments, biomarkers are detected at the protein level. For example, the presence or amount of biomarker protein in a sample is determined (e.g., to determine the presence or level of biomarker expression or localization). In some embodiments, reagents are provided for the detection and/or quantification of biomarker proteins. Suitable reagents include primary antibodies (e.g., that bind to the biomarkers), secondary antibodies (e.g., that bind primary antibodies), antibody fragments, aptamers, etc. Protein detection reagents may be labeled (e.g., fluorescently) or unlabeled, and may by free in solution or immobilized (e.g., on a bead, well, surface, chip, etc.).

In some embodiments, biomarker capture reagents are provided to localize, concentrate, aggregate, etc. a biomarker. For example, in some embodiments a biomarker capture reagent that interacts with the biomarker is linked to a solid support (e.g., a bead, surface, resin, column, and the like) that allows manipulation by the user on a macroscopic scale. Often, the solid support allows the use of a mechanical means to isolate and purify the biomarker from a heterogeneous solution. For example, when linked to a bead, separation is achieved by removing the bead from the heterogeneous solution, e.g., by physical movement.

In embodiments in which the bead is magnetic or paramagnetic, a magnetic field is used to achieve physical separation of the capture reagent (and thus the target) from the heterogeneous solution. Magnetic beads used to isolate targets are described in the art, e.g., as described in European Patent Application No. 87309308, incorporated herein in its entirety for all purposes.

Compositions for use in the diagnostic methods or testing steps described herein include, but are not limited to, probes, amplification oligonucleotides, and antibodies. Any of the detection and/or diagnostic reagents used in embodiments described herein may be provided alone or in combination with other compositions in the form of a kit. Kits may include any and all components necessary or sufficient for assays including, but not limited to, the detection reagents, buffers, control reagents (e.g., tissue samples, positive and negative control sample, etc.), solid supports, labels, written and/or pictorial instructions and product information, inhibitors, labeling and/or detection reagents, package environmental controls (e.g., ice, desiccants, etc.), and the like. In some embodiments, the kits provide a sub-set of the required components, wherein it is expected that the user will supply the remaining components. In some embodiments, the kits comprise two or more separate containers wherein each container houses a subset of the components to be delivered.

In some embodiments, a computer-based analysis program is used to translate the raw data generated by the detection assay (*e.g.*, the presence, absence, or amount of expression a biomarker) into data of predictive value for a clinician. In some embodiments, computer analysis combines various data into a single score or value that is predictive and/or diagnostic. The clinician can access the predictive data using any suitable means. Thus, in some preferred embodiments, the present invention provides the further benefit that the clinician, who is not likely to be trained in genetics or molecular biology, need not understand the raw data. The data is presented directly to the clinician in its most useful form. The clinician is then able to immediately utilize the information in order to optimize the care of the subject. Contemplated herein are any methods capable of receiving, processing, and transmitting the information to and from laboratories conducting the assays, information providers, medical personal, and subjects. For example, in some embodiments of the present invention, a sample (*e.g.*, a biopsy, cell, or blood sample) is obtained from a subject and submitted to a profiling service (*e.g.*, clinical lab at a medical facility, third-party testing service, genomic profiling business, etc. to generate raw data. Where the sample comprises a tissue or other biological sample, the subject may visit a medical center to have the sample obtained and sent to the profiling center, or subjects may collect the sample themselves and

directly send it to a profiling center. In some embodiments, a report is generated (e.g., by a clinician, by a testing center, by a computer or other automated analysis system, etc.). A report may contain test results, diagnoses, and/or treatment recommendations.

EXPERIMENTAL

Materials and Methods

Mice and tumor inoculation

Female C57BL/6 mice ranging from 6 to 8 weeks were purchased from Taconic Farms. CD45.1 and Rag2$^{-/-}$ mice on the C57BL/6 background were obtained from Taconic Farms and bred at the University of Chicago. 2C/Rag2$^{-/-}$ and P14/Rag2$^{-/-}$ mice have been previously described (Brown et al., 2006; incorporated by reference in its entirety). pLCK-CreERT2 x ROSA-YFP mice were generated and have been described (Evaristo et al., 2016; incorporated by reference in its entirety). B16.SIY.dsRed (Kline et al., 2012; incorporated by reference in its entirety), C1498.SIY.GFP (Zhang et al., 2009; incorporated by reference in its entirety), and MC57.SIY.GFP (Spiotto et al., 2002; incorporated by reference in its entirety) tumor cells were engineered to express either dsRed or GFP in frame with the H2-K^{b}-restricted model antigen SIYRYYGL. The 1969.SIY.GFP cell line was engineered by retroviral transduction of the 1969 cell line (Diamond et al., 2011; incorporated by reference in its entirety) using the pLEGFP plasmid expressing cDNA for SIYRYYGL (Spiotto et al., 2002; incorporated by reference in its entirety). For experiments, mice 6 to 9 weeks of age and received 2x10^{6} tumor cells subcutaneously on either the left flank or both the left and right flank. All mice were maintained according to the National Institute of Health Animal Care guidelines and studied under IACUC-approved protocols.

To generate the targeting construct for the Egr2^{EGFP} knock-in reporter mice, a 12.6kb mouse genomic DNA fragment including the *egr2* gene was excised with SacII and cloned into a pEasy-Flox vector adjacent to the thymidine kinase (TK) selection marker. A cassette containing IRES2-eGFP and a LoxP-flanked neomycin selection marker was inserted into an NheI site between the translation stop codon (TGA) and the polyadenylation signal of the *egr2* gene. ES cell clones from 129 mice were electroporated and selected for Neomycin resistance. ES cell clones were verified for homologous insertion in the endogenous locus by PCR and southern blot with 5' and 3' probes. Mice were backcrossed to C57BL/6 for over 8 generations.

TIL isolation

Tumors were harvested from mice at the indicated time points. Tumors were dissociated through a 50 μm filter and washed with PBS. TILs were further enriched by layering Ficoll-Hypaque beneath the cell suspension followed by centrifugation without breaks for 30 min at 400 x g. The buffy-layer was isolated and washed twice with PBS before staining. For isolating specific cell populations by FACS, tumors were pooled when indicated and the cell layer was re-purified by Ficoll-Hypaque centrifugation twice. For day 28 tumors, after Ficoll-Hypaque separation, T cells were further purified by negative bead selection according to manufacturer's instructions (MAGNISORT, eBiosciences). Cells were then washed with PBS, stained at 4°C for 15 minutes before resuspending in complete DMEM (cDMEM: 10% FBS, 100U/mL Penicillin-Streptomycin, 1% MEM Non-Essential Amino Acids, 50 μM β-ME, 0.01M MOPS), and were sorted into either RLT lysis buffer (QIAGEN) or cDMEM depending on the experimental assay. Cells sorted into RLT buffer were put directly on dry ice as soon as the sort was finished.

Flow cytometry and antibodies

Cell suspensions were washed twice in PBS before staining an FACS buffer (10% FBS, 2mM EDTA, 0.001% NaN_3). Cells were stained for 30 min on ice and fixed in 1% PFA. Antibodies against the following molecules were used: CD3 (17A2, AX700), 2B4 (2B4, FITC), CD127 (A7R34, PE), OX-40 (OX-86, PE), 4-1BB (17B5, Biotin, APC), CD160 (7H1, PE-Cy7), LAG-3 (C9B7W, PerCPeFluor710), PD-1 (RMP1-30, PE-Cy7), NRP1 (3E12, BV421), GITR (DTA-1, FITC), ICOS (7E.17G9, BV421), KLRG-1 (2F1, eF450, BV605), TIGIT (1G9, APC), TIM-3 (RMT3-23, PE), CD4 (RM4-5, BV605), CD45.1 (A20, FITC), CD45.2 (104, PE), CD8α (53-6.7, BV711). Fixable Viability Dye 506 (eBioscience) was used for live/dead discrimination. Staining of SIY-specific T cells was performed utilizing the SIYRYYGL-Pentamer (PE) (Proimmune); a SIINFEKL-pentamer (PE) was used as a non-specific control. All flow cytometric analysis was conducted on an LSRFortessa (BD) and analyzed using FlowJo software (Tree Star).

Quantitative real-time PCR

Total RNA was extracted from sorted cell populations using the RNEasy Micro Kit (QIAGEN) following the manufacturer's protocol. cDNA was synthesized using the High

Capacity cDNA Reverse Transcription kit (Applied Biosystems) according to manufacturer's instructions. Transcript levels were determined using primer-probe sets (**Tables 1a and 1b**) developed through the online ProbeFinder Software and the Universal Probe Library (Roche) with the exception of IL-2 (Mm00434256_m1) and 18S (Hs99999901_s1). To minimize batch effect, when possible, all samples probed for a gene were run on the same 96-well qRT-PCR plate. All primer-probe sets either contained a primer spanning an exon-exon boundary or primers spanning an intron. Expression levels of transcripts were normalized to 18S expression.

Table 1a. Primer Sequences

#	Wilson	IMGT	Sequence	SEQ ID NO:
0	Cβ1.1	TRBC1	CTCAAACAAGGAGACCTTGGGTGG	1
1	Vβ1	TRVB5	CAGACAGCTCCAAGCTACTTTTAC	2
2	Vβ2	TRVB1	ATGAGCCAGGGCAGAACCTTGTAC	3
3	Vβ3	TRVB26	GAAATTCAGTCCTCTGAGGCAGGA	4
4	Vβ4	TRVB2	CTAAAGCCTGATGACTCGGCCACA	5
5	Vβ5.1	TRVB12-2	CTTTGGAGCTAGAGGACTCTGCCG	6
6	Vβ5.2	TRVB12-1	CCTTGGAACTGGAGGACTCTGCTA	7
7	Vβ6	TRVB19	GCCCAGAAGAACGAGATGGCCGTT	8
8	Vβ7	TRVB29	GGATTCTGCTAAAACAAACCAGACATCTGT	9
9	Vβ8.1	TRVB13-3	GCTTCCCTTTCTCAGACAGCTGTA	10
10	Vβ8.2	TRVB13-2	GCTACCCCCTCTCAGACATCAGTG	11
11	Vβ8.3	TRVB13-3	GGCTTCTCCCTCTCAGACATCTT	12
12	Vβ9	TRVB17	CTCTCTCTACATTGGCTCTGCAGG	13
13	Vβ10	TRVB4	CTTCGAATCAAGTCTGTAGAGCCG	14
14	Vβ11	TRVB16	TGAAGATCCAGAGCAGCGGGCCCC	15
15	Vβ12	TRVB15	CCACTCTGAAGATTCAACCTACAGAACCC	16
16	Vβ13	TRVB14	CAAGATCCAGTCTGCAAAGCAGGG	17
17	Vβ14	TRVB31	GCACGGAGAAGCTGCTTCTCAGCC	18
18	Vβ15	TRVB20	GCATATCTTGAAGACAGAGGC	19
19	Vβ16	TRVB3	CTCTGAAAATCCAACCCACAGCACTGG	20
20	Vβ17	TRVB24	TCTGAAGAAGACGACTCAGCACTG	21
21	Vβ18	TRVB30	GCAAGGCCTGGAGACAGCAGTATC	22

Table 1b. Primer/Probe

Gene	SEQ ID NO:	Primer1	Primer2	SEQ ID NO:	Roche Probe #
Lag3	23	tgctttgggaagctccagt	gctgcagggaagatggac	42	79
Tnfrsf9	24	ccggtcttaagcacagacct	gaacggtactggcgtctgtc	43	108
Egr2	25	ctacccggtggaagacctc	aatgttgatcatgccatctcc	44	60
Sema7a	26	tcaatcggctgcaagatgt	cgcagacagctgagtagttcc	45	15
Crtam	27	agatccaacaacgaggagaca	tcatgcaacgcttagactgg	46	71
Ccl1	28	tcaccatgaaacccactgc	agcagcagctattggagacc	47	71
Ngn	29	caccctagcctaacctcaacc	tgaaaacctcctcccctctt	48	45

Arl3	30	ctggcagatccagtcctgtt	acccagttcatgccatcct	49	100
Exph5	31	atgagggaggagagcggtat	cagcttgttgtccaaatcgtc	50	67
Fhl2	32	agaaaaccatcatgccaggt	acaggtgaagcaggtctcgt	51	74
Nrn1	33	atcctcgcggtgcaaata	gcccttaaagactgcatcaca	52	108
Ptgfrn	34	ccggggagatctcatcaaa	tcgaaggccatgtcatctg	53	12
Rankl	35	tgaagacacactacctgactcctg	cccacaatgtgttgcagttc	54	88
Hif1a	36	gctgctcactgtgaaggaagt	tggggaatgcattttaccat	55	2
Egr3	37	caatctgtaccccgaggaga	ccgatgtccatcacattctct	56	74
Tnfa	38	ctgtagcccacgtcgtagc	ttgagatccatgccgttg	57	25
Gzmb	39	gctgctcactgtgaaggaagt	tggggaatgcattttaccat	58	2
Ccl1	40	tcaccatgaaacccactgc	agcagcagctattggagacc	59	71
Ccl22	41	tcttgctgtggcaattcaga	gcagagggtgacggatgtag	60	74

In vivo proliferation assay

In vivo proliferation was measured by a BrdU pulse 24 hours prior to flow cytometric analysis. Each mouse received 0.8 mg BrdU injected i.p. (intraperitoneal) on day 12 after tumor inoculation. TILs were isolated and surface stain was performed as described above. Following surface staining, cells were fixed and permeabilized using the Foxp3 staining kit (BD), according to manufacturer's protocol, and incubated with 100 µl PBS/DNase solution (300 µg/ml) for 30 minutes at 37 °C. Cells were washed and incubated for 30 minutes at room temperature with anti-BrdU (FITC, Bu20a) and then washed with and resuspended in PBS.

In vitro stimulation assays

Tissue culture-treated 96-well round bottom plates were coated with anti-CD3ε (1 µg/ml; 2C11) in DPBS overnight at 4°C or for 2 hours at 37°C. Cells were sorted into cold cDMEM media and put on ice as soon as the sort was finished. Cells were then pelleted, resuspended in 50 µl cDMEM and incubated with soluble anti-CD28 (2 µg/ml; PV-1) for 10-12 hours for a final volume of 100 µl. After stimulation supernatants were removed for ELISA or bead-based immunoassay (LegendPlex), and cells were washed once with DPBS and resuspended in 15 µl of RNAlater Stabilization Solution (QIAGEN) or 300 µl of RLT buffer. Cells were stored at -80°C until RNA isolation was performed.

Protein quantification

Measurement of protein concentration was determined either by a standard ELISA or bead-based immunoassay (LEGENDplex, BioLegend). ELISAs were performed according to

manufacturer's protocol (Ready-SET-Go ELISA; eBioscience) on supernatants from in vitro stimulations. Absorbance values were obtained at 450 nm using an Emax microplate reader (Molecular Devices) and IL-2 concentration was determined by standard curve. Protein concentration values were normalized to the number of sorted cells plated. LEGENDplex assays were performed according to manufacturer's protocols. IL-2 concentration (Figure 4B) was confirmed by both methods in separate experiments with no significant difference in IL-2 concentration between the two methods.

Spectratype analysis and sequencing

Mice were injected with $2x10^6$ B16.SIY.dsRed tumor cells. 14 days later, tumors were harvested and specific $CD8^+$ TIL subpopulations were sorted into RLT buffer (QIAGEN) and immediately frozen. cDNA was synthesized from sorted cell populations and CDR3 regions were amplified by PCR with 21 different Vβ-5' primers paired with a FAM-Cβ1.1 primer (Table 1). Three Vβ PCR reactions did not reach significant amplification for analysis and were removed from the analysis. For sequencing, Cβ-Vβ PCR products were purified using the QIAquick PCR purification kit (QIAGEN) and sequenced at the University of Chicago Genomics Core Facility. Cβ-Vβ PCR products were analyzed by capillary electrophoresis at the University of Chicago Genomics core and CDR3 peaks were aligned using the Liz500 ladder. Spectratype graphs were displayed using the GeneiousR9 software (Kearse et al., 2012). To generate the frequency profile for each Vβ spectratype, the area under each peak was measured using peak studio (fodorlab.uncc.edu/software/peakstudio). The Hamming Distance (Currier and Robinson, 2001; incorporated by reference in its entirety) was calculated between each Vβ spectratype from each $CD8^+$ spleen and TIL population within a given mouse. To determine significance between the HD from each comparison the HDs for each Vβ from mice were averaged and a One-Way ANOVA with Dunn's correction for multiple comparisons was performed.

TCR transgenic T cell transfer experiments

Cell suspensions were generated from spleens and lymph nodes from congenic 2C/$Rag2^{-/-}$/CD45.1/2 and/or P14/$Rag2^{-/-}$/CD45.2 mice and T cells were purified by $CD8^+$ negative selection (Miltenyi Biotechnologies) over magnetic columns according to the manufacturer's protocol. TCR Transgenic (Tg) T cells were washed with PBS, resuspended

at a concentration of $10x10^6$/ml and $1x10^6$ TCR Tg cells were adoptively transferred into CD45.1 tumor bearing mice by tail vein transfer in a volume of 0.1 mL. After indicated times, 2C T cells and corresponding host $CD8^+$ T cells were sorted and stimulated as described above.

In vitro cytotoxicity assay

Per individual experiment, 10 C57BL/6 mice were injected s.c. (subcutaneous) with 2 x 10^6 B16.SIY cells on both left and right flanks. On day 14, all 20 tumors were pooled and dissociated using the Tumor Dissociation Kit (Miltenyi Biotec) following the manufacturer's protocol. Tumor cell suspensions were washed 3-5 times with PBS and TILs were enriched for by Ficoll-Hypaque gradient centrifugation. TILs were stained, sorted and put directly on ice. TILs were titrated and added directly to a 96-well plate containing 50,000 P815 mastocytoma cells and 1 μg/mL anti-CD3. For a positive control, OT-I cells were isolated from OT-I/$Rag2^{-/-}$ mice and stimulated with plate-bound anti-CD3 (0.25 μg/mL), anti-CD28 (2 μg/mL) and 100 U/mL IL-2 for 2-3 days. For a negative control, P815 cells were cultured alone or cultured with naïve $CD8^+$ T cells isolated from lymph nodes. After 12 hours of incubation, cells were stained for Thy1, CD45, CD8α, Fixable Viability Dye 450 (eBioscience) and/or propidium Iodide.

Gene expression analysis

Total RNA for the $CD8^+$ TIL subpopulations was isolated following the manufacturer's protocol (RNEasy Micro Kit: QIAGEN) from sorted cells pooled from 10 mice. Samples were analyzed by the University of Chicago Genomics Facility using Illumina MouseRef8 microarray chips. Two experimental replicates were performed, and the results were log_2 transformed and averaged. Probe sets that revealed a 1.5-fold difference abs(log_2(ratio)> 1.5)) relative to $CD8^+$4-1BB$^-$LAG-3$^-$PD-1$^-$ cells were identified and used for subsequent analysis. The microarray data are available in the Gene Expression Omnibus database (ncbi.nlm.nih.gov/gds) under accession number GSE79919. For cross-study comparisons, log2-fold change values were extracted using the GEO2R online software from the hypofunctional $CD8^+$ TIL data set, GSE79858 ((GSM2107353, GSM2107353 and GSM2107355) versus (GSM2107350, GSM2107351, GSM210732)) and the $CD8^+$ T cell exhausted data set, GSE41870 ((GSM1026819, GSM1026820, GSM1026821) versus (GSM1026786, GSM1026787, GSM1026788, GSM1026789)). Upregulated genes showing

a 2-fold difference were used for analysis. Multiple genes names with from the GEO2R extracted data were identified and matched to gene names from the Illumina data set. The rank-rank hypergeometric overlap (RRHO) analysis (Plaisier et al., 2010; incorporated by reference in its entirety) was conducted at systems.crump.ucla.edu/rankrank/index.php and the associated Bioconductor package "RRHO" (Rosenblatt and Stein, 2014; incorporated by reference in its entirety).

Gene Ontology enrichment analysis

In a pair-wise fashion, shared upregulated genes were used as the input for the ClueGO software with the Cytoscape application (Shannon et al., 2003; incorporated by reference in its entirety). Both the Biological Process and Immune System Process Gene Ontology Annotations were used for analysis. Only pathways with a Bonferroni step down correction p-value > 0.01 were considered when generating pathway nodes. Non-redundant pathways with the greatest number of genes found within each node were used as examples in Figure 6A.

Antibody and FTY720 treatments

Mice were treated i.p. with 100 μg/mouse of anti-4-1BB (Bio-X-Cell; LOB12.3) antibody and/or 100 μg/mouse anti-LAG-3 (Bio-X-Cell; C9B7W). For tumor outgrowth experiments, mice were treated on day 7, 10, 13 and 16 after tumor inoculation. For *ex vivo* functional experiments mice were treated on day 7, 10 and 13 and cells were sorted on day 14. For experiments blocking lymph node egress, 25 μg of FTY720 was given by gavage one day prior to first antibody treatment (day 6) and continued every day until endpoint on day 14.

Results

4-1BB and LAG-3 identify a major population of $CD8^+$ TILs

To determine whether 4-1BB and LAG-3 could identify dysfunctional $CD8^+$ TILs, the expression pattern of LAG-3 and 4-1BB was examined using the well-characterized B16.SIY model of melanoma. On day 7 following tumor inoculation, the 4-1BB^+LAG-3^+ population comprised 15.8% of all $CD8^+$ TILs. The frequency of this population significantly increased to 44% by day 21. The frequency of 4-1BB^-LAG-3^+ (4^-L^+) population also increased 1.9-fold from day 7 to day 14 to comprise 25% of the $CD8^+$ TIL compartment. In contrast, the

frequency of the 4-1BB$^-$LAG-3$^-$ (4$^-$L$^-$) population decreased by 2.7-fold by day 21. There was no significant increase in the proportion or number of 4-1BB$^+$LAG-3$^-$ CD8$^+$ TILs within the time frame of the experiment (Figure 1A and B). Similar patterns were seen when analyzing absolute numbers of cell subsets (Figure 1C and D). Acquisition of these phenotypes was specific for the tumor microenvironment, as they were not observed in the spleen or tumor-draining lymph node (TdLN) (Figure 1A). These data indicate that the tumor microenvironment preferentially supports the induced co-expression of LAG-3 and 4-1BB.

The selective increase in cell numbers and proportional shift towards the 4-1BB$^-$LAG-3$^+$ and 4-1BB$^+$LAG-3$^+$ populations during tumor progression indicated that expansion of these populations was occurring within the tumor microenvironment. CD8$^+$ TILs were stained for Ki67 at day 14 after tumor inoculation and analyzed by flow cytometry. 81% of 4-1BB$^-$LAG-3$^+$ cells and 85% of 4-1BB$^+$LAG-3$^+$ cells were Ki67$^+$ compared to only 32% of the 4-1BB$^-$LAG-3$^-$ TILs (Figure 1E). Mice were pulsed with BrdU on day 12, and 24 hours later the CD8$^+$ TIL subpopulations were analyzed for BrdU incorporation. Indeed, the 4-1BB$^-$LAG-3$^+$ and 4-1BB$^+$LAG-3$^+$ populations incorporated more BrdU compared to the 4-1BB$^-$LAG-3$^-$ population (Figure 1F). These data indicate that once CD8$^+$ T cells arrive at the tumor site, a fraction of TILs expands within the tumor, and that these expanding TILs are identified by increased expression of 4-1BB and LAG-3.

To determine if upregulation of LAG-3 and 4-1BB was simply a product of the B16.SIY tumor model or if it is a more general feature of CD8$^+$ T cells within tumors, T cells from three additional progressively growing tumor models, C1498.SIY, MC38.SIY, EL4.SIY and B16F10 parental were analyzed. TILs were analyzed for expression of 4-1BB and LAG-3 at day 14. A pattern of expression was found that is similar to that seen in CD8$^+$ TILs isolated from B16.SIY tumors (Figure 1G and I). The results from the B16F10 parental tumor confirm that presence of SIY is not required to see co-expression of 4-1BB and LAG-3. In order to determine whether the 4-1BB$^+$LAG-3$^+$ TIL subset was generated only in progressing tumors or also in tumors that were rejected, T cell phenotypes in the 1969.SIY and MC57.SIY fibrosarcoma tumor models were analyzed, which are more immunogenic and undergo spontaneous rejection. Distinctly fewer 4-1BB$^+$LAG-3$^+$ cells were found among the CD8$^+$ TIL compartment in the 1969.SIY and MC57.SIY tumors (Figure H and I). Over time, co-expression of 4-1BB and LAG-3 was maintained in B16.SIY tumors but not MC57.SIY tumors (Figure 1J). These data indicate that the acquisition of the LAG-3$^+$4-1BB$^+$ TIL phenotype preferentially occurs within the tumor microenvironment and only upon conditions of tumor progression rather than regression.

CD8$^+$4-1BB$^+$LAG-3$^+$ TILs express Egr2 and multiple Egr2 gene targets

Experiments conducted during development of embodiments herein to determine whether Egr2 expression itself was also characteristic of T cells within the CD8$^+$ TIL compartment; an Egr2-IRES-GFP (Egr2^{GFP}) knock-in reporter mouse was utilized. Approximately 14% of all CD8$^+$ TILs were GFP$^+$ on both day 7 and day 14 (Figure 2A). To confirm that Egr2 is faithfully reported, CD8$^+$ TILs expressing high and low levels of EGFP were sorted and screened for Egr2 and several Egr2 targets by qRT-PCR. The Egr2-GFP^{hi} population expressed greater levels of Egr2 and many Egr2-target genes previously defined using in vitro anergy models. These include *Tnfrsf9*, *Lag3*, *Ngn*, *Sema7a*, *Crtam*, *Ccl1* and *Nrn1* (Figure 2B). Expression of 4-1BB and LAG-3 in the Egr2-GFP^{hi} CD8$^+$ TILs was confirmed by flow cytometry. The majority of Egr2-GFP^{hi} cells expressed LAG-3 and/or 4-1BB. The Egr2GFP^{lo} cells also showed expression of 4-1BB and LAG-3 on a subpopulation at day 14 (Figure 2C). This result indicates either that CD8$^+$ TILs expressing Egr2 encompass only a subset of the TILs expressing LAG-3 and/or 4-1BB, or that Egr2 is transiently expressed and is subsequently downregulated after the induction of LAG-3 and 4-1BB.

Using Egr2 target genes from in vitro anergic CD4$^+$ T cell clones (Zheng et al., 2013; incorporated by reference in its entirety), the Egr2-driven transcriptional program was examined in sorted 4-1BB$^-$LAG-3$^-$ and 4-1BB$^+$LAG-3$^+$ cells by qRT-PCR. Of the 43 Egr2 target genes examined, 10 showed detectably increased expression in 4-1BB$^+$LAG-3$^+$ population, while expression of a similar subset of genes was increased in the 4-1BB$^-$LAG-3$^+$ population (Figure 2D). Collectively, these data demonstrate that Egr2 is expressed in a subpopulation of CD8$^+$ TILs expressing LAG-3 and/or 4-1BB, and that a subset of known Egr2 targets was detected in these larger T cell populations as a whole.

It was next examined whether Egr2 was required for expression of LAG-3 and 4-1BB among CD8$^+$ TIL *in vivo*. To this end Egr2$^{flox/flox}$ X pLCK-CreERT2 x ROSA-YFP mice were utilized, in which oral tamoxifen administration results in a fraction of the CD8$^+$ T cells deleting Egr2 and expressing YFP (Figure 2E). This allowed comparison of both Egr2-sufficient (YFP$^-$) and Egr2-deficient (YFP$^+$) CD8$^+$ within the same tumor. To determine that Egr2 was in fact deleted from the YFP$^+$ fraction, both YFP$^+$ and YFP$^-$ CD8$^+$ TILs were sorted and *Egr2* transcripts were measured directly *ex vivo* and upon *ex vivo* stimulation. The YFP$^+$ CD8$^+$ TILs expressed substantially less *Egr2* transcripts compared to the YFP$^-$ counterparts (Figure 2E). To determine if Egr2 is required for 4-1BB and LAG-3 expression, CD8$^+$ TILs were analyzed at day 7 and 14 after tumor inoculation and compared the YFP$^+$ and YFP$^-$ populations to mice not treated with tamoxifen. At day 7, the YFP$^+$ fraction expressed less 4-

1BB and LAG-3 compared to the YFP^- population and the WT $CD8^+$ TILs. However, expression of 4-1BB and LAG-3 was not significantly different at day 14 (Figure 2F). This indicates that other transcriptional regulators compensate and contribute to the expression of LAG-3 and 4-1BB, especially at later time points.

Egr3 has been shown to have overlapping function with Egr2 (Safford et al., 2005; incorporated by reference in its entirety) and HIF1α can contribute to 4-1BB expression (Palazón et al., 2012). To investigate whether these transcription factors may compensate for 4-1BB and/or LAG-3 expression we sorted $Egr2GFP^{hi}$ and $Egr2GFP^{lo}$ $CD8^+$ TILs expressing 4-1BB and LAG-3 on day 7 and analyzed expression of *Egr3* and *HIF1α* by qRT-PCR. *Egr3* and *HIF1α* were indeed expressed in both the $Egr2GFP^{hi}$ and $Egr2GFP^{lo}$ populations. It was confirmed differential expression of Egr2 and CCL1 to between the $Egr2GFP^{hi}$ and $Egr2GFP^{lo}$ populations to assure sort purity (Figure 2G). Together, these data indicate that Egr2 contributes to upregulation of 4-1BB and LAG-3 expression at early time points, but that other transcriptional regulators compensate and drive expression of LAG-3 and 4-1BB as the T cell-tumor interaction progresses.

$CD8^+$4-1BB$^+$LAG-3$^+$ TILs are oligoclonal and enriched for tumor antigen specificity

Not all T cells in the tumor microenvironment are specific for tumor-associated antigens, as memory T cells specific for irrelevant antigens are often found among TIL, and non-specific T cell trafficking has been documented *in vivo* (Harlin et al., 2006; incorporated by reference in its entirety). Experiments conducted during development of embodiments herein to determine whether 4-1BB$^+$LAG-3$^+$ $CD8^+$ TILs are tumor-antigen specific. LAG-3, 4-1BB and Egr2 are upregulated after TCR stimulation and experiments indicate that this population expands within the tumor microenvironment *in situ*. Three complementary techniques were employed. First, the $CD8^+$ TILs were isolated based on LAG-3 and 4-1BB expression by cell sorting and performed TCRβ spectratype analysis. Compared to the 4-1BB$^-$LAG-3$^-$ TILs and $CD8^+$ splenocytes, the 4-1BB$^+$LAG-3$^+$ TILs had a non-Gaussian distribution and shared one or two dominant peaks (Figure 3A). Analysis of several Vβs displaying one dominant peak revealed that Vβ7 contained a single CDR3β sequence shared between the 4-1BB$^-$LAG-3$^+$ and 4-1BB$^+$LAG-3$^+$ populations, indicating a clonal relationship (Figure 3A). To measure the oligoclonality of the CDR3β repertoires the Hamming Distance (HD) was calculated for each Vβ between the $CD8^+$ TIL subpopulations and the splenic $CD8^+$ population within three separate mice (Figure 8). By transforming each spectratype into area under the curve frequency profiles the Hamming Distance computes the changes in

frequency and reports a value of comparison between 0 and 1, with 0 indicating a completely identical frequency profile and 1 signifying a completely discordant profile. As a control, the HD of the splenic $CD8^+$ populations between different mice was calculated (Figure 3B, black bar). Since the splenic $CD8^+$ spectratypes are largely Gaussian this value represents the HD between two similar distributions. Analysis of the HD between the $CD8^+$ TIL subpopulations revealed that the 4-$1BB^+$LAG-3^+ and 4-$1BB^-$LAG-3^+ but not the 4-$1BB^-$LAG-3^- CDR3β distributions are significantly different (less Gaussian) compared to the splenic $CD8^+$ population (Figure 3B). These data indicate that the 4-$1BB^+$LAG-3^+ and 4-$1BB^-$LAG-3^+ populations are oligoclonal expanded subsets of TILs, indicating antigen specificity in these subpopulations.

As a second approach, the B16.SIY melanoma and MC38.SIY adenocarcinoma models were utilized. $CD8^+$ T cells specific for the H-$2K^b$-restricted SIY epitope (SIYRYYGL) were monitored. SIYRYYGL/K^b pentamer$^+$ (H-$2K^b$/SIY) cells were found in expanded numbers within B16.SIY and MC38.SIY tumors at day 14 after tumor inoculation (Figure 3C). Nearly 47% of the H-$2K^b$/SIY^+ cells expressed both 4-1BB and LAG-3, in contrast to 32% of the H-$2K^b$/SIY^- population (Figure 3C and E). This enrichment of antigen-specific $CD8^+$ TILs in the 4-$1BB^+$LAG-3^+ populations indicates that these markers identify tumor antigen-specific TILs. The H-$2K^b$/SIY^- cells also contained significant numbers of 4-$1BB^+$LAG-3^+ cells, which is consistent with the notion that tumor antigens other than SIY are also recognized by subsets of $CD8^+$ TILs *in vivo* (Figure 3C). H-$2K^b$/SIY^+ cells in the spleen or TdLN did not co-express 4-1BB and LAG-3, indicating that this phenotype is acquired within the tumor microenvironment.

These features were also analyzed in the context of tumor-antigen specific $CD8^+$ TILs in two spontaneously rejected tumor models. To this end, H-$2K^b$/SIY-specific $CD8^+$ TILs cells were evaluated from MC57.SIY and 1969.SIY tumors. At day 14 after tumor inoculation, approximately 5% of the H-$2K^b$/SIY-specific $CD8^+$ TILs were found in the 4-$1BB^+$LAG-3^+ fraction. As with the B16.SIY tumors, no H-$2K^b$/SIY-specific CD8 T cells co-expressed 4-1BB and LAG-3 in the TdLN or spleen (not shown) (Figure 3D). Unlike the B16.SIY and MC38.SIY tumors, no significant enrichment of 4-$1BB^+$LAG-3^+ H-$2K^b$/SIY-specific $CD8^+$ TILs was observed (Figure 3D and E). These data indicate that tumor antigen specificity per se does not determine dysfunctionality, and that this is a feature unique to the microenvironment of progressing tumors.

As a third measure to determine if tumor-antigen specific $CD8^+$ T cells acquire the 4-$1BB^+$LAG-3^+ phenotype, congenically marked 2C and P14 transgenic (Tg) T cells, isolated

from 2C/Rag2$^{-/-}$ and P14/Rag2$^{-/-}$ mice, were transferred into tumor-bearing hosts. The 2C TCR is specific for the SIY model antigen expressed by B16.SIY tumor cells, while P14 is an irrelevant TCR specific for the LCMV-derived gp_{33-41} epitope; both TCRs are H-2K^b-restricted. 2C and P14 Tg CD8$^+$ T cells were transferred via tail vein 7 days after tumor inoculation. Seven days after transfer, tumors and TdLNs were extracted and the phenotypic profile of the transferred populations was analyzed. This system allowed for the analysis of two T cell populations with defined antigen specificities within the same tumor microenvironment, as well as the polyclonal host CD8$^+$ T cells. The 2C T cells were more efficiently recruited and expanded within the tumor microenvironment compared to the P14 T cells and encompassed a large fraction of the total CD8$^+$ TIL population (Figure 3F). Of the 2C T cells, nearly all expressed LAG-3 and or 4-1BB while this was true for only a small percentage of the P14 cells (Figure 3G and H). Consistent with the SIY-K^b pentamer analysis, the co-expression of LAG-3 and 4-1BB on 2C T cells was not observed in the TdLN. Together, these results demonstrate that the 4-1BB$^+$LAG-3$^+$ phenotype is a property of tumor antigen-specific TIL under conditions of tumor progression.

CD8$^+$ TILs expressing LAG-3 and 4-1BB exhibit defective IL-2 production yet produce IFN-γ and Treg-recruiting chemokines

Based on the characteristics of the *in vitro* T cell anergy model that led to the identification of Egr2 as an important regulator, experiments conducted during development of embodiments herein to determine whether the tumor-antigen specific 4-1BB$^+$LAG-3$^+$ CD8$^+$ TIL population is dysfunctional in their capacity to produce IL-2. To this end each subpopulation was sorted and stimulated with anti-CD3 and anti-CD28 mAb and analyzed IL-2 production by qRT-PCR and ELISA. Since nearly all CD8$^+$ TILs displayed an activated phenotype, CD8$^+$CD44$^+$ splenocytes wer used as a positive control. Indeed, the 4-1BB$^+$LAG-3$^+$ cells showed a 100-fold reduction in *Il-2* mRNA and as much as a 40-fold reduction in IL-2 protein levels compared to the 4-1BB$^-$LAG-3$^-$ population (Figure 4A and 4B). As a second approach, Egr2^{hi} TIL (which are also largely 4-1BB$^+$LAG-3$^+$) was examined by utilizing the Egr2-GFP reporter mice. Indeed, *ex vivo* stimulated Egr2-GFP^{hi} CD8$^+$ TILs also exhibited reduced *Il-2* transcript compared to Egr2-GFP^{lo} cells (Figure 4C). As a final approach, congenically marked 2C T cells were adoptively transferred intravenously into tumor-bearing hosts and recovered the 2C T cells 7 days later from the tumor and TdLN. 2C T cells isolated from tumors exhibited a reduced capacity to produce *Il-2* transcripts, at a level equivalent to 4-1BB$^+$LAG-3$^+$ TILs, compared to 2C CD44$^+$ T cells isolated from the TdLN (Figure 4D). In

chronic infection models, expression of PD-1 has been suggested to identify intrinsically dysfunctional or "exhausted" $CD8^+$ T cells. To determine if PD-1 alone might be sufficient to identify cells that lack the capacity to produce IL-2, $CD8^+$ TILs that lacked expression of LAG-3 and 4-1BB were isolated and tested for the ability of the PD-1^+ fraction to produce IL-2. Approximately ~10% of $CD8^+$ TILs were 4-$1BB^-$LAG-3^-PD-1^+ on day 14 and 21 (Figure 4E and F). Upon ex vivo stimulation, this population retained the capacity to produce *Il-2* mRNA at a level comparable to the 4-$1BB^-$LAG-3^- cells (Figure 4G). These results indicate that PD-1 expression alone is not sufficient to identify dysfunctional TIL in the tumor microenvironment.

To further examine functional alterations during tumor progression protein levels of IL-2, IFN-γ and TNF-α wer tested after TCR stimulation. As the loss of the ability of $CD8^+$ TILs to produce cytokines is suggested to be a temporal process reported initiated following entry into the tumor microenvironment (Waugh et al., 2016; Schietinger et al., 2016; incorporated by reference in their entireties) or progressively after 30 days in the chronic LCMV model (Wherry et al., 2007; incorporated by reference in its entirety), cytokine production was tested on day 7, 14, 21 and 28. The 4-$1BB^+$LAG-3^+ population lost the capacity to produce IL-2 as early as day 7 while the 4-$1BB^-$LAG-3^+ population lost IL-2 production between day 7 and day 14 (Figure 5A). The 4-$1BB^-$LAG-3^- population did not lose the ability to produce IL-2 at any time point tested (Figure 5A), supporting the notion that this population is not tumor antigen specific and that differentiation into the dysfunctional state is an antigen-dependent process (Schietinger et al., 2016; incorporated by reference in its entirety). The 4-$1BB^+$LAG-3^+ population produced more IFN-γ at all time points after day 7 compared to their negative counterparts, albeit with a slight decrease in IFN-γ production over time. While the increase in IFN-γ was maintained until later time points, TNF-α production was lost by day 28 (Figure 5A).

Experiments were conducted during development of embodiments herein to evaluate production of cytokines directly in the tumor without *in vitro* restimulation, which may more closely reflect which T cells were receiving TCR stimulation *in situ*. Each T cell population was sorted directly *ex vivo* without any culturing and mRNA levels were measured by qRT-PCR. Elevated *Ifn-γ* and *Gzmb* transcripts were observed from the 4-$1BB^+$LAG-3^+ subpopulation, along with a slight decrease in *Tnf-α* levels, compared to the 4-$1BB^-$LAG-3^- cells (Figure 5B). Production of IFN-γ in primary TILs was confirmed by injecting tumors with Brefeldin A prior to analysis by intracellular cytokine staining. Consistent with the mRNA expression, the 4-$1BB^+$LAG-3^+ population produced significantly greater amounts of

IFN-γ protein (Figure 5C). Thus, the 4-1BB$^+$LAG-3$^+$ TIL are not completely devoid of functionality, as they continue to produce IFN-γ despite defective production of IL-2. This phenotype is consistent with *in vitro* T cell anergy models (Jenkins et al., 1987; incorporated by reference in its entirety).

To test whether the 4-1BB$^+$LAG-3$^+$ population still retains cytotoxic capacity, re-directed lysis was performed by co-culturing anti-CD3 bound P815 mastocytoma target cells with the different CD8$^+$ TIL subpopulations directly after sorting. 4-1BB$^+$LAG-3$^+$ CD8$^+$ TILs isolated from day 14 tumors were able to lyse target cells at a comparable efficacy to *in vitro* primed OT-I cells. 4-1BB$^+$LAG-3$^+$ TILs isolated from day 21 tumors were still able to lyse target cells, albeit to a lesser extent compared to primed OT-I cells (Figure 5D).

CD8$^+$ T cells in the tumor can be the source of the chemokine CCL22 that recruits FoxP3$^+$ regulatory T cells (Tregs) to the tumor microenvironment (Spranger et al., 2013; incorporated by reference in its entirety). In addition, the chemokine *Ccl1* was an Egr2 target in anergic T cells (Zheng et al., 2013; incorporated by reference in its entirety), and it has been suggested that CCL1 also contribute to Treg recruitment in the tumor context in vivo (Hoelzinger et al., 2010; incorporated by reference in its entirety). However, whether all CD8$^+$ T cells in the tumor produce these chemokines or if they are only produced by subpopulations of T cells had not been determined. To address this the CD8$^+$ TIL phenotypic subpopulations were analyzed for *Ccl1* and *Ccl22* mRNA expression directly *ex vivo* by qRT-PCR. Indeed, the 4-1BB$^+$LAG-3$^+$ TIL population produced substantially greater *Ccl1* and *Ccl22* compared to their negative counterparts or to splenic CD8$^+$CD44$^+$ T cells (Figure 4K). As a control, expression of a distinct chemokine *Ccl5* was found not to be differentially expressed.

Together, these data show that co-expression of 4-1BB and LAG-3 delineates tumor antigen-specific CD8$^+$ TIL that lack the ability to produce IL-2 yet retain the ability to produce IFN-γ, kill target cells *in vitro,* and secrete chemokines capable of Treg recruitment. Given the fact that IFN-γ is responsible for the upregulation of PD-L1 and IDO in the tumor microenvironment, and that chemokines produced by CD8$^+$ TIL contribute to Treg recruitment (Spranger et al., 2013; incorporated by reference in its entirety), these data indicate that the 4-1BB$^+$LAG-3$^+$ population contributes to the network of immune suppressive mechanisms within the tumor microenvironment that limit the efficacy of anti-tumor immunity.

Gene expression profiling reveals that CD8$^+$4-1BB$^+$LAG-3$^+$ TILs express an extensive array of additional co-stimulatory and co-inhibitory receptors

Having in hand surface markers that define tumor antigen-specific dysfunctional CD8$^+$ TILs, experiments conducted during development of embodiments herein to compare the gene expression profile of this population to other published profiles of dysfunctional CD8$^+$ T cells to determine genes that regulate or are differentially expressed in cells in this dysfunctional state. To this end, a cross-study comparison was conducted of the transcriptional profiles of the "dysfunctional" 4-1BB$^+$LAG-3$^+$ CD8$^+$ TILs, "hypofunctional" CD8$^+$ TILs from a study utilizing the murine CT26 tumor model (Waugh et al., 2016; incorporated by reference in its entirety) and LCMV "exhausted" GP33 specific CD8$^+$ T cells (Doering et al., 2012; incorporated by reference in its entirety). The results are depicted in Table 2. Only genes with a 2-fold increase over controls from each study independently were considered. Over a 2-fold greater number of genes was found to be shared between the dysfunctional TIL dataset and the previously published hypofunctional CD8$^+$ TIL data, than with the exhausted T cell profile (Figure 6A). In addition, a rank-rank hypergeometric overlap (RRHO) analysis indicated a greater statistically significant overlap (Figure 10A) and a greater correlation (Figure 10B) between the current dysfunctional TIL and the published hypofunctional CD8$^+$ TIL gene expression profiles compared to the virally-induced exhausted CD8$^+$ T cell profile, indicating a more similar molecular program between CD8$^+$ T cells isolate from tumors compared to chronic viral infection.

Table 2. Differentially regulated genes in *CD8$^+$4-1BB$^+$LAG-3$^+$ TILs*

Gene	Gene Description	Log2-Fold Change	Gene Symbol	Gene Description	Log2-Fold Change
GLDC	glycine decarboxylase	11.25109772	CRY2	cryptochrome circadian clock 2	-1.546648257
GZMD	Granzyme D	10.66720027	KCMF1	potassium channel modulatory factor 1	-1.546835341
SLC17A6	solute carrier family 17 member 6	8.946467699	RHOB	ras homolog family member B	-1.548813112
IL1R2	interleukin 1 receptor type 2	7.595353131	KRT15	keratin 15	-1.549018071
LTF	lactotransferrin	7.530211233	RRAD	RRAD, Ras related glycolysis inhibitor and calcium channel regulator	-1.549530357
NRGN	neurogranin	7.334049768	C3	complement component 3	-1.54996

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GZME	granzyme E	7.160375687		ITFG3	Description Not Found	-1.550162812
RPL6	ribosomal protein L6	7.142107057		HAAO	3-hydroxyanthranilate 3,4-dioxygenase	-1.550553207
NRN1	neuritin 1	7.087993146		RNF138	ring finger protein 138	-1.551449524
LPL	lipoprotein lipase	7.004501392		UNC93B1	unc-93 homolog B1 (C. elegans)	-1.551767491
CLGN	calmegin	6.933690655		ANKZF1	ankyrin repeat and zinc finger domain containing 1	-1.552214097
CD70	CD70 molecule	6.906890596		IFITM3	interferon induced transmembrane protein 3	-1.552644542
AREG	amphiregulin	6.712870868		TXNIP	thioredoxin interacting protein	-1.552785452
ZRANB3	zinc finger RANBP2-type containing 3	6.595443985		LMAN1L	lectin, mannose binding 1 like	-1.554588852
ASNS	asparagine synthetase (glutamine-hydrolyzing)	6.59496878		ALDH3B1	aldehyde dehydrogenase 3 family member B1	-1.554711558
FANCD2	Fanconi anemia complementation group D2	6.353146826		GIP	gastric inhibitory polypeptide	-1.555511104
GM156	predicted gene 156(Gm156)	6.293701542		COX7A2L	cytochrome c oxidase subunit 7A2 like	-1.555572553
ACAA1B	acetyl-Coenzyme A acyltransferase 1B(Acaa1b)	6.293701542		APPL2	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 2	-1.555598704
IGF2BP3	insulin like growth factor 2 mRNA binding protein 3	6.186857067		KLHL22	kelch like family member 22	-1.555929583
GZMG	granzyme G	6.093813673		OLFR272	olfactory receptor 272(Olfr272)	-1.557482156
CIB2	calcium and integrin binding family member 2	6.007868243		LRRC29	leucine rich repeat containing 29	-1.559366716
ATG9B	autophagy related 9B	5.986410935		A630095E13RIK	Description Not Found	-1.560714954
XKR8	XK related 8	5.977279924		OLFR194	olfactory receptor 194(Olfr194)	-1.560714954
EPDR1	ependymin related 1	5.956521363		OLFR1013	olfactory receptor 1013(Olfr1013)	-1.560714954
SPP1	secreted phosphoprotein 1	5.797769502		GLRA4	glycine receptor alpha 4	-1.56071

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RGS8	regulator of G-protein signaling 8	5.753805672		P2RY6	pyrimidinergic receptor P2Y6	-1.560714954
MDFIC	MyoD family inhibitor domain containing	5.730639956		RASGEF1B	RasGEF domain family member 1B	-1.560714954
DMWD	dystrophia myotonica, WD repeat containing	5.687200695		IL22RA2	interleukin 22 receptor subunit alpha 2	-1.560714954
KIF11	kinesin family member 11	5.669593751		LIN7C	lin-7 homolog C, crumbs cell polarity complex component	-1.560714954
LGI2	leucine rich repeat LGI family member 2	5.655351829		DMRT1	doublesex and mab-3 related transcription factor 1	-1.560714954
ZFP41	ZFP41 zinc finger protein	5.615445725		TSPAN12	tetraspanin 12	-1.560714954
MLKL	mixed lineage kinase domain-like	5.605849867		PAK3	p21 (RAC1) activated kinase 3	-1.560714954
CENPH	centromere protein H	5.563768278		COL2A1	collagen type II alpha 1 chain	-1.560714954
SERPINF1	serpin family F member 1	5.5360529		SLC37A1	solute carrier family 37 member 1	-1.560714954
UNC13B	unc-13 homolog B (C. elegans)	5.503030646		PSD3	pleckstrin and Sec7 domain containing 3	-1.560714954
MLANA	melan-A	5.496654083		RDH5	retinol dehydrogenase 5	-1.560714954
PES1	pescadillo ribosomal biogenesis factor 1	5.484376709		ABCA3	ATP binding cassette subfamily A member 3	-1.561263453
2900026A02RIK	Description Not Found	5.477353527		PLA2G4E	phospholipase A2 group IVE	-1.561650879
OSR2	odd-skipped related transciption factor 2	5.416164165		DDIT3	DNA damage inducible transcript 3	-1.563566526
MPP6	membrane palmitoylated protein 6	5.408506442		ZFP12	zinc finger protein 12(Zfp12)	-1.564308646
HIST1H3C	histone cluster 1, H3c	5.397460726		PIGYL	phosphatidylinositol glycan anchor biosynthesis, class Y-like(Pigyl)	-1.564585219
PI4K2B	phosphatidylinositol 4-kinase type 2 beta	5.375039431		CCDC97	coiled-coil domain containing 97	-1.565355117
SH3YL1	SH3 and SYLF domain containing 1	5.375039431		OLFR1112	olfactory receptor 1112(Olfr1112)	-1.56589319
RAD51	RAD51 recombinase	5.371558863		ACTN2	actinin alpha 2	-1.566931646

ZBTB32	zinc finger and BTB domain containing 32	5.318316841		POLG	polymerase (DNA) gamma, catalytic subunit	-1.567265595
MSC	musculin	5.285402219		FBXO32	F-box protein 32	-1.567281905
TG	thyroglobulin	5.259272487		MRPL15	mitochondrial ribosomal protein L15	-1.570722678
RSPH1	radial spoke head 1 homolog	5.236492618		FCHSD2	FCH and double SH3 domains 2	-1.571821211
ARL11	ADP ribosylation factor like GTPase 11	5.21916852		RECQL	RecQ like helicase	-1.572889668
NUDT11	nudix hydrolase 11	5.215290306		NDUFB11	NADH:ubiquinone oxidoreductase subunit B11	-1.572889668
APBB1	amyloid beta precursor protein binding family B member 1	5.197708158		SOX8	SRY-box 8	-1.573341535
SPINK2	serine peptidase inhibitor, Kazal type 2	5.189824559		1700030J22RIK	Description Not Found	-1.57662394
HMGN3	high mobility group nucleosomal binding domain 3	5.168922782		EMB	embigin	-1.577890585
FAM20B	family with sequence similarity 20 member B	5.12722055		CELSR1	cadherin EGF LAG seven-pass G-type receptor 1	-1.578201987
CDC25C	cell division cycle 25C	5.11997861		COL1A2	collagen type I alpha 2 chain	-1.580682782
FAM20A	family with sequence similarity 20 member A	5.108524457		1700080E11RIK	Description Not Found	-1.581046002
PPP1R16B	protein phosphatase 1 regulatory subunit 16B	5.09592442		GALNT12	polypeptide N-acetylgalactosaminyltransferase 12	-1.581363645
SBNO1	strawberry notch homolog 1 (Drosophila)	5.050936965		RMND5B	required for meiotic nuclear division 5 homolog B	-1.583960816
ST14	suppression of tumorigenicity 14	5.026800059		LRRC28	leucine rich repeat containing 28	-1.583987499
LRRC49	leucine rich repeat containing 49	5.024704311		OLFR622	olfactory receptor 622(Olfr622)	-1.584962501
TIAM1	T-cell lymphoma invasion and metastasis 1	5.004501392		OLFR339	olfactory receptor 339(Olfr339)	-1.584962501
APLF	aprataxin and PNKP like factor	4.951867504		NEIL3	nei like DNA glycosylase 3	-1.584962501
PGPEP1	pyroglutamyl-peptidase I	4.927185358		SNX24	sorting nexin 24	-1.584962501
ALCAM	activated leukocyte cell adhesion molecule	4.909293086		SLC7A11	solute carrier family 7 member 11	-1.58496

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B9D1	B9 domain containing 1	4.906890596		FOXJ1	forkhead box J1	-1.584962501
SCIN	scinderin	4.87282876		TAF3	TATA-box binding protein associated factor 3	-1.584962501
EXOC3L	exocyst complex component 3-like(Exoc3l)	4.844013973		MATN2	matrilin 2	-1.584962501
SLC35D3	solute carrier family 35 member D3	4.840463234		ADHFE1	alcohol dehydrogenase, iron containing 1	-1.586280668
ALDOC	aldolase, fructose-bisphosphate C	4.832890014		NANOS1	nanos C2HC-type zinc finger 1	-1.586914831
TMEM205	transmembrane protein 205	4.830182468		PPP2R5B	protein phosphatase 2 regulatory subunit B'beta	-1.586914831
PLEKHA8	pleckstrin homology domain containing A8	4.820178962		USP22	ubiquitin specific peptidase 22	-1.588703598
SPC25	SPC25, NDC80 kinetochore complex component	4.817623258		DAGLB	diacylglycerol lipase beta	-1.588817933
PCYT1B	phosphate cytidylyltransferase 1, choline, beta	4.749534268		KCTD6	potassium channel tetramerization domain containing 6	-1.589690033
SLC6A8	solute carrier family 6 member 8	4.749534268		ACTL6B	actin like 6B	-1.591351555
TUBB6	tubulin beta 6 class V	4.749241128		FAM129B	family with sequence similarity 129 member B	-1.5915039
BSPRY	B-box and SPRY domain containing	4.711494907		APOE	apolipoprotein E	-1.591683393
ICA1	islet cell autoantigen 1	4.708739041		GPR18	G protein-coupled receptor 18	-1.592384168
TNFSF13B	tumor necrosis factor superfamily member 13b	4.703211467		GSTP2	glutathione S-transferase, pi 2(Gstp2)	-1.592559885
GSTCD	glutathione S-transferase C-terminal domain containing	4.700439718		GPR114	Description Not Found	-1.593829527
CCNB1	cyclin B1	4.699051844		CHUK	conserved helix-loop-helix ubiquitous kinase	-1.594823937
4930539E08RIK	Description Not Found	4.693211287		TAS1R3	taste 1 receptor member 3	-1.596595048
SRXN1	sulfiredoxin 1	4.66106548		SLC7A7	solute carrier family 7 member 7	-1.596935142
SERF1	small EDRK-rich factor 1(Serf1)	4.632268216		SPIB	Spi-B transcription factor	-1.597677703
CCDC77	coiled-coil domain	4.62935		POLR3A	polymerase (RNA) III	-

	containing 77	662			subunit A	1.59958 8488
RHBDF1	rhomboid 5 homolog 1	4.62643 9137		OLFR952	olfactory receptor 952(Olfr952)	- 1.59967 9175
REEP3	receptor accessory protein 3	4.59991 2842		1700021F05 RIK	Description Not Found	- 1.60162 3253
ITGA3	integrin subunit alpha 3	4.59096 1241		CCDC79	Description Not Found	- 1.60219 5565
SCCPDH	saccharopine dehydrogenase (putative)	4.59096 1241		FAM134B	family with sequence similarity 134 member B	- 1.60271 5966
MYADM	myeloid associated differentiation marker	4.58796 4989		SEMA3B	semaphorin 3B	- 1.60288 4409
FAM132A	family with sequence similarity 132 member A	4.58195 3751		FA2H	fatty acid 2-hydroxylase	- 1.60449 4406
FOXRED2	FAD dependent oxidoreductase domain containing 2	4.57288 9668		ULK1	unc-51 like autophagy activating kinase 1	- 1.60465 3903
CENPK	centromere protein K	4.56985 5608		MCOLN1	mucolipin 1	- 1.60624 2992
DCXR	dicarbonyl and L-xylulose reductase	4.56224 2424		BMP5	bone morphogenetic protein 5	- 1.60676 0033
TSPAN6	tetraspanin 6	4.54225 805		ANKRD50	ankyrin repeat domain 50	- 1.60713 7028
UPP1	uridine phosphorylase 1	4.53838 296		OLFR560	olfactory receptor 560(Olfr560)	- 1.60880 9243
DOK4	docking protein 4	4.52042 2249		OLFR366	olfactory receptor 366(Olfr366)	- 1.60880 9243
ELOVL4	ELOVL fatty acid elongase 4	4.50143 9145		OLFR273	olfactory receptor 273(Olfr273)	- 1.60880 9243
KNDC1	kinase non-catalytic C-lobe domain containing 1	4.49979 0117		FHIT	fragile histidine triad	- 1.60880 9243
KRT17	keratin 17	4.49185 3096		AQP11	aquaporin 11	- 1.60880 9243
CHST2	carbohydrate sulfotransferase 2	4.48731 5031		TMEM176 A	transmembrane protein 176A	- 1.60880 9243
TPX2	TPX2, microtubule nucleation factor	4.47573 3431		ENAH	enabled homolog (Drosophila)	- 1.60880 9243
DUSP14	dual specificity phosphatase 14	4.45614 9035		CLDN6	claudin 6	- 1.60880 9243
BGN	biglycan	4.44956 1375		SP1	Sp1 transcription factor	- 1.60880 9243

FKBP9	FK506 binding protein 9	4.44294 3496		SP140	SP140 nuclear body protein	-1.60880 9243
CAPN5	calpain 5	4.38543 1037		RASGRP3	RAS guanyl releasing protein 3	-1.60880 9243
SLC1A4	solute carrier family 1 member 4	4.37503 9431		HIF3A	hypoxia inducible factor 3 alpha subunit	-1.60942 2664
IDI2	isopentenyl-diphosphate delta isomerase 2	4.35755 2005		FYCO1	FYVE and coiled-coil domain containing 1	-1.61122 0598
AKR1E1	aldo-keto reductase family 1, member E1(Akr1e1)	4.34659 6388		FBXL12	F-box and leucine rich repeat protein 12	-1.61193 68
GNB4	G protein subunit beta 4	4.33608 8936		KLRA10	killer cell lectin-like receptor subfamily A, member 10(Klra10)	-1.61848 4777
CPNE2	copine 2	4.31864 0898		ABAT	4-aminobutyrate aminotransferase	-1.62058 641
FAM132B	family with sequence similarity 132, member B(Fam132b)	4.25927 2487		AMHR2	anti-Mullerian hormone receptor type 2	-1.62058 641
SLC6A12	solute carrier family 6 member 12	4.25927 2487		DDX3Y	DEAD-box helicase 3, Y-linked	-1.62064 9859
CPLX1	complexin 1	4.24031 4329		LGALS4	galectin 4	-1.62155 0215
PDCD1	programmed cell death 1	4.22110 3725		SPG20	spastic paraplegia 20 (Troyer syndrome)	-1.62165 3602
UTF1	undifferentiated embryonic cell transcription factor 1	4.20163 3861		CTRL	chymotrypsin like	-1.62729 369
WDR60	WD repeat domain 60	4.14974 712		GREM2	gremlin 2, DAN family BMP antagonist	-1.62792 7342
EGFL7	EGF like domain multiple 7	4.13750 3524		ZMAT3	zinc finger matrin-type 3	-1.62836 2075
ASPM	abnormal spindle microtubule assembly	4.13339 9125		AP4M1	adaptor related protein complex 4 mu 1 subunit	-1.62889 8157
TMBIM1	transmembrane BAX inhibitor motif containing 1	4.10462 8811		NT5C2	5'-nucleotidase, cytosolic II	-1.63059 747
KNTC1	kinetochore associated 1	4.09395 2772		TMIE	transmembrane inner ear	-1.63160 6148
1700019D03RIK	Description Not Found	4.08746 2841		OLFR556	olfactory receptor 556(Olfr556)	-1.63226 8216
TM4SF5	transmembrane 4 L six family member 5	4.08746 2841		OLFR463	olfactory receptor 463(Olfr463)	-1.63226 8216
BIRC5	baculoviral IAP repeat containing 5	4.02790 5997		CTS3	cathepsin 3(Cts3)	-1.63226

						8216
SYNGR3	synaptogyrin 3	4.022367813		OAS1B	2'-5' oligoadenylate synthetase 1B(Oas1b)	-1.632268216
PLSCR4	phospholipid scramblase 4	4		KCNF1	potassium voltage-gated channel modifier subfamily F member 1	-1.632268216
KIF15	kinesin family member 15	3.962376898		GCGR	glucagon receptor	-1.632268216
TICAM2	toll like receptor adaptor molecule 2	3.958842675		NR1I3	nuclear receptor subfamily 1 group I member 3	-1.632268216
CENPM	centromere protein M	3.957682486		FSTL1	follistatin like 1	-1.632268216
KIF4	kinesin family member 4(Kif4)	3.956097191		ASAP3	ArfGAP with SH3 domain, ankyrin repeat and PH domain 3	-1.632268216
E2F2	E2F transcription factor 2	3.93191939		IHH	indian hedgehog	-1.632268216
MSN	moesin	3.930737338		SEMA3A	semaphorin 3A	-1.632268216
PTPRA	protein tyrosine phosphatase, receptor type A	3.928989949		RAMP1	receptor activity modifying protein 1	-1.632575446
BC026585	cDNA sequence BC026585(BC026585)	3.882643049		NFKBID	NFKB inhibitor delta	-1.633158642
IQGAP3	IQ motif containing GTPase activating protein 3	3.867896464		KLK15	kallikrein related peptidase 15	-1.633773522
CD244	CD244 molecule	3.867896464		CYP1B1	cytochrome P450 family 1 subfamily B member 1	-1.634684534
HIST1H3G	histone cluster 1, H3g	3.837943242		DNAJA1	DnaJ heat shock protein family (Hsp40) member A1	-1.635111002
SLC15A3	solute carrier family 15 member 3	3.832890014		SDSL	serine dehydratase like	-1.635807742
GIPC2	GIPC PDZ domain containing family member 2	3.817623258		CCDC137	coiled-coil domain containing 137	-1.636838653
UTP15	UTP15, small subunit processome component	3.812498225		ZSWIM4	zinc finger SWIM-type containing 4	-1.638152805
PDIA6	protein disulfide isomerase family A member 6	3.812498225		BBC3	BCL2 binding component 3	-1.638336813
JDP2	Jun dimerization protein 2	3.807354922		SOCS3	suppressor of cytokine signaling 3	-1.638876738
MESDC1	mesoderm development candidate 1	3.806723946		2900092C05RIK	Description Not Found	-1.639157339
GAS2	growth arrest specific 2	3.80219		CSRNP2	cysteine and serine rich	-

		3217			nuclear protein 2	1.63938 3642
IL4I1	interleukin 4 induced 1	3.80219 3217		BLOC1S3	biogenesis of lysosomal organelles complex 1 subunit 3	- 1.63958 5785
PHF19	PHD finger protein 19	3.80219 3217		ELL	elongation factor for RNA polymerase II	- 1.64021 945
CKAP2L	cytoskeleton associated protein 2 like	3.79701 2978		GTF3C4	general transcription factor IIIC subunit 4	- 1.64065 8029
GSTT1	glutathione S-transferase theta 1	3.79181 4071		MYLPF	myosin light chain, phosphorylatable, fast skeletal muscle	- 1.64066 0074
ADAM3	a disintegrin and metallopeptidase domain 3 (cyritestin)(Adam3)	3.78135 9714		CYP2A12	cytochrome P450, family 2, subfamily a, polypeptide 12(Cyp2a12)	- 1.64194 7141
SLAMF7	SLAM family member 7	3.78135 9714		RNF139	ring finger protein 139	- 1.64201 0395
MCPT8	mast cell protease 8(Mcpt8)	3.77082 9046		C78339	Description Not Found	- 1.64357 3868
DGKG	diacylglycerol kinase gamma	3.76553 4746		EDEM1	ER degradation enhancing alpha-mannosidase like protein 1	- 1.64385 619
NLGN2	neuroligin 2	3.71699 0894		UBE2E1	ubiquitin conjugating enzyme E2 E1	- 1.64585 9791
SERPINE2	serpin family E member 2	3.69488 0193		PALMD	palmdelphin	- 1.64632 2067
IL10	interleukin 10	3.68929 9161		AMICA1	adhesion molecule, interacts with CXADR antigen 1(Amica1)	- 1.64747 8619
SLC6A13	solute carrier family 6 member 13	3.68929 9161		KLHL11	kelch like family member 11	- 1.65061 1828
STAU2	staufen double-stranded RNA binding protein 2	3.66675 6592		IFNGR2	interferon gamma receptor 2 (interferon gamma transducer 1)	- 1.65105 0175
ARHGDIG	Rho GDP dissociation inhibitor gamma	3.65535 1829		DECR1	2,4-dienoyl-CoA reductase 1, mitochondrial	- 1.65140 6438
TK1	thymidine kinase 1	3.63747 7097		SAMD3	sterile alpha motif domain containing 3	- 1.65321 3853
PCYT1A	phosphate cytidylyltransferase 1, choline, alpha	3.61772 8231		9130409I23 RIK	Description Not Found	- 1.65535 1829
LAMB3	laminin subunit beta 3	3.60880 9243		2010107G1 2RIK	Description Not Found	- 1.65535 1829
UBE2N	ubiquitin conjugating enzyme E2 N	3.59096 1241		ZFP354B	zinc finger protein 354B(Zfp354b)	- 1.65535 1829
STARD8	StAR related lipid transfer domain containing 8	3.57893 8713		TAS2R143	taste receptor, type 2, member 143(Tas2r143)	- 1.65535 1829

PRR5	proline rich 5	3.578938713		OLFR65	olfactory receptor 65(Olfr65)	-1.655351829
BDH2	3-hydroxybutyrate dehydrogenase, type 2	3.554588852		NRP	neural regeneration protein(Nrp)	-1.655351829
FAM124B	family with sequence similarity 124 member B	3.548436625		DOK3	docking protein 3	-1.655351829
MGAT3	mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase	3.548436625		HIGD1A	HIG1 hypoxia inducible domain family member 1A	-1.655351829
LAG3	lymphocyte activating 3	3.542346309		CCDC13	coiled-coil domain containing 13	-1.655351829
GDPD5	glycerophosphodiester phosphodiesterase domain containing 5	3.538812733		ANGPTL2	angiopoietin like 2	-1.655351829
RNF168	ring finger protein 168	3.5360529		CNGB3	cyclic nucleotide gated channel beta 3	-1.655351829
LYPLA1	lysophospholipase I	3.529820947		HOXD4	homeobox D4	-1.655351829
TUBGCP4	tubulin gamma complex associated protein 4	3.523561956		KIFC3	kinesin family member C3	-1.655351829
PYGL	phosphorylase, glycogen, liver	3.51412226		AMACR	alpha-methylacyl-CoA racemase	-1.655351829
CCL3	C-C motif chemokine ligand 3	3.510281539		2310014L17RIK	Description Not Found	-1.655707015
BCAT1	branched chain amino acid transaminase 1	3.508163667		BRAP	BRCA1 associated protein	-1.657090723
ATP6V0A1	ATPase H+ transporting V0 subunit a1	3.501439145		SLC39A1	solute carrier family 39 member 1	-1.657631089
EIF4E	eukaryotic translation initiation factor 4E	3.498250868		OLFR419	olfactory receptor 419(Olfr419)	-1.65813796
HIST1H4B	histone cluster 1, H4b	3.491853096		NHP2L1	NHP2 non-histone chromosome protein 2-like 1 (S. cerevisiae)(Nhp2l1)	-1.658298045
LAD1	ladinin 1	3.49085426		STOML2	stomatin like 2	-1.659357735
ITGAV	integrin subunit alpha V	3.485426827		SAMM50	SAMM50 sorting and assembly machinery component	-1.662400762
MRPL47	mitochondrial ribosomal protein L47	3.485426827		CCDC91	coiled-coil domain containing 91	-1.6632299
CAMK2N1	calcium/calmodulin dependent protein kinase II inhibitor 1	3.484460783		ATF3	activating transcription factor 3	-1.663483642
UEVLD	UEV and lactate/malate	3.46597		RAI1	retinoic acid induced 1	-

	dehyrogenase domains	4465				1.66388 5989
SFXN4	sideroflexin 4	3.46270 6751		RRAS2	related RAS viral (r-ras) oncogene homolog 2	- 1.66582 6896
2810417H1 3RIK	Description Not Found	3.46163 4298		UROS	uroporphyrinogen III synthase	- 1.66592 3156
RAD51AP1	RAD51 associated protein 1	3.45943 1619		SCOC	short coiled-coil protein	- 1.66627 2349
FUT4	fucosyltransferase 4	3.45285 8965		DUSP10	dual specificity phosphatase 10	- 1.66648 5948
CTNNBIP1	catenin beta interacting protein 1	3.44625 623		CYB5R4	cytochrome b5 reductase 4	- 1.66675 6592
ZBTB8OS	zinc finger and BTB domain containing 8 opposite strand	3.42626 4755		9930104L0 6RIK	Description Not Found	- 1.66715 0978
LYSMD4	LysM domain containing 4	3.42259 008		ZFP579	zinc finger protein 579(Zfp579)	- 1.66902 3741
DIAP3	Description Not Found	3.40599 236		RGP1	RGP1 homolog, RAB6A GEF complex partner 1	- 1.66939 3721
PTGIS	prostaglandin I2 (prostacyclin) synthase	3.39917 1094		PIAS2	protein inhibitor of activated STAT 2	- 1.67213 7196
MOAP1	modulator of apoptosis 1	3.39231 7423		METTL1	methyltransferase like 1	- 1.67242 5342
SLC27A3	solute carrier family 27 member 3	3.39231 7423		POU5F1	POU class 5 homeobox 1	- 1.67385 4965
MRPL39	mitochondrial ribosomal protein L39	3.37149 2175		SERPINB6 C	serine (or cysteine) peptidase inhibitor, clade B, member 6c(Serpinb6c)	- 1.67393 2658
WTAP	Wilms tumor 1 associated protein	3.36457 2432		STXBP4	syntaxin binding protein 4	- 1.67555 2278
RAD54L	RAD54-like (S. cerevisiae)	3.35658 9854		RIMS3	regulating synaptic membrane exocytosis 3	- 1.67612 0648
CETN4	centrin 4(Cetn4)	3.33628 3388		XYLT2	xylosyltransferase 2	- 1.67697 6793
CEP55	centrosomal protein 55	3.32912 3596		TAS2R107	taste receptor, type 2, member 107(Tas2r107)	- 1.67807 1905
CYP4F39	cytochrome P450, family 4, subfamily f, polypeptide 39(Cyp4f39)	3.32192 8095		SKP1A	S-phase kinase-associated protein 1A(Skp1a)	- 1.67807 1905
PTPN5	protein tyrosine phosphatase, non-receptor type 5	3.31469 6526		OLFR165	olfactory receptor 165(Olfr165)	- 1.67807 1905
TUBE1	tubulin epsilon 1	3.29278 1749		OLFR111	olfactory receptor 111(Olfr111)	- 1.67807 1905

TCAM1	testicular cell adhesion molecule 1(Tcam1)	3.28540 2219		CYP4A12A	cytochrome P450, family 4, subfamily a, polypeptide 12a(Cyp4a12a)	- 1.67807 1905
MID1IP1	MID1 interacting protein 1	3.26303 4406		TLR6	toll like receptor 6	- 1.67807 1905
ABHD6	abhydrolase domain containing 6	3.26068 2276		KCNS3	potassium voltage-gated channel modifier subfamily S member 3	- 1.67807 1905
ZCCHC4	zinc finger CCHC-type containing 4	3.25550 0733		FARSA	phenylalanyl-tRNA synthetase alpha subunit	- 1.67807 1905
MGST3	microsomal glutathione S-transferase 3	3.25353 624		SLC2A4	solute carrier family 2 member 4	- 1.67807 1905
BC022687	cDNA sequence BC022687(BC022687)	3.24792 7513		GDPD4	glycerophosphodiester phosphodiesterase domain containing 4	- 1.67807 1905
ACSF3	acyl-CoA synthetase family member 3	3.24325 855		RCAN1	regulator of calcineurin 1	- 1.67807 1905
ADAM8	ADAM metallopeptidase domain 8	3.24031 4329		CCDC82	coiled-coil domain containing 82	- 1.67807 1905
SGCB	sarcoglycan beta	3.23703 4772		CDYL2	chromodomain protein, Y-like 2	- 1.67807 1905
SOCS2	suppressor of cytokine signaling 2	3.23266 0757		MBD5	methyl-CpG binding domain protein 5	- 1.67807 1905
HIST1H2A G	histone cluster 1, H2ag	3.22300 0387		ACSL1	acyl-CoA synthetase long-chain family member 1	- 1.67807 1905
CRMP1	collapsin response mediator protein 1	3.20163 3861		OTUB2	OTU deubiquitinase, ubiquitin aldehyde binding 2	- 1.67807 1905
RPS19BP1	ribosomal protein S19 binding protein 1	3.20163 3861		NPPA	natriuretic peptide A	- 1.67807 1905
1700020L2 4RIK	Description Not Found	3.19377 1743		LY96	lymphocyte antigen 96	- 1.67959 4789
CCDC109B	coiled-coil domain containing 109B(Ccdc109b)	3.18127 6986		OLFR351	olfactory receptor 351(Olfr351)	- 1.68073 0557
UBE2C	ubiquitin conjugating enzyme E2 C	3.17791 7792		TGFBR1	transforming growth factor beta receptor 1	- 1.68106 8055
SLC25A16	solute carrier family 25 member 16	3.17791 7792		KLHL6	kelch like family member 6	- 1.68353 1539
ARHGAP1 9	Rho GTPase activating protein 19	3.16770 5534		ELMO2	engulfment and cell motility 2	- 1.68369 6454
TYMS-PS	thymidylate synthase, pseudogene(Tyms-ps)	3.16636 2514		POLR3D	polymerase (RNA) III subunit D	- 1.68394 2043
IL3RA	interleukin 3 receptor	3.14579		RALGPS1	Ral GEF with PH domain	-

	subunit alpha	3675			and SH3 binding motif 1	1.68552 4532
TMEM53	transmembrane protein 53	3.14159 6278		ATL2	atlastin GTPase 2	- 1.68573 1341
THNSL2	threonine synthase like 2	3.14159 6278		RAD52	RAD52 homolog, DNA repair protein	- 1.68952 3672
2810408M0 9RIK	Description Not Found	3.12928 3017		GPC1	glypican 1	- 1.68964 6894
ADAMDEC 1	ADAM like decysin 1	3.12101 5401		ARHGAP1 5	Rho GTPase activating protein 15	- 1.69080 4518
ASB2	ankyrin repeat and SOCS box containing 2	3.11879 2343		GPRC5B	G protein-coupled receptor class C group 5 member B	- 1.69399 9744
SLC37A4	solute carrier family 37 member 4	3.11270 0133		ZBTB1	zinc finger and BTB domain containing 1	- 1.69404 6727
NICN1	nicolin 1	3.10847 8268		NARFL	nuclear prelamin A recognition factor like	- 1.69488 0193
2310067B1 0RIK	Description Not Found	3.08746 2841		SLC26A6	solute carrier family 26 member 6	- 1.69525 2347
PIGL	phosphatidylinositol glycan anchor biosynthesis class L	3.07723 9787		MAPKBP1	mitogen-activated protein kinase binding protein 1	- 1.69590 8738
1190005I06 RIK	Description Not Found	3.07038 9328		RAB6B	RAB6B, member RAS oncogene family	- 1.69754 1036
DHFR	dihydrofolate reductase	3.07038 9328		ARL2	ADP ribosylation factor like GTPase 2	- 1.70034 9879
FABP5	fatty acid binding protein 5	3.06608 919		ZFP646	zinc finger protein 646(Zfp646)	- 1.70043 9718
POMT2	protein O-mannosyltransferase 2	3.05579 4286		SELENBP2	selenium binding protein 2(Selenbp2)	- 1.70043 9718
F2RL2	coagulation factor II thrombin receptor like 2	3.05311 1336		ACOT3	acyl-CoA thioesterase 3(Acot3)	- 1.70043 9718
GRB7	growth factor receptor bound protein 7	3.04885 2907		REG3G	regenerating family member 3 gamma	- 1.70043 9718
SNX21	sorting nexin family member 21	3.04439 4119		GAB1	GRB2 associated binding protein 1	- 1.70043 9718
SUFU	SUFU negative regulator of hedgehog signaling	3.04439 4119		LCN10	lipocalin 10	- 1.70043 9718
RFC3	replication factor C subunit 3	3.02928 8361		MTHFD2L	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2-like	- 1.70043 9718
CLDN12	claudin 12	3.01792 1908		PTCD3	pentatricopeptide repeat domain 3	- 1.70043 9718

C1QTNF6	C1q and tumor necrosis factor related protein 6	3.01445 0679		NTHL1	nth-like DNA glycosylase 1	-1.70043 9718
PLCXD1	phosphatidylinositol specific phospholipase C X domain containing 1	2.99095 486		NUDT3	nudix hydrolase 3	-1.70043 9718
SULT4A1	sulfotransferase family 4A member 1	2.99095 486		CLEC12A	C-type lectin domain family 12 member A	-1.70043 9718
CTTNBP2N L	CTTNBP2 N-terminal like	2.98185 2653		ZBTB3	zinc finger and BTB domain containing 3	-1.70043 9718
SNX5	sorting nexin 5	2.97727 9924		AMT	aminomethyltransferase	-1.70043 9718
HPS5	HPS5, biogenesis of lysosomal organelles complex 2 subunit 2	2.97269 2654		ZDHHC14	zinc finger DHHC-type containing 14	-1.70043 9718
WISP1	WNT1 inducible signaling pathway protein 1	2.96809 0752		NKX2-5	NK2 homeobox 5	-1.70049 1519
PTPN9	protein tyrosine phosphatase, non-receptor type 9	2.96347 4124		FOXA3	forkhead box A3	-1.70281 5694
USP37	ubiquitin specific peptidase 37	2.95419 631		WASF1	WAS protein family member 1	-1.70641 2734
SH3BGRL	SH3 domain binding glutamate rich protein like	2.93545 9748		OLFR690	olfactory receptor 690(Olfr690)	-1.70719 2688
NCALD	neurocalcin delta	2.93545 9748		ENTPD5	ectonucleoside triphosphate diphosphohydrolase 5	-1.70776 4551
CDC42EP4	CDC42 effector protein 4	2.91647 6644		PCDHGA4	protocadherin gamma subfamily A, 4	-1.70904 2655
IGFBP7	insulin like growth factor binding protein 7	2.91055 3168		TCF12	transcription factor 12	-1.71030 8209
ABHD4	abhydrolase domain containing 4	2.90886 8748		MTRR	5-methyltetrahydrofolate-homocysteine methyltransferase reductase	-1.71149 4907
CSF1	colony stimulating factor 1	2.90689 0596		CDKN1C	cyclin dependent kinase inhibitor 1C	-1.71169 0028
COX7A1	cytochrome c oxidase subunit 7A1	2.89724 0426		PRICKLE1	prickle planar cell polarity protein 1	-1.71341 0822
TTYH2	tweety family member 2	2.89239 1026		ATXN7L1	ataxin 7 like 1	-1.71669 984
ACO1	aconitase 1	2.87774 425		SLCO3A1	solute carrier organic anion transporter family member 3A1	-1.71923 5762
BARD1	BRCA1 associated RING domain 1	2.86789 6464		TMEM110	transmembrane protein 110	-1.72004 6704
GPN1	GPN-loop GTPase 1	2.86789		KLF2	Kruppel like factor 2	-

		6464				1.72137 4729
PTTG1	pituitary tumor-transforming 1	2.86789 6464		FGG	fibrinogen gamma chain	- 1.72246 6024
2810408A1 1RIK	Description Not Found	2.85798 0995		ASAH2	N-acylsphingosine amidohydrolase 2	- 1.72246 6024
BBX	BBX, HMG-box containing	2.85798 0995		LAP3	leucine aminopeptidase 3	- 1.72246 6024
LTBP3	latent transforming growth factor beta binding protein 3	2.83794 3242		STAB2	stabilin 2	- 1.72246 6024
ACTG2	actin, gamma 2, smooth muscle, enteric	2.82781 9025		IL22RA1	interleukin 22 receptor subunit alpha 1	- 1.72246 6024
ISLR	immunoglobulin superfamily containing leucine rich repeat	2.82781 9025		SERINC4	serine incorporator 4	- 1.72246 6024
NARS2	asparaginyl-tRNA synthetase 2, mitochondrial (putative)	2.82308 7408		GPR180	G protein-coupled receptor 180	- 1.72246 6024
ICAM4	intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)	2.81452 379		TIPARP	TCDD inducible poly(ADP-ribose) polymerase	- 1.72246 6024
ABCB8	ATP binding cassette subfamily B member 8	2.81335 8991		USP11	ubiquitin specific peptidase 11	- 1.72246 6024
IDI1	isopentenyl-diphosphate delta isomerase 1	2.81178 2922		TRIP6	thyroid hormone receptor interactor 6	- 1.72246 6024
GLS2	glutaminase 2	2.79701 2978		KCNH2	potassium voltage-gated channel subfamily H member 2	- 1.72246 6024
HDAC8	histone deacetylase 8	2.79701 2978		ESR2	estrogen receptor 2	- 1.72246 6024
BRIP1	BRCA1 interacting protein C-terminal helicase 1	2.79701 2978		FGF13	fibroblast growth factor 13	- 1.72263 9247
USP6NL	USP6 N-terminal like	2.79441 5866		KBTBD7	kelch repeat and BTB domain containing 7	- 1.72423 7927
TLCD2	TLC domain containing 2	2.79181 4071		UHRF1BP1	UHRF1 binding protein 1	- 1.72583 5292
GUCY1A3	guanylate cyclase 1 soluble subunit alpha	2.78750 2763		BCAM	basal cell adhesion molecule (Lutheran blood group)	- 1.72650 9704
OCA2	OCA2 melanosomal transmembrane protein	2.78659 6362		ELOVL6	ELOVL fatty acid elongase 6	- 1.72656 5554
VAT1	vesicle amine transport 1	2.77250 2543		PPM1K	protein phosphatase, Mg2+/Mn2+ dependent 1K	- 1.72664 3643
HIST1H2A B	histone cluster 1, H2ab	2.76791 4142		SPATA6	spermatogenesis associated 6	- 1.72767 3077

PIGC	phosphatidylinositol glycan anchor biosynthesis class C	2.76022 0946		NAV1	neuron navigator 1	- 1.72792 0455
PARG	poly(ADP-ribose) glycohydrolase	2.75655 8208		ANK3	ankyrin 3, node of Ranvier (ankyrin G)	- 1.72792 0455
ESCO2	establishment of sister chromatid cohesion N-acetyltransferase 2	2.75488 7502		KCNAB1	potassium voltage-gated channel subfamily A member regulatory beta subunit 1	- 1.72792 0455
HIPK2	homeodomain interacting protein kinase 2	2.75488 7502		CYP27A1	cytochrome P450 family 27 subfamily A member 1	- 1.72792 0455
IMPA1	inositol monophosphatase 1	2.75294 5007		MAP4K4	mitogen-activated protein kinase kinase kinase kinase 4	- 1.72975 6006
COQ4	coenzyme Q4	2.74416 1096		ANKRD7	ankyrin repeat domain 7	- 1.73064 6873
ZBTB7A	zinc finger and BTB domain containing 7A	2.74416 1096		IFRD1	interferon related developmental regulator 1	- 1.73244 7522
GAMT	guanidinoacetate N-methyltransferase	2.74416 1096		ALX3	ALX homeobox 3	- 1.73335 4341
BIK	BCL2 interacting killer	2.74416 1096		SNURF	SNRPN upstream reading frame	- 1.73335 4341
PMS1	PMS1 homolog 1, mismatch repair system component	2.73335 4341		AMZ2	archaelysin family metallopeptidase 2	- 1.73350 053
HAVCR2	hepatitis A virus cellular receptor 2	2.72976 9667		ROGDI	rogdi homolog	- 1.73419 198
FHL2	four and a half LIM domains 2	2.72725 4747		DAGLA	diacylglycerol lipase alpha	- 1.73447 1203
CHAF1A	chromatin assembly factor 1 subunit A	2.72524 8783		4930432K2 1RIK	Description Not Found	- 1.73624 3886
2810004N2 3RIK	Description Not Found	2.72246 6024		KRCC1	lysine rich coiled-coil 1	- 1.73665 741
TBC1D14	TBC1 domain family member 14	2.72246 6024		OLFR1331	olfactory receptor 1331(Olfr1331)	- 1.73682 6447
EHD2	EH domain containing 2	2.71149 4907		SLC25A25	solute carrier family 25 member 25	- 1.73690 749
APH1A	aph-1 homolog A, gamma-secretase subunit	2.70597 7902		CXCR4	C-X-C motif chemokine receptor 4	- 1.73777 9353
TMEM2	transmembrane protein 2	2.70321 1467		EPB4.1L3	Description Not Found	- 1.73876 7837
LCAT	lecithin-cholesterol acyltransferase	2.70043 9718		CEP164	centrosomal protein 164	- 1.73879 5736
FBXO15	F-box protein 15	2.68929		AGER	advanced glycosylation	-

		9161			end product-specific receptor	1.73961488
ADAP1	ArfGAP with dual PH domains 1	2.674391397		B3GALT5	beta-1,3-galactosyltransferase 5	-1.740215306
PPAPDC1B	Description Not Found	2.666756592		OLFR450	olfactory receptor 450(Olfr450)	-1.74228265
CD48	CD48 molecule	2.666756592		ZFP780B	zinc finger protein 780B(Zfp780b)	-1.744161096
CAMK4	calcium/calmodulin dependent protein kinase IV	2.655351829		OLFR485	olfactory receptor 485(Olfr485)	-1.744161096
SAC3D1	SAC3 domain containing 1	2.64385619		OLFR47	olfactory receptor 47(Olfr47)	-1.744161096
ECHDC2	enoyl-CoA hydratase domain containing 2	2.640725033		CYP4F18	cytochrome P450, family 4, subfamily f, polypeptide 18(Cyp4f18)	-1.744161096
INCENP	inner centromere protein	2.638460117		PLOD2	procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	-1.744161096
INTS9	integrator complex subunit 9	2.634920268		OSBPL1A	oxysterol binding protein like 1A	-1.744161096
KLRA17	killer cell lectin-like receptor, subfamily A, member 17(Klra17)	2.632268216		CHRNA5	cholinergic receptor nicotinic alpha 5 subunit	-1.744161096
MAN2B2	mannosidase alpha class 2B member 2	2.632268216		TSSK4	testis specific serine kinase 4	-1.744161096
DOLK	dolichol kinase	2.632268216		ALKBH8	alkB homolog 8, tRNA methyltransferase	-1.744161096
SAP30BP	SAP30 binding protein	2.632268216		GPX2	glutathione peroxidase 2	-1.744161096
RTN1	reticulon 1	2.627898616		ATG4D	autophagy related 4D cysteine peptidase	-1.744161096
ADAM15	ADAM metallopeptidase domain 15	2.626439137		SCRN3	secernin 3	-1.744161096
STAG3	stromal antigen 3	2.62058641		NOTCH3	notch 3	-1.744161096
NUDT2	nudix hydrolase 2	2.610775705		OLFR113	olfactory receptor 113(Olfr113)	-1.744357436
GLT8D2	glycosyltransferase 8 domain containing 2	2.609988757		CD28	CD28 molecule	-1.744605653
CAPSL	calcyphosine like	2.608809243		SAG	S-antigen; retina and pineal gland (arrestin)	-1.745224161
CALR	calreticulin	2.608809243		AGTRAP	angiotensin II receptor associated protein	-1.749107415

CRYBG3	crystallin beta-gamma domain containing 3	2.605393551		BLK	BLK proto-oncogene, Src family tyrosine kinase	-1.749534268
DIXDC1	DIX domain containing 1	2.596940379		MGAT5	mannosyl (alpha-1,6-)-glycoprotein beta-1,6-N-acetyl-glucosaminyltransferase	-1.749534268
TACSTD2	tumor-associated calcium signal transducer 2	2.593926161		RNF2	ring finger protein 2	-1.750890228
TRP53RK	Description Not Found	2.588066506		COL14A1	collagen type XIV alpha 1 chain	-1.752093722
PDCD1LG2	programmed cell death 1 ligand 2	2.584962501		PLEKHG3	pleckstrin homology and RhoGEF domain containing G3	-1.752109698
SEC23IP	SEC23 interacting protein	2.584962501		ARHGEF18	Rho/Rac guanine nucleotide exchange factor 18	-1.754100479
ORM1	orosomucoid 1	2.584962501		LEF1	lymphoid enhancer binding factor 1	-1.754887502
ZFP322A	zinc finger protein 322A(Zfp322a)	2.575024164		COMMD9	COMM domain containing 9	-1.754907 09
4931406C07RIK	Description Not Found	2.560714954		SLC20A1	solute carrier family 20 member 1	-1.758637847
ZFP382	zinc finger protein 382(Zfp382)	2.560714954		ACTR5	ARP5 actin-related protein 5 homolog	-1.759244091
CLIP2	CAP-Gly domain containing linker protein 2	2.560714954		UBQLN3	ubiquilin 3	-1.765109548
TNFAIP8L1	TNF alpha induced protein 8 like 1	2.560714954		ZFP770	zinc finger protein 770(Zfp770)	-1.765534746
NRCAM	neuronal cell adhesion molecule	2.560714954		PCDHB18	protocadherin beta 18(Pcdhb18)	-1.765534746
HPSE	heparanase	2.560714954		OLFR700	olfactory receptor 700(Olfr700)	-1.765534746
RTKN	rhotekin	2.558985655		FOXP4	forkhead box P4	-1.765534746
DLGAP5	DLG associated protein 5	2.550125328		CDC34	cell division cycle 34	-1.765534746
ENPP2	ectonucleotide pyrophosphatase/phosphodiesterase 2	2.548436625		HIST1H1E	histone cluster 1, H1e	-1.765534746
GCNT1	glucosaminyl (N-acetyl) transferase 1, core 2	2.548436625		G6PC2	glucose-6-phosphatase catalytic subunit 2	-1.765534746
SASS6	SAS-6 centriolar assembly protein	2.548436625		FUT1	fucosyltransferase 1 (H blood group)	-1.765534746
AMIGO3	adhesion molecule with	2.54843		ZFP69	ZFP69 zinc finger protein	-

	Ig-like domain 3	6625				1.76553 4746
APH1B	aph-1 homolog B, gamma-secretase subunit	2.54843 6625		WBSCR27	Williams Beuren syndrome chromosome region 27	- 1.76553 4746
ABCC5	ATP binding cassette subfamily C member 5	2.54784 6505		METTL8	methyltransferase like 8	- 1.76688 0868
YIPF6	Yip1 domain family member 6	2.54380 5176		TMEM170	transmembrane protein 170(Tmem170)	- 1.76746 2508
FFAR1	free fatty acid receptor 1	2.53605 29		TRP53INP1	transformation related protein 53 inducible nuclear protein 1(Trp53inp1)	- 1.76751 8474
TSSK6	testis specific serine kinase 6	2.53605 29		H2-Q5	histocompatibility 2, Q region locus 5(H2-Q5)	- 1.76967 6967
ETV6	ETS variant 6	2.53538 5323		ADCK1	aarF domain containing kinase 1	- 1.77003 3995
PTGDS	prostaglandin D2 synthase	2.52983 8423		IMPAD1	inositol monophosphatase domain containing 1	- 1.77143 4505
SH3D19	SH3 domain containing 19	2.52356 1956		E4F1	E4F transcription factor 1	- 1.77242 7885
KIF5C	kinesin family member 5C	2.51829 8014		ZFYVE20	Description Not Found	- 1.77294 2676
PTGER2	prostaglandin E receptor 2	2.51727 5693		PNPLA6	patatin like phospholipase domain containing 6	- 1.77507 4114
INSR	insulin receptor	2.51096 1919		TRIB3	tribbles pseudokinase 3	- 1.77521 5233
MAPK6	mitogen-activated protein kinase 6	2.50462 0392		GM614	predicted gene 614(Gm614)	- 1.77610 3988
OXSR1	oxidative stress responsive 1	2.50221 1192		D5ERTD57 9E	DNA segment, Chr 5, ERATO Doi 579, expressed(D5Ertd579e)	- 1.77630 6798
EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit	2.50143 9145		SCAND1	SCAN domain containing 1	- 1.77785 827
BNIP1	BCL2 interacting protein 1	2.49825 0868		ASB13	ankyrin repeat and SOCS box containing 13	- 1.78220 5107
LPCAT4	lysophosphatidylcholine acyltransferase 4	2.49528 5165		ARHGEF4	Rho guanine nucleotide exchange factor 4	- 1.78407 2601
PPAP2C	Description Not Found	2.48542 6827		H1FNT	H1 histone family member N, testis specific	- 1.78485 543
IFNA12	interferon alpha 12(Ifna12)	2.48542 6827		BLOC1S1	biogenesis of lysosomal organelles complex 1 subunit 1	- 1.78491 1393
DCLK1	doublecortin like kinase 1	2.48542 6827		ZFYVE27	zinc finger FYVE-type containing 27	- 1.78510

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MX1	MX dynamin like GTPase 1	2.485426827		RHOX4B	reproductive homeobox 4B(Rhox4b)	-1.786596362
SMTN	smoothelin	2.485426827		OLFR1134	olfactory receptor 1134(Olfr1134)	-1.786596362
PLA2G15	phospholipase A2 group XV	2.48194563		CAR11	carbonic anhydrase 11(Car11)	-1.786596362
OLFR192	olfactory receptor 192(Olfr192)	2.472487771		LRRIQ4	leucine rich repeats and IQ motif containing 4	-1.786596362
ITGB5	integrin subunit beta 5	2.472487771		CASP12	caspase 12 (gene/pseudogene)	-1.786596362
RAPSN	receptor associated protein of the synapse	2.465974465		ODF3L1	outer dense fiber of sperm tails 3 like 1	-1.786596362
SNX3	sorting nexin 3	2.459431619		CCDC3	coiled-coil domain containing 3	-1.786596362
FERMT2	fermitin family member 2	2.459431619		SSPN	sarcospan	-1.786596362
CCR5	C-C motif chemokine receptor 5 (gene/pseudogene)	2.444410478		KLK1	kallikrein 1	-1.786596362
UPK1A	uroplakin 1A	2.439623138		SENP7	SUMO1/sentrin specific peptidase 7	-1.786897131
BCL2L2	BCL2 like 2	2.43629512		CAML	calcium modulating ligand(Caml)	-1.787735284
2610002M06RIK	Description Not Found	2.432959407		YEATS2	YEATS domain containing 2	-1.788627083
CENPN	centromere protein N	2.432959407		SERPINF2	serpin family F member 2	-1.791814071
HBEGF	heparin binding EGF like growth factor	2.43096254		KCNMB1	potassium calcium-activated channel subfamily M regulatory beta subunit 1	-1.792597191
TYMS	thymidylate synthetase	2.427103287		FCHO2	FCH domain only 2	-1.792666489
MGA	MGA, MAX dimerization protein	2.426939834		BBS9	Bardet-Biedl syndrome 9	-1.792734984
RAI14	retinoic acid induced 14	2.426264755		OLFR323	olfactory receptor 323(Olfr323)	-1.794609131
CFI	complement factor I	2.419538892		CD247	CD247 molecule	-1.796081585
PLK4	polo like kinase 4	2.419538892		HIST2H2AA1	histone cluster 2, H2aa1(Hist2h2aa1)	-1.796847743

SLC6A9	solute carrier family 6 member 9	2.41953 8892		PDK1	pyruvate dehydrogenase kinase 1	- 1.80056 3818
TMED2	transmembrane p24 trafficking protein 2	2.41953 8892		NRARP	NOTCH-regulated ankyrin repeat protein	- 1.80304 9246
TMEM120 B	transmembrane protein 120B	2.41857 423		BTBD11	BTB domain containing 11	- 1.80479 3263
TRIM36	tripartite motif containing 36	2.41785 2515		CSF2RA	colony stimulating factor 2 receptor alpha subunit	- 1.80508 9518
CCDC93	coiled-coil domain containing 93	2.41616 4165		DEXI	Dexi homolog	- 1.80699 8156
SLC25A35	solute carrier family 25 member 35	2.40936 7225		OLFR1276	olfactory receptor 1276(Olfr1276)	- 1.80735 4922
BNC1	basonuclin 1	2.40599 236		TCSTV3	2-cell-stage, variable group, member 3(Tcstv3)	- 1.80735 4922
FOXL2	forkhead box L2	2.40599 236		SPRR2D	small proline rich protein 2D	- 1.80735 4922
TFPI2	tissue factor pathway inhibitor 2	2.40599 236		SEMA4G	semaphorin 4G	- 1.80735 4922
NET1	neuroepithelial cell transforming 1	2.40599 236		KCNK9	potassium two pore domain channel subfamily K member 9	- 1.80735 4922
SLCO2A1	solute carrier organic anion transporter family member 2A1	2.40599 236		SNAPC3	small nuclear RNA activating complex polypeptide 3	- 1.80738 5513
A730008H2 3RIK	Description Not Found	2.39927 5037		AXIN2	axin 2	- 1.80842 9403
CDKN2B	cyclin dependent kinase inhibitor 2B	2.39726 4578		PCNXL3	Description Not Found	- 1.80899 5133
ZFP532	zinc finger protein 532(Zfp532)	2.39313 8801		KLHL7	kelch like family member 7	- 1.80901 6035
GTSE1	G2 and S-phase expressed 1	2.39242 8431		ZFP281	zinc finger protein 281(Zfp281)	- 1.81155 6991
CCDC14	coiled-coil domain containing 14	2.39231 7423		CHRNB2	cholinergic receptor nicotinic beta 2 subunit	- 1.81249 8225
ADAT1	adenosine deaminase, tRNA specific 1	2.39231 7423		TBC1D15	TBC1 domain family member 15	- 1.81290 9044
DGKH	diacylglycerol kinase eta	2.39231 7423		GALNT9	polypeptide N-acetylgalactosaminyltransferase 9	- 1.81340 7449
ZRSR1	zinc finger CCCH-type, RNA binding motif and serine/arginine rich 1	2.39231 7423		DYNC1I1	dynein cytoplasmic 1 intermediate chain 1	- 1.81343 4179
NFE2	nuclear factor, erythroid 2	2.39152 9377		MYH8	myosin heavy chain 8	- 1.81403

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CD63	CD63 molecule	2.38785 3137		CEP57	centrosomal protein 57	- 1.81568 4972
MIB1	mindbomb E3 ubiquitin protein ligase 1	2.38645 559		LTK	leukocyte receptor tyrosine kinase	- 1.81762 3258
TSN	translin	2.38234 9023		COMMD2	COMM domain containing 2	- 1.81762 3258
2510003E0 4RIK	Description Not Found	2.37851 1623		MEF2C	myocyte enhancer factor 2C	- 1.81762 3258
BC043934	cDNA sequence BC043934(BC043934)	2.37851 1623		LONRF2	LON peptidase N-terminal domain and ring finger 2	- 1.81794 1412
AHCYL1	adenosylhomocysteinase like 1	2.36673 4247		PDCD6IP	programmed cell death 6 interacting protein	- 1.82057 5529
OLFR731	olfactory receptor 731(Olfr731)	2.36457 2432		DHX16	DEAH-box helicase 16	- 1.82066 1084
CDKN2A	cyclin dependent kinase inhibitor 2A	2.36457 2432		ZFYVE19	zinc finger FYVE-type containing 19	- 1.82528 1028
SLC29A4	solute carrier family 29 member 4	2.36457 2432		H2-T10	histocompatibility 2, T region locus 10(H2-T10)	- 1.82621 8639
SLC4A10	solute carrier family 4 member 10	2.36457 2432		ARID1A	AT-rich interaction domain 1A	- 1.82704 3205
CYCS	cytochrome c, somatic	2.35187 2866		NOD1	nucleotide binding oligomerization domain containing 1	- 1.82718 5706
COL5A1	collagen type V alpha 1	2.35049 7247		2610318N0 2RIK	Description Not Found	- 1.82781 9025
UTRN	utrophin	2.35049 7247		BC048644	cDNA sequence BC048644(BC048644)	- 1.82781 9025
AURKA	aurora kinase A	2.34967 8136		CDC42EP2	CDC42 effector protein 2	- 1.82781 9025
KREMEN2	kringle containing transmembrane protein 2	2.34943 1709		CCL25	C-C motif chemokine ligand 25	- 1.82781 9025
FGL2	fibrinogen like 2	2.34640 9407		TBX6	T-box 6	- 1.82781 9025
NCAM1	neural cell adhesion molecule 1	2.34340 7822		PLEKHG4	pleckstrin homology and RhoGEF domain containing G4	- 1.82781 9025
ALG8	ALG8, alpha-1,3-glucosyltransferase	2.34340 7822		RAD18	RAD18, E3 ubiquitin protein ligase	- 1.83064 2494
OLFR703	olfactory receptor 703(Olfr703)	2.33628 3388		SLC12A9	solute carrier family 12 member 9	- 1.83080 7586
SLC39A10	solute carrier family 39	2.33628		NR1D2	nuclear receptor subfamily	-

	member 10	3388			1 group D member 2	1.837943242
HIST1H2AH	histone cluster 1, H2ah	2.322141712		NLK	nemo like kinase	-1.840170811
TSGA8	testis specific gene A8(Tsga8)	2.321928095		TTC37	tetratricopeptide repeat domain 37	-1.840462743
ELOVL2	ELOVL fatty acid elongase 2	2.321928095		DLG3	discs large MAGUK scaffold protein 3	-1.841507525
MLF1	myeloid leukemia factor 1	2.321928095		PCF11	PCF11 cleavage and polyadenylation factor subunit	-1.843349827
FZD6	frizzled class receptor 6	2.321928095		HIST1H4D	histone cluster 1, H4d	-1.846386944
PLD1	phospholipase D1	2.321928095		PEX26	peroxisomal biogenesis factor 26	-1.847440096
IFRD2	interferon-related developmental regulator 2	2.321928095		CYP2B10	cytochrome P450, family 2, subfamily b, polypeptide 10(Cyp2b10)	-1.847996907
OLA1	Obg-like ATPase 1	2.321928095		GDF3	growth differentiation factor 3	-1.847996907
ASPA	aspartoacylase	2.321928095		GPR33	G protein-coupled receptor 33 (gene/pseudogene)	-1.847996907
TGFB3	transforming growth factor beta 3	2.321928095		TDG	thymine DNA glycosylase	-1.847996907
PKIG	protein kinase (cAMP-dependent, catalytic) inhibitor gamma	2.314696526		HIPK3	homeodomain interacting protein kinase 3	-1.847996907
TNFRSF4	tumor necrosis factor receptor superfamily member 4	2.308832886		PAPOLA	poly(A) polymerase alpha	-1.847996907
IQCB1	IQ motif containing B1	2.307984443		MAPK4	mitogen-activated protein kinase 4	-1.847996907
SLC16A11	solute carrier family 16 member 11	2.307662797		FRAT2	frequently rearranged in advanced T-cell lymphomas 2	-1.84969115
1190002N15RIK	Description Not Found	2.307428525		HEXIM1	hexamethylene bisacetamide inducible 1	-1.851035845
LCE1L	late cornified envelope 1L(Lce1l)	2.307428525		TATDN2	TatD DNase domain containing 2	-1.851433223
RGS13	regulator of G-protein signaling 13	2.307428525		KLRB1C	killer cell lectin-like receptor subfamily B member 1C(Klrb1c)	-1.854253843
FBXW8	F-box and WD repeat domain containing 8	2.299987517		SLC16A9	solute carrier family 16 member 9	-1.855083462
SNCA	synuclein alpha	2.296457407		ACBD4	acyl-CoA binding domain containing 4	-1.855739032

OSGIN1	oxidative stress induced growth inhibitor 1	2.294491702		REXO1	RNA exonuclease 1 homolog	-1.857980995
BC004004	cDNA sequence BC004004(BC004004)	2.292781749		OLFR1442	olfactory receptor 1442(Olfr1442)	-1.859286959
WNT10A	Wnt family member 10A	2.292781749		PHOSPHO1	phosphoethanolamine/phosphocholine phosphatase	-1.859747926
THG1L	tRNA-histidine guanylyltransferase 1 like	2.292781749		ITPKA	inositol-trisphosphate 3-kinase A	-1.859881803
MLH1	mutL homolog 1	2.292781749		ZFHX2	zinc finger homeobox 2	-1.860513882
RRM2	ribonucleotide reductase regulatory subunit M2	2.289435485		TOR1A	torsin family 1 member A	-1.860949348
SHISA4	shisa family member 4	2.277984747		CDKAL1	CDK5 regulatory subunit associated protein 1 like 1	-1.862794137
DDAH2	dimethylarginine dimethylaminohydrolase 2	2.277984747		SMAD1	SMAD family member 1	-1.863462947
APBA1	amyloid beta precursor protein binding family A member 1	2.269085766		ZC3H13	zinc finger CCCH-type containing 13	-1.863535399
MMAB	methylmalonic aciduria (cobalamin deficiency) cblB type	2.264911693		ZSCAN20	zinc finger and SCAN domain containing 20	-1.863962106
DIAP1	Description Not Found	2.263034406		EPB4.1L4A	Description Not Found	-1.867896464
CAR14	carbonic anhydrase 14(Car14)	2.263034406		ZFP280C	zinc finger protein 280C(Zfp280c)	-1.867896464
C2	complement component 2	2.263034406		GM1322	predicted gene 1322(Gm1322)	-1.867896464
MAG	myelin associated glycoprotein	2.263034406		OLFR472	olfactory receptor 472(Olfr472)	-1.867896464
KCNIP3	potassium voltage-gated channel interacting protein 3	2.263034406		OLFR171	olfactory receptor 171(Olfr171)	-1.867896464
CFD	complement factor D	2.263034406		OLFR1249	olfactory receptor 1249(Olfr1249)	-1.867896464
CCNE1	cyclin E1	2.262723645		PRH1	proline rich protein HaeIII subfamily 1	-1.867896464
RYR1	ryanodine receptor 1	2.261305322		ARSI	arylsulfatase family member I	-1.867896464
PROC	protein C, inactivator of coagulation factors Va and VIIIa	2.255500733		KRT7	keratin 7	-1.867896464
ZFP27	zinc finger protein 27(Zfp27)	2.247927513		PCGF3	polycomb group ring finger 3	-1.86789

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TBX1	T-box 1	2.24792 7513		PCTP	phosphatidylcholine transfer protein	- 1.86789 6464
DHRS13	dehydrogenase/reductase 13	2.24792 7513		CALD1	caldesmon 1	- 1.86789 6464
HSPG2	heparan sulfate proteoglycan 2	2.24792 7513		TREML2	triggering receptor expressed on myeloid cells like 2	- 1.86789 6464
FRMD8	FERM domain containing 8	2.24777 312		RTN4RL1	reticulon 4 receptor like 1	- 1.86789 6464
MIOX	myo-inositol oxygenase	2.24057 9987		PARVA	parvin alpha	- 1.86847 9018
LYRM1	LYR motif containing 1	2.23266 0757		NPCD	neuronal pentraxin chromo domain(Npcd)	- 1.87190 2039
STAP1	signal transducing adaptor family member 1	2.23266 0757		RFXANK	regulatory factor X associated ankyrin containing protein	- 1.87206 109
NAT2	N-acetyltransferase 2	2.23266 0757		MAP3K14	mitogen-activated protein kinase kinase kinase 14	- 1.87229 1304
SRGAP3	SLIT-ROBO Rho GTPase activating protein 3	2.23266 0757		KLHL9	kelch like family member 9	- 1.87452 8943
NXT2	nuclear transport factor 2 like export factor 2	2.23266 0757		SESN1	sestrin 1	- 1.87526 0951
RCOR1	REST corepressor 1	2.23266 0757		ADAMTS7	ADAM metallopeptidase with thrombospondin type 1 motif 7	- 1.87940 4807
SRR	serine racemase	2.23083 6503		SNAPC1	small nuclear RNA activating complex polypeptide 1	- 1.88488 993
IKBKAP	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	2.22617 7109		ADAR	adenosine deaminase, RNA specific	- 1.88529 9379
AI597479	expressed sequence AI597479(AI597479)	2.22581 9675		LCE1C	late cornified envelope 1C	- 1.88562 6461
POP1	POP1 homolog, ribonuclease P/MRP subunit	2.22496 6365		FBXO21	F-box protein 21	- 1.88615 5099
SLC35E4	solute carrier family 35 member E4	2.21723 0716		2610524H0 6RIK	Description Not Found	- 1.88752 5271
XAB2	XPA binding protein 2	2.21723 0716		1700016K1 9RIK	Description Not Found	- 1.88752 5271
MREG	melanoregulin	2.21292 58		ZFP715	zinc finger protein 715(Zfp715)	- 1.88752 5271
FKBP11	FK506 binding protein 11	2.21072 1954		OLFR446	olfactory receptor 446(Olfr446)	- 1.88752

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IGF2BP2	insulin like growth factor 2 mRNA binding protein 2	2.20778 9851		PTK7	protein tyrosine kinase 7 (inactive)	- 1.88752 5271
NUP133	nucleoporin 133	2.20744 7199		TMEM117	transmembrane protein 117	- 1.88752 5271
OLFR1183	olfactory receptor 1183(Olfr1183)	2.20163 3861		ITIH2	inter-alpha-trypsin inhibitor heavy chain 2	- 1.88752 5271
IL1F6	interleukin 1 family, member 6(Il1f6)	2.20163 3861		TAGLN3	transgelin 3	- 1.88752 5271
OTX1	orthodenticle homeobox 1	2.20163 3861		IFI203	interferon activated gene 203(Ifi203)	- 1.88764 4112
MSH3	mutS homolog 3	2.20163 3861		ATP1B1	ATPase Na+/K+ transporting subunit beta 1	- 1.88766 4186
SCN4B	sodium voltage-gated channel beta subunit 4	2.20163 3861		BLCAP	bladder cancer associated protein	- 1.88859 6201
CROCC	ciliary rootlet coiled-coil, rootletin	2.20163 3861		IGF1R	insulin like growth factor 1 receptor	- 1.89024 137
NSUN2	NOP2/Sun RNA methyltransferase family member 2	2.19434 9986		HMG20A	high mobility group 20A	- 1.89057 9593
GAS2L1	growth arrest specific 2 like 1	2.19377 1743		WDR24	WD repeat domain 24	- 1.89152 7175
3110007F17 RIK	Description Not Found	2.19074 0399		CDX4	caudal type homeobox 4	- 1.89265 5439
DEFB15	defensin beta 15(Defb15)	2.18586 6545		CLDN18	claudin 18	- 1.89344 9375
C1QTNF2	C1q and tumor necrosis factor related protein 2	2.18586 6545		IL4RA	interleukin 4 receptor, alpha(Il4ra)	- 1.89536 9594
RAP1GAP	RAP1 GTPase activating protein	2.18586 6545		RETNLA	resistin like alpha(Retnla)	- 1.89573 9477
SNTB1	syntrophin beta 1	2.18586 6545		AA388235	expressed sequence AA388235(AA388235)	- 1.89573 9477
FAH	fumarylacetoacetate hydrolase	2.18292 5576		ZC3H6	zinc finger CCCH-type containing 6	- 1.89612 7489
AVPI1	arginine vasopressin induced 1	2.17439 3775		D930015E0 6RIK	RIKEN cDNA D930015E06 gene(D930015E06Rik)	- 1.89965 6973
RPA2	replication protein A2	2.17275 1912		NPFFR2	neuropeptide FF receptor 2	- 1.90207 3579
BRCA2	BRCA2, DNA repair associated	2.16873 2488		IRAK1	interleukin 1 receptor associated kinase 1	- 1.90243 374
RBM47	RNA binding motif	2.16591		CWF19L2	CWF19-like 2, cell cycle	-

	protein 47	1939			control (S. pombe)	1.90370 4505
MSL3L2	male-specific lethal 3-like 2 (Drosophila)(Msl3l2)	2.15906 1455		STK40	serine/threonine kinase 40	- 1.90396 4448
TNFRSF9	tumor necrosis factor receptor superfamily member 9	2.15607 1704		MARS2	methionyl-tRNA synthetase 2, mitochondrial	- 1.90457 1951
TRF	transferrin(Trf)	2.15458 8207		RAB5A	RAB5A, member RAS oncogene family	- 1.90635 0687
ZDHHC15	zinc finger DHHC-type containing 15	2.15437 2546		OLFR1037	olfactory receptor 1037(Olfr1037)	- 1.90689 0596
IGJ	Description Not Found	2.15380 5336		ARHGAP2 2	Rho GTPase activating protein 22	- 1.90689 0596
FBXO27	F-box protein 27	2.15380 5336		DENND1B	DENN domain containing 1B	- 1.90689 0596
ZDHHC24	zinc finger DHHC-type containing 24	2.15380 5336		EAPP	E2F associated phosphoprotein	- 1.90689 0596
SPCS2	signal peptidase complex subunit 2	2.15380 5336		ANKRD13 D	ankyrin repeat domain 13D	- 1.90689 0596
UCN3	urocortin 3	2.15380 5336		EFCAB2	EF-hand calcium binding domain 2	- 1.90689 0596
SLC35A1	solute carrier family 35 member A1	2.15380 5336		HOXC9	homeobox C9	- 1.90689 0596
PODXL	podocalyxin like	2.15380 5336		SENP6	SUMO1/sentrin specific peptidase 6	- 1.90795 6932
FAM154B	Description Not Found	2.15379 2145		SIDT1	SID1 transmembrane family member 1	- 1.90828 6674
NRP1	neuropilin 1	2.14747 0553		2310057J18 RIK	Description Not Found	- 1.91647 6644
ERGIC1	endoplasmic reticulum-golgi intermediate compartment 1	2.14710 4727		SPRYD4	SPRY domain containing 4	- 1.91647 6644
RNF26	ring finger protein 26	2.14681 0011		LY6D	lymphocyte antigen 6 complex, locus D	- 1.91647 6644
LCN3	lipocalin 3(Lcn3)	2.13750 3524		PPARGC1B	PPARG coactivator 1 beta	- 1.91729 1956
FMO1	flavin containing monooxygenase 1	2.13750 3524		SH3TC1	SH3 domain and tetratricopeptide repeats 1	- 1.91790 6346
RAB20	RAB20, member RAS oncogene family	2.13750 3524		FOXO1	forkhead box O1	- 1.92020 9106
KATNAL1	katanin catalytic subunit A1 like 1	2.13750 3524		DHX40	DEAH-box helicase 40	- 1.92062 3917

GPR107	G protein-coupled receptor 107	2.136424717		RECQL5	RecQ like helicase 5	-1.920664575
MELK	maternal embryonic leucine zipper kinase	2.133399125		RBM15	RNA binding motif protein 15	-1.922616041
KCTD9	potassium channel tetramerization domain containing 9	2.13207329		EGLN2	egl-9 family hypoxia inducible factor 2	-1.924079933
PBK	PDZ binding kinase	2.130417144		GPR112	Description Not Found	-1.925999419
ENPP5	ectonucleotide pyrophosphatase/phosphodiesterase 5 (putative)	2.124112676		OLFR829	olfactory receptor 829(Olfr829)	-1.925999419
ZDHHC16	zinc finger DHHC-type containing 16	2.12361008		OLFR684	olfactory receptor 684(Olfr684)	-1.925999419
OLFR1346	olfactory receptor 1346(Olfr1346)	2.121015401		RETN	resistin	-1.925999419
MILL1	MHC I like leukocyte 1(Mill1)	2.121015401		ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	-1.925999419
RHCG	Rh family C glycoprotein	2.121015401		FES	FES proto-oncogene, tyrosine kinase	-1.925999419
CLDN1	claudin 1	2.121015401		KIF13A	kinesin family member 13A	-1.925999419
LHX3	LIM homeobox 3	2.121015401		TRPT1	tRNA phosphotransferase 1	-1.926457816
TUBB2A	tubulin beta 2A class IIa	2.121015401		PLCB2	phospholipase C beta 2	-1.927343833
GSG2	germ cell associated 2, haspin	2.119412265		NADSYN1	NAD synthetase 1	-1.929674394
HYAL2	hyaluronoglucosaminidase 2	2.107345942		4833420G17RIK	Description Not Found	-1.93060469
1700003F12RIK	Description Not Found	2.10433666		P2RY10	purinergic receptor P2Y10	-1.930737338
RUSC2	RUN and SH3 domain containing 2	2.10433666		PPAPDC3	Description Not Found	-1.935459748
LRRIQ3	leucine rich repeats and IQ motif containing 3	2.10433666		DIP2B	disco interacting protein 2 homolog B	-1.935459748
CHSY1	chondroitin sulfate synthase 1	2.10433666		RHAG	Rh-associated glycoprotein	-1.935459748
DUSP23	dual specificity phosphatase 23	2.10433666		EMID1	EMI domain containing 1	-1.935459748
RRAGB	Ras related GTP binding	2.10433		RNF4	ring finger protein 4	-

	B	666				1.93883 4579
KCNAB3	potassium voltage-gated channel subfamily A regulatory beta subunit 3	2.10433 666		UBL5	ubiquitin like 5	- 1.93895 2478
GRPEL2	GrpE like 2, mitochondrial	2.10312 9681		PROSC	proline synthetase cotranscribed homolog (bacterial)	- 1.94016 675
TRAF2	TNF receptor associated factor 2	2.10202 9095		FZD5	frizzled class receptor 5	- 1.94250 3137
COQ7	coenzyme Q7, hydroxylase	2.10020 5246		UBE2D1	ubiquitin conjugating enzyme E2 D1	- 1.94277 5467
TMEM126 B	transmembrane protein 126B	2.09918 7297		KLRA7	killer cell lectin-like receptor, subfamily A, member 7(Klra7)	- 1.94351 0757
SGPL1	sphingosine-1-phosphate lyase 1	2.09711 2667		TMEM63C	transmembrane protein 63C	- 1.94425 562
CAPN2	calpain 2	2.09644 7979		2810006K2 3RIK	Description Not Found	- 1.94485 8446
CHEK2	checkpoint kinase 2	2.08845 7439		OLFR672	olfactory receptor 672(Olfr672)	- 1.94485 8446
GLRP1	glutamine repeat protein 1(Glrp1)	2.08746 2841		OLFR1347	olfactory receptor 1347(Olfr1347)	- 1.94485 8446
RTN4R	reticulon 4 receptor	2.08746 2841		MTTP	microsomal triglyceride transfer protein	- 1.94485 8446
TRIM37	tripartite motif containing 37	2.08746 2841		MSX1	msh homeobox 1	- 1.94485 8446
NUCB2	nucleobindin 2	2.08746 2841		BSND	barttin CLCNK type accessory beta subunit	- 1.94485 8446
UBE2T	ubiquitin conjugating enzyme E2 T	2.07361 6696		MARK1	microtubule affinity regulating kinase 1	- 1.94485 8446
CREB3L3	cAMP responsive element binding protein 3 like 3	2.07038 9328		CHRNB1	cholinergic receptor nicotinic beta 1 subunit	- 1.94485 8446
CHRM4	cholinergic receptor muscarinic 4	2.07038 9328		CRYL1	crystallin lambda 1	- 1.94641 9425
SLC16A13	solute carrier family 16 member 13	2.07038 9328		TEC	tec protein tyrosine kinase	- 1.94733 0641
OLFML2B	olfactomedin like 2B	2.07038 9328		XKR6	XK related 6	- 1.95031 589
CSNK1G1	casein kinase 1 gamma 1	2.07038 9328		ARC	activity-regulated cytoskeleton-associated protein	- 1.95363 6949
S100A14	S100 calcium binding protein A14	2.07038 9328		WFDC10	WAP four-disulfide core domain 10(Wfdc10)	- 1.95419 631

SMYD4	SET and MYND domain containing 4	2.070389328		OLFR866	olfactory receptor 866(Olfr866)	-1.959768144
CH25H	cholesterol 25-hydroxylase	2.070389328		WIPI2	WD repeat domain, phosphoinositide interacting 2	-1.960171668
TEX2	testis expressed 2	2.067875748		OLFR948	olfactory receptor 948(Olfr948)	-1.963474124
SYN1	synapsin I	2.063429187		CRTAM	cytotoxic and regulatory T-cell molecule	-1.963474124
CYP3A13	cytochrome P450, family 3, subfamily a, polypeptide 13(Cyp3a13)	2.060581758		CCDC116	coiled-coil domain containing 116	-1.963474124
CBX8	chromobox 8	2.060297534		ALAS2	5'-aminolevulinate synthase 2	-1.963474124
TOR2A	torsin family 2 member A	2.056535553		SDC4	syndecan 4	-1.963474124
E230025N22RIK	Riken cDNA E230025N22 gene(E230025N22Rik)	2.053111336		LENG1	leukocyte receptor cluster member 1	-1.963474124
OLFR963	olfactory receptor 963(Olfr963)	2.053111336		TRIM65	tripartite motif containing 65	-1.963474124
OLFR694	olfactory receptor 694(Olfr694)	2.053111336		ADRA2B	adrenoceptor alpha 2B	-1.963474124
AKR1B8	aldo-keto reductase family 1, member B8(Akr1b8)	2.053111336		CPSF4	cleavage and polyadenylation specific factor 4	-1.964016356
UGDH	UDP-glucose 6-dehydrogenase	2.053111336		LRCH1	leucine rich repeats and calponin homology domain containing 1	-1.966068313
CLPB	ClpB homolog, mitochondrial AAA ATPase chaperonin	2.053111336		CPXM1	carboxypeptidase X (M14 family), member 1	-1.96782195
KLHDC9	kelch domain containing 9	2.053111336		PARP6	poly(ADP-ribose) polymerase family member 6	-1.968362498
MCPH1	microcephalin 1	2.051211057		GTF3C2	general transcription factor IIIC subunit 2	-1.975687807
IL2RA	interleukin 2 receptor subunit alpha	2.049225103		NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like, E3 ubiquitin protein ligase	-1.978518523
CAR9	carbonic anhydrase 9(Car9)	2.044394119		DICER1	dicer 1, ribonuclease III	-1.97959126
USP10	ubiquitin specific peptidase 10	2.044394119		GBA2	glucosylceramidase beta 2	-1.980387638
FASTKD2	FAST kinase domains 2	2.044394119		OLFR1269	olfactory receptor 1269(Olfr1269)	-1.98185

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STRA13	stimulated by retinoic acid 13	2.04439 4119		EAR10	eosinophil-associated, ribonuclease A family, member 10(Ear10)	- 1.98185 2653
HIST1H2A D	histone cluster 1, H2ad	2.04411 1161		ADAM5	ADAM metallopeptidase domain 5 (pseudogene)	- 1.98185 2653
PLA1A	phospholipase A1 member A	2.03715 7781		MED1	mediator complex subunit 1	- 1.98185 2653
MCM3	minichromosome maintenance complex component 3	2.03646 2274		FGFRL1	fibroblast growth factor receptor-like 1	- 1.98185 2653
PIF1	PIF1 5'-to-3' DNA helicase	2.03609 4966		EXTL1	exostosin like glycosyltransferase 1	- 1.98185 2653
GALR1	galanin receptor 1	2.03562 391		ZFHX3	zinc finger homeobox 3	- 1.98185 2653
DLD	dihydrolipoamide dehydrogenase	2.03562 391		FBXO30	F-box protein 30	- 1.98185 2653
GGCX	gamma-glutamyl carboxylase	2.03562 391		RNF112	ring finger protein 112	- 1.98468 1148
CEP68	centrosomal protein 68	2.03562 391		PARP3	poly(ADP-ribose) polymerase family member 3	- 1.98599 548
MMP11	matrix metallopeptidase 11	2.03562 391		AIRE	autoimmune regulator	- 1.98641 0935
STMN1	stathmin 1	2.03331 6653		CYB561D1	cytochrome b561 family member D1	- 1.98710 7951
SLCO4A1	solute carrier organic anion transporter family member 4A1	2.03217 627		TRAPPC5	trafficking protein particle complex 5	- 1.98726 9174
TIAL1	TIA1 cytotoxic granule-associated RNA binding protein-like 1	2.02888 965		RFTN2	raftlin family member 2	- 1.98749 308
0610009B2 2RIK	Description Not Found	2.01792 1908		FRAT1	frequently rearranged in advanced T-cell lymphomas 1	- 1.99989 4159
GM1673	predicted gene 1673(Gm1673)	2.01792 1908		DMC1	DNA meiotic recombinase 1	-2
CCL26	C-C motif chemokine ligand 26	2.01792 1908		RIPK4	receptor interacting serine/threonine kinase 4	-2
ZWILCH	zwilch kinetochore protein	2.01792 1908		PVR	poliovirus receptor	-2
GABRA1	gamma-aminobutyric acid type A receptor alpha1 subunit	2.01792 1908		LPIN2	lipin 2	-2
ACP2	acid phosphatase 2, lysosomal	2.01714 3376		THAP2	THAP domain containing 2	-2
FAM131A	family with sequence similarity 131 member A	2.01321 9985		SHE	Src homology 2 domain containing E	-2
PXMP4	peroxisomal membrane protein 4	2.01249 7517		ARHGAP2 5	Rho GTPase activating protein 25	- 2.00561 8551

CDC6	cell division cycle 6	2.01116 6077		CSF1R	colony stimulating factor 1 receptor	- 2.00635 0699
AXL	AXL receptor tyrosine kinase	2.00813 1619		ZFP1	ZFP1 zinc finger protein	- 2.00790 4843
RBBP7	RB binding protein 7, chromatin remodeling factor	2.00674 6832		SFN	stratifin	- 2.00898 8783
PABPC4	poly(A) binding protein cytoplasmic 4	2.00526 0152		COL17A1	collagen type XVII alpha 1	- 2.01038 6372
HIST1H2A K	histone cluster 1, H2ak	2.00330 7679		XKRX	XK related, X-linked	- 2.01056 96
MTFMT	mitochondrial methionyl-tRNA formyltransferase	2.00175 4595		BRD8	bromodomain containing 8	- 2.01346 226
ZFP449	zinc finger protein 449(Zfp449)	2		ZFP213	zinc finger protein 213(Zfp213)	- 2.01353 2276
D930020B1 8RIK	RIKEN cDNA D930020B18 gene(D930020B18Rik)	2		ZFY2	zinc finger protein 2, Y-linked(Zfy2)	- 2.01565 7249
LCE1D	late cornified envelope 1D	2		MAP3K3	mitogen-activated protein kinase kinase kinase 3	- 2.01612 652
UCN	urocortin	2		ZFP445	zinc finger protein 445(Zfp445)	- 2.01792 1908
SYT4	synaptotagmin 4	2		MTAP7D3	MAP7 domain containing 3(Mtap7d3)	- 2.01792 1908
GPR132	G protein-coupled receptor 132	2		TMPRSS11 A	transmembrane protease, serine 11A	- 2.01792 1908
SDHD	succinate dehydrogenase complex subunit D	2		OLFM2	olfactomedin 2	- 2.01792 1908
PANK3	pantothenate kinase 3	2		GRM4	glutamate metabotropic receptor 4	- 2.01792 1908
SBSN	suprabasin	1.99095 486		ONECUT2	one cut homeobox 2	- 2.01792 1908
WDR59	WD repeat domain 59	1.98997 6974		HNRNPH3	heterogeneous nuclear ribonucleoprotein H3	- 2.01792 1908
MTMR9	myotubularin related protein 9	1.98784 4644		ZMYM5	zinc finger MYM-type containing 5	- 2.02020 4421
IL15RA	interleukin 15 receptor subunit alpha	1.98562 8881		RAPGEF6	Rap guanine nucleotide exchange factor 6	- 2.02095 3989
RHBDF2	rhomboid 5 homolog 2	1.98468 1148		CD34	CD34 molecule	- 2.02671 4044
NHLRC2	NHL repeat containing 2	1.98375 117		ACVR2B	activin A receptor type 2B	- 2.02671

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NMRAL1	NmrA-like family domain containing 1	1.98337 0163		RILP	Rab interacting lysosomal protein	- 2.02680 0059
OLFR120	olfactory receptor 120(Olfr120)	1.98185 2653		EMR1	Description Not Found	- 2.03121 8731
OLFR1051	olfactory receptor 1051(Olfr1051)	1.98185 2653		DNAJA2	DnaJ heat shock protein family (Hsp40) member A2	- 2.03129 1874
PCDHGA9	protocadherin gamma subfamily A, 9	1.98185 2653		SEMA4B	semaphorin 4B	- 2.03198 5281
FST	follistatin	1.98185 2653		1700015E1 3RIK	Description Not Found	- 2.03562 391
RECQL4	RecQ like helicase 4	1.97661 1605		RHOX1	reproductive homeobox 1(Rhox1)	- 2.03562 391
NFKBIL1	NFKB inhibitor like 1	1.97096 9489		TCP11	t-complex 11	- 2.03562 391
TUBD1	tubulin delta 1	1.96436 7355		FBXW11	F-box and WD repeat domain containing 11	- 2.03562 391
FSD1	fibronectin type III and SPRY domain containing 1	1.96347 4124		ALX1	ALX homeobox 1	- 2.03562 391
GDF5	growth differentiation factor 5	1.96347 4124		BST1	bone marrow stromal cell antigen 1	- 2.03562 391
TREML4	triggering receptor expressed on myeloid cells like 4	1.96347 4124		GPR83	G protein-coupled receptor 83	- 2.03562 391
SORD	sorbitol dehydrogenase	1.96347 4124		RECK	reversion inducing cysteine rich protein with kazal motifs	- 2.03611 2118
HEBP1	heme binding protein 1	1.96347 4124		ABHD14B	abhydrolase domain containing 14B	- 2.04046 0993
KDELR2	KDEL endoplasmic reticulum protein retention receptor 2	1.96155 465		GPRC6A	G protein-coupled receptor class C group 6 member A	- 2.04212 2888
TRPV4	transient receptor potential cation channel subfamily V member 4	1.95884 2675		GRAMD3	GRAM domain containing 3	- 2.04229 6131
ABHD5	abhydrolase domain containing 5	1.95738 9419		IMPACT	impact RWD domain protein	- 2.04243 6285
YOD1	YOD1 deubiquitinase	1.95419 631		TOP1	topoisomerase (DNA) I	- 2.04439 4119
MAGOHB	mago homolog B, exon junction complex core component	1.95293 2368		NACC2	NACC family member 2	- 2.04439 4119
TSPAN2	tetraspanin 2	1.95176 103		PKNOX1	PBX/knotted 1 homeobox 1	- 2.04579 7958
LDB3	LIM domain binding 3	1.94850		TMEM79	transmembrane protein 79	-

		842				2.04662 8729
1700067P10 RIK	Description Not Found	1.94485 8446		MYCBP2	MYC binding protein 2, E3 ubiquitin protein ligase	- 2.04736 8853
9530091C0 8RIK	Description Not Found	1.94485 8446		MAS1	MAS1 proto-oncogene, G protein-coupled receptor	- 2.04805 5651
RHOJ	ras homolog family member J	1.94485 8446		GEMIN6	gem nuclear organelle associated protein 6	- 2.05311 1336
SFRP1	secreted frizzled related protein 1	1.94485 8446		TMEM100	transmembrane protein 100	- 2.05311 1336
XPNPEP2	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound	1.94485 8446		FOXI1	forkhead box I1	- 2.05311 1336
RNASE4	ribonuclease A family member 4	1.93545 9748		OPLAH	5-oxoprolinase (ATP-hydrolysing)	- 2.05311 1336
NAPSA	napsin A aspartic peptidase	1.93158 6931		BC094916	Description Not Found	- 2.05833 7935
TIMM22	translocase of inner mitochondrial membrane 22 homolog (yeast)	1.93120 2999		GZMM	granzyme M	- 2.06119 3332
MTCH2	mitochondrial carrier 2	1.92977 4464		RCOR2	REST corepressor 2	- 2.06280 495
ADCK4	aarF domain containing kinase 4	1.92792 1426		NR2E1	nuclear receptor subfamily 2 group E member 1	- 2.06366 268
PDSS1	prenyl (decaprenyl) diphosphate synthase, subunit 1	1.92624 5513		NT5DC1	5'-nucleotidase domain containing 1	- 2.06599 4119
ZFP94	zinc finger protein 94(Zfp94)	1.92599 9419		SCN8A	sodium voltage-gated channel alpha subunit 8	- 2.06750 099
FABP9	fatty acid binding protein 9	1.92599 9419		CBX7	chromobox 7	- 2.06750 099
RNF170	ring finger protein 170	1.92599 9419		FHAD1	forkhead associated phosphopeptide binding domain 1	- 2.06811 4527
TLR3	toll like receptor 3	1.92599 9419		KCNQ3	potassium voltage-gated channel subfamily Q member 3	- 2.06888 5643
LIPH	lipase H	1.92599 9419		BC025920	zinc finger protein pseudogene(BC025920)	- 2.07038 9328
PLEKHA7	pleckstrin homology domain containing A7	1.92599 9419		FCGR1	Fc receptor, IgG, high affinity I(Fcgr1)	- 2.07038 9328
LXN	latexin	1.92446 06		SYN3	synapsin III	- 2.07038 9328
PPCS	phosphopantothenoylcys teine synthetase	1.92294 738		KLHL5	kelch like family member 5	- 2.07038 9328

BTRC	beta-transducin repeat containing E3 ubiquitin protein ligase	1.92065845		EDA2R	ectodysplasin A2 receptor	-2.070389328
APIP	APAF1 interacting protein	1.920326443		STK38	serine/threonine kinase 38	-2.070389328
ANK1	ankyrin 1	1.916476644		CDKN2D	cyclin dependent kinase inhibitor 2D	-2.072205467
TOMM70A	translocase of outer mitochondrial membrane 70 homolog A (yeast)(Tomm70a)	1.913107017		IL6ST	interleukin 6 signal transducer	-2.072660321
ABCB1B	ATP-binding cassette, sub-family B (MDR/TAP), member 1B(Abcb1b)	1.908033945		OLFR427	olfactory receptor 427(Olfr427)	-2.074318985
ACN9	Description Not Found	1.906890596		BAIAP2	BAI1 associated protein 2	-2.078951341
DLX1AS	distal-less homeobox 1, antisense(Dlx1as)	1.906890596		TIMP2	TIMP metallopeptidase inhibitor 2	-2.079805224
MRGPRD	MAS related GPR family member D	1.906890596		CDCP1	CUB domain containing protein 1	-2.083991945
WDHD1	WD repeat and HMG-box DNA binding protein 1	1.906890596		RGS14	regulator of G-protein signaling 14	-2.084198537
USP46	ubiquitin specific peptidase 46	1.906890596		VASP	vasodilator-stimulated phosphoprotein	-2.086359868
PKN3	protein kinase N3	1.906890596		ZFP318	zinc finger protein 318(Zfp318)	-2.087462841
OSCAR	osteoclast associated, immunoglobulin-like receptor	1.906890596		PSG25	pregnancy-specific glycoprotein 25(Psg25)	-2.087462841
CDK2	cyclin dependent kinase 2	1.906746727		PDZD8	PDZ domain containing 8	-2.087462841
TRIM62	tripartite motif containing 62	1.905520967		DET1	de-etiolated homolog 1 (Arabidopsis)	-2.087462841
SQLE	squalene epoxidase	1.903767694		CHST3	carbohydrate sulfotransferase 3	-2.087462841
MCM10	minichromosome maintenance 10 replication initiation factor	1.89598378		EHHADH	enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase	-2.087462841
CCDC90B	coiled-coil domain containing 90B	1.894803124		FCGRT	Fc fragment of IgG receptor and transporter	-2.090735607
SPATS1	spermatogenesis associated serine rich 1	1.892848083		CFP	complement factor properdin	-2.09437407
GPNMB	glycoprotein nmb	1.891427809		SOCS6	suppressor of cytokine signaling 6	-2.09463

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MST1	macrophage stimulating 1	1.88993148		SYT11	synaptotagmin 11	-2.09592442
LTB4R1	leukotriene B4 receptor 1(Ltb4r1)	1.887644112		MBTPS2	membrane bound transcription factor peptidase, site 2	-2.09592442
DNAJC5B	DnaJ heat shock protein family (Hsp40) member C5 beta	1.887525271		MEFV	Mediterranean fever	-2.097059135
PCDHGC4	protocadherin gamma subfamily C, 4	1.887525271		SRPK2	SRSF protein kinase 2	-2.10044313
HMX2	H6 family homeobox 2	1.887525271		DUSP16	dual specificity phosphatase 16	-2.102740277
NDUFAB1	NADH:ubiquinone oxidoreductase subunit AB1	1.887525271		SLC6A7	solute carrier family 6 member 7	-2.103129681
MGP	matrix Gla protein	1.887525271		HBB-B1	hemoglobin, beta adult major chain(Hbb-b1)	-2.10433666
ZKSCAN2	zinc finger with KRAB and SCAN domains 2	1.887525271		TNPO3	transportin 3	-2.10433666
CCDC51	coiled-coil domain containing 51	1.887525271		CSNK2B	casein kinase 2 beta	-2.10433666
CTSK	cathepsin K	1.887525271		BCAS1	breast carcinoma amplified sequence 1	-2.10433666
PRDM9	PR domain 9	1.887525271		INO80	INO80 complex subunit	-2.10433666
C8A	complement component 8 alpha subunit	1.887525271		MPG	N-methylpurine DNA glycosylase	-2.10433666
NEUROG1	neurogenin 1	1.887082413		FOXP1	forkhead box P1	-2.107557734
NUSAP1	nucleolar and spindle associated protein 1	1.886951242		USP21	ubiquitin specific peptidase 21	-2.107658353
LZIC	leucine zipper and CTNNBIP1 domain containing	1.877899051		LIMS1	LIM zinc finger domain containing 1	-2.112700133
ZFP609	zinc finger protein 609(Zfp609)	1.87774425		FXYD1	FXYD domain containing ion transport regulator 1	-2.112700133
GPR87	G protein-coupled receptor 87	1.87774425		POU3F1	POU class 3 homeobox 1	-2.113574207
GMPPB	GDP-mannose pyrophosphorylase B	1.871523637		OLFR591	olfactory receptor 591(Olfr591)	-2.114494844
TMEM115	transmembrane protein 115	1.870364796		GRAMD4	GRAM domain containing 4	-2.114673101
DSN1	DSN1 homolog, MIS12	1.86847		BCL2	BCL2, apoptosis regulator	-

	kinetochore complex component	9018				2.11587 8669
A530099J1 9RIK	Description Not Found	1.86789 6464		PELI3	pellino E3 ubiquitin protein ligase family member 3	- 2.11891 5146
1700007K0 9RIK	Description Not Found	1.86789 6464		PPP1CB	protein phosphatase 1 catalytic subunit beta	- 2.11923 6221
1810043G0 2RIK	Description Not Found	1.86789 6464		TFF2	trefoil factor 2	- 2.12101 5401
UCHL1	ubiquitin C-terminal hydrolase L1	1.86789 6464		GCA	grancalcin	- 2.12101 5401
PTCH2	patched 2	1.86789 6464		LYL1	LYL1, basic helix-loop-helix family member	- 2.12101 5401
APBB3	amyloid beta precursor protein binding family B member 3	1.86789 6464		ATG4B	autophagy related 4B cysteine peptidase	- 2.12101 5401
PTER	phosphotriesterase related	1.86789 6464		CCDC102A	coiled-coil domain containing 102A	- 2.12101 5401
PRKCE	protein kinase C epsilon	1.86789 6464		ATP2A1	ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 1	- 2.12101 5401
PLEKHM3	pleckstrin homology domain containing M3	1.86789 6464		TERF2	telomeric repeat binding factor 2	- 2.12358 5568
HIST1H4C	histone cluster 1, H4c	1.86789 6464		LCN5	lipocalin 5(Lcn5)	- 2.12443 2612
PLS3	plastin 3	1.86789 6464		TM6SF1	transmembrane 6 superfamily member 1	- 2.12453 3495
DUSP4	dual specificity phosphatase 4	1.86768 6654		SSBP2	single stranded DNA binding protein 2	- 2.12928 3017
SCLY	selenocysteine lyase	1.86280 2277		KRTAP6-2	keratin associated protein 6-2	- 2.13750 3524
RPRD1A	regulation of nuclear pre-mRNA domain containing 1A	1.86177 7838		CRHBP	corticotropin releasing hormone binding protein	- 2.13750 3524
CCRL2	C-C motif chemokine receptor like 2	1.86175 579		TOPBP1	topoisomerase (DNA) II binding protein 1	- 2.13750 3524
CCT7	chaperonin containing TCP1 subunit 7	1.86163 6037		SLC35A3	solute carrier family 35 member A3	- 2.13750 3524
ZFP217	zinc finger protein 217(Zfp217)	1.86109 7096		CACNB4	calcium voltage-gated channel auxiliary subunit beta 4	- 2.13750 3524
ACTN4	actinin alpha 4	1.85968 9938		TASP1	taspase 1	- 2.13750 3524
KCNA3	potassium voltage-gated channel subfamily A	1.85913 5363		HMBOX1	homeobox containing 1	- 2.14531

	member 3					3833
CUL7	cullin 7	1.858597911		ZFP62	ZFP62 zinc finger protein	-2.145677455
LRRC59	leucine rich repeat containing 59	1.857543219		PCDHB4	protocadherin beta 4	-2.148666128
PHTF2	putative homeodomain transcription factor 2	1.855602651		SLC35F3	solute carrier family 35 member F3	-2.15120644
KDELC1	KDEL motif containing 1	1.852556218		AW549877	expressed sequence AW549877(AW549877)	-2.151324826
SEC24D	SEC24 homolog D, COPII coat complex component	1.8483841		GIMAP9	GTPase, IMAP family member 9(Gimap9)	-2.152400921
OLFR222	olfactory receptor 222(Olfr222)	1.847996907		ZFP329	zinc finger protein 329(Zfp329)	-2.153805336
OLFR118	olfactory receptor 118(Olfr118)	1.847996907		KRT74	keratin 74	-2.153805336
CASKIN2	CASK interacting protein 2	1.847996907		REG3A	regenerating family member 3 alpha	-2.153805336
TPK1	thiamin pyrophosphokinase 1	1.847996907		RAB4A	RAB4A, member RAS oncogene family	-2.154308231
NOL3	nucleolar protein 3	1.847996907		CECR5	cat eye syndrome chromosome region, candidate 5	-2.155682653
UBA6	ubiquitin like modifier activating enzyme 6	1.847388943		ESM1	endothelial cell specific molecule 1	-2.157156463
RAVER1	ribonucleoprotein, PTB binding 1	1.846151947		HS6ST1	heparan sulfate 6-O-sulfotransferase 1	-2.164820712
NAT10	N-acetyltransferase 10	1.843300131		DDB2	damage specific DNA binding protein 2	-2.168338824
HIST1H3H	histone cluster 1, H3h	1.842055889		5430435G22RIK	Description Not Found	-2.169925001
SNX8	sorting nexin 8	1.840985134		ALOX12B	arachidonate 12-lipoxygenase, 12R type	-2.169925001
POLR3K	polymerase (RNA) III subunit K	1.839538616		SLC34A3	solute carrier family 34 member 3	-2.169925001
WDR55	WD repeat domain 55	1.835957408		TNS4	tensin 4	-2.169925001
WDR93	WD repeat domain 93	1.830541464		CANX	calnexin	-2.169925001
PLSCR1	phospholipid scramblase 1	1.828635636		BET1	Bet1 golgi vesicular membrane trafficking protein	-2.169925001
ARL6	ADP ribosylation factor	1.82781		BEST2	bestrophin 2	-

	like GTPase 6	9025				2.16992 5001
NOL9	nucleolar protein 9	1.82781 9025		USP28	ubiquitin specific peptidase 28	- 2.17299 8154
PNKD	paroxysmal nonkinesigenic dyskinesia	1.82781 9025		PDE4B	phosphodiesterase 4B	- 2.17361 4018
TMEM139	transmembrane protein 139	1.82781 9025		CNOT4	CCR4-NOT transcription complex subunit 4	- 2.17791 7792
ASPH	aspartate beta-hydroxylase	1.82781 9025		NECAP1	NECAP endocytosis associated 1	- 2.17804 3245
LZTFL1	leucine zipper transcription factor like 1	1.82781 9025		JUN	Jun proto-oncogene, AP-1 transcription factor subunit	- 2.17856 5309
RHEBL1	Ras homolog enriched in brain like 1	1.82781 9025		SLC10A7	solute carrier family 10 member 7	- 2.17990 909
CHCHD5	coiled-coil-helix-coiled-coil-helix domain containing 5	1.82552 849		IL17A	interleukin 17A	- 2.18170 2586
GPD2	glycerol-3-phosphate dehydrogenase 2	1.82414 8697		ERICH1	glutamate rich 1	- 2.18228 6216
STK39	serine/threonine kinase 39	1.82360 8879		HN1L	hematological and neurological expressed 1-like	- 2.18586 6545
MAGED2	MAGE family member D2	1.82086 3253		SLFNL1	schlafen like 1	- 2.18586 6545
TBC1D9B	TBC1 domain family member 9B	1.81321 9568		MYOD1	myogenic differentiation 1	- 2.18586 6545
LSS	lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	1.80954 0228		TRIM35	tripartite motif containing 35	- 2.18586 6545
OLFR859	olfactory receptor 859(Olfr859)	1.80735 4922		CHRNE	cholinergic receptor nicotinic epsilon subunit	- 2.18639 7884
OLFR1225	olfactory receptor 1225(Olfr1225)	1.80735 4922		PHF21A	PHD finger protein 21A	- 2.19094 3197
IFNA11	interferon alpha 11(Ifna11)	1.80735 4922		HIST1H2A E	histone cluster 1, H2ae	- 2.19669 8179
ARG1	arginase 1	1.80735 4922		SATB1	SATB homeobox 1	- 2.19865 9952
ASCL3	achaete-scute family bHLH transcription factor 3	1.80735 4922		LCN8	lipocalin 8	- 2.20163 3861
AGA	aspartylglucosaminidase	1.80735 4922		ABCG5	ATP binding cassette subfamily G member 5	- 2.20163 3861
MAP3K12	mitogen-activated protein kinase kinase kinase 12	1.80653 0545		KRBA1	KRAB-A domain containing 1	- 2.20295 9029

COMMD10	COMM domain containing 10	1.802771724		CD274	CD274 molecule	-2.206081393
STYX	serine/threonine/tyrosine interacting protein	1.801251483		DYRK2	dual specificity tyrosine phosphorylation regulated kinase 2	-2.206730511
EPHA6	EPH receptor A6	1.797583147		ZFP292	zinc finger protein 292(Zfp292)	-2.209453366
SERPINA3F	serine (or cysteine) peptidase inhibitor, clade A, member 3F(Serpina3f)	1.794445043		PRX	periaxin	-2.209453366
PUS10	pseudouridylate synthase 10	1.791814071		SPAG1	sperm associated antigen 1	-2.209453366
RASL12	RAS like family 12	1.791652715		ASGR2	asialoglycoprotein receptor 2	-2.209784456
MRPL51	mitochondrial ribosomal protein L51	1.787631232		PTEN	phosphatase and tensin homolog	-2.215013513
OLFR1306	olfactory receptor 1306(Olfr1306)	1.786596362		IL1A	interleukin 1 alpha	-2.217230716
BCL2A1C	B cell leukemia/lymphoma 2 related protein A1c(Bcl2a1c)	1.786596362		TPCN2	two pore segment channel 2	-2.217230716
HOXD1	homeobox D1	1.786596362		IKBKB	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	-2.217230716
MEMO1	mediator of cell motility 1	1.786596362		ST6GAL1	ST6 beta-galactoside alpha-2,6-sialyltransferase 1	-2.218342351
ARCN1	archain 1	1.786596362		TMEM161A	transmembrane protein 161A	-2.232660757
NUDT10	nudix hydrolase 10	1.786596362		STK32B	serine/threonine kinase 32B	-2.232660757
SLC4A4	solute carrier family 4 member 4	1.786596362		CHST14	carbohydrate sulfotransferase 14	-2.232660757
DHRS4	dehydrogenase/reductase 4	1.786596362		AQP3	aquaporin 3 (Gill blood group)	-2.232660757
TOM1	target of myb1 membrane trafficking protein	1.786596362		RASSF3	Ras association domain family member 3	-2.233505898
TST	thiosulfate sulfurtransferase	1.786596362		OTUD7B	OTU deubiquitinase 7B	-2.242923867
RIPK2	receptor interacting serine/threonine kinase 2	1.784428584		AP3M2	adaptor related protein complex 3 mu 2 subunit	-2.247481244
NAIP2	NLR family, apoptosis inhibitory protein 2(Naip2)	1.780351745		PSMA6	proteasome subunit alpha 6	-2.247927513

OLFR133	olfactory receptor 133(Olfr133)	1.77946 628		PRCC	papillary renal cell carcinoma (translocation-associated)	-2.24792 7513
NBR1	NBR1, autophagy cargo receptor	1.77699 5396		ZFP688	zinc finger protein 688(Zfp688)	-2.26221 8541
GLIS1	GLIS family zinc finger 1	1.77651 2203		DOCK11	dedicator of cytokinesis 11	-2.26221 8541
SLC35A2	solute carrier family 35 member A2	1.77623 2819		PLA2G4F	phospholipase A2 group IVF	-2.26303 4406
AU022252	expressed sequence AU022252(AU022252)	1.77455 9318		MYPN	myopalladin	-2.26303 4406
OLFR64	olfactory receptor 64(Olfr64)	1.77399 1786		FRS2	fibroblast growth factor receptor substrate 2	-2.26303 4406
PPAPDC2	Description Not Found	1.77198 3065		STARD6	StAR related lipid transfer domain containing 6	-2.26303 4406
DIS3	DIS3 homolog, exosome endoribonuclease and 3'-5' exoribonuclease	1.77137 5295		WSCD2	WSC domain containing 2	-2.27065 3766
4931440F15 RIK	Description Not Found	1.77082 9046		TLE1	transducin like enhancer of split 1	-2.27263 1746
ZFP771	zinc finger protein 771(Zfp771)	1.77019 569		HDHD3	haloacid dehalogenase like hydrolase domain containing 3	-2.27296 6802
HMBS	hydroxymethylbilane synthase	1.76967 6967		1700029J07 RIK	Description Not Found	-2.27798 4747
RCC1	regulator of chromosome condensation 1	1.76826 7605		CLEC2D	C-type lectin domain family 2 member D	-2.27798 4747
SPAG5	sperm associated antigen 5	1.76798 0257		PPM1G	protein phosphatase, Mg2+/Mn2+ dependent 1G	-2.27798 4747
TSPAN31	tetraspanin 31	1.76762 6782		CDKN1B	cyclin dependent kinase inhibitor 1B	-2.28097 0508
PCDHGB8	protocadherin gamma subfamily B, 8(Pcdhgb8)	1.76553 4746		OASL1	2'-5' oligoadenylate synthetase-like 1(Oasl1)	-2.28169 825
PRL2B1	prolactin family 2, subfamily b, member 1(Prl2b1)	1.76553 4746		G0S2	G0/G1 switch 2	-2.28204 5463
OBOX5	oocyte specific homeobox 5(Obox5)	1.76553 4746		TMEM17	transmembrane protein 17	-2.28540 2219
PIK3R3	phosphoinositide-3-kinase regulatory subunit 3	1.76553 4746		BLVRB	biliverdin reductase B	-2.29061 9427
MAP3K4	mitogen-activated protein kinase kinase kinase 4	1.76553 4746		GOSR1	golgi SNAP receptor complex member 1	-2.29089 7209
LRRC30	leucine rich repeat containing 30	1.76553 4746		ZFP26	zinc finger protein 26(Zfp26)	-2.29278

						1749
EN2	engrailed homeobox 2	1.76553 4746		CXCL2	C-X-C motif chemokine ligand 2	- 2.29278 1749
HOOK3	hook microtubule-tethering protein 3	1.76553 4746		SNX7	sorting nexin 7	- 2.29278 1749
MYO9A	myosin IXA	1.76553 4746		ZDHHC23	zinc finger DHHC-type containing 23	- 2.29278 1749
STX7	syntaxin 7	1.76506 0364		GALNT6	polypeptide N-acetylgalactosaminyltransferase 6	- 2.29278 1749
ATM	ATM serine/threonine kinase	1.76350 4031		AMPD1	adenosine monophosphate deaminase 1	- 2.29784 4157
KCNK6	potassium two pore domain channel subfamily K member 6	1.76338 5753		GIMAP5	GTPase, IMAP family member 5	- 2.30324 6615
PQLC3	PQ loop repeat containing 3	1.75995 4577		ATP5F1	ATP synthase, H+ transporting, mitochondrial Fo complex subunit B1	- 2.30539 9163
KIFAP3	kinesin associated protein 3	1.75884 3168		LHFPL2	lipoma HMGIC fusion partner-like 2	- 2.30742 8525
E2F4	E2F transcription factor 4	1.75775 2886		KIF1B	kinesin family member 1B	- 2.31323 1129
ETV5	ETS variant 5	1.75770 9335		TLE6	transducin like enhancer of split 6	- 2.32192 8095
GTF2E2	general transcription factor IIE subunit 2	1.75666 387		SHF	Src homology 2 domain containing F	- 2.33069 1998
GPR150	G protein-coupled receptor 150	1.75547 927		NGFR	nerve growth factor receptor	- 2.33143 8521
E130308A19RIK	RIKEN cDNA E130308A19 gene(E130308A19Rik)	1.75488 7502		KLRA4	killer cell lectin-like receptor, subfamily A, member 4(Klra4)	- 2.33448 5632
DPYSL4	dihydropyrimidinase like 4	1.75488 7502		ITGAE	integrin subunit alpha E	- 2.33594 8972
FNBP1	formin binding protein 1	1.75468 902		PQLC2	PQ loop repeat containing 2	- 2.33614 1568
TMOD4	tropomodulin 4	1.75406 4107		KLRB1A	killer cell lectin-like receptor subfamily B member 1A(Klrb1a)	- 2.33628 3388
ERLIN1	ER lipid raft associated 1	1.75115 4691		IRF9	interferon regulatory factor 9	- 2.33630 8285
ENOPH1	enolase-phosphatase 1	1.74844 7442		GATA3	GATA binding protein 3	- 2.33897 1433
RAB31	RAB31, member RAS oncogene family	1.74621 5332		RSAD2	radical S-adenosyl methionine domain containing 2	- 2.33997 952

HOXA6	homeobox A6	1.745184623		RNF215	ring finger protein 215	-2.341976415
TAS2R126	taste receptor, type 2, member 126(Tas2r126)	1.744161096		IL7R	interleukin 7 receptor	-2.343395577
AGXT2	alanine--glyoxylate aminotransferase 2	1.744161096		ACP5	acid phosphatase 5, tartrate resistant	-2.345270806
STK32C	serine/threonine kinase 32C	1.744161096		STYXL1	serine/threonine/tyrosine interacting-like 1	-2.346956889
P2RY2	purinergic receptor P2Y2	1.744161096		NOXO1	NADPH oxidase organizer 1	-2.35030956
NWD1	NACHT and WD repeat domain containing 1	1.744161096		IGFALS	insulin like growth factor binding protein acid labile subunit	-2.358664554
UQCRQ	ubiquinol-cytochrome c reductase complex III subunit VII	1.744161096		STIM1	stromal interaction molecule 1	-2.359335599
PPP1R3A	protein phosphatase 1 regulatory subunit 3A	1.744161096		TMEM186	transmembrane protein 186	-2.361030771
GOLT1A	golgi transport 1A	1.744161096		OLFR1043	olfactory receptor 1043(Olfr1043)	-2.364572432
EZH1	enhancer of zeste 1 polycomb repressive complex 2 subunit	1.744161096		D8ERTD82E	DNA segment, Chr 8, ERATO Doi 82, expressed(D8Ertd82e)	-2.364572432
MTHFD2	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	1.744154314		MYOG	myogenin	-2.364572432
PGRMC1	progesterone receptor membrane component 1	1.742545062		NCLN	nicalin	-2.364572432
DNAJB12	DnaJ heat shock protein family (Hsp40) member B12	1.741863621		MTSS1	metastasis suppressor 1	-2.364572432
DNAJC11	DnaJ heat shock protein family (Hsp40) member C11	1.738767837		TRMU	tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase	-2.364572432
TOMM6	translocase of outer mitochondrial membrane 6	1.738448709		EMILIN2	elastin microfibril interfacer 2	-2.369119767
RPS6KL1	ribosomal protein S6 kinase like 1	1.738393453		MPV17L	MPV17 mitochondrial inner membrane protein like	-2.371558863
CDC73	cell division cycle 73	1.73665741		WWC2	WW and C2 domain containing 2	-2.371558863
NDC80	NDC80, kinetochore complex component	1.732078892		TMEM178	transmembrane protein 178(Tmem178)	-2.374005585
TACC3	transforming acidic coiled-coil containing	1.731372884		TPCN1	two pore segment channel 1	-2.37523

	protein 3					2208
CPSF3	cleavage and polyadenylation specific factor 3	1.72792 6568		LRRC45	leucine rich repeat containing 45	- 2.37720 7351
ARID3A	AT-rich interaction domain 3A	1.72647 1722		1110059G1 0RIK	Description Not Found	- 2.37791 5929
LLPH	LLP homolog, long-term synaptic facilitation	1.72610 7859		MCOLN2	mucolipin 2	- 2.37851 1623
PCNA	proliferating cell nuclear antigen	1.72544 1599		DDX58	DEXD/H-box helicase 58	- 2.37851 1623
GJC2	gap junction protein gamma 2	1.72297 8517		H2-OA	histocompatibility 2, O region alpha locus(H2-Oa)	- 2.38232 9516
OLFR373	olfactory receptor 373(Olfr373)	1.72246 6024		RARG	retinoic acid receptor gamma	- 2.38882 7772
H2-T24	histocompatibility 2, T region locus 24(H2-T24)	1.72246 6024		SERPINB1 A	serine (or cysteine) peptidase inhibitor, clade B, member 1a(Serpinb1a)	- 2.39231 7423
AKAP7	A-kinase anchoring protein 7	1.72246 6024		GHRL	ghrelin/obestatin prepropeptide	- 2.39231 7423
NDUFB7	NADH:ubiquinone oxidoreductase subunit B7	1.72246 6024		ZMAT4	zinc finger matrin-type 4	- 2.39231 7423
PRR11	proline rich 11	1.72246 6024		BTBD6	BTB domain containing 6	- 2.39289 7478
TJP1	tight junction protein 1	1.72246 6024		KLRA16	killer cell lectin-like receptor, subfamily A, member 16(Klra16)	- 2.39453 4969
S100A3	S100 calcium binding protein A3	1.72246 6024		EPS15L1	epidermal growth factor receptor pathway substrate 15 like 1	- 2.39701 2831
KRT78	keratin 78	1.71872 9711		VCPIP1	valosin containing protein interacting protein 1	- 2.39730 3585
GMDS	GDP-mannose 4,6-dehydratase	1.71790 4741		RRP7A	ribosomal RNA processing 7 homolog A	- 2.40499 2223
PDGFB	platelet derived growth factor subunit B	1.71440 0534		IL1B	interleukin 1 beta	- 2.40599 236
SLC36A1	solute carrier family 36 member 1	1.71429 7338		NAT14	N-acetyltransferase 14 (putative)	- 2.40599 236
RSU1	Ras suppressor protein 1	1.71264 7036		SLC40A1	solute carrier family 40 member 1	- 2.40599 236
STX12	syntaxin 12	1.71191 1478		RAB37	RAB37, member RAS oncogene family	- 2.40599 236
SLC25A34	solute carrier family 25 member 34	1.71149 4907		IL17RA	interleukin 17 receptor A	- 2.40599 236
AFG3L2	AFG3 like matrix AAA	1.71105		BACE1	beta-secretase 1	-

	peptidase subunit 2	7				2.40599236
RPL24	ribosomal protein L24	1.709193708		CTNS	cystinosin, lysosomal cystine transporter	-2.40599236
UBE3C	ubiquitin protein ligase E3C	1.708789682		IFIT3	interferon induced protein with tetratricopeptide repeats 3	-2.411404504
CAR12	carbonic anhydrase 12(Car12)	1.70867626		ZFYVE21	zinc finger FYVE-type containing 21	-2.412378292
ZFP207	zinc finger protein 207(Zfp207)	1.707603009		1700016D06RIK	Description Not Found	-2.419538892
XIST	X inactive specific transcript (non-protein coding)	1.706065607		STK25	serine/threonine kinase 25	-2.419538892
NCAPD2	non-SMC condensin I complex subunit D2	1.705012178		PLEKHJ1	pleckstrin homology domain containing J1	-2.419538892
ZSWIM2	zinc finger SWIM-type containing 2	1.704802998		TGIF2	TGFB induced factor homeobox 2	-2.419538892
CASP1	caspase 1	1.70065942		SLC25A29	solute carrier family 25 member 29	-2.419538892
OLFR701	olfactory receptor 701(Olfr701)	1.700439718		DAPL1	death associated protein like 1	-2.419661316
CBLC	Cbl proto-oncogene C	1.700439718		P2RX4	purinergic receptor P2X 4	-2.425748008
HIST1H2AC	histone cluster 1, H2ac	1.700439718		1700001O22RIK	Description Not Found	-2.426264755
EPHA10	EPH receptor A10	1.700439718		C9	complement component 9	-2.429615964
NDUFC2	NADH:ubiquinone oxidoreductase subunit C2	1.700439718		KLF13	Kruppel like factor 13	-2.430628023
DLG1	discs large MAGUK scaffold protein 1	1.700439718		GADD45A	growth arrest and DNA damage inducible alpha	-2.432591239
SCN10A	sodium voltage-gated channel alpha subunit 10	1.700439718		OLFR788	olfactory receptor 788(Olfr788)	-2.432959407
RGL3	ral guanine nucleotide dissociation stimulator like 3	1.700439718		FADS6	fatty acid desaturase 6	-2.432959407
TMCO3	transmembrane and coiled-coil domains 3	1.700439718		CHCHD2	coiled-coil-helix-coiled-coil-helix domain containing 2	-2.432959407
BCL2L14	BCL2 like 14	1.700439718		MPPE1	metallophosphoesterase 1	-2.432959407
THOP1	thimet oligopeptidase 1	1.700290033		CHAC1	ChaC glutathione specific gamma-glutamylcyclotransferase 1	-2.432959407

MTIF3	mitochondrial translational initiation factor 3	1.698305331		2310011J03RIK	Description Not Found	-2.435017448
XDH	xanthine dehydrogenase	1.697717724		LRSAM1	leucine rich repeat and sterile alpha motif containing 1	-2.437473925
ANXA9	annexin A9	1.697184071		SIRPA	signal regulatory protein alpha	-2.443125132
OLFR1502	olfactory receptor 1502(Olfr1502)	1.694046727		CYP24A1	cytochrome P450 family 24 subfamily A member 1	-2.44625623
HCFC2	host cell factor C2	1.693780609		NQO1	NAD(P)H quinone dehydrogenase 1	-2.44625623
DIDO1	death inducer-obliterator 1	1.693596948		HRH4	histamine receptor H4	-2.44625623
PGAM1	phosphoglycerate mutase 1	1.689846917		NUDCD1	NudC domain containing 1	-2.44625623
RASGEF1C	RasGEF domain family member 1C	1.689299161		CCND1	cyclin D1	-2.447924527
SLC25A42	solute carrier family 25 member 42	1.686774817		ADAM22	ADAM metallopeptidase domain 22	-2.452858965
CPT2	carnitine palmitoyltransferase 2	1.686364794		MDK	midkine (neurite growth-promoting factor 2)	-2.456149035
MAD2L1	MAD2 mitotic arrest deficient-like 1 (yeast)	1.686161103		STX1A	syntaxin 1A	-2.456729828
NQO2	NAD(P)H quinone dehydrogenase 2	1.685558757		HEMK1	HemK methyltransferase family member 1	-2.459431619
HIP1R	huntingtin interacting protein 1 related	1.685473307		B4GALT7	beta-1,4-galactosyltransferase 7	-2.459431619
ALOX12E	arachidonate lipoxygenase, epidermal(Alox12e)	1.684373244		ASXL2	additional sex combs like 2, transcriptional regulator	-2.459431619
LMAN1	lectin, mannose binding 1	1.683514205		TLR7	toll like receptor 7	-2.46052038
ASB3	ankyrin repeat and SOCS box containing 3	1.680142991		TDP1	tyrosyl-DNA phosphodiesterase 1	-2.464461869
XKR5	XK related 5	1.679254438		1700025G04RIK	Description Not Found	-2.469303076
ZFP235	zinc finger protein 235(Zfp235)	1.678071905		SLC16A6	solute carrier family 16 member 6	-2.471045434
OLFR971	olfactory receptor 971(Olfr971)	1.678071905		DOXL2	diamine oxidase-like protein 2(Doxl2)	-2.472487771
OLFR374	olfactory receptor 374(Olfr374)	1.678071905		PKD1L3	polycystin 1 like 3, transient receptor potential	-2.47248

					channel interacting	7771
NOS1AP	nitric oxide synthase 1 adaptor protein	1.67807 1905		ZC3H11A	zinc finger CCCH-type containing 11A	- 2.47248 7771
GALM	galactose mutarotase	1.67807 1905		LY6K	lymphocyte antigen 6 complex, locus K	- 2.47248 7771
MEGF9	multiple EGF like domains 9	1.67807 1905		KLF7	Kruppel like factor 7	- 2.47475 5307
CCDC66	coiled-coil domain containing 66	1.67807 1905		BTLA	B and T lymphocyte associated	- 2.47560 4026
LRRC40	leucine rich repeat containing 40	1.67807 1905		CDON	cell adhesion associated, oncogene regulated	- 2.48542 6827
RALA	RALA Ras like proto-oncogene A	1.67807 1905		DDC	dopa decarboxylase	- 2.48542 6827
YIPF4	Yip1 domain family member 4	1.67807 1905		GTF2A2	general transcription factor IIA subunit 2	- 2.48542 6827
TAL2	T-cell acute lymphocytic leukemia 2	1.67807 1905		DTX4	deltex E3 ubiquitin ligase 4	- 2.48542 6827
LRRC8A	leucine rich repeat containing 8 family member A	1.67807 1905		GSTK1	glutathione S-transferase kappa 1	- 2.48619 5934
APOM	apolipoprotein M	1.67807 1905		OLFR213	olfactory receptor 213(Olfr213)	- 2.48912 5048
KCNG3	potassium voltage-gated channel modifier subfamily G member 3	1.67807 1905		PDE5A	phosphodiesterase 5A	- 2.49057 1469
CNN1	calponin 1	1.67807 1905		TOB1	transducer of ERBB2, 1	- 2.49676 3907
STAC2	SH3 and cysteine rich domain 2	1.67807 1905		1700109H0 8RIK	Description Not Found	- 2.49825 0868
SFRP2	secreted frizzled related protein 2	1.67807 1905		LEFTY1	left-right determination factor 1	- 2.49825 0868
SERPINB9 E	serine (or cysteine) peptidase inhibitor, clade B, member 9e(Serpinb9e)	1.67016 9131		SNAPC4	small nuclear RNA activating complex polypeptide 4	- 2.50087 8922
TFB1M	transcription factor B1, mitochondrial	1.66894 6692		RNF41	ring finger protein 41	- 2.50355 1585
SLC25A10	solute carrier family 25 member 10	1.66885 6925		KLHL34	kelch like family member 34	- 2.50462 0392
BID	BH3 interacting domain death agonist	1.66799 2567		SSH2	slingshot protein phosphatase 2	- 2.50549 2762
MRPS27	mitochondrial ribosomal protein S27	1.66729 5766		CAMK2B	calcium/calmodulin dependent protein kinase II beta	- 2.50704 7355

NEDD4	neural precursor cell expressed, developmentally down-regulated 4, E3 ubiquitin protein ligase	1.66675 6592		IRF7	interferon regulatory factor 7	-2.50759 0939
VANGL2	VANGL planar cell polarity protein 2	1.66675 6592		SCML4	sex comb on midleg-like 4 (Drosophila)	-2.52311 8672
UBE2R2	ubiquitin conjugating enzyme E2 R2	1.66664 1116		EPB4.1	Description Not Found	-2.52356 1956
KLHL30	kelch like family member 30	1.66651 9523		PARP12	poly(ADP-ribose) polymerase family member 12	-2.52356 1956
FBXO36	F-box protein 36	1.66558 8375		CACNB3	calcium voltage-gated channel auxiliary subunit beta 3	-2.52987 7218
DCT	dopachrome tautomerase	1.66401 6818		NRG4	neuregulin 4	-2.53318 567
CCDC120	coiled-coil domain containing 120	1.66393 1727		OLFR1383	olfactory receptor 1383(Olfr1383)	-2.53605 29
TMEM38B	transmembrane protein 38B	1.66345 5268		PTGR1	prostaglandin reductase 1	-2.53605 29
ENDOD1	endonuclease domain containing 1	1.66332 7923		NFAM1	NFAT activating protein with ITAM motif 1	-2.53605 29
PTPRD	protein tyrosine phosphatase, receptor type D	1.66321 5776		ARL4C	ADP ribosylation factor like GTPase 4C	-2.53605 29
ARL3	ADP ribosylation factor like GTPase 3	1.66169 0196		LACE1	lactation elevated 1	-2.53605 29
CDC37	cell division cycle 37	1.66156 7827		CDC14B	cell division cycle 14B	-2.54535 0645
MKKS	McKusick-Kaufman syndrome	1.66106 548		GUCA1A	guanylate cyclase activator 1A	-2.54843 6625
CHN2	chimerin 2	1.66099 8764		KIF21B	kinesin family member 21B	-2.55458 8852
CRTAP	cartilage associated protein	1.65943 1912		ARID3B	AT-rich interaction domain 3B	-2.55808 7884
CXCR6	C-X-C motif chemokine receptor 6	1.65751 5938		HBA-A1	hemoglobin alpha, adult chain 1(Hba-a1)	-2.56071 4954
BUB1B	BUB1 mitotic checkpoint serine/threonine kinase B	1.65691 495		CSF2RB2	colony stimulating factor 2 receptor, beta 2, low-affinity (granulocyte-macrophage)(Csf2rb2)	-2.56071 4954
B430306N03RIK	RIKEN cDNA B430306N03 gene(B430306N03Rik)	1.65535 1829		ATP6V1B1	ATPase H+ transporting V1 subunit B1	-2.56071 4954
OLFR1262	olfactory receptor 1262(Olfr1262)	1.65535 1829		PCSK1N	proprotein convertase subtilisin/kexin type 1	-2.56071

					inhibitor	4954
SLC38A5	solute carrier family 38 member 5	1.65535 1829		ZFP667	zinc finger protein 667(Zfp667)	- 2.56667 0372
VAT1L	vesicle amine transport 1-like	1.65535 1829		SH3BP1	SH3 domain binding protein 1	- 2.56673 4604
HOXB7	homeobox B7	1.65535 1829		FFAR2	free fatty acid receptor 2	- 2.57288 9668
GAN	gigaxonin	1.65535 1829		EEF2K	eukaryotic elongation factor 2 kinase	- 2.57288 9668
MMP28	matrix metallopeptidase 28	1.65535 1829		SLPI	secretory leukocyte peptidase inhibitor	- 2.57472 1828
METTL10	methyltransferase like 10	1.65535 1829		CMA1	chymase 1	- 2.58496 2501
SIX4	SIX homeobox 4	1.65535 1829		ASCL1	achaete-scute family bHLH transcription factor 1	- 2.58496 2501
TDRD6	tudor domain containing 6	1.65535 1829		ACPP	acid phosphatase, prostate	- 2.58496 2501
COMMD5	COMM domain containing 5	1.65460 4999		CLCNKB	chloride voltage-gated channel Kb	- 2.59693 5142
PRDX4	peroxiredoxin 4	1.65192 3925		FBXW7	F-box and WD repeat domain containing 7	- 2.59693 5142
HS3ST3A1	heparan sulfate-glucosamine 3-sulfotransferase 3A1	1.64929 8274		OLIG3	oligodendrocyte transcription factor 3	- 2.59693 5142
CALCA	calcitonin related polypeptide alpha	1.64906 7786		WHRN	whirlin	- 2.60678 9951
SLC12A2	solute carrier family 12 member 2	1.64844 9243		DNAJC14	DnaJ heat shock protein family (Hsp40) member C14	- 2.60880 9243
TJP2	tight junction protein 2	1.64414 5647		PIGT	phosphatidylinositol glycan anchor biosynthesis class T	- 2.61103 1218
LRRC16B	Description Not Found	1.64385 619		AP1G2	adaptor related protein complex 1 gamma 2 subunit	- 2.61470 9844
AP3S2	adaptor related protein complex 3 sigma 2 subunit	1.64385 619		SAA2	serum amyloid A2	- 2.62058 641
PSMD9	proteasome 26S subunit, non-ATPase 9	1.64385 619		USP30	ubiquitin specific peptidase 30	- 2.62058 641
PARD6G	par-6 family cell polarity regulator gamma	1.64337 9419		RPE65	retinal pigment epithelium specific protein 65	- 2.63226 8216
CIAPIN1	cytokine induced apoptosis inhibitor 1	1.64321 9709		CML1	Description Not Found	- 2.63489 1632
CKAP5	cytoskeleton associated	1.64274		SLC6A19	solute carrier family 6	-

	protein 5	7156			member 19	2.64093 0751
E430025E2 1RIK	RIKEN cDNA E430025E21 gene(E430025E21Rik)	1.64190 2626		FGF15	fibroblast growth factor 15(Fgf15)	- 2.64385 619
PIAS3	protein inhibitor of activated STAT 3	1.64188 4484		HERC3	HECT and RLD domain containing E3 ubiquitin protein ligase 3	- 2.64385 619
USP1	ubiquitin specific peptidase 1	1.64023 3791		ADAMTSL 4	ADAMTS like 4	- 2.64385 619
RAB3GAP2	RAB3 GTPase activating non-catalytic protein subunit 2	1.63959 2623		HYAL3	hyaluronoglucosaminidase 3	- 2.64385 619
CSRP2	cysteine and glycine rich protein 2	1.63904 6229		SLC15A2	solute carrier family 15 member 2	- 2.64821 7996
MOV10	Mov10 RISC complex RNA helicase	1.63807 3837		UFSP1	UFM1-specific peptidase 1 (inactive)	- 2.64955 3823
GM1965	predicted gene 1965(Gm1965)	1.63788 1562		6430573F11 RIK	Description Not Found	- 2.65535 1829
POMGNT1	protein O-linked mannose N-acetylglucosaminyltransf erase 1 (beta 1,2-)	1.63623 7884		DNM3OS	DNM3 opposite strand/antisense RNA	- 2.65535 1829
FIGNL1	fidgetin like 1	1.63395 0492		F2RL1	F2R like trypsin receptor 1	- 2.65535 1829
TMEM177	transmembrane protein 177	1.63347 5547		SNX33	sorting nexin 33	- 2.66665 4581
ALX4	ALX homeobox 4	1.63286 4872		CXCL9	C-X-C motif chemokine ligand 9	- 2.66675 6592
OLFR533	olfactory receptor 533(Olfr533)	1.63226 8216		TEAD2	TEA domain transcription factor 2	- 2.66675 6592
H2-M10.3	histocompatibility 2, M region locus 10.3(H2-M10.3)	1.63226 8216		QSOX1	quiescin sulfhydryl oxidase 1	- 2.66675 6592
GPX7	glutathione peroxidase 7	1.63226 8216		TLR13	toll-like receptor 13(Tlr13)	- 2.67807 1905
STXBP6	syntaxin binding protein 6	1.63226 8216		SCD3	stearoyl-coenzyme A desaturase 3(Scd3)	- 2.67807 1905
RAB33A	RAB33A, member RAS oncogene family	1.63226 8216		SDC3	syndecan 3	- 2.67807 1905
PDCL3	phosducin like 3	1.63226 8216		GRPR	gastrin releasing peptide receptor	- 2.67807 1905
GPR20	G protein-coupled receptor 20	1.63226 8216		MAFK	MAF bZIP transcription factor K	- 2.67807 1905
GSTA2	glutathione S-transferase alpha 2	1.63226 8216		DIRC2	disrupted in renal carcinoma 2	- 2.67807

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ADCY10	adenylate cyclase 10 (soluble)	1.63226 8216		ZCCHC12	zinc finger CCHC-type containing 12	- 2.67833 354
PEX12	peroxisomal biogenesis factor 12	1.63226 8216		ADCY6	adenylate cyclase 6	- 2.68088 6921
IQCC	IQ motif containing C	1.63226 8216		ECM1	extracellular matrix protein 1	- 2.68345 512
ENPP1	ectonucleotide pyrophosphatase/phosph odiesterase 1	1.63208 6279		AFP	alpha fetoprotein	- 2.68929 9161
ADAL	adenosine deaminase-like	1.63066 4126		GP5	glycoprotein V platelet	- 2.68929 9161
SCRN2	secernin 2	1.63056 6247		GAB3	GRB2 associated binding protein 3	- 2.69140 5681
CEP78	centrosomal protein 78	1.62985 1642		USP2	ubiquitin specific peptidase 2	- 2.69333 4369
SLC25A15	solute carrier family 25 member 15	1.62979 8606		PLXNB1	plexin B1	- 2.70043 9718
ADSSL1	adenylosuccinate synthase like 1	1.62827 2149		PODXL2	podocalyxin like 2	- 2.70079 9925
TM6SF2	transmembrane 6 superfamily member 2	1.62775 8638		RAD9B	RAD9 checkpoint clamp component B	- 2.70103 836
TUBG1	tubulin gamma 1	1.62451 1879		AKAP10	A-kinase anchoring protein 10	- 2.70597 7902
FASTK	Fas activated serine/threonine kinase	1.62333 6662		PIGW	phosphatidylinositol glycan anchor biosynthesis class W	- 2.71699 0894
RBBP5	RB binding protein 5, histone lysine methyltransferase complex subunit	1.62216 3711		COL12A1	collagen type XII alpha 1 chain	- 2.72246 6024
1700071K0 1RIK	Description Not Found	1.62146 5074		GPR137B	G protein-coupled receptor 137B	- 2.73335 4341
SLC25A33	solute carrier family 25 member 33	1.62128 2718		IMMP2L	inner mitochondrial membrane peptidase subunit 2	- 2.73335 4341
MDM4	MDM4, p53 regulator	1.62058 641		PIK3CB	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	- 2.73732 0423
TOP2A	topoisomerase (DNA) II alpha	1.62037 4948		TGFBI	transforming growth factor beta induced	- 2.74027 6443
OLFR139	olfactory receptor 139(Olfr139)	1.61973 1323		ZFP106	zinc finger protein 106(Zfp106)	- 2.74416 1096
PAPLN	papilin, proteoglycan like sulfated glycoprotein	1.61876 2248		ARNTL	aryl hydrocarbon receptor nuclear translocator like	- 2.74416 1096

PACSIN2	protein kinase C and casein kinase substrate in neurons 2	1.617401771		HS3ST3B1	heparan sulfate-glucosamine 3-sulfotransferase 3B1	-2.744161096
TRDMT1	tRNA aspartic acid methyltransferase 1	1.615239219		OASL2	2'-5' oligoadenylate synthetase-like 2(Oasl2)	-2.744892108
4932438H23RIK	Description Not Found	1.614681809		PRDX6	peroxiredoxin 6	-2.75084462
SPAG9	sperm associated antigen 9	1.614567709		RASA2	RAS p21 protein activator 2	-2.751203108
RPA3	replication protein A3	1.61436984		HOXB2	homeobox B2	-2.754887502
GNPTAB	N-acetylglucosamine-1-phosphate transferase alpha and beta subunits	1.613298199		TULP3	tubby like protein 3	-2.754887502
SNX9	sorting nexin 9	1.609251493		MFRP	membrane frizzled-related protein	-2.754887502
OLFR550	olfactory receptor 550(Olfr550)	1.609195813		MEN1	menin 1	-2.757556689
ZFP160	zinc finger protein 160(Zfp160)	1.608809243		C330021F23RIK	RIKEN cDNA C330021F23 gene(C330021F23Rik)	-2.762199201
TAS2R129	taste receptor, type 2, member 129(Tas2r129)	1.608809243		CSTAD	CSA-conditional, T cell activation-dependent protein(Cstad)	-2.765534746
OLFR371	olfactory receptor 371(Olfr371)	1.608809243		ALDH5A1	aldehyde dehydrogenase 5 family member A1	-2.773022439
OLFR281	olfactory receptor 281(Olfr281)	1.608809243		EPM2AIP1	EPM2A interacting protein 1	-2.773468928
OLFR195	olfactory receptor 195(Olfr195)	1.608809243		PDE8B	phosphodiesterase 8B	-2.776103988
OLFR142	olfactory receptor 142(Olfr142)	1.608809243		DMRTA1	DMRT like family A1	-2.776184379
PRSS3	protease, serine 3	1.608809243		LYPD6B	LY6/PLAUR domain containing 6B	-2.780048768
CX3CL1	C-X3-C motif chemokine ligand 1	1.608809243		CD300E	CD300e molecule	-2.786596362
TMPRSS6	transmembrane protease, serine 6	1.608809243		NPFF	neuropeptide FF-amide peptide precursor	-2.786596362
ALK	anaplastic lymphoma receptor tyrosine kinase	1.608809243		FASTKD1	FAST kinase domains 1	-2.793765229
ITGA9	integrin subunit alpha 9	1.608809243		OLFR802	olfactory receptor 802(Olfr802)	-2.797012978
TIMM13	translocase of inner mitochondrial membrane	1.608809243		HIVEP1	human immunodeficiency virus type I enhancer	-2.79701

	13				binding protein 1	2978
MSH5	mutS homolog 5	1.60880 9243		HIC1	hypermethylated in cancer 1	- 2.79701 2978
XPO4	exportin 4	1.60581 8241		TRIM33	tripartite motif containing 33	- 2.80200 9226
MED21	mediator complex subunit 21	1.60330 9406		SELL	selectin L	- 2.80327 4253
CHST12	carbohydrate sulfotransferase 12	1.60261 2589		EPHX1	epoxide hydrolase 1	- 2.80375 8579
6030408B1 6RIK	Description Not Found	1.60219 5565		BCL9	B-cell CLL/lymphoma 9	- 2.80735 4922
SLU7	SLU7 homolog, splicing factor	1.60154 8066		STAT2	signal transducer and activator of transcription 2	- 2.80852 1822
CDK5RAP2	CDK5 regulatory subunit associated protein 2	1.60112 0229		ELMO3	engulfment and cell motility 3	- 2.81249 8225
CASP7	caspase 7	1.60024 02		HDC	histidine decarboxylase	- 2.81516 7456
KIF22	kinesin family member 22	1.59901 1705		AI317395	Description Not Found	- 2.81762 3258
E2F1	E2F transcription factor 1	1.59844 9678		RPL14	ribosomal protein L14	- 2.81762 3258
MXI1	MAX interactor 1, dimerization protein	1.59769 0116		SNAI1	snail family transcriptional repressor 1	- 2.81825 6244
DONSON	downstream neighbor of SON	1.59693 5142		NUPR1	nuclear protein 1, transcriptional regulator	- 2.82781 9025
TBX22	T-box 22	1.59693 5142		IGSF8	immunoglobulin superfamily member 8	- 2.82781 9025
INPPL1	inositol polyphosphate phosphatase like 1	1.59630 0192		SLC12A7	solute carrier family 12 member 7	- 2.82781 9025
CSE1L	chromosome segregation 1 like	1.59586 273		RENBP	renin binding protein	- 2.83743 1463
NDFIP2	Nedd4 family interacting protein 2	1.59470 9608		ZFP553	zinc finger protein 553(Zfp553)	- 2.83794 3242
LYPD6	LY6/PLAUR domain containing 6	1.59296 2293		LRFN2	leucine rich repeat and fibronectin type III domain containing 2	- 2.83794 3242
DDX49	DEAD-box helicase 49	1.59219 0323		HP	haptoglobin	- 2.83973 7506
MGLL	monoglyceride lipase	1.59094 8822		TOMM40	translocase of outer mitochondrial membrane 40	- 2.84799 6907
NR4A3	nuclear receptor	1.59092		GABARAP	GABA type A receptor	-

	subfamily 4 group A member 3	994		L2	associated protein like 2	2.847996907
LRRN3	leucine rich repeat neuronal 3	1.590360181		TMEM86A	transmembrane protein 86A	-2.855497819
PTPRK	protein tyrosine phosphatase, receptor type K	1.587927102		LRP1	LDL receptor related protein 1	-2.857980995
OLFR1212	olfactory receptor 1212(Olfr1212)	1.584962501		ATXN1	ataxin 1	-2.857980995
KLHL2	kelch like family member 2	1.584962501		FAS	Fas cell surface death receptor	-2.861524641
UBE2G2	ubiquitin conjugating enzyme E2 G2	1.584962501		ZDHHC18	zinc finger DHHC-type containing 18	-2.882740655
GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A	1.584962501		LARGE	Description Not Found	-2.887525271
INHA	inhibin alpha subunit	1.584962501		SP5	Sp5 transcription factor	-2.887525271
RNPC3	RNA binding region (RNP1, RRM) containing 3	1.584962501		ATG7	autophagy related 7	-2.895440528
XKR7	XK related 7	1.584962501		DNAJC27	DnaJ heat shock protein family (Hsp40) member C27	-2.897240426
STX19	syntaxin 19	1.584962501		PCSK4	proprotein convertase subtilisin/kexin type 4	-2.900866808
SLC5A5	solute carrier family 5 member 5	1.584962501		RNF141	ring finger protein 141	-2.902073579
VPS37C	VPS37C, ESCRT-I subunit	1.584022655		GRAP2	GRB2-related adaptor protein 2	-2.904150467
ERMP1	endoplasmic reticulum metallopeptidase 1	1.582531434		VIPR1	vasoactive intestinal peptide receptor 1	-2.904484098
ZFP790	zinc finger protein 790(Zfp790)	1.581046002		CAR15	carbonic anhydrase 15(Car15)	-2.906890596
AA467197	expressed sequence AA467197(AA467197)	1.579947242		RELL2	RELT like 2	-2.906890596
UBE2Z	ubiquitin conjugating enzyme E2 Z	1.57976541		HECA	hdc homolog, cell cycle regulator	-2.916545968
SOAT2	sterol O-acyltransferase 2	1.577460518		DPM1	dolichyl-phosphate mannosyltransferase polypeptide 1, catalytic subunit	-2.933100475
ZMAT5	zinc finger matrin-type 5	1.576986214		AOC2	amine oxidase, copper containing 2	-2.936235748
CDCA3	cell division cycle associated 3	1.576323153		HIST2H2BE	histone cluster 2, H2be	-2.93632

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NEUROD2	neuronal differentiation 2	1.576266476		ACAD10	acyl-CoA dehydrogenase family member 10	-2.942514505
WDR35	WD repeat domain 35	1.576120636		NT5E	5'-nucleotidase ecto	-2.944039663
TWSG1	twisted gastrulation BMP signaling modulator 1	1.5758728		SSH1	slingshot protein phosphatase 1	-2.944858446
PPT1	palmitoyl-protein thioesterase 1	1.575321868		SEMA4F	ssemaphorin 4F	-2.948329995
IRF8	interferon regulatory factor 8	1.574489283		NKD2	naked cuticle homolog 2	-2.953960396
PLEKHG5	pleckstrin homology and RhoGEF domain containing G5	1.574066379		TCEB3	transcription elongation factor B subunit 3	-2.95419631
CDC20	cell division cycle 20	1.573718243		HDAC4	histone deacetylase 4	-2.95419631
MFI2	antigen p97 (melanoma associated) identified by monoclonal antibodies 133.2 and 96.5(Mfi2)	1.572889668		PCNX	pecanex homolog (Drosophila)(Pcnx)	-2.972692654
HDAC9	histone deacetylase 9	1.571625208		ARL5C	ADP ribosylation factor like GTPase 5C	-2.972692654
ASF1B	anti-silencing function 1B histone chaperone	1.570544039		1600014C10RIK	Description Not Found	-2.981852653
B3GNT1	Description Not Found	1.569171715		ANKRD23	ankyrin repeat domain 23	-2.981852653
SLC25A14	solute carrier family 25 member 14	1.569127395		CLOCK	clock circadian regulator	-2.985543793
FYN	FYN proto-oncogene, Src family tyrosine kinase	1.567462919		SFI1	SFI1 centrin binding protein	-2.986410935
SERPINB6B	serine (or cysteine) peptidase inhibitor, clade B, member 6b(Serpinb6b)	1.567348435		HEY1	hes related family bHLH transcription factor with YRPW motif 1	-2.987632559
TOP1MT	topoisomerase (DNA) I, mitochondrial	1.567180597		ATP11C	ATPase phospholipid transporting 11C	-2.99095486
CCDC50	coiled-coil domain containing 50	1.566273906		NUDCD3	NudC domain containing 3	-3
ZFP414	zinc finger protein 414(Zfp414)	1.565776574		CDC25A	cell division cycle 25A	-3.000238201
OGFOD2	2-oxoglutarate and iron dependent oxygenase domain containing 2	1.565512016		OLFR135	olfactory receptor 135(Olfr135)	-3.017921908
CTNNAL1	catenin alpha like 1	1.563586461		RC3H1	ring finger and CCCH-type domains 1	-3.019621529

CREB3L2	cAMP responsive element binding protein 3 like 2	1.56136 1122		NSG2	neuron specific gene family member 2(Nsg2)	- 3.02046 6888
OLFR492	olfactory receptor 492(Olfr492)	1.56071 4954		ID1	inhibitor of DNA binding 1, HLH protein	- 3.02680 0059
OLFR1312	olfactory receptor 1312(Olfr1312)	1.56071 4954		CYP2D22	cytochrome P450, family 2, subfamily d, polypeptide 22(Cyp2d22)	- 3.04428 2215
UPK2	uroplakin 2	1.56071 4954		H2AFJ	H2A histone family member J	- 3.04429 7135
RESP18	regulated endocrine specific protein 18	1.56071 4954		TGFBR3	transforming growth factor beta receptor 3	- 3.05311 1336
CRCT1	cysteine rich C-terminal 1	1.56071 4954		IRS2	insulin receptor substrate 2	- 3.06177 6198
NEUROD4	neuronal differentiation 4	1.56071 4954		ADCY7	adenylate cyclase 7	- 3.06608 919
SENP1	SUMO1/sentrin specific peptidase 1	1.56071 4954		HYI	hydroxypyruvate isomerase (putative)	- 3.07231 5809
MR1	major histocompatibility complex, class I-related	1.56071 4954		TRIP4	thyroid hormone receptor interactor 4	- 3.07895 1341
BIVM	basic, immunoglobulin-like variable motif containing	1.56071 4954		D730001G1 8RIK	RIKEN cDNA D730001G18 gene(D730001G18Rik)	- 3.08746 2841
KPNA2	karyopherin subunit alpha 2	1.56071 4954		PRR7	proline rich 7 (synaptic)	- 3.08746 2841
BAG2	BCL2 associated athanogene 2	1.56071 4954		GFPT2	glutamine-fructose-6-phosphate transaminase 2	- 3.09592 442
SLC12A8	solute carrier family 12 member 8	1.56071 4954		SCMH1	sex comb on midleg homolog 1 (Drosophila)	- 3.10013 6671
SCN7A	sodium voltage-gated channel alpha subunit 7	1.56071 4954		ANKRD12	ankyrin repeat domain 12	- 3.10745 6458
SLC5A7	solute carrier family 5 member 7	1.56071 4954		PTPRV	protein tyrosine phosphatase, receptor type, V(Ptprv)	- 3.11270 0133
ENPEP	glutamyl aminopeptidase	1.56071 4954		TMEM135	transmembrane protein 135	- 3.11270 0133
ANGPTL4	angiopoietin like 4	1.56060 777		AKAP3	A-kinase anchoring protein 3	- 3.11460 665
OSBPL3	oxysterol binding protein like 3	1.55977 8376		CBR2	carbonyl reductase 2(Cbr2)	- 3.12928 3017
MCFD2	multiple coagulation factor deficiency 2	1.55961 7874		CXCL16	C-X-C motif chemokine ligand 16	- 3.12928 3017
MAP2K1	mitogen-activated protein kinase kinase 1	1.55855 6708		MBTD1	mbt domain containing 1	- 3.14567

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ING2	inhibitor of growth family member 2	1.55722 3521		UBE2J2	ubiquitin conjugating enzyme E2 J2	- 3.16188 7682
CDCA5	cell division cycle associated 5	1.55643 411		STK36	serine/threonine kinase 36	- 3.16188 7682
MAP3K7	mitogen-activated protein kinase kinase kinase 7	1.55446 3905		SLC14A1	solute carrier family 14 member 1 (Kidd blood group)	- 3.16922 072
GSTT3	glutathione S-transferase, theta 3(Gstt3)	1.55048 277		CTSE	cathepsin E	- 3.17791 7792
PFN2	profilin 2	1.54969 0793		HSD3B7	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 7	- 3.17791 7792
HPS4	HPS4, biogenesis of lysosomal organelles complex 3 subunit 2	1.54911 5647		3010003L2 1RIK	Description Not Found	- 3.17924 9632
CAPN8	calpain 8	1.54843 6625		BAI1	Description Not Found	- 3.18646 1055
RAB11FIP5	RAB11 family interacting protein 5	1.54843 6625		ZFP451	zinc finger protein 451(Zfp451)	- 3.18771 1618
CD9	CD9 molecule	1.54842 9184		CCDC28B	coiled-coil domain containing 28B	- 3.19220 7249
CCR6	C-C motif chemokine receptor 6	1.54825 0633		MCF2L	MCF.2 cell line derived transforming sequence like	- 3.19967 2345
ALG2	ALG2, alpha-1,3/1,6-mannosyltransferase	1.54799 2668		BCL6	B-cell CLL/lymphoma 6	- 3.20102 4389
BCDIN3D	BCDIN3 domain containing RNA methyltransferase	1.54604 6129		PFKFB4	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4	- 3.20493 5584
NT5DC3	5'-nucleotidase domain containing 3	1.54522 349		PROS1	protein S (alpha)	- 3.20945 3366
DNAJC18	DnaJ heat shock protein family (Hsp40) member C18	1.54462 6916		CTSH	cathepsin H	- 3.21628 737
SH3RF1	SH3 domain containing ring finger 1	1.54415 6019		CRTC3	CREB regulated transcription coactivator 3	- 3.21723 0716
RGS16	regulator of G-protein signaling 16	1.54138 2294		TNKS	tankyrase	- 3.21723 0716
NCAPH	non-SMC condensin I complex subunit H	1.54078 8228		GRM6	glutamate metabotropic receptor 6	- 3.22496 6365
USP14	ubiquitin specific peptidase 14	1.54033 3713		SPSB1	splA/ryanodine receptor domain and SOCS box containing 1	- 3.25550 0733
RFT1	RFT1 homolog	1.54031 759		PARP8	poly(ADP-ribose) polymerase family member 8	- 3.26303 4406

SLC31A1	solute carrier family 31 member 1	1.540275536		KCNRG	potassium channel regulator	-3.263034406
TCTEX1D2	Tctex1 domain containing 2	1.538332378		POU6F1	POU class 6 homeobox 1	-3.268517714
TTF2	transcription termination factor 2	1.537871953		REV3L	REV3 like, DNA directed polymerase zeta catalytic subunit	-3.270528942
ZFP7	zinc finger protein 7(Zfp7)	1.5360529		TCF7	transcription factor 7 (T-cell specific, HMG-box)	-3.272419178
G6PD2	glucose-6-phosphate dehydrogenase 2(G6pd2)	1.5360529		NME4	NME/NM23 nucleoside diphosphate kinase 4	-3.283551423
DEFB14	defensin beta 14(Defb14)	1.5360529		PLAUR	plasminogen activator, urokinase receptor	-3.285402219
SLC18A3	solute carrier family 18 member A3	1.5360529		CD4	CD4 molecule	-3.285402219
AHNAK2	AHNAK nucleoprotein 2	1.5360529		ZMYND11	zinc finger MYND-type containing 11	-3.293186363
HOXC12	homeobox C12	1.5360529		ARMCX5	armadillo repeat containing, X-linked 5	-3.298404158
CEACAM16	carcinoembryonic antigen related cell adhesion molecule 16	1.5360529		LPHN1	Description Not Found	-3.300123725
MOSPD3	motile sperm domain containing 3	1.5360529		PIK3IP1	phosphoinositide-3-kinase interacting protein 1	-3.307428525
DCTN1	dynactin subunit 1	1.5360529		ERDR1	erythroid differentiation regulator 1(Erdr1)	-3.317651188
MYB	MYB proto-oncogene, transcription factor	1.5360529		PLD4	phospholipase D family member 4	-3.328444792
GLIPR1L2	GLI pathogenesis-related 1 like 2	1.5360529		BMF	Bcl2 modifying factor	-3.336283388
ALDH1A3	aldehyde dehydrogenase 1 family member A3	1.5360529		GALNT11	polypeptide N-acetylgalactosaminyltransferase 11	-3.345118795
SLC2A8	solute carrier family 2 member 8	1.5360529		LCN2	lipocalin 2	-3.378511623
SRC	SRC proto-oncogene, non-receptor tyrosine kinase	1.5360529		PAG1	phosphoprotein membrane anchor with glycosphingolipid microdomains 1	-3.385431037
ZCCHC17	zinc finger CCHC-type containing 17	1.535618518		DTX1	deltex E3 ubiquitin ligase 1	-3.425576064
HNRNPUL1	heterogeneous nuclear ribonucleoprotein U like 1	1.534420207		RFFL	ring finger and FYVE-like domain containing E3 ubiquitin protein ligase	-3.426684082
TRIM68	tripartite motif	1.53305		MAFF	MAF bZIP transcription	-

	containing 68	7052			factor F	3.429615964
TPST1	tyrosylprotein sulfotransferase 1	1.53140111		TOR1AIP2	torsin 1A interacting protein 2	-3.432316325
OLFR922	olfactory receptor 922(Olfr922)	1.531260941		SNN	stannin	-3.432316325
FIG4	FIG4 phosphoinositide 5-phosphatase	1.530442167		CLEC4N	C-type lectin domain family 4, member n(Clec4n)	-3.433567144
SETMAR	SET domain and mariner transposase fusion gene	1.530442167		RREB1	ras responsive element binding protein 1	-3.443780274
GSTM5	glutathione S-transferase mu 5	1.530053218		CCDC84	coiled-coil domain containing 84	-3.445188687
TUBA3B	tubulin, alpha 3B(Tuba3b)	1.527986221		ID3	inhibitor of DNA binding 3, HLH protein	-3.46350285
PDCL	phosducin like	1.527807072		BC065397	cDNA sequence BC065397(BC065397)	-3.465974465
SMPDL3B	sphingomyelin phosphodiesterase acid like 3B	1.527243888		VRK1	vaccinia related kinase 1	-3.46760555
ABHD14A	abhydrolase domain containing 14A	1.527213882		HOXD13	homeobox D13	-3.491853096
TIPIN	TIMELESS interacting protein	1.526972991		MAPK8IP2	mitogen-activated protein kinase 8 interacting protein 2	-3.491853096
DSCC1	DNA replication and sister chromatid cohesion 1	1.525986429		HOXA5	homeobox A5	-3.517275693
PSMD1	proteasome 26S subunit, non-ATPase 1	1.525574957		HIST1H1A	histone cluster 1, H1a	-3.523561956
BZRAP1	benzodiazepine receptor associated protein 1(Bzrap1)	1.524166255		MAML1	mastermind like transcriptional coactivator 1	-3.523603553
ENO3	enolase 3	1.523778831		PTPDC1	protein tyrosine phosphatase domain containing 1	-3.526694846
E330034G19RIK	RIKEN cDNA E330034G19 gene(E330034G19Rik)	1.523561956		TNFRSF12A	tumor necrosis factor receptor superfamily member 12A	-3.528725998
GABRP	gamma-aminobutyric acid type A receptor pi subunit	1.523561956		TNIP2	TNFAIP3 interacting protein 2	-3.539158811
SLC14A2	solute carrier family 14 member 2	1.523561956		HIST2H4	histone cluster 2, H4(Hist2h4)	-3.540773411
YWHAE	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	1.522478712		PIM2	Pim-2 proto-oncogene, serine/threonine kinase	-3.557655155
EHBP1L1	EH domain binding	1.52228		DOK7	docking protein 7	-

	protein 1 like 1	2169				3.56778 1854
CHGB	chromogranin B	1.51924 262		TNFSF14	tumor necrosis factor superfamily member 14	- 3.58889 5735
TXNRD2	thioredoxin reductase 2	1.51900 8256		TDRKH	tudor and KH domain containing	- 3.59096 1241
NCF1	neutrophil cytosolic factor 1	1.51887 3761		FIBCD1	fibrinogen C domain containing 1	- 3.60865 6121
OAF	out at first homolog	1.51743 1856		RBBP9	RB binding protein 9, serine hydrolase	- 3.60880 9243
FAM110A	family with sequence similarity 110 member A	1.51726 3583		DERL1	derlin 1	- 3.61765 1119
ANGEL1	angel homolog 1 (Drosophila)	1.51583 2566		LENG9	leukocyte receptor cluster member 9	- 3.62058 641
RTN4IP1	reticulon 4 interacting protein 1	1.51576 0776		TRPC2	transient receptor potential cation channel subfamily C member 2, pseudogene	- 3.62058 641
LAMP2	lysosomal associated membrane protein 2	1.51570 9038		CCDC134	coiled-coil domain containing 134	- 3.63226 8216
KRT4	keratin 4	1.51429 9789		OAS2	2'-5'-oligoadenylate synthetase 2	- 3.63226 8216
PAFAH1B3	platelet activating factor acetylhydrolase 1b catalytic subunit 3	1.51429 35		2410127L1 7RIK	Description Not Found	- 3.64673 8698
STT3A	STT3A, catalytic subunit of the oligosaccharyltransferas e complex	1.51353 7695		RSAD1	radical S-adenosyl methionine domain containing 1	- 3.64922 0471
PRKAR1B	protein kinase cAMP-dependent type I regulatory subunit beta	1.51340 003		H2-DMB1	histocompatibility 2, class II, locus Mb1(H2-DMb1)	- 3.64961 5459
HIST1H2B B	histone cluster 1, H2bb	1.51294 1595		IFT81	intraflagellar transport 81	- 3.67383 9056
ZFP39	zinc finger protein 39(Zfp39)	1.51138 5424		MID1	midline 1	- 3.68369 6454
PLK1	polo like kinase 1	1.51115 1166		DEPDC1B	DEP domain containing 1B	- 3.68369 6454
1700028P14 RIK	Description Not Found	1.51096 1919		SMAD3	SMAD family member 3	- 3.71629 6166
D10BWG13 79E	Description Not Found	1.51096 1919		UBTD1	ubiquitin domain containing 1	- 3.71699 0894
TREM3	triggering receptor expressed on myeloid cells 3(Trem3)	1.51096 1919		FBXO44	F-box protein 44	- 3.73876 7837
GM128	predicted gene 128(Gm128)	1.51096 1919		KCNMB4	potassium calcium-activated channel	- 3.74195

					subfamily M regulatory beta subunit 4	1111
OLFR741	olfactory receptor 741(Olfr741)	1.51096 1919		FAIM3	Description Not Found	- 3.75488 7502
OLFR523	olfactory receptor 523(Olfr523)	1.51096 1919		CCM2	CCM2 scaffolding protein	- 3.75488 7502
DCPP1	demilune cell and parotid protein 1(Dcpp1)	1.51096 1919		DAG1	dystroglycan 1	- 3.76022 0946
RPRML	reprimo like	1.51096 1919		FCGR3	Fc receptor, IgG, low affinity III(Fcgr3)	- 3.77610 3988
CHRD	chordin	1.51096 1919		ZNRF1	zinc and ring finger 1, E3 ubiquitin protein ligase	- 3.77610 3988
C5AR1	complement component 5a receptor 1	1.51096 1919		TLR1	toll like receptor 1	- 3.78659 6362
APOA2	apolipoprotein A2	1.51096 1919		HSD17B11	hydroxysteroid 17-beta dehydrogenase 11	- 3.78920 7575
PRG2	proteoglycan 2, pro eosinophil major basic protein	1.51096 1919		ZPBP	zona pellucida binding protein	- 3.88752 5271
VCAM1	vascular cell adhesion molecule 1	1.51096 1919		ZSWIM3	zinc finger SWIM-type containing 3	- 3.89239 1026
LY6G5B	lymphocyte antigen 6 complex, locus G5B	1.51096 1919		SOCS1	suppressor of cytokine signaling 1	- 3.89239 1026
AIM2	absent in melanoma 2	1.51096 1919		KLF9	Kruppel like factor 9	- 3.90202 1342
DMBX1	diencephalon/mesencephalon homeobox 1	1.51096 1919		AHSA2	AHA1, activator of heat shock 90kDa protein ATPase homolog 2 (yeast)	- 3.90476 0449
HCN2	hyperpolarization activated cyclic nucleotide gated potassium channel 2	1.51096 1919		DDHD1	DDHD domain containing 1	- 3.91408 6097
MRGPRF	MAS related GPR family member F	1.51096 1919		CNKSR3	CNKSR family member 3	- 3.93073 7338
CYTH4	cytohesin 4	1.51096 1919		CPEB2	cytoplasmic polyadenylation element binding protein 2	- 4.01751 6295
ANGPTL3	angiopoietin like 3	1.51096 1919		TRP53BP2	transformation related protein 53 binding protein 2(Trp53bp2)	- 4.02193 2279
DHX29	DEAH-box helicase 29	1.51066 7738		FAM178A	family with sequence similarity 178, member A(Fam178a)	- 4.03562 391
PMPCB	peptidase, mitochondrial processing beta subunit	1.50947 7625		RCN3	reticulocalbin 3	- 4.03562 391
HRH3	histamine receptor H3	1.50855 4002		SPTLC2	serine palmitoyltransferase long chain base subunit 2	- 4.04001

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ZFP282	zinc finger protein 282(Zfp282)	1.50741 9453		ZFP810	zinc finger protein 810(Zfp810)	- 4.07038 9328
TBC1D7	TBC1 domain family member 7	1.50484 7821		NAGA	alpha-N-acetylgalactosaminidase	- 4.07467 6686
ARSB	arylsulfatase B	1.50484 5728		KLRA20	killer cell lectin-like receptor subfamily A, member 20(Klra20)	- 4.07895 1341
RAD17	RAD17 checkpoint clamp loader component	1.50417 7542		STK11IP	serine/threonine kinase 11 interacting protein	- 4.08321 3368
CMTM7	CKLF like MARVEL transmembrane domain containing 7	1.50329 7831		KLF4	Kruppel like factor 4	- 4.08430 6687
NFKB2	nuclear factor kappa B subunit 2	1.50036 3085		INADL	Description Not Found	- 4.08666 7018
TOP3A	topoisomerase (DNA) III alpha	- 1.50007 357		URM1	ubiquitin related modifier 1	- 4.09070 78
RAB33B	RAB33B, member RAS oncogene family	- 1.50054 042		PELI1	pellino E3 ubiquitin protein ligase 1	- 4.09381 3673
LYSMD1	LysM domain containing 1	- 1.50061 4885		FBLN1	fibulin 1	- 4.09803 2083
POLG2	polymerase (DNA) gamma 2, accessory subunit	- 1.50070 7646		HR	hair growth associated	- 4.13545 2784
TGIF1	TGFB induced factor homeobox 1	- 1.50119 6523		ASB6	ankyrin repeat and SOCS box containing 6	- 4.13750 3524
RELL1	RELT like 1	- 1.50300 255		SLC27A5	solute carrier family 27 member 5	- 4.14159 6278
CYP26B1	cytochrome P450 family 26 subfamily B member 1	- 1.50439 813		PPP1R3F	protein phosphatase 1 regulatory subunit 3F	- 4.14974 712
PTRH2	peptidyl-tRNA hydrolase 2	- 1.50467 8598		AB124611	cDNA sequence AB124611(AB124611)	- 4.17337 3402
ZKSCAN3	zinc finger with KRAB and SCAN domains 3	- 1.50491 6722		CD40	CD40 molecule	- 4.18189 7643
SP8	Sp8 transcription factor	- 1.50599 9092		SMAD5	SMAD family member 5	- 4.18388 3459
SAMD14	sterile alpha motif domain containing 14	- 1.50627 2343		COL23A1	collagen type XXIII alpha 1 chain	- 4.22110 3725
MX2	MX dynamin like GTPase 2	- 1.50726 8463		ZFP595	zinc finger protein 595(Zfp595)	- 4.22881 8691
OCRL	OCRL, inositol polyphosphate-5-phosphatase	- 1.50763 8755		PECAM1	platelet and endothelial cell adhesion molecule 1	- 4.23278 9973
SYNJ2BP	synaptojanin 2 binding	-		TMEM138	transmembrane protein	-

	protein	1.507669173			138	4.241228289
CPLX4	complexin 4	-1.508554002		RFX2	regulatory factor X2	-4.244125943
LGALS9	galectin 9	-1.509246723		KCTD12	potassium channel tetramerization domain containing 12	-4.247846204
TAZ	tafazzin	-1.509269953		TRIM56	tripartite motif containing 56	-4.262008929
2310002L09RIK	Description Not Found	-1.511961919		EIF4EBP2	eukaryotic translation initiation factor 4E binding protein 2	-4.263034406
ZFP97	zinc finger protein 97(Zfp97)	-1.511961919		RALGPS2	Ral GEF with PH domain and SH3 binding motif 2	-4.279842694
OLFR1494	olfactory receptor 1494(Olfr1494)	-1.511961919		TGM2	transglutaminase 2	-4.293161941
BC030867	cDNA sequence BC030867(BC030867)	-1.511961919		ENC1	ectodermal-neural cortex 1	-4.311067102
CEACAM9	carcinoembryonic antigen-related cell adhesion molecule 9(Ceacam9)	-1.511961919		LRIG1	leucine rich repeats and immunoglobulin like domains 1	-4.375039431
LRIT1	leucine rich repeat, Ig-like and transmembrane domains 1	-1.511961919		PRM1	protamine 1	-4.375039431
KLK5	kallikrein related peptidase 5	-1.511961919		DUSP7	dual specificity phosphatase 7	-4.383538076
KRT27	keratin 27	-1.511961919		SERTAD3	SERTA domain containing 3	-4.399171094
CACNG4	calcium voltage-gated channel auxiliary subunit gamma 4	-1.511961919		KCNC1	potassium voltage-gated channel subfamily C member 1	-4.409390936
IL13RA1	interleukin 13 receptor subunit alpha 1	-1.511961919		UBE2D3	ubiquitin conjugating enzyme E2 D3	-4.462706751
TMEM121	transmembrane protein 121	-1.511961919		SEPP1	selenoprotein P, plasma, 1	-4.463383458
HIST1H2AA	histone cluster 1, H2aa	-1.511961919		ADRB2	adrenoceptor beta 2	-4.463910999
MPZL3	myelin protein zero like 3	-1.511961919		PPP1R13B	protein phosphatase 1 regulatory subunit 13B	-4.471417658
TGFB2	transforming growth factor beta 2	-1.511961919		ARRDC3	arrestin domain containing 3	-4.504620392
IFT74	intraflagellar transport 74	-1.511961919		GNGT2	G protein subunit gamma transducin 2	-4.531381461
FCRL1	Fc receptor like 1	-1.51096		SIAH1A	seven in absentia 1A(Siah1a)	-4.53915

		1919				8811
ADRB1	adrenoceptor beta 1	-1.51096 1919		XPC	XPC complex subunit, DNA damage recognition and repair factor	-4.56376 8278
MAGI2	membrane associated guanylate kinase, WW and PDZ domain containing 2	-1.51096 1919		HIPK1	homeodomain interacting protein kinase 1	-4.68369 6454
SCG5	secretogranin V	-1.51096 1919		H2-OB	histocompatibility 2, O region beta locus(H2-Ob)	-4.70043 9718
GCK	glucokinase	-1.51096 1919		BACH2	BTB domain and CNC homolog 2	-4.71699 0894
ASB10	ankyrin repeat and SOCS box containing 10	-1.51096 1919		MAP1LC3 A	microtubule associated protein 1 light chain 3 alpha	-4.72246 6024
SELE	selectin E	-1.51096 1919		LRRFIP1	LRR binding FLII interacting protein 1	-4.76155 1232
IGFBP3	insulin like growth factor binding protein 3	-1.51096 1919		ATP10D	ATPase phospholipid transporting 10D (putative)	-4.76658 1958
TPT1	tumor protein, translationally-controlled 1	-1.51096 1919		IGFBP4	insulin like growth factor binding protein 4	-4.79099 3785
ROCK1	Rho associated coiled-coil containing protein kinase 1	-1.51096 1919		TMEM108	transmembrane protein 108	-4.86542 3978
OGFRL1	opioid growth factor receptor-like 1	-1.51096 1919		PTK2	protein tyrosine kinase 2	-4.87571 9796
TMEM38A	transmembrane protein 38A	-1.51096 1919		CLEC11A	C-type lectin domain family 11 member A	-4.89724 0426
RLTPR	Description Not Found	-1.51227 339		LRP12	LDL receptor related protein 12	-4.95502 9571
ITPKC	inositol-trisphosphate 3-kinase C	-1.51238 9725		GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group)	-4.95884 2675
TLE4	transducin like enhancer of split 4	-1.51341 989		F10	coagulation factor X	-4.96578 4285
PDE4D	phosphodiesterase 4D	-1.51366 7908		DBP	D-box binding PAR bZIP transcription factor	-4.96654 9451
A130010J1 5RIK	Description Not Found	-1.51429 6211		ABCG1	ATP binding cassette subfamily G member 1	-5.00225 2452
RNF167	ring finger protein 167	-1.51476 5492		WDR78	WD repeat domain 78	-5.01792 1908
CCBL1	Description Not Found	-1.51562 6494		DNAJC6	DnaJ heat shock protein family (Hsp40) member C6	-5.01792 1908
HSD17B1	hydroxysteroid 17-beta dehydrogenase 1	-1.51687 5069		AFF4	AF4/FMR2 family member 4	-5.03342 3002

OSM	oncostatin M	-1.517234668		TNFRSF26	tumor necrosis factor receptor superfamily, member 26(Tnfrsf26)	-5.040015679
RHPN1	rhophilin, Rho GTPase binding protein 1	-1.517275693		GFOD2	glucose-fructose oxidoreductase domain containing 2	-5.070389328
TAS2R105	taste receptor, type 2, member 105(Tas2r105)	-1.517431856		TYROBP	TYRO protein tyrosine kinase binding protein	-5.114783447
NIPBL	NIPBL, cohesin loading factor	-1.517569618		TMEM176B	transmembrane protein 176B	-5.118941073
CXCR3	C-X-C motif chemokine receptor 3	-1.519325267		ZFP710	zinc finger protein 710(Zfp710)	-5.159871337
SMURF1	SMAD specific E3 ubiquitin protein ligase 1	-1.520263252		ENPP4	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)	-5.181897643
RNF208	ring finger protein 208	-1.52126647		MAPK8	mitogen-activated protein kinase 8	-5.259272487
ITGA5	integrin subunit alpha 5	-1.523517983		TNFRSF25	tumor necrosis factor receptor superfamily member 25	-5.289096702
USP18	ubiquitin specific peptidase 18	-1.524814077		LCN4	lipocalin 4(Lcn4)	-5.366322214
PIP5K1A	phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	-1.525074369		CRIM1	cysteine rich transmembrane BMP regulator 1	-5.369815424
STRBP	spermatid perinuclear RNA binding protein	-1.52561213		RTP4	receptor transporter protein 4	-5.444600814
GRAMD2	GRAM domain containing 2	-1.52652805		PRNP	prion protein	-5.495055528
ZFP101	zinc finger protein 101(Zfp101)	-1.526555668		ZFP747	zinc finger protein 747(Zfp747)	-5.496654083
RUNDC1	RUN domain containing 1	-1.526563287		CD7	CD7 molecule	-5.504620392
SLC13A3	solute carrier family 13 member 3	-1.528487927		ARHGAP26	Rho GTPase activating protein 26	-5.548436625
CCDC94	coiled-coil domain containing 94	-1.528487927		S100A9	S100 calcium binding protein A9	-5.557655155
MRPS14	mitochondrial ribosomal protein S14	-1.528962318		AQP9	aquaporin 9	-5.572889668
NEU4	neuraminidase 4 (sialidase)	-1.529820947		CXCR5	C-X-C motif chemokine receptor 5	-5.573647187
PCGF1	polycomb group ring finger 1	-1.53059536		CCNO	cyclin O	-5.574404309
PNPLA7	patatin like phospholipase domain	-1.53207		LYNX1	Ly6/neurotoxin 1	-5.66675

	containing 7	883				6592
SPATA19	spermatogenesis associated 19	-1.533014103		CLDN10	claudin 10	-5.782015335
AP4B1	adaptor related protein complex 4 beta 1 subunit	-1.533821865		AMIGO2	adhesion molecule with Ig-like domain 2	-5.83541884
BC068281	cDNA sequence BC068281(BC068281)	-1.5360529		CD79B	CD79b molecule	-5.94016675
GK2	glycerol kinase 2	-1.5360529		USP53	ubiquitin specific peptidase 53	-5.980710829
PIGM	phosphatidylinositol glycan anchor biosynthesis class M	-1.5360529		IKBKE	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon	-6.005624549
FKBP6	FK506 binding protein 6	-1.5360529		ALOX5AP	arachidonate 5-lipoxygenase activating protein	-6.008988783
EVI5	ecotropic viral integration site 5	-1.5360529		GGT1	gamma-glutamyltransferase 1	-6.010108453
BCL11A	B-cell CLL/lymphoma 11A	-1.5360529		CAMK2D	calcium/calmodulin dependent protein kinase II delta	-6.047669251
PER1	period circadian clock 1	-1.537278499		RAB3D	RAB3D, member RAS oncogene family	-6.156841525
BTBD9	BTB domain containing 9	-1.537451456		MAP3K8	mitogen-activated protein kinase kinase kinase 8	-6.376776572
USP38	ubiquitin specific peptidase 38	-1.537763627		NOTCH4	notch 4	-6.495055528
LRRC57	leucine rich repeat containing 57	-1.538083341		MACROD1	MACRO domain containing 1	-6.581200582
5830415F09RIK	Description Not Found	-1.53855912		RNF144A	ring finger protein 144A	-6.632268216
EGR2	early growth response 2	-1.540038325		PDE2A	phosphodiesterase 2A	-6.86913112
GMEB2	glucocorticoid modulatory element binding protein 2	-1.541122795		THA1	threonine aldolase 1(Tha1)	-6.885086225
PIK3R4	phosphoinositide-3-kinase regulatory subunit 4	-1.541975323		APP	amyloid beta precursor protein	-6.940754047
KRR1	KRR1, small subunit processome component homolog	-1.54225805		FAM109A	family with sequence similarity 109 member A	-6.968666793
COL9A1	collagen type IX alpha 1	-1.54225805		LRG1	leucine rich alpha-2-glycoprotein 1	-6.995484519
POLD4	polymerase (DNA) delta 4, accessory subunit	-1.542654605		IL11RA1	interleukin 11 receptor, alpha chain 1(Il11ra1)	-7.016251155
ACSS2	acyl-CoA synthetase	-		CNR2	cannabinoid receptor 2	-

	short-chain family member 2	1.544045378				7.213347282
PDLIM1	PDZ and LIM domain 1	-1.544785186		NUAK2	NUAK family kinase 2	-7.369815424
A430107P09RIK	Description Not Found	-1.544921568		GPR146	G protein-coupled receptor 146	-7.577806447
SLC38A11	solute carrier family 38 member 11	-1.546222547				

***Log2Fold Change = log2(4+L+/4–L–)**

To investigate the molecular pathways between these three populations, gene ontology networks were grouped into nodes and the most significant pathways within each node were determined (Figure 6A). Gene ontology (GO) terms shared between our dysfunctional T cell dataset and the published hypofunctional T cell dataset were greatly enriched in cell cycle genes, consistent with the observation that the dysfunctional population is largely Ki67$^+$. GO terms shared between dysfunctional and exhausted gene sets encompassed effector programs such as regulation of cell killing, chemotaxis, interferon-γ production. GO terms shared between hypofunctional and exhausted gene sets consisted of cell cycle pathways, negative regulation of lymphocytes, and interferon-γ production. These data indicate that while some conserved molecular programs likely exist in these dysfunctional differentiation states, many pathways may be differentially regulated between chronic viral infections and in the tumor context.

While many inhibitory receptors, including *Pdcd1* (PD-1), *Havcr2* (TIM-3), *Cd244* (2B4), *Klre1*, and *Lag3* were shared between all data sets; the co-stimulatory receptors *Tnfrsf4* (OX-40) and *Tnfrsf9* (4-1BB) were upregulated in dysfunctional and hypofunctional CD8$^+$ TIL data sets. Therefore, to enrich in potential markers and therapeutic targets on tumor specific CD8$^+$ TILs, the complete cell surface phenotype of the 4-1BB$^+$LAG-3$^+$ CD8 TIL population was characterized. Comparing the different CD8$^+$ TIL subpopulations, several additional upregulated co-stimulatory receptors were found: *Tnfrsf18* (GITR), *Nkg2d* (KLRK1) and *Cd27*. The transcript for *Nrp1* (neuropilin-1), which encodes for a cell surface receptor protein implicated in CD4$^+$ Treg function (Sarris et al., 2008; incorporated by reference in its entirety), was also highly expressed. Expression of many of these molecules was confirmed by flow cytometry at day 7, 14 and 21 after tumor inoculation (Figure 6C). The analysis was extended to include the co-stimulatory molecules ICOS and CD160 and the inhibitory

receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT) because ICOS and CD160 were close to the cutoff value and no probe was present for TIGIT in the gene array. In addition, recent reports indicate that targeting these receptors can be therapeutic in murine models of cancer (Johnston et al., 2014; Fan et al., 2014; incorporated by reference in their entireties). PD-1, TIGIT, TIM-3, CD27 and NRP1 were expressed the majority of the 4-1BB$^+$LAG-3$^+$ TIL population and expression was maintained over time. 2B4, CD160, CTLA4, OX-40, and GITR subdivided a lesser fraction of the 4-1BB$^+$LAG-3$^+$ population. The expression of several inhibitory receptors, 2B4, TIM3 and CD160 increased over this 3-week time frame while expression of the co-stimulatory receptors, ICOS and OX-40, decreased (Figure 6C).

To address if the dysfunctional CD8$^+$ TILs are terminally-differentiated short term effector cells or memory-like cells, the expression of KLRG-1 and IL-7Rα (Joshi et al., 2007). Most of the CD8$^+$ TIL were negative for KLRG-1 expression and there was no difference between the 4-1BB$^+$LAG-3$^+$ and 4-1BB$^-$LAG-3$^-$ populations. However, the majority of the 4-1BB$^+$LAG-3$^+$ TIL did not express the IL-7 receptor (IL-7Rα) compared to their negative counter parts (Figure 6D). These results indicate that the 4-1BB$^-$LAG-3$^-$ TIL, which are not apparently specific for antigens expressed in the tumor microenvironment, are more memory-like, yet at the same time the tumor antigen-specific LAG-3$^+$4-1BB$^+$ subset has not fully acquired a terminal effector phenotype.

Functional relevance of genes that are differentially regulated in CD8$^+$4-1BB$^+$LAG-3$^+$ TILs

The gene array results in Table 2 provide a list of genes characterizing *CD8$^+$4-1BB$^+$LAG-3$^+$ TILs*. The list includes therapeutic targets and additional markers of anti-tumor immunity. Experiments conducted during development of embodiments herein to test the functional relevance of these additional targets/markers (Figure 11). Data indicate that the array has identified targets for immunotherapy, using knockout mice (e.g., PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, and TMEM126A, CRTAM, Sema7a, etc.). Experiments demonstrate that Nrn1 and CRTAM are negative regulators of the anti-tumor immune response, as knockout mice lacking either of these molecules showed improved immune-mediated tumor control in vivo. In contrast, Sema7a is a positive regulator of anti-tumor immune responses, as knockout mice lacking this molecule show diminished immune-mediated tumor control in vivo (Figure 11). These experiments indicate that agonists of Sema7a signaling and antagonists of Nrn1 and/or CRTAM should be useful therapeutics for the treatment of cancer.

Targeting 4-1BB and LAG-3 exerts anti-tumor activity in vivo and normalizes the function and phenotypic composition of CD8$^+$ TILs

Experiments were conducted during development of embodiments herein to assess whether targeting these receptors might have therapeutic utility. To this end, an agonistic anti-4-1BB mAb was administered alone or in combination with a blocking anti-LAG-3 mAb in mice bearing established B16.SIY tumors. While each antibody treatment alone had some therapeutic effect as reflected by slower tumor growth, the combination was particularly potent (Figure 7A). Analysis of the tumor microenvironment revealed that improved tumor control with the combination therapy was accompanied by an increase in the number of CD8$^+$ TILs specific for the SIY antigen (Figure 7B), consistent with results reported previously with anti-PD-L1 + anti-CTLA-4 mAb (Spranger et al., 2014b; Twyman-Saint Victor et al., 2015; incorporated by reference in their entireties).

It was next examined whether the therapeutic effect of anti-4-1BB + anti-LAG-3 mAbs was associated with a loss of phenotypic markers defining dysfunctional T cells in the steady state. Due to concern that re-analyzing the T cells for expression of LAG-3 and 4-1BB might be problematic, as the administered Abs could theoretically modulate the target receptors from the cell surface, the coordinate expression of additional receptors as identified above by gene expression profiling was taken advantage of. Preliminary analyses of the bulk TIL subpopulations revealed decreased expression of NRP1 and 2B4 following anti-LAG-3 + anti-4-1BB treatment (data not shown). Co-expression of 2B4 and NRP1 on SIY-reactive CD8$^+$ TILs identified by pentamer staining was analyzed. A 2.7-fold-decrease in the co-expression of 2B4 and NRP1 was observed upon anti-4-1BB + and anti-LAG-3 mAb treatment (Figure 7C), indicating a loss of the surface phenotype associated with T cell dysfunction. To determine whether this change was accompanied by a shift towards an effector phenotype, expression of KLGR-1 was examined. Indeed, a marked increase in KLGR-1 expression was observed on the SIY-reactive TIL following treatment, and a 3.7-fold increase in the KLRG-1^{hi}IL-7RA^{lo} population was observed (Figure 7D).

To eliminate the possibility that treatment with anti-LAG-3 + anti-4-1BB mAbs was not altering the phenotype of T cells already within the tumor but rather was supporting recruitment of newly primed functional T cells from secondary lymphoid organs, the S1PR inhibitor FTY720, which prevents T cell egress from lymph nodes (Halin et al., 2005; incorporated by reference in its entirety), was utilized. The efficacy of anti-PD-L1-based immunotherapies was preserved in the presence of FTY720, arguing for re-functionalization

of TIL as the major mechanism of action (Spranger et al., 2014a; incorporated by reference in its entirety). FTY720 administration was started on day 6 after tumor inoculation, 24 hours before the start of anti-LAG-3 + anti-4-1BB treatment, and continued every day until TIL analysis on day 14. Peripheral blood analyzed at the same time point revealed marked depletion of circulating T cells (Figure 9). Despite this loss of circulating T cells, the down regulation of 2B4 and NRP1 and the shift towards the KLRG1^{hi}IL-7RA^{lo} phenotype was nonetheless preserved (Figure 7E and F).

To examine functional restoration of the TIL, the KLRG-1^{lo}IL-7RA^{lo} and KLRG-1^{hi}IL-7RA^{lo} CD8^{+} TIL populations were sorted from B16.SIY tumors on day 14 following treatment and analyzed for IL-2 after restimulation *in vitro*. Indeed, the KLRG-1^{lo}IL-7RA^{lo} and KLRG-1^{hi}IL-7RA^{lo} populations showed an increased capacity to produce IL-2 upon stimulation (Figure 7G). The relative level of *Il-2* mRNA was comparable between the two CD8^{+} TIL populations and control CD8^{+}CD44^{+} TdLN T cells. Collectively, these data indicate that anti-4-1BB/anti-LAG-3 combinatorial treatment induces significant changes in the phenotype profile and promotes functional restoration of tumor antigen-specific CD8^{+} T cells already present within the tumor microenvironment.

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CLAIMS

1. A method of treating a subject with cancer comprising administering an agent that specifically targets dysfunctional tumor antigen-specific $CD8^+$ T cells.

2. The method of claim 1, wherein the subject suffers from a solid tumor cancer.

3. The method of claim 2, wherein the tumor allows T cell infiltration, but is resistant to immunotherapies.

4. The method of claim 2, wherein the tumor environment comprises dysfunctional tumor antigen-specific $CD8^+$ T cells.

5. The method of claim 1, comprising contacting the dysfunctional tumor antigen-specific $CD8^+$ T cells with an anti-4-1BB and/or anti-LAG3 agent.

6. The method of claim 5, wherein the anti-4-1BB and/or anti-LAG3 agent is an antibody, antibody fragment, or antibody mimetic molecule.

7. The method of claim 1, further comprising co-administration of an additional therapeutic agent.

8. The method of claim 7, wherein the additional therapeutic agent is a chemotherapeutic or an immunotherapeutic agent.

9. The method of claim 8, wherein the additional therapeutic agent is an immunotherapeutic agent selected from the list consisting of cell-based therapies, monoclonal antibody (mAb) therapy, cytokine therapy, and adjuvant treatment.

10. The method of claim 9, wherein the immunotherapeutic agent is a mAb therapy selected from the list consisting of anti-CTLA-4 monoclonal antibodies and/or anti-PD-L1 monoclonal antibodies.

11. The method of claim 9, wherein the immunotherapeutic agent is a cell-based therapy selected from the list consisting of dendritic-cell therapy and T-cell therapy.

12. The method of claim 7, wherein the additional therapeutic agent targets one of the receptors listed in Table 2.

13. The method of claim 7, wherein the additional therapeutic agent targets PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, TMEM126A, CRTAM and/or Sema7a.

14. The method of claim 1, comprising contacting the dysfunctional tumor antigen-specific $CD8^+$ T cells with a therapeutic agent that targets one of the receptors listed in Table 2.

15. The method of claim 14, wherein the therapeutic agent targets PD-1, TIM-3, OX-40ICOS, TIGIT, CD244, TNFRSF18, Nrn1, Nrp1, KLRG1, GM156, GPNMB, GPR65, TMEM205, TMEM126A, CRTAM and/or Sema7a.

16. The method of claim 15, wherein the therapeutic agent is an anti-Nrn1 antibody, antibody fragment, or antibody mimetic molecule.

17. The method of claim 15, wherein the therapeutic agent is an anti-Sema7a antibody, antibody fragment, or antibody mimetic molecule.

18. The method of claim 15, wherein the therapeutic agent is an anti-CRTAM antibody, antibody fragment, or antibody mimetic molecule.

19. A composition comprising: (a) one or more of an anti-4-1BB agent, an anti-LAG-3 agent, an anti-Nrn1 agent, an anti-Sema7a agent, and an anti-CRTAM agent; and (b) an immunotherapeutic agent, said composition formulated for therapeutic delivery to a subject.

20. The composition of claim 19, wherein the anti-4-1BB agent, anti-LAG-3 agent, anti-Nrn1 agent, anti-Sema7a agent, and/or anti-CRTAM agent is an antibody, antibody fragment, or antibody mimetic molecule.

21. A method comprising: (a) testing $CD8^+$ T cells from a cell population to determine whether they co-express LAG-3 and 4-1BB; and (b) administering an anti-Nrn1 agent, an anti-Sema7a agent, and an anti-CRTAM agent.

22. The method of claim 21, wherein the anti-Nrn1 agent, anti-Sema7a agent, and/or anti-CRTAM agent is an antibody, antibody fragment, or antibody mimetic molecule.

23. The method of claim 21, wherein said testing is performed *in vitro*.

24. A method of identifying dysfunctional T cells by testing said cells for co-expression of 4-1BB and LAG-3.

FIG. 1A

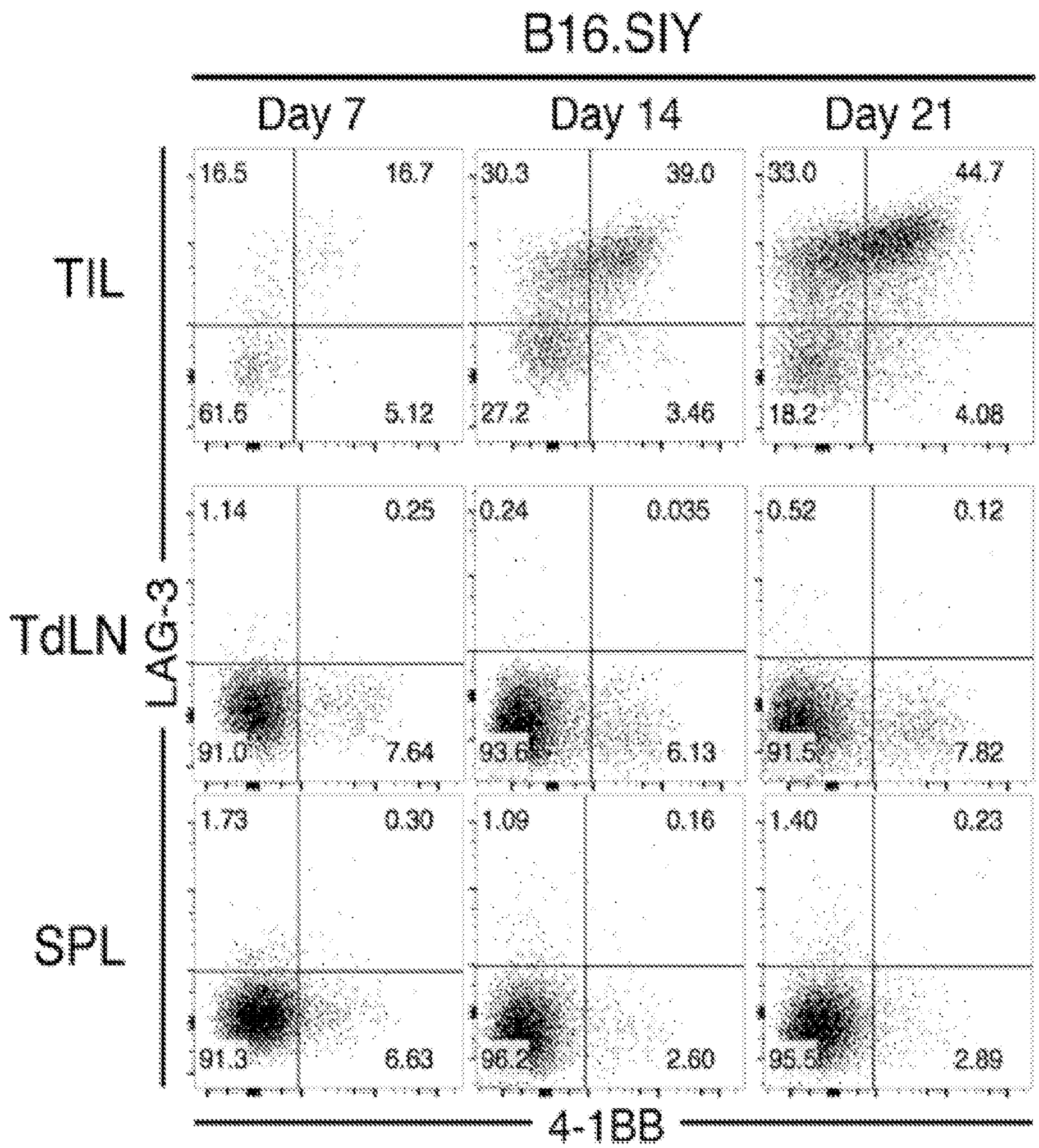

B16.SIY
Day 7
Day 14
Day 21
TIL
TdLN
SPL
LAG-3
4-1BB
16.5
16.7
30.3
39.0
33.0
44.7
61.6
5.12
27.2
3.46
18.2
4.08
1.14
0.25
0.24
0.035
0.52
0.12
91.0
7.64
93.6
6.13
91.5
7.82
1.73
0.30
1.09
0.16
1.40
0.23
91.3
6.63
96.2
2.60
95.5
2.89

FIG. 1B

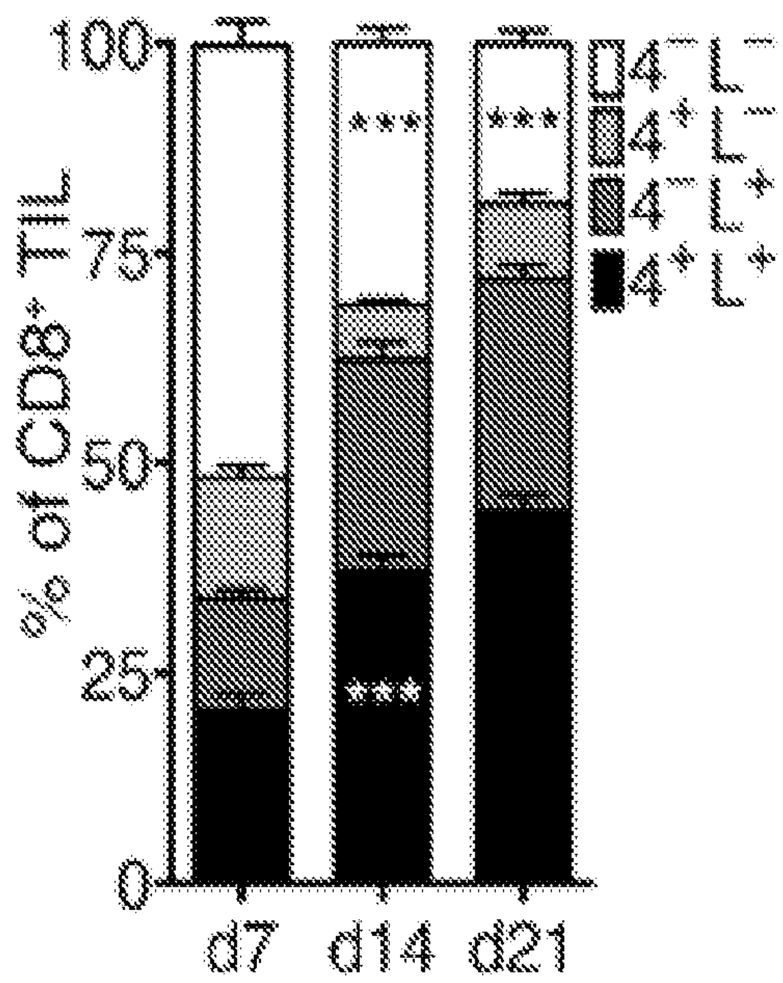

% of CD8+ TIL
100
75
50
25
0
d7
d14
d21
4- L-
4+ L-
4- L+
4+ L+

FIG. 1C

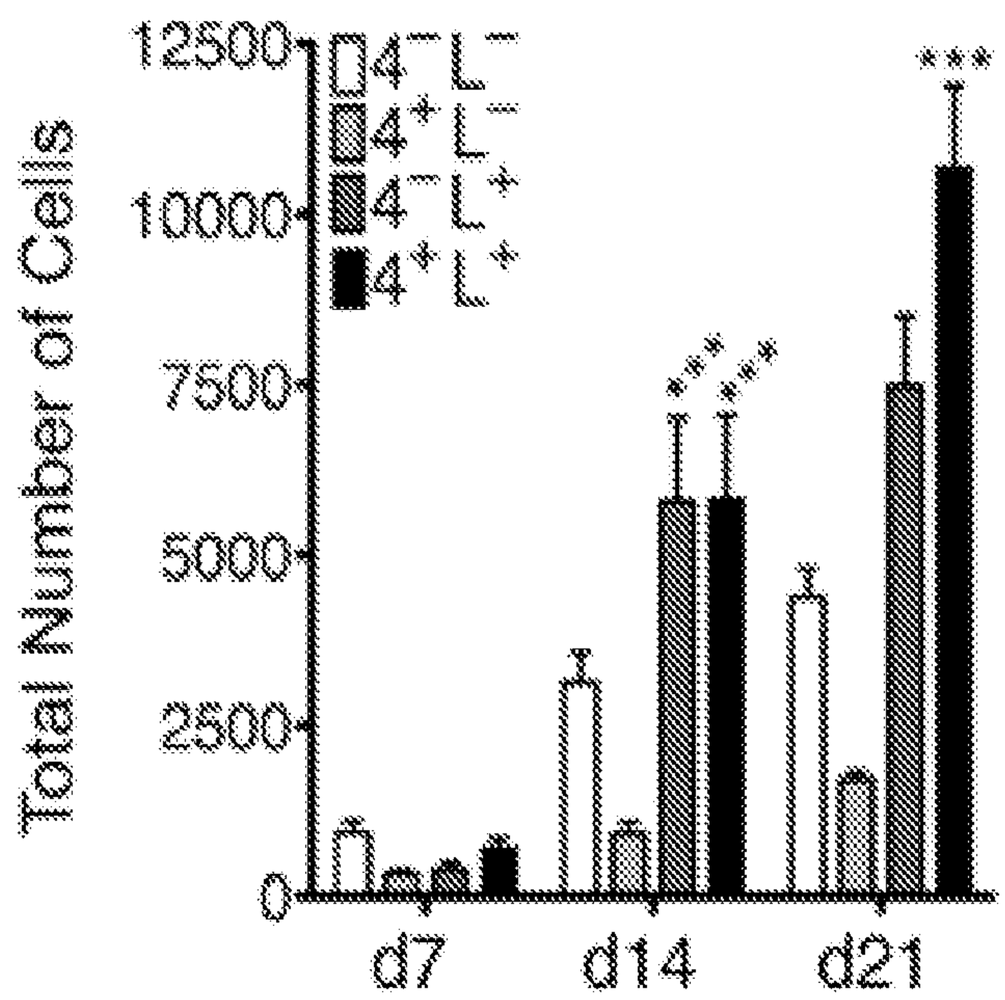

Total Number of Cells
12500
10000
7500
5000
2500
0
d7
d14
d21
4- L-
4+ L-
4- L+
4+ L+

FIG. 1D

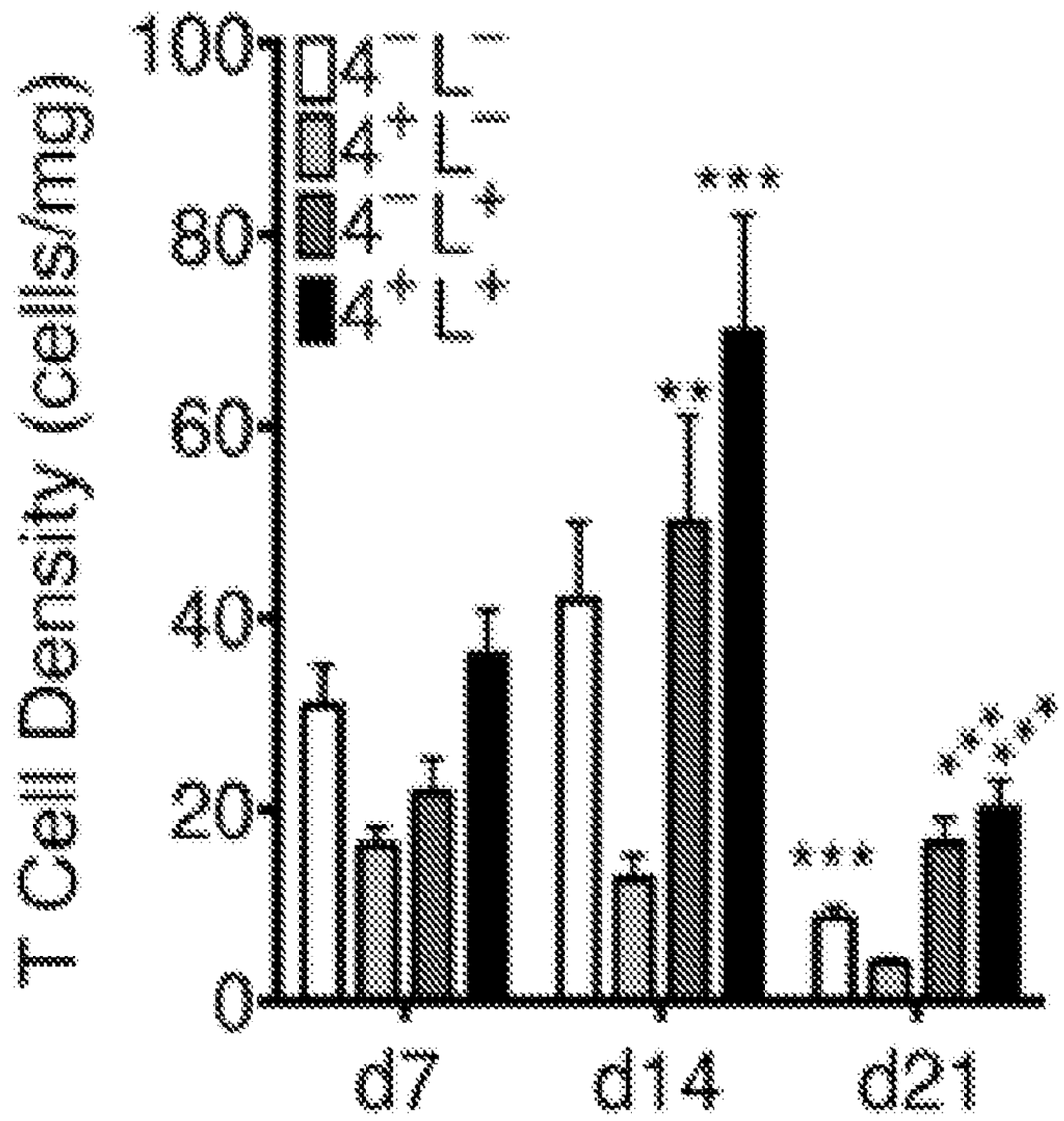

T Cell Density (cells/mg)
100
80
60
40
20
0
d7
d14
d21
4⁻L⁻
4⁺L⁻
4⁻L⁺
4⁺L⁺
***
**
***
***
***

FIG. 1E

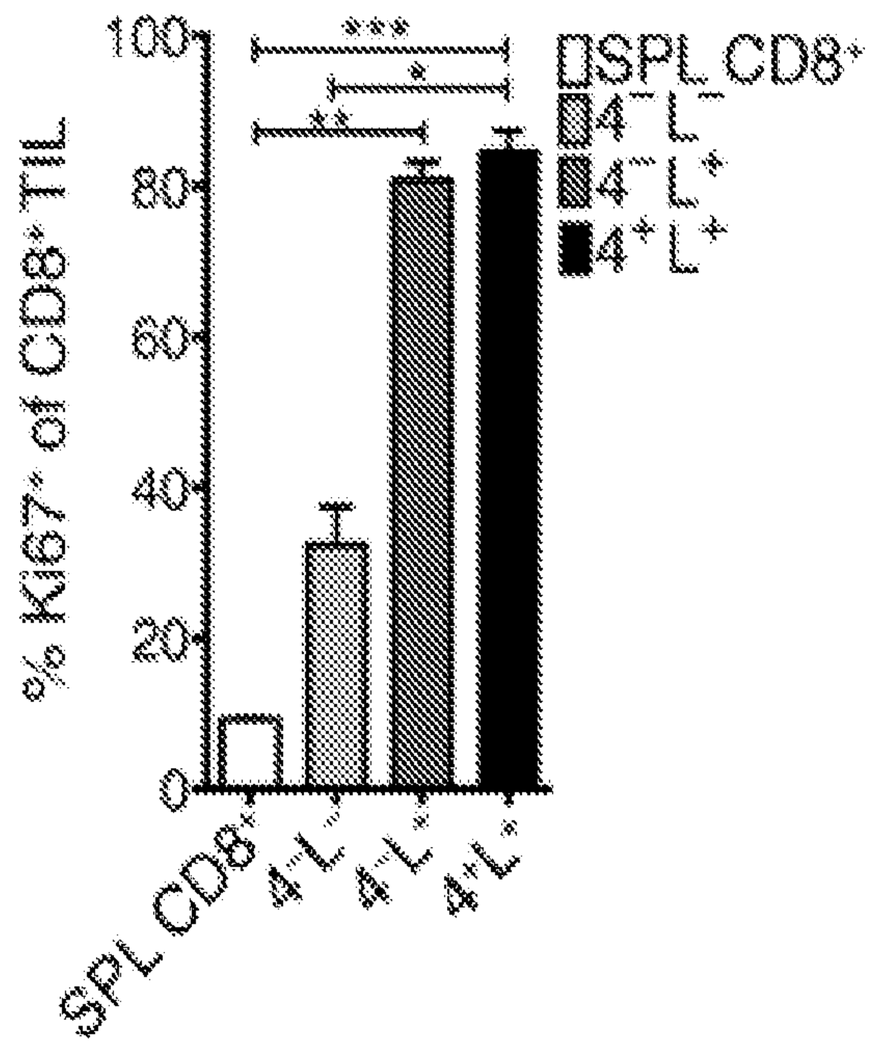

% Ki67⁺ of CD8⁺ TIL
100
80
60
40
20
0
SPL CD8⁺
4⁺L⁻
4⁺L⁺
4⁺L⁺
***
*
**
SPL CD8⁺
4⁻L⁻
4⁻L⁺
4⁺L⁺

FIG. 1F

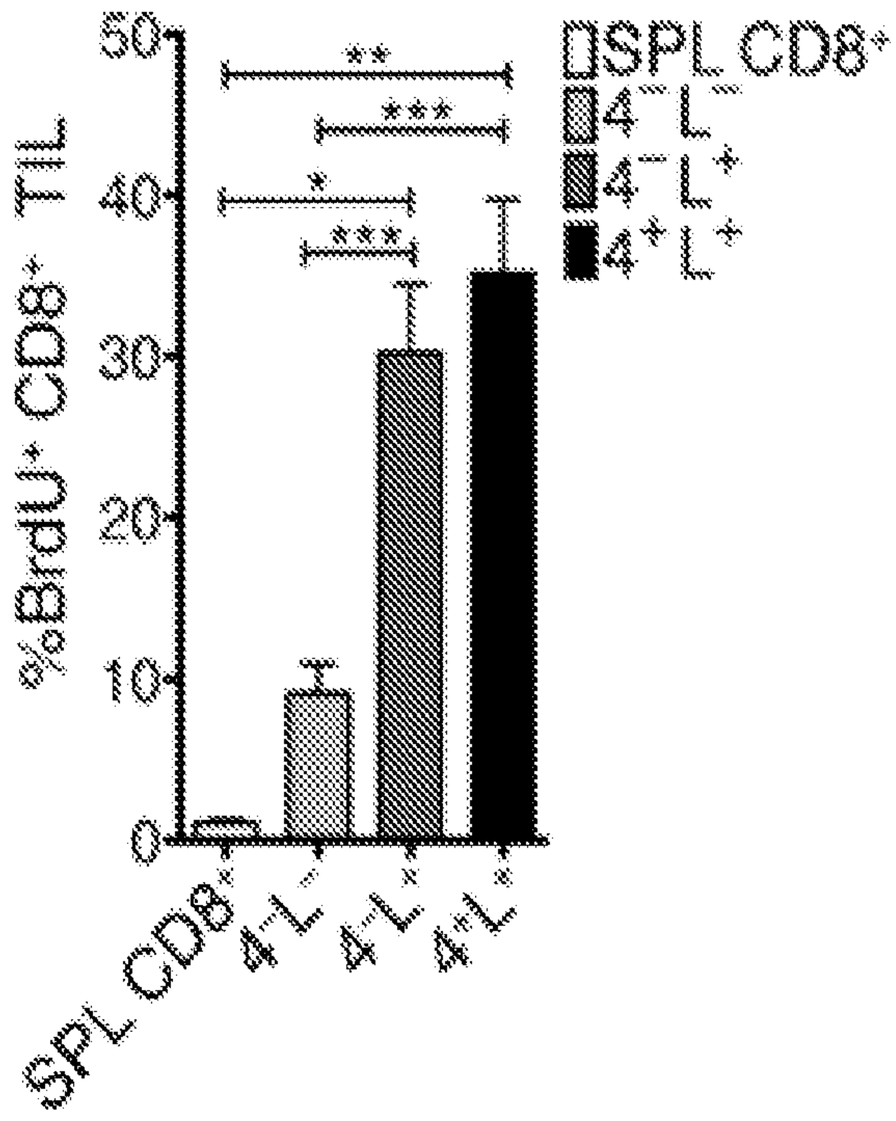

%BrdU+ CD8+ TIL
50
40
30
20
10
0
SPL CD8+
4-L-
4-L+
4+L-
4+L+
SPL CD8+
4-L-
4-L+
4+L-
4+L+

FIG. 1J

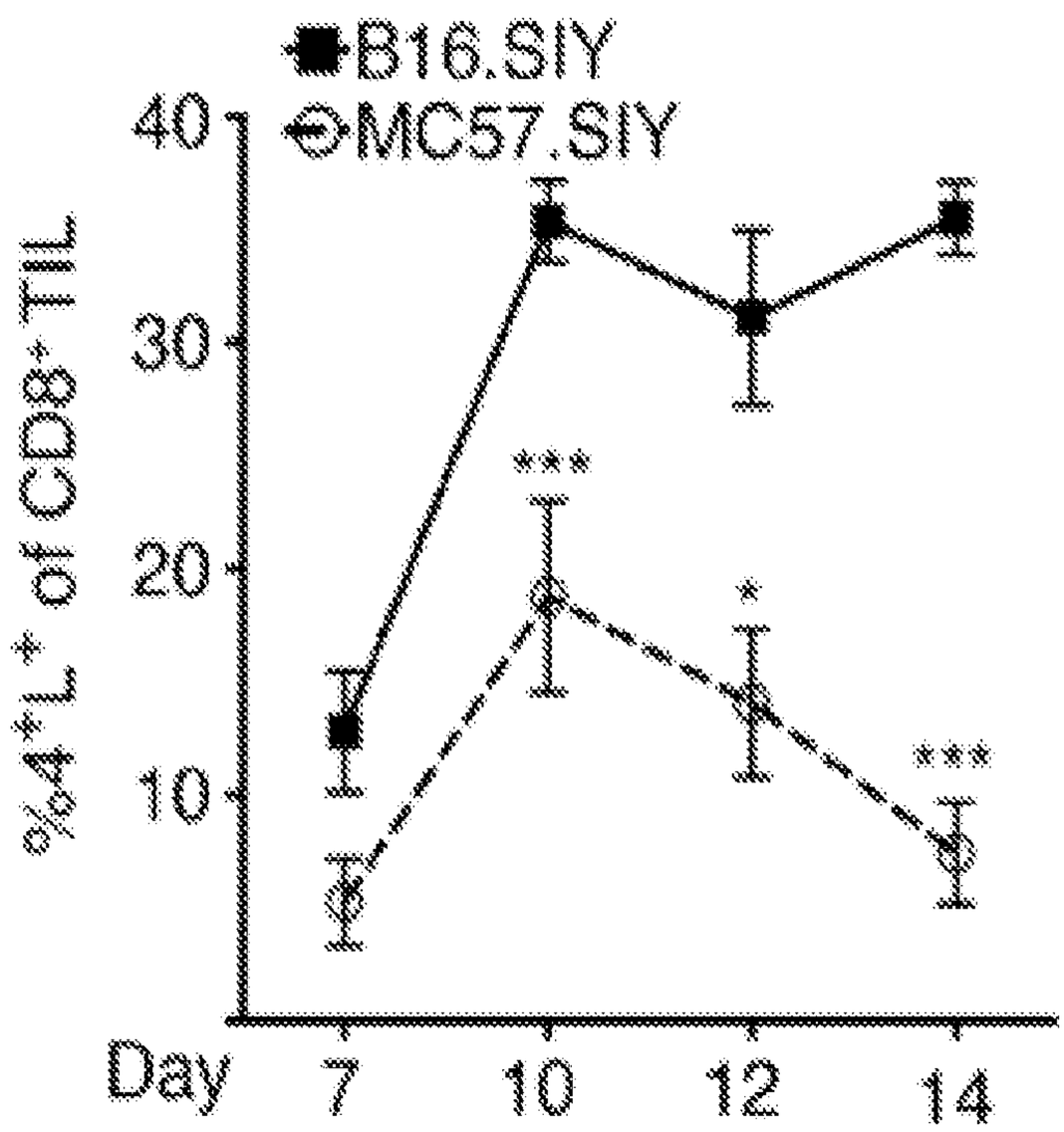

B16.SIY
MC57.SIY
%4+L+ of CD8+ TIL
40
30
20
10
Day
7
10
12
14

FIG. 1G

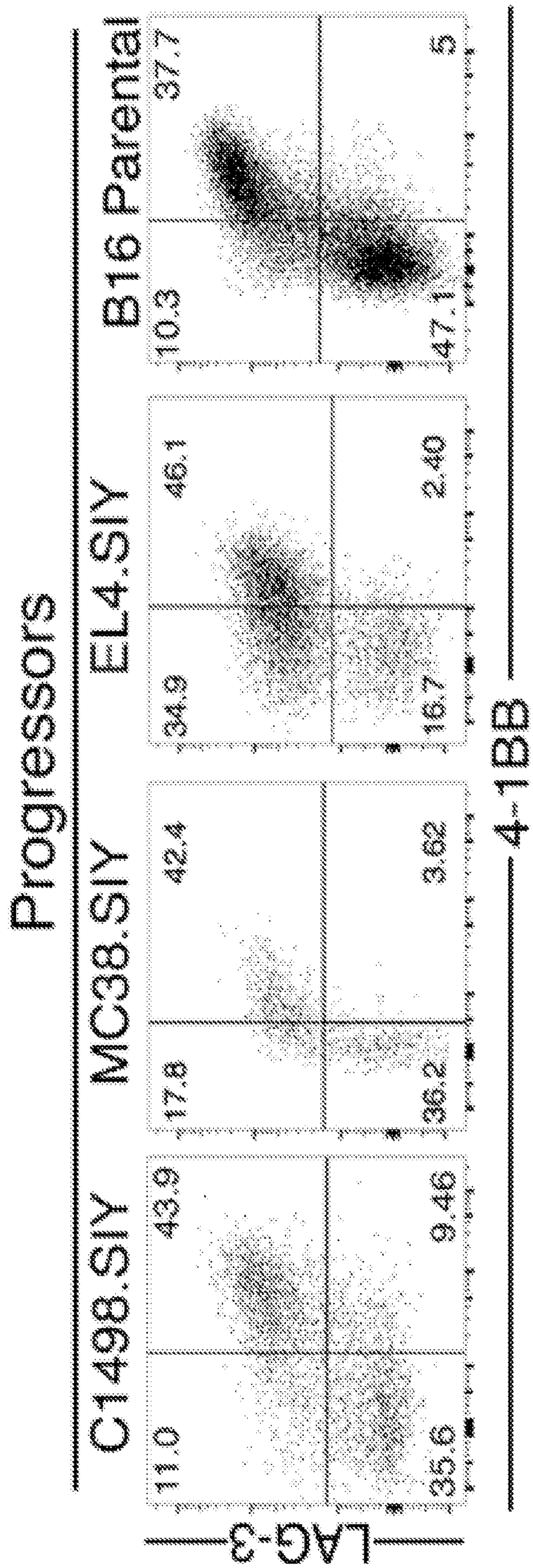

Progressors
C1498.SIY
MC38.SIY
EL4.SIY
B16 Parental
LAG-3
4-1BB
11.0
43.9
17.8
42.4
34.9
46.1
10.3
37.7
35.6
9.46
36.2
3.62
16.7
2.40
47.1
5

FIG. 1H

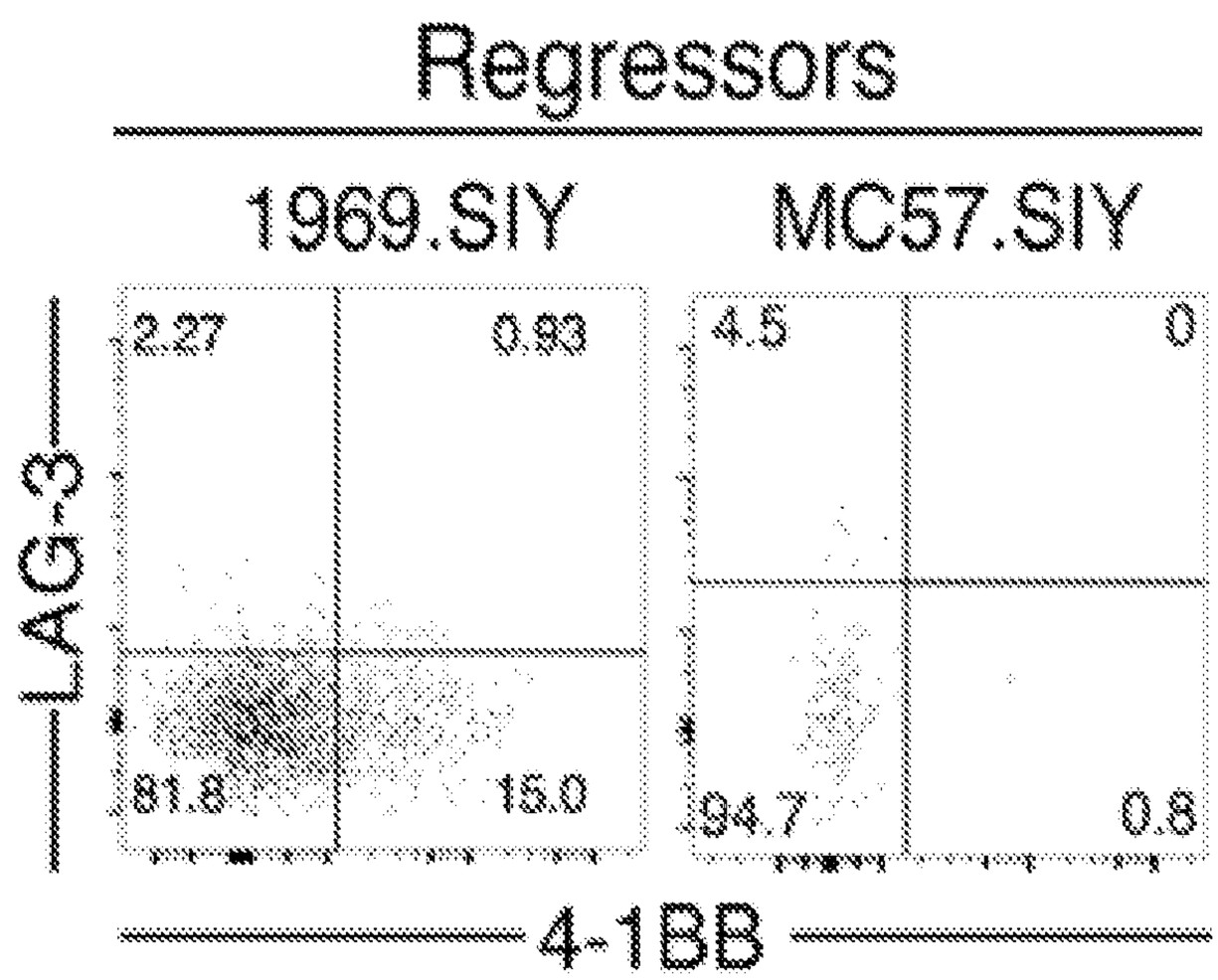

Regressors
1969.SIY
MC57.SIY
LAG-3
4-1BB
2.27
0.93
81.8
15.0
4.5
0
94.7
0.8

FIG. 1I

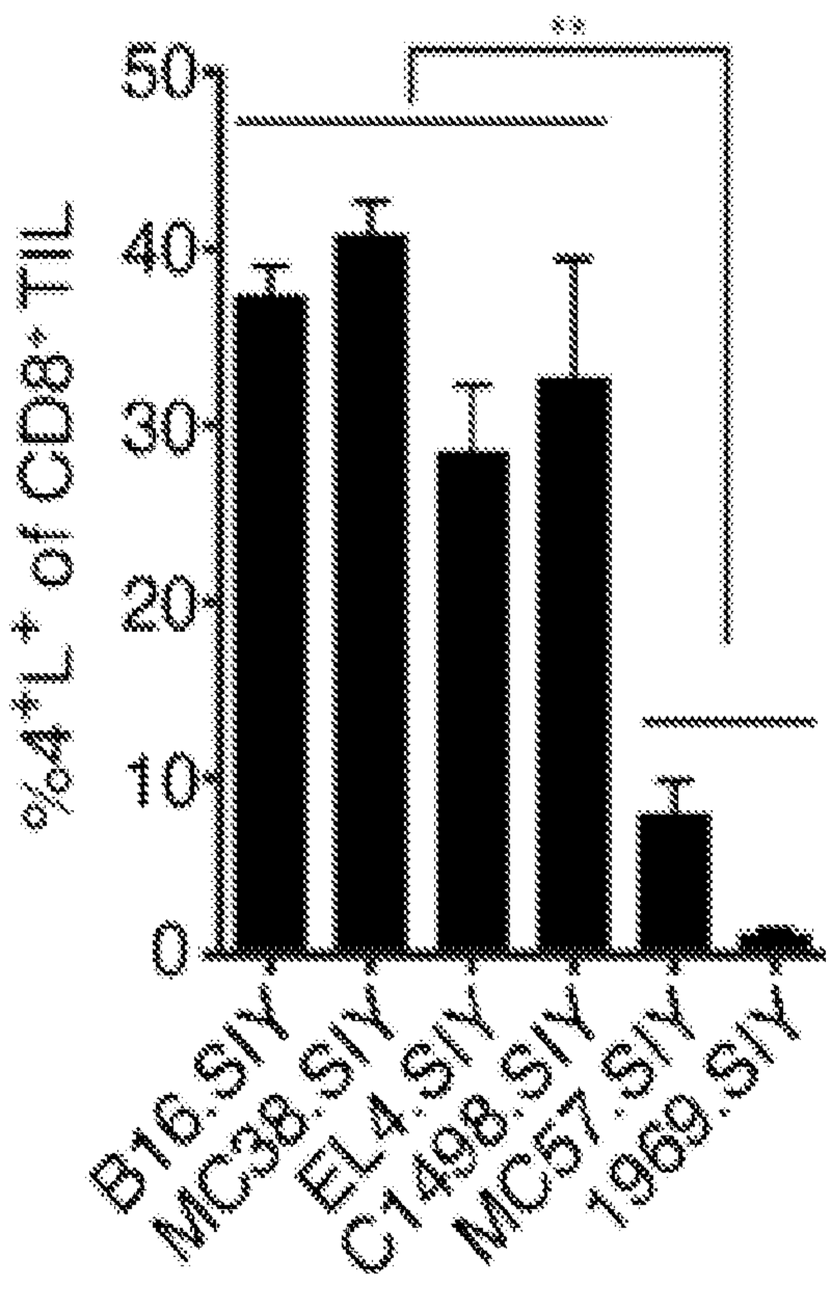

%4-1BL+ of CD8+ TIL
50
40
30
20
10
0
**
B16.SIY
MC38.SIY
EL4.SIY
C1498.SIY
MC57.SIY
1969.SIY

FIG. 2A

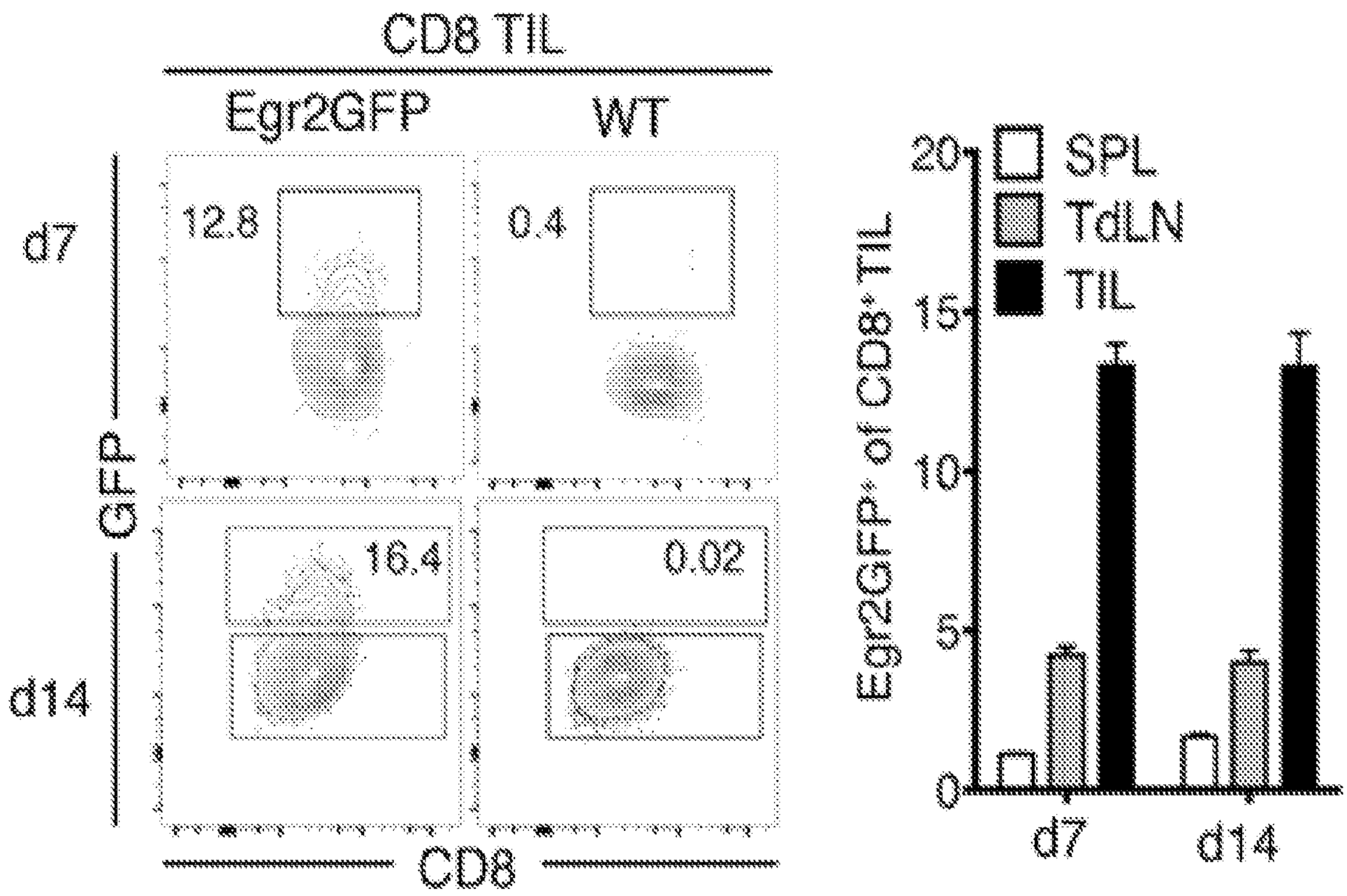

CD8 TIL
Egr2GFP
WT
d7
d14
GFP
12.8
0.4
16.4
0.02
CD8
SPL
TdLN
TIL
Egr2GFP+ of CD8+ TIL
20
15
10
5
0
d7
d14

FIG. 2B

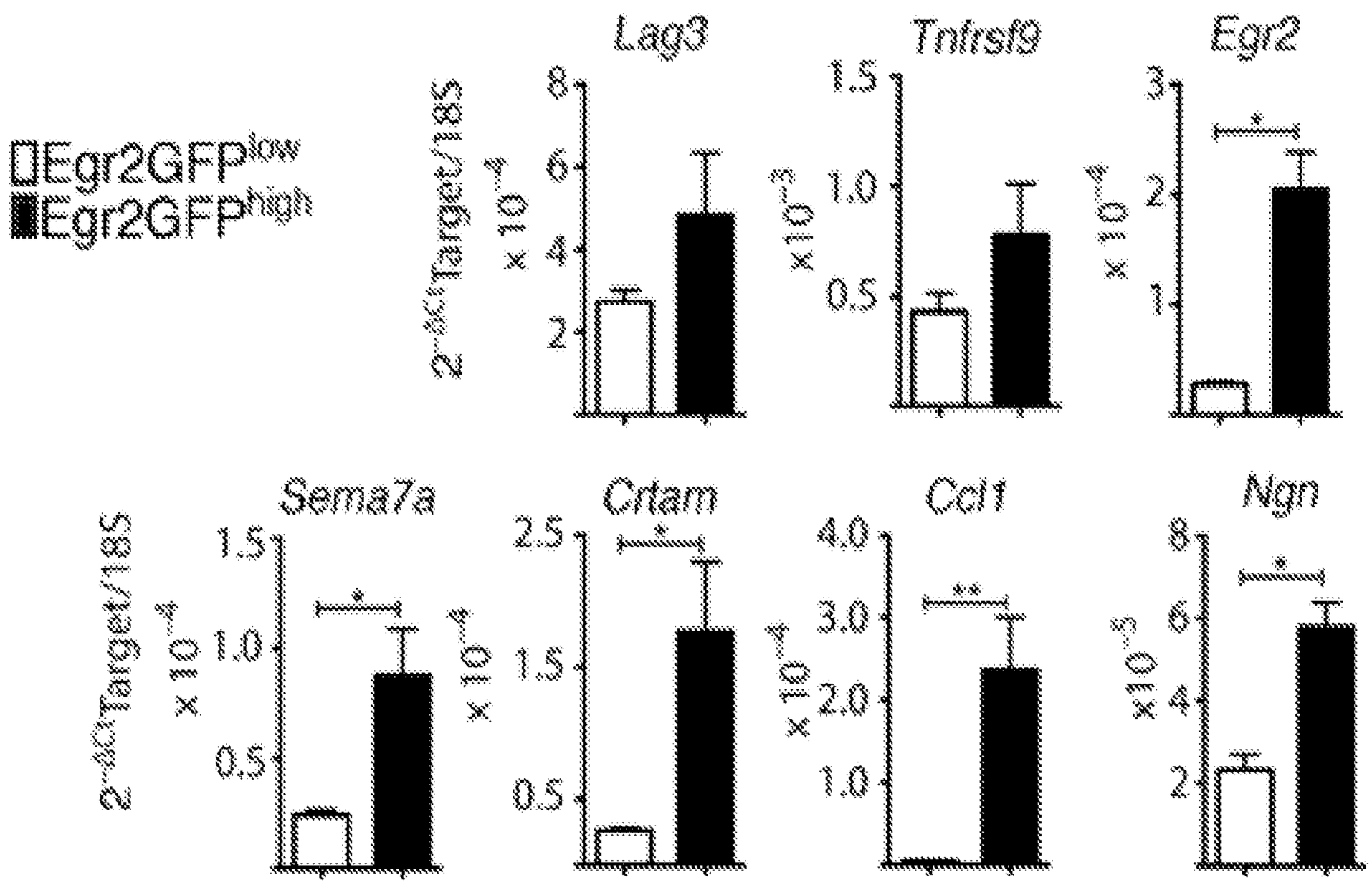

Egr2GFP^low
Egr2GFP^high
Lag3
Tnfrsf9
Egr2
Sema7a
Cntam
Ccl1
Ngn
2^-ΔΔCt Target/18S
x 10^-4
x 10^-3
*
**

FIG. 2C

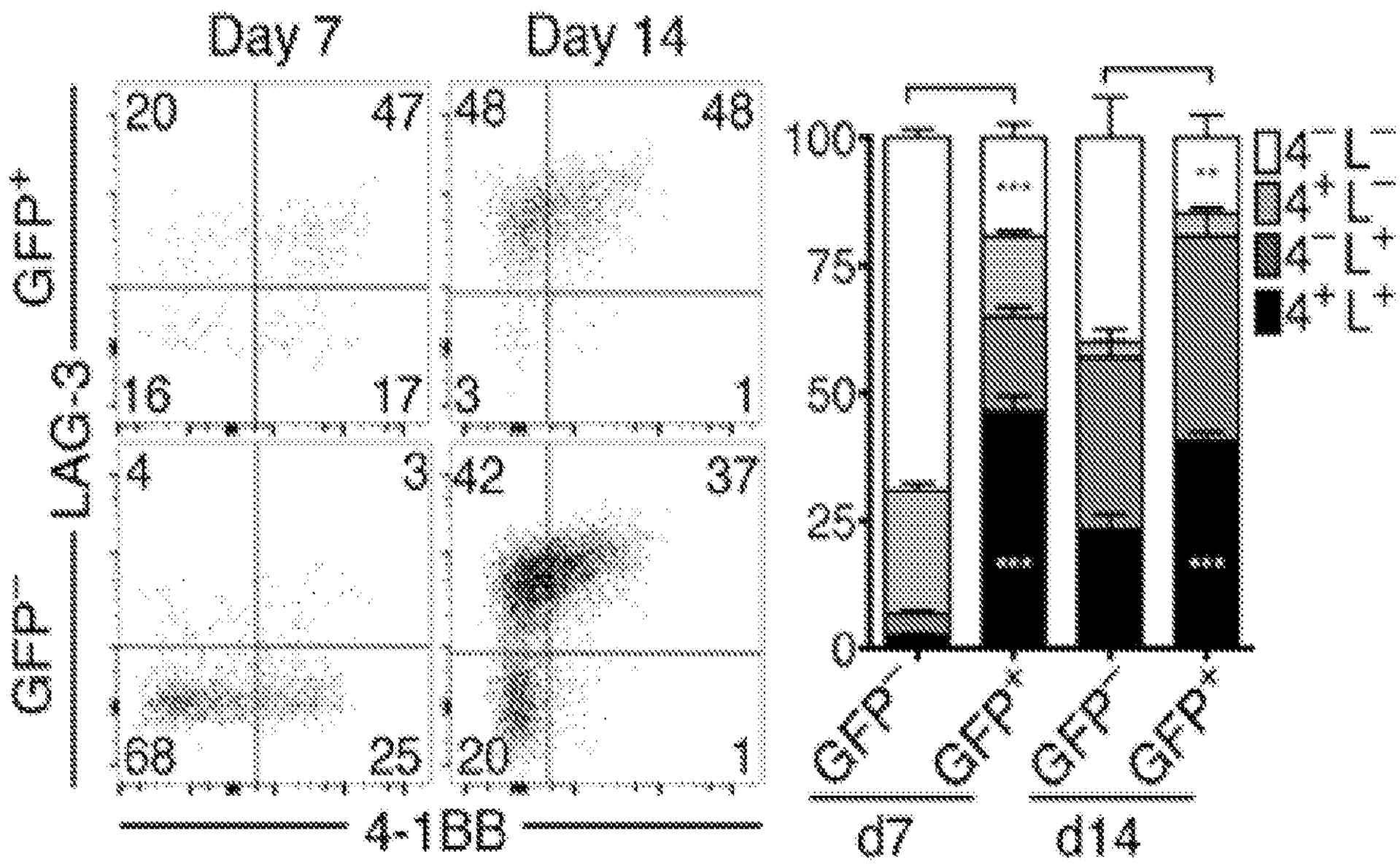

Day 7
Day 14
GFP+
GFP−
LAG-3
20
47
16
17
4
3
68
25
48
48
3
1
42
37
20
1
4-1BB
100
75
50
25
0
GFP−
GFP+
GFP−
GFP+
d7
d14

FIG. 2D

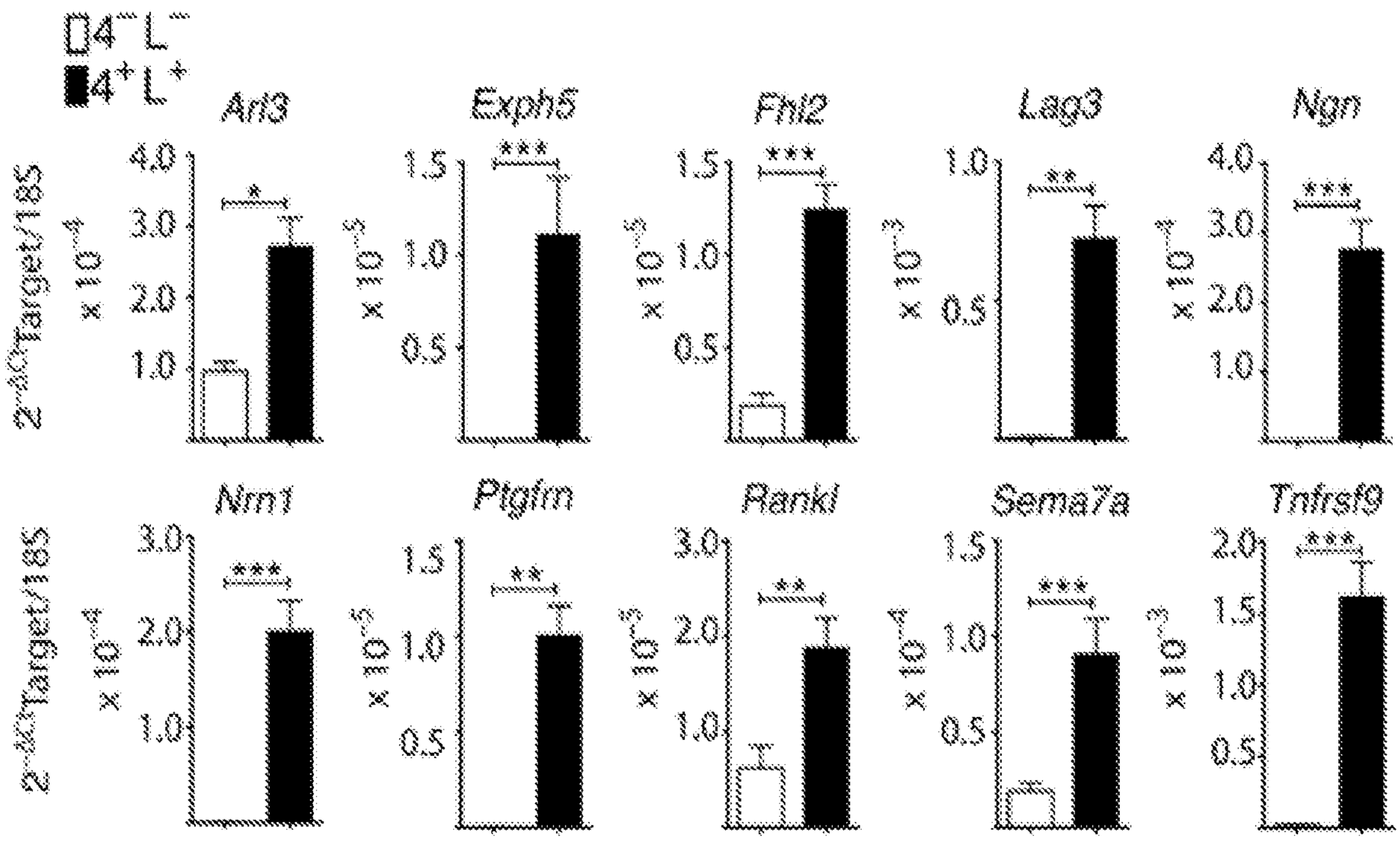

CD4⁻L⁻
CD4⁺L⁺
Arl3
Exph5
Fhl2
Lag3
Ngn
Nrn1
Ptglrn
Rankl
Sema7a
Tnfrsf9
2^-ΔCt Target/18S
×10^-4
×10^-3
*
**
***

FIG. 2E

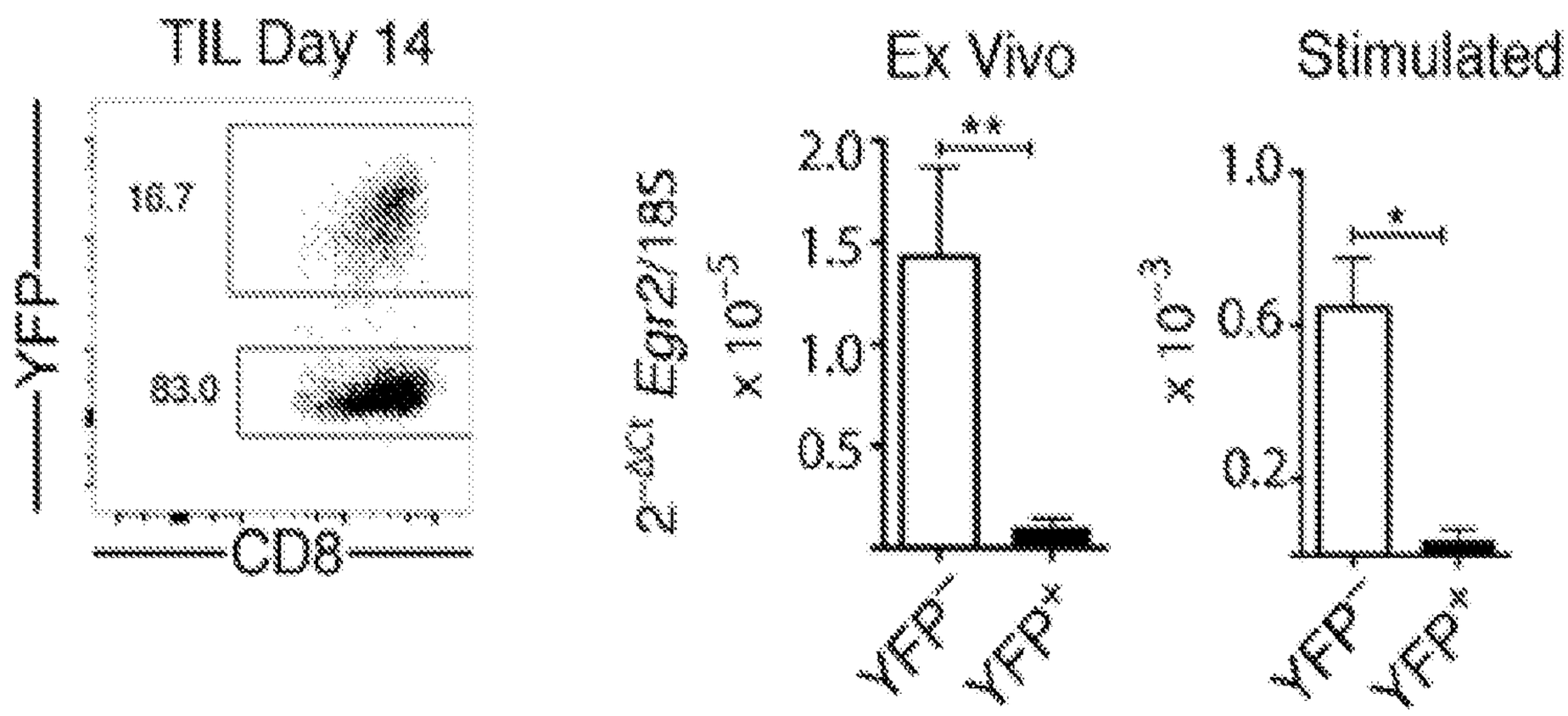

TIL Day 14
Ex Vivo
Stimulated
YFP
CD8
16.7
83.0
2^-ΔCt Egr2/18S
x 10^-5
2.0
1.5
1.0
0.5
**
YFP-
YFP+
x 10^-3
1.0
0.6
0.2
*

FIG. 2F

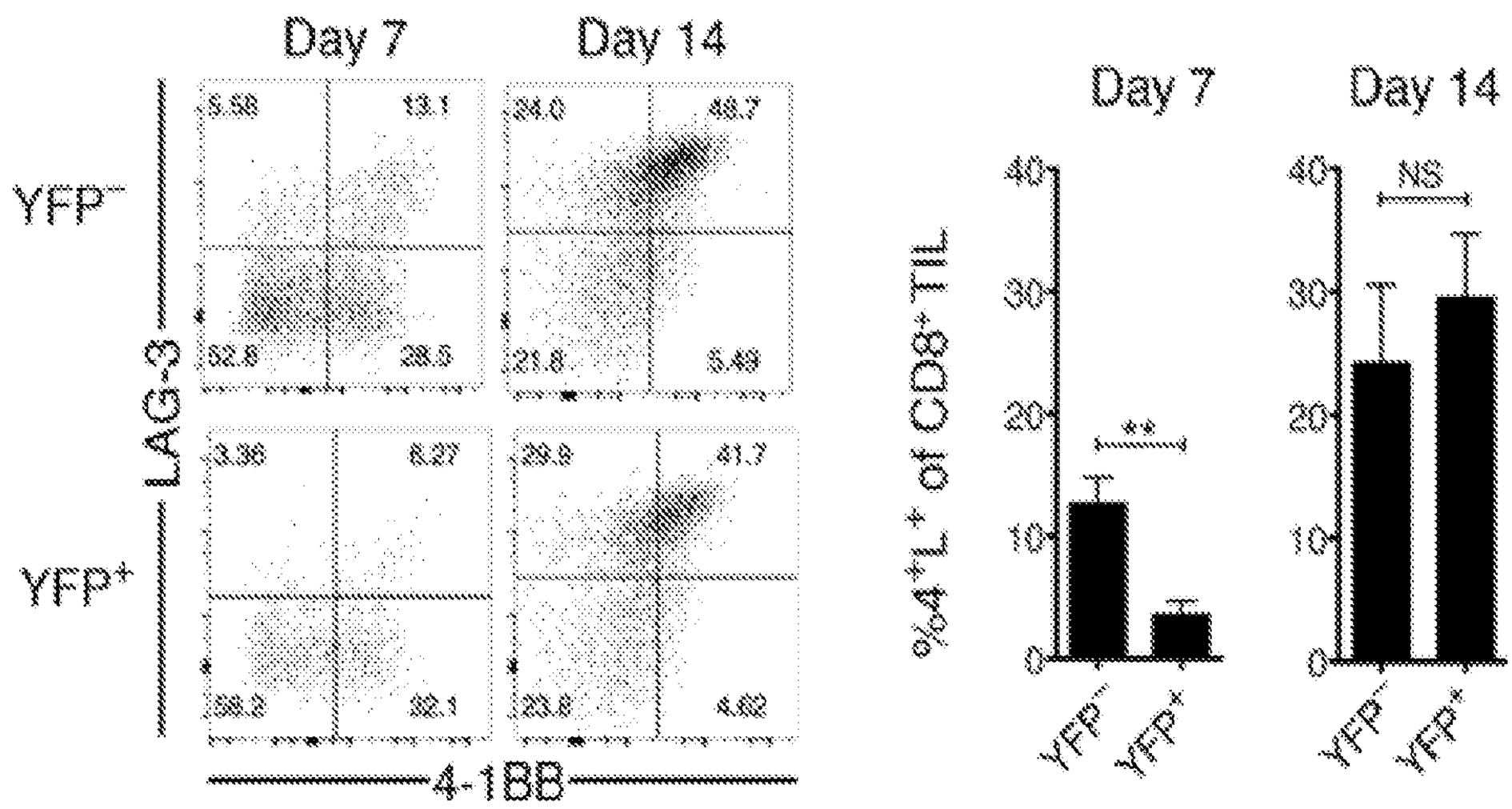

Day 7
Day 14
YFP-
YFP+
LAG-3
4-1BB
5.58
13.1
52.8
28.5
24.0
48.7
21.8
6.49
3.36
8.27
58.2
32.1
29.6
41.7
23.6
4.62
%4+L+ of CD8+ TIL
40
30
20
10
0
**
NS
YFP-
YFP+

FIG. 2G

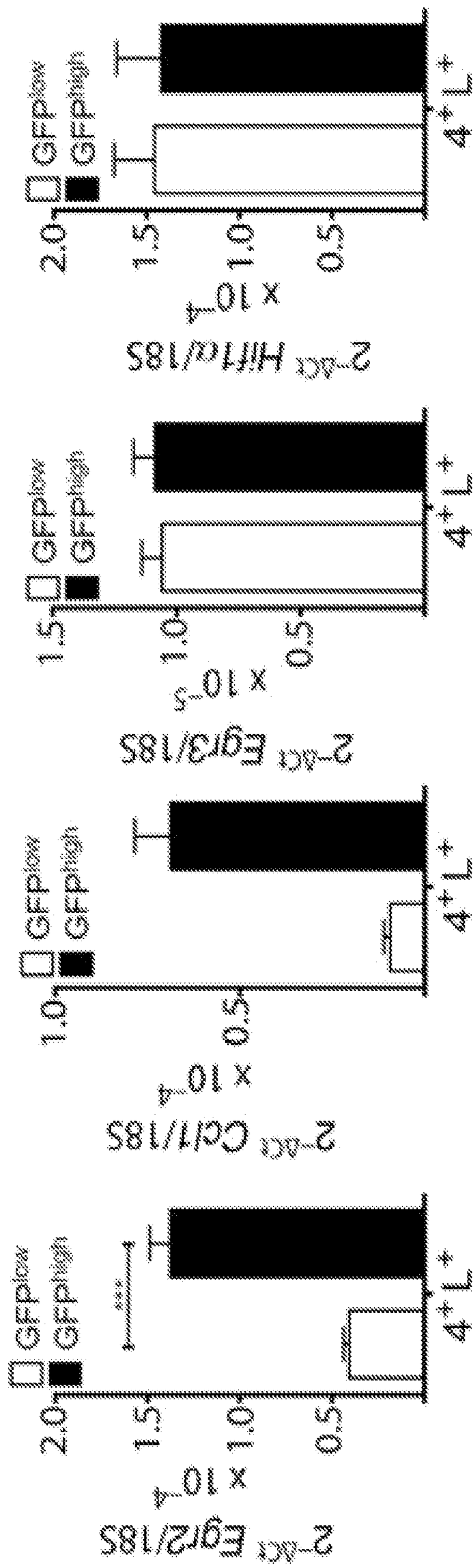

2-ΔΔct Egr2/18S
x 10-4
2.0
1.5
1.0
0.5
GFPlow
GFPhigh
4+L+
2-ΔΔct Egr3/18S
x 10-5
1.5
1.0
0.5
GFPlow
GFPhigh
4+L+
2-ΔΔct Cd1/18S
x 10-4
1.0
0.5
GFPlow
GFPhigh
4+L+
2-ΔΔct Hif1α/18S
x 10-4
2.0
1.5
1.0
0.5
GFPlow
GFPhigh
4+L+

FIG. 3A

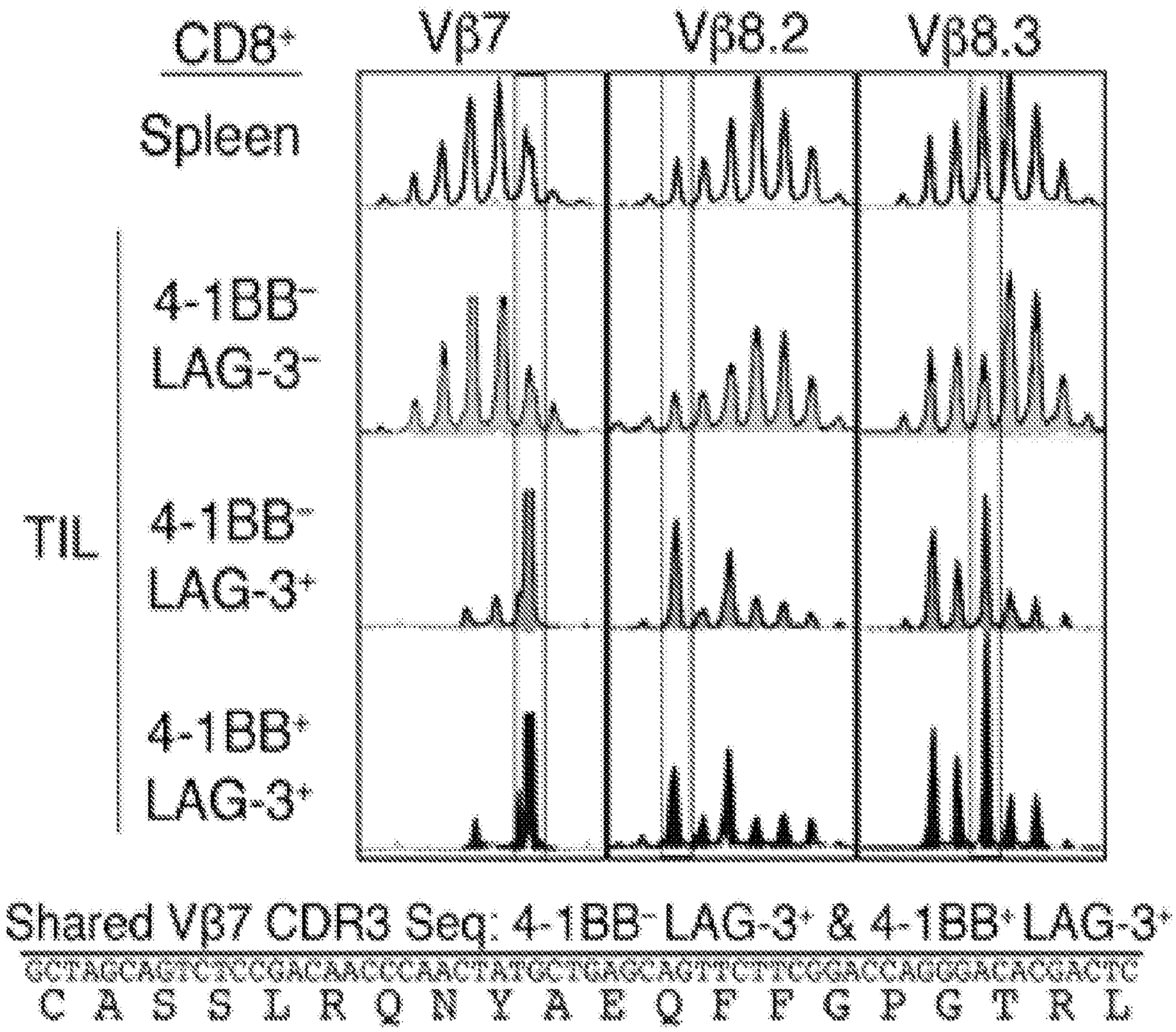

CD8+
Vβ7
Vβ8.2
Vβ8.3
Spleen
TIL
4-1BB−
LAG-3−
4-1BB−
LAG-3+
4-1BB+
LAG-3+
Shared Vβ7 CDR3 Seq: 4-1BB− LAG-3+ & 4-1BB+ LAG-3+
GCTAGCAGTCTTCCGACAACCCAACTATGCTGAGCAGTTCTTCGGACCAGGGACACGACTC
C A S S L R Q N Y A E Q F F G P G T R L

FIG. 3B

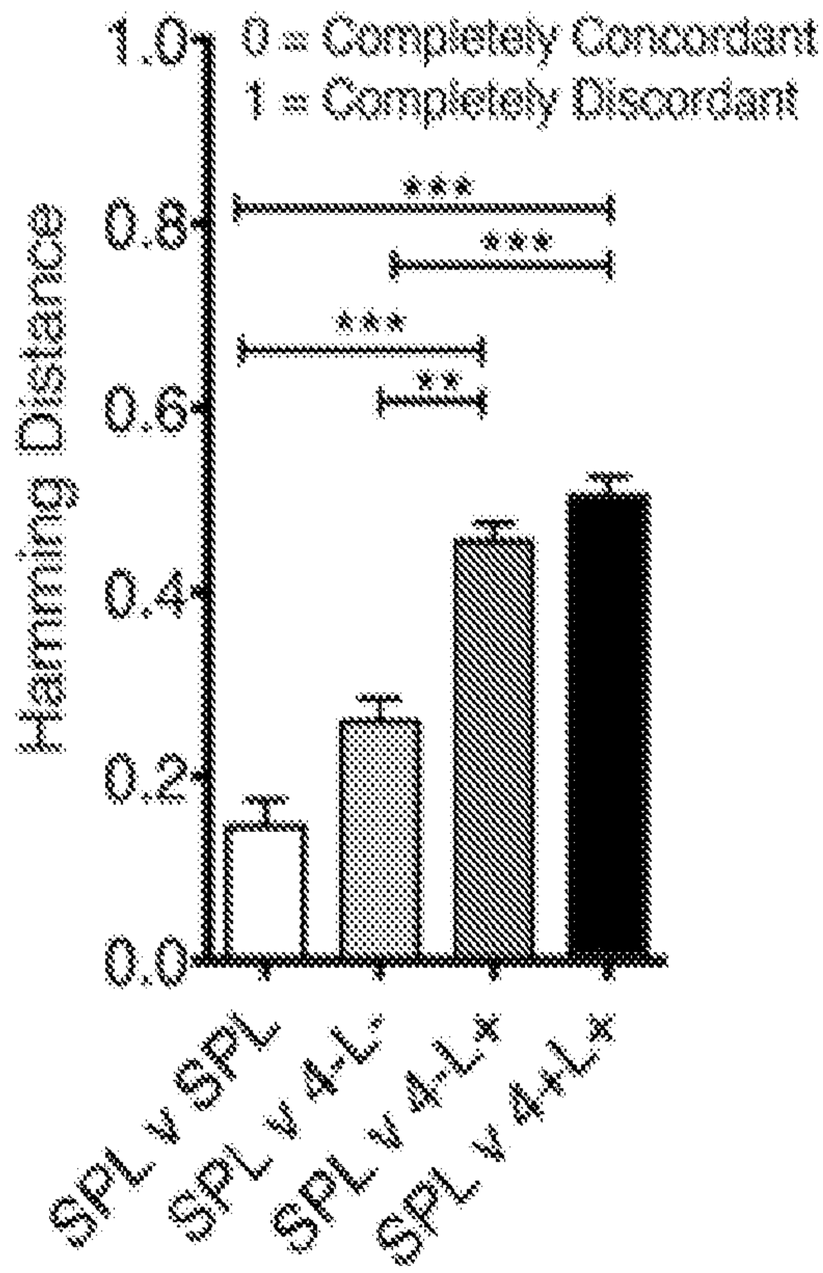

0 = Completely Concordant
1 = Completely Discordant
Hamming Distance
1.0
0.8
0.6
0.4
0.2
0.0
***
***
***
**
SPL v SPL
SPL v 4-L-
SPL v 4-L+
SPL v 4+L+

FIG. 3C

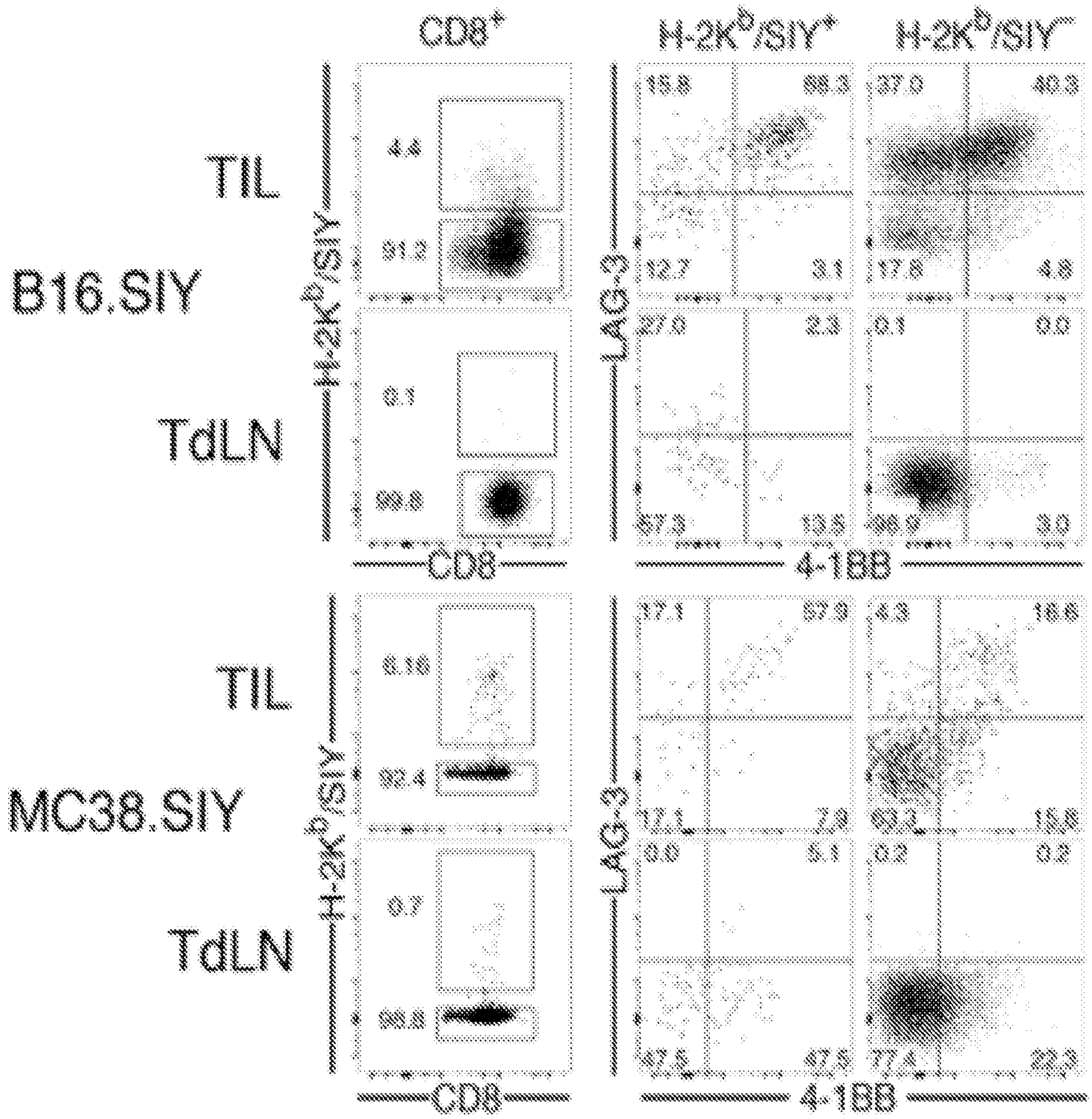

CD8+
H-2Kb/SIY+
H-2Kb/SIY−
B16.SIY
TIL
TdLN
MC38.SIY
TIL
TdLN
H-2Kb/SIY
LAG-3
CD8
4-1BB
4.6
91.2
0.1
99.8
15.8
99.3
37.0
40.3
12.7
3.1
17.8
4.8
27.0
2.3
0.1
0.0
57.3
10.5
99.9
3.0
8.18
92.4
0.7
99.8
17.1
67.9
4.3
18.6
12.1
2.9
92.1
19.8
0.0
5.1
0.2
0.2
87.6
87.6
77.4
22.3

FIG. 3D

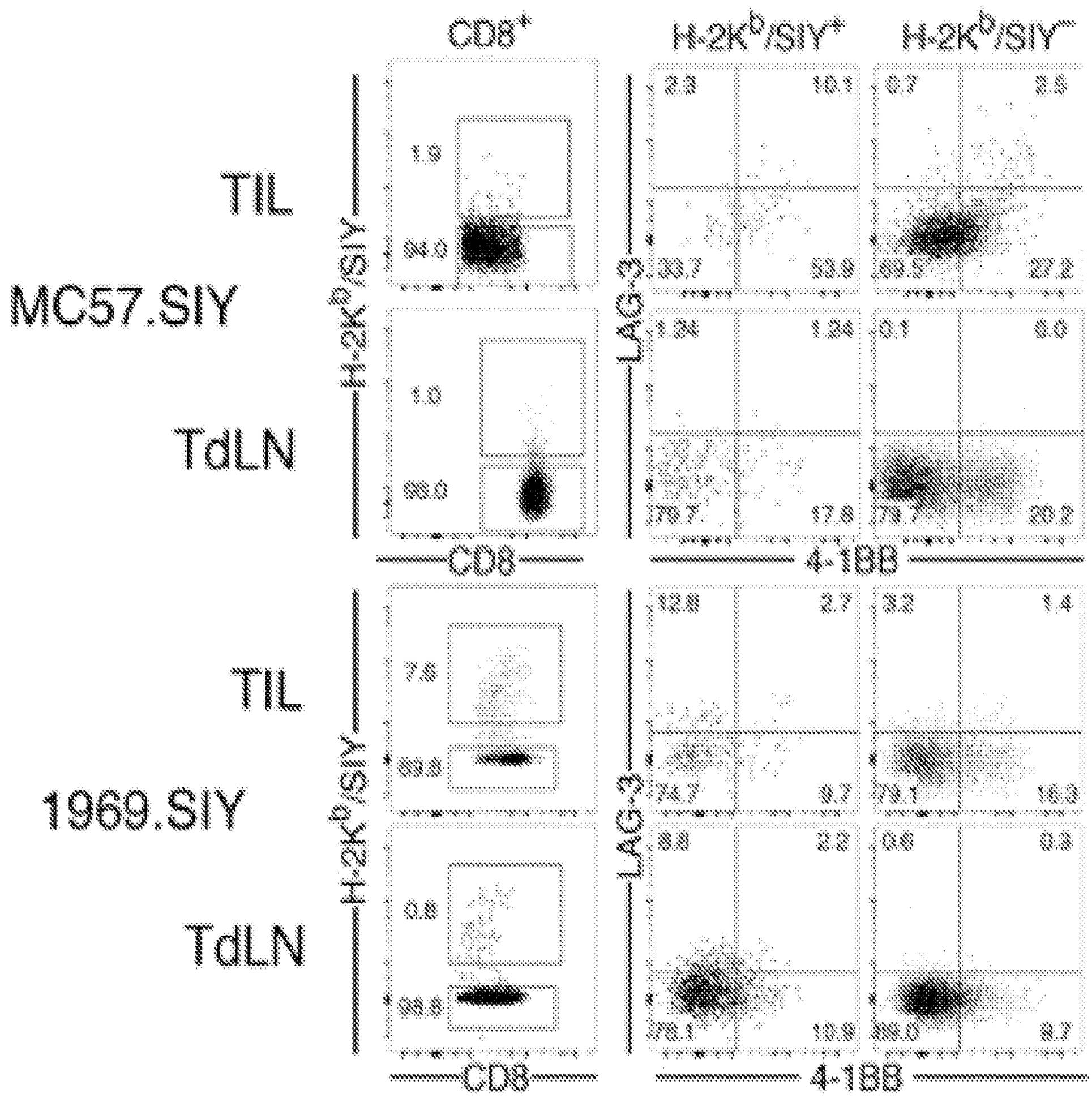

CD8+
H-2Kb/SIY+
H-2Kb/SIY−
MC57.SIY
TIL
TdLN
1969.SIY
TIL
TdLN
H-2Kb/SIY
LAG-3
CD8
4-1BB
2.3
10.1
0.7
2.5
1.9
94.0
80.7
93.0
69.5
27.2
1.24
1.24
0.1
0.0
1.0
98.0
79.7
17.8
79.7
20.2
12.8
2.7
3.2
1.4
7.6
89.9
74.7
9.7
79.1
16.3
8.8
2.2
0.6
0.3
0.8
99.0
78.1
10.9
89.0
8.7

FIG. 3E

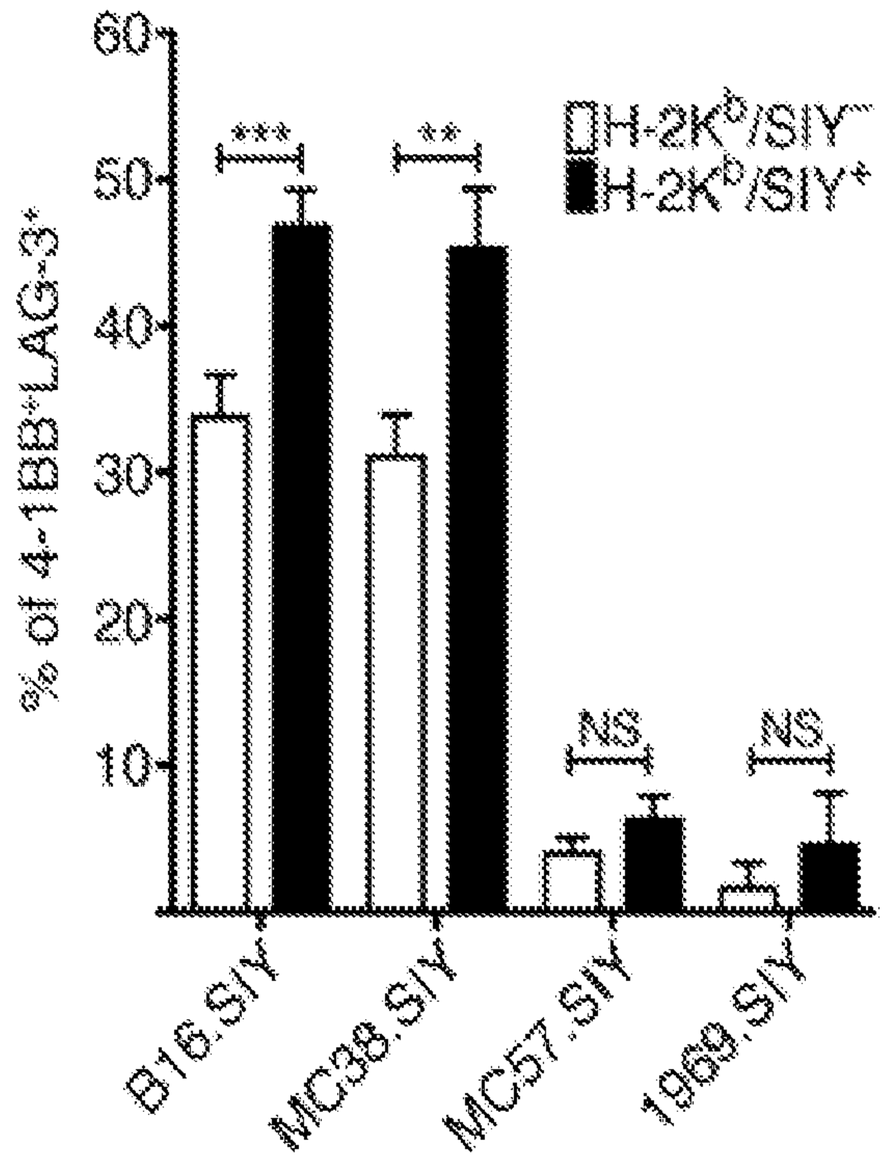

% of 4-1BB+LAG-3+
60
50
40
30
20
10
***
**
NS
NS
H-2Kb/SIY−
H-2Kb/SIY+
B16.SIY
MC38.SIY
MC57.SIY
1969.SIY

FIG. 3F

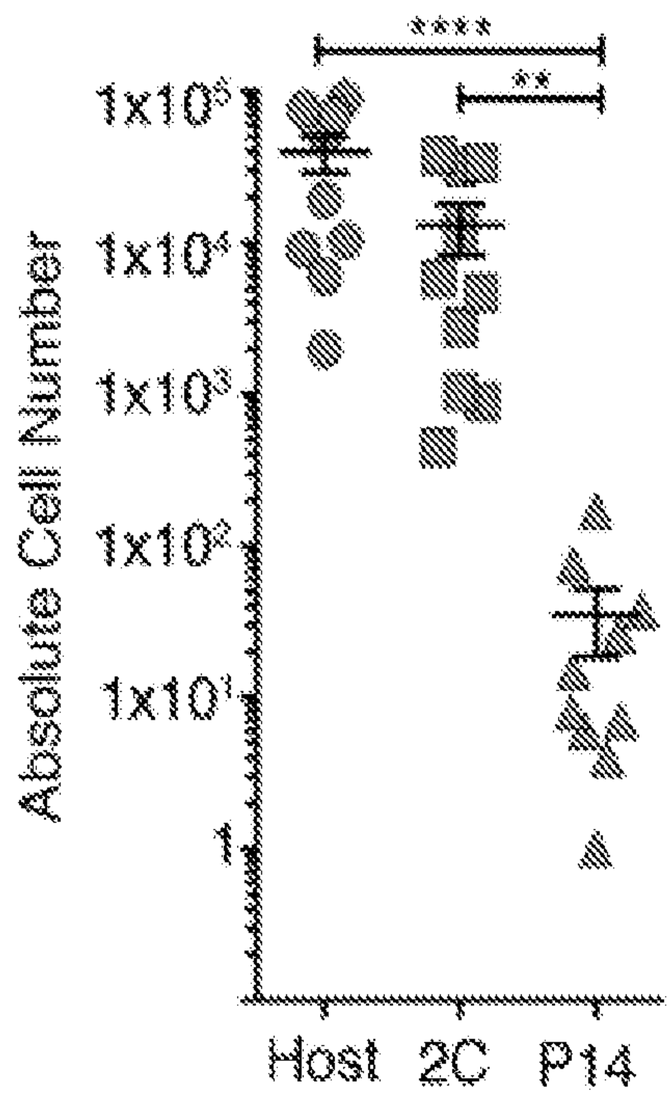

Absolute Cell Number
1x10^5
1x10^4
1x10^3
1x10^2
1x10^1
1
****
**
Host
2C
P14

FIG. 3G

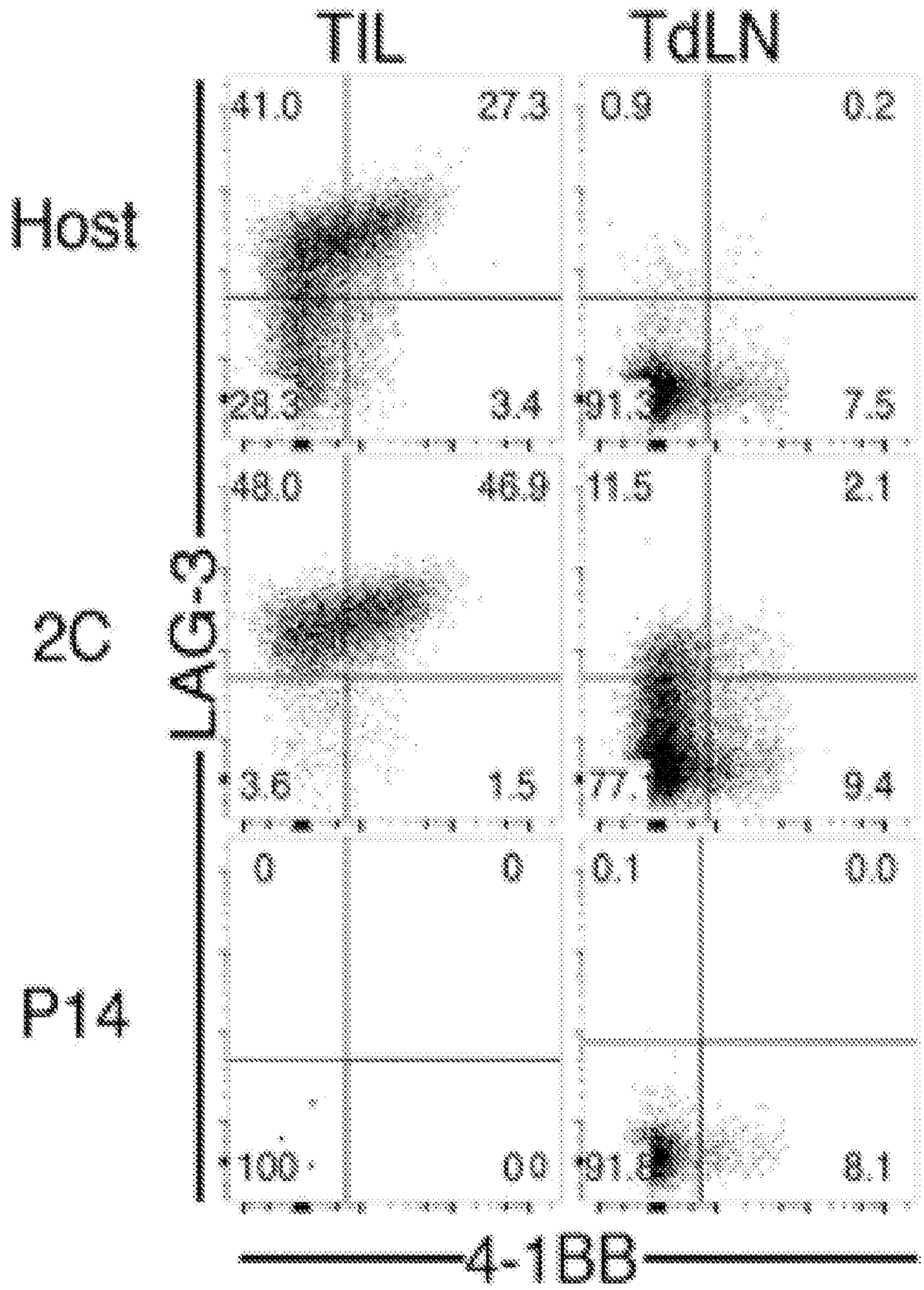

TIL
TdLN
Host
2C
P14
LAG-3
41.0
27.3
0.9
0.2
28.3
3.4
91.3
7.5
48.0
46.9
11.5
2.1
3.6
1.5
77.
9.4
0
0
0.1
0.0
100
00
91.8
8.1
4-1BB

FIG. 3H

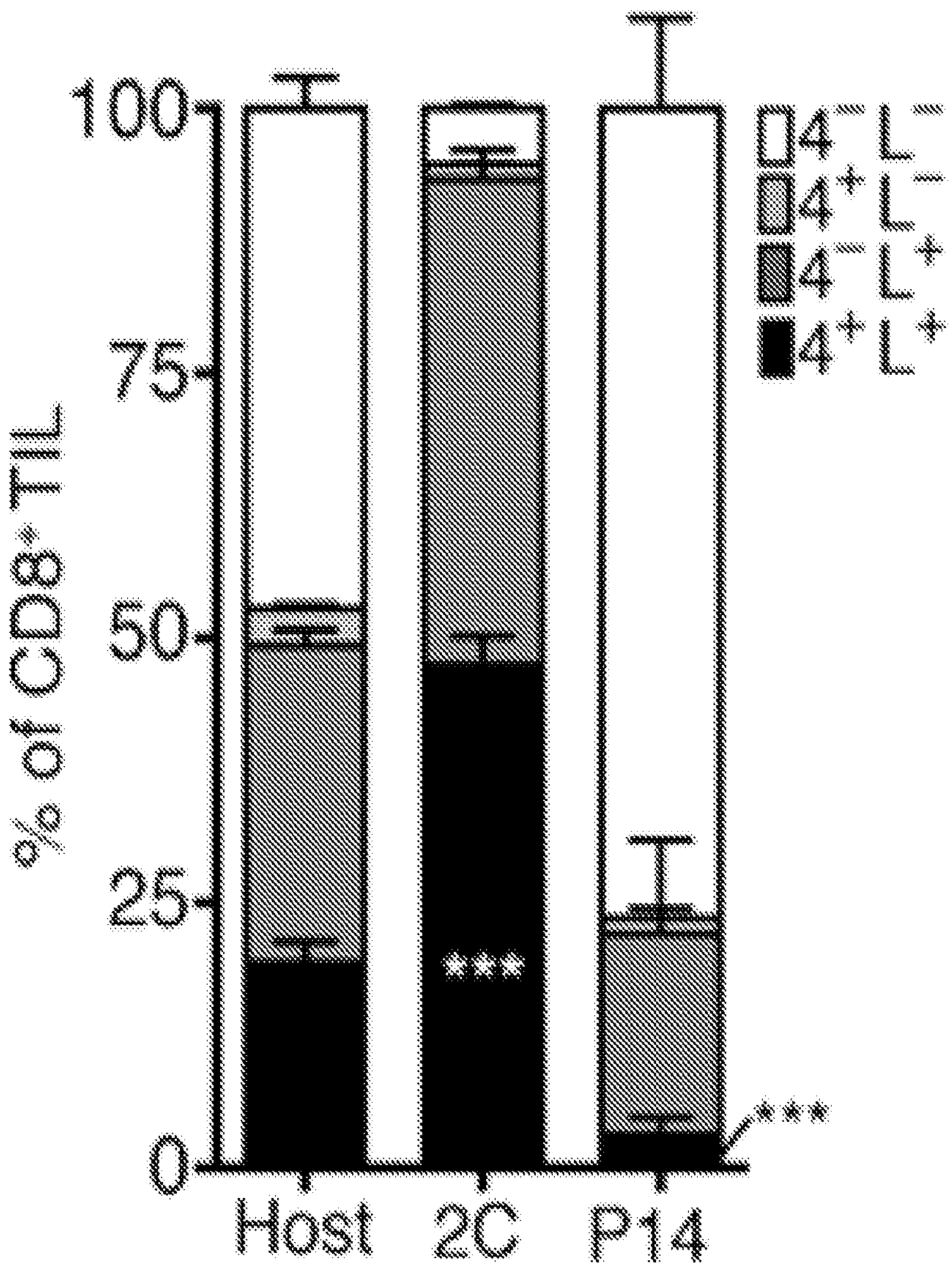


FIG. 4A

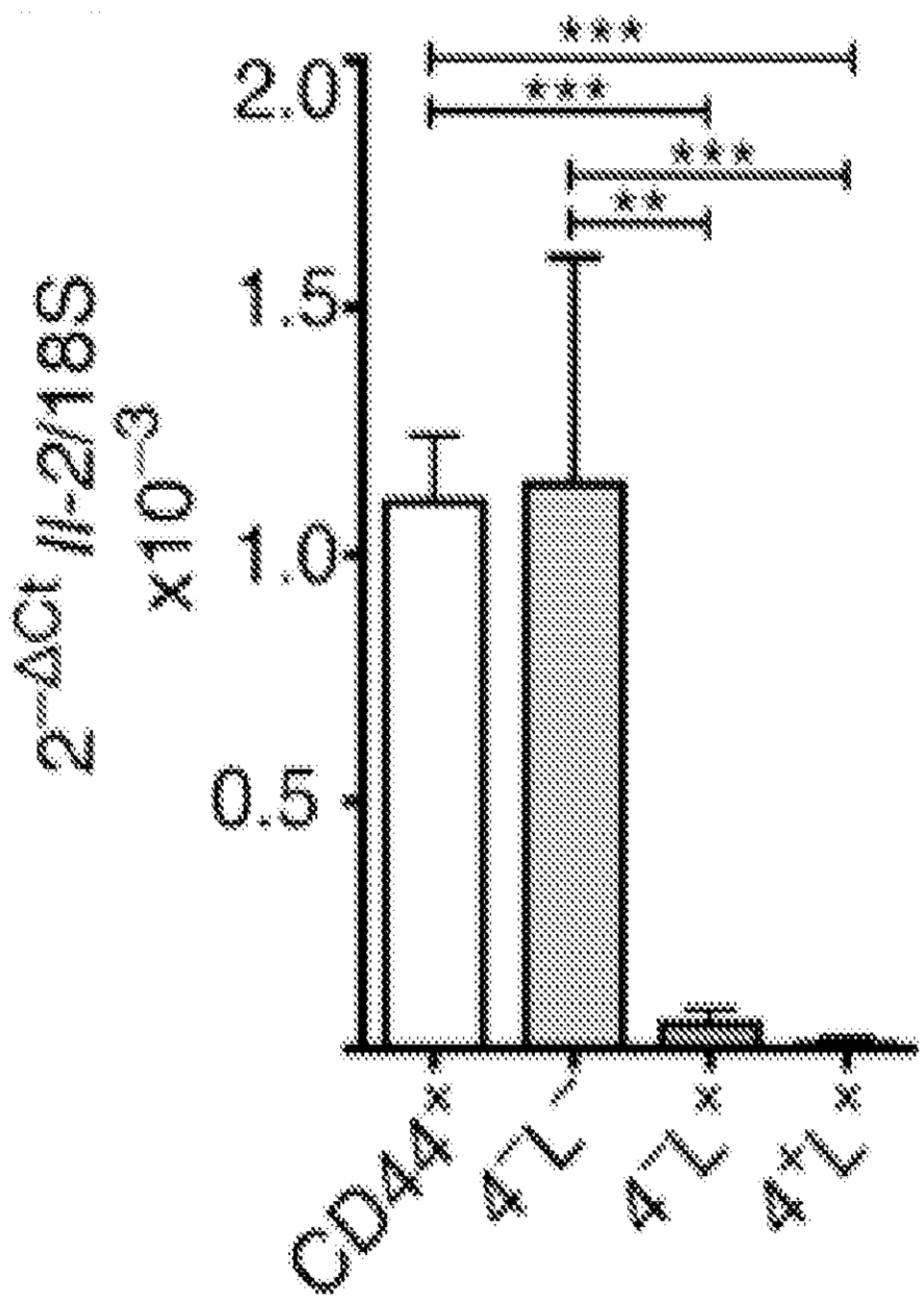

2.0
1.5
1.0
0.5
2^-ΔCt IL-2/18S
x10^-3
***
***
***
**
CD4+
4T1
4T1+
4T1+

FIG. 4B

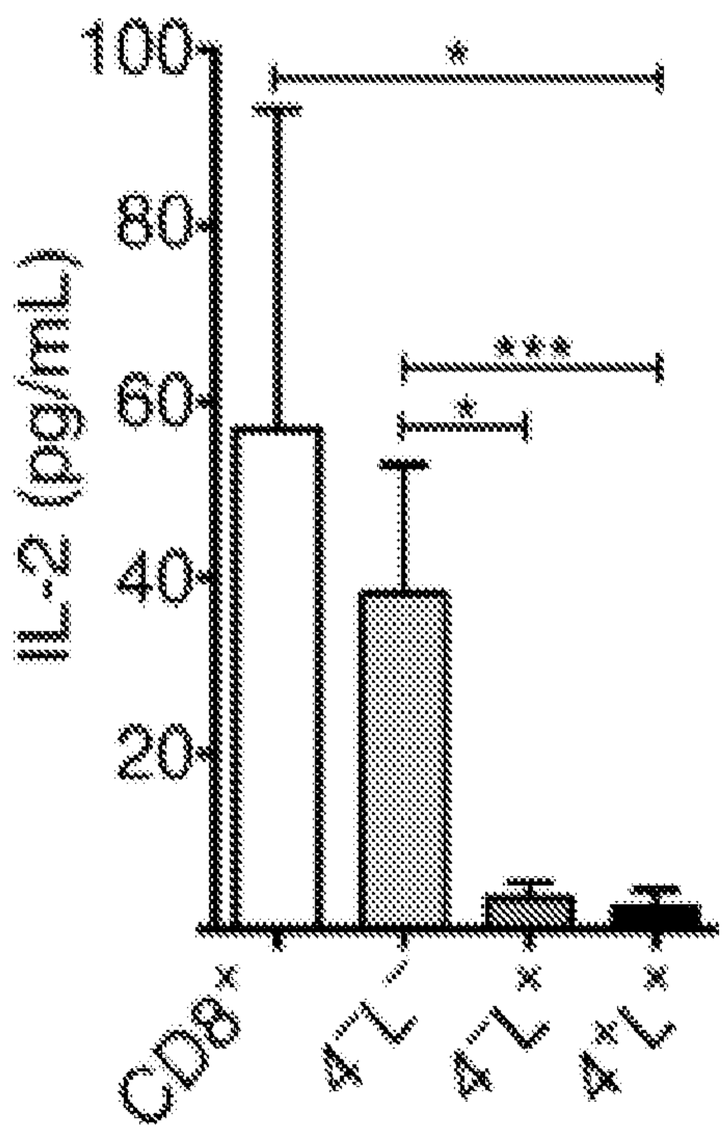

100
80
60
40
20
IL-2 (pg/mL)
*
***
*
CD8+
4T1
4T1+
4T1+

FIG. 4C

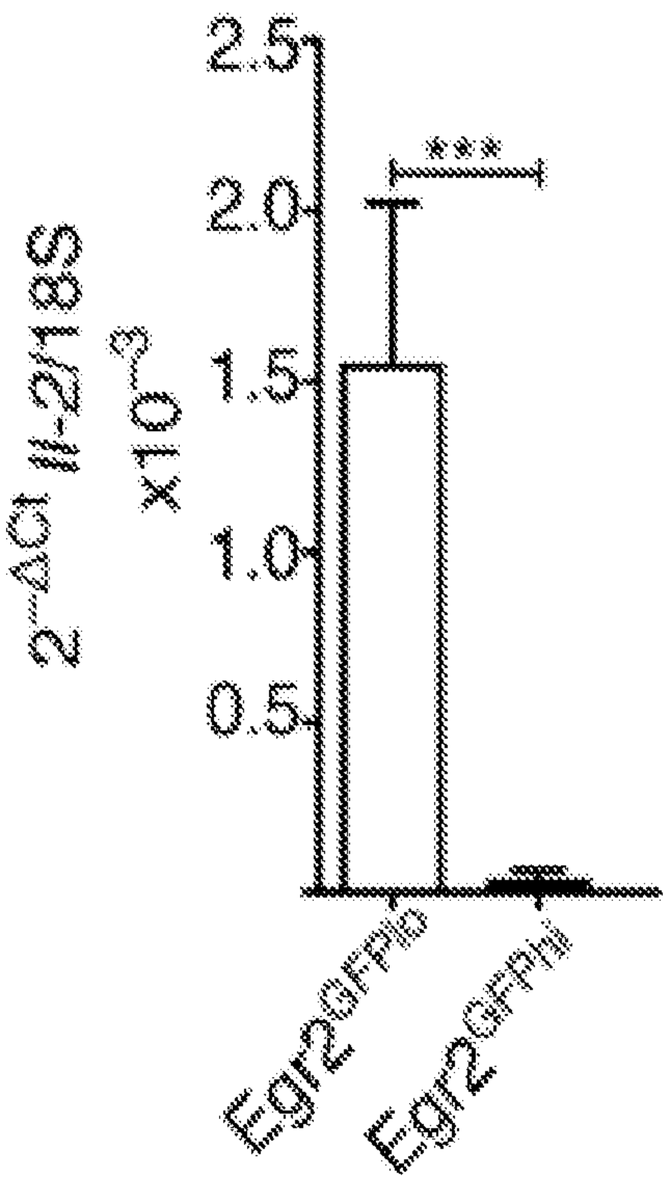

2.5
2.0
1.5
1.0
0.5
2^-ΔCt Il-2/18S
x10^-3
***
Egr2^GFPlo
Egr2^GFPhi

FIG. 4D

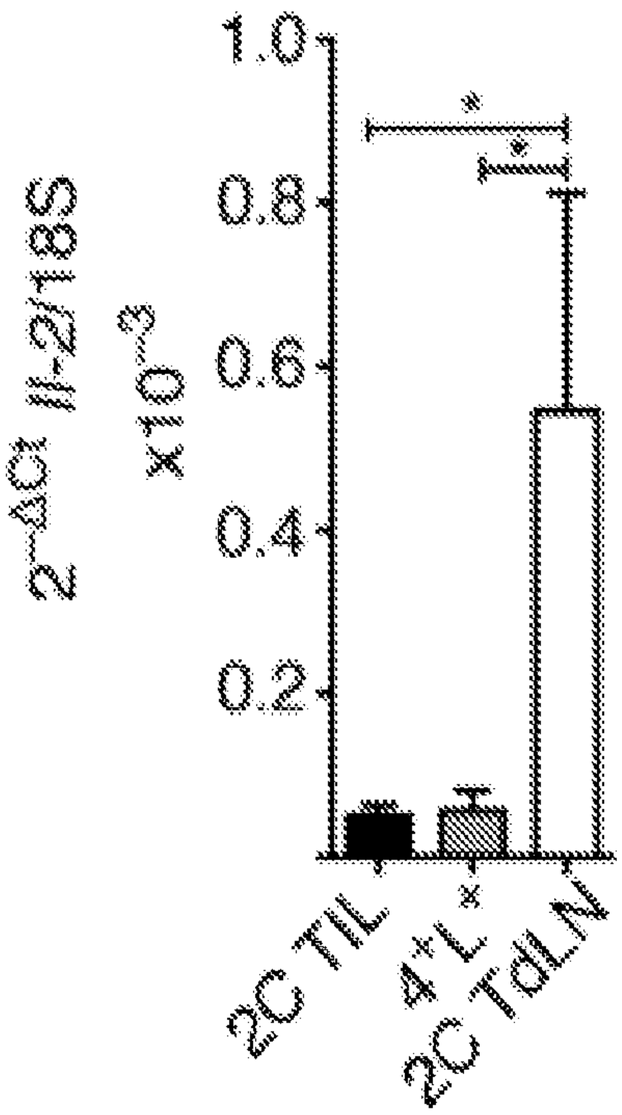

1.0
0.8
0.6
0.4
0.2
2^-ΔCt Il-2/18S
x10^-3
*
*
2C TIL
4+L
2C TdLN

FIG. 4E

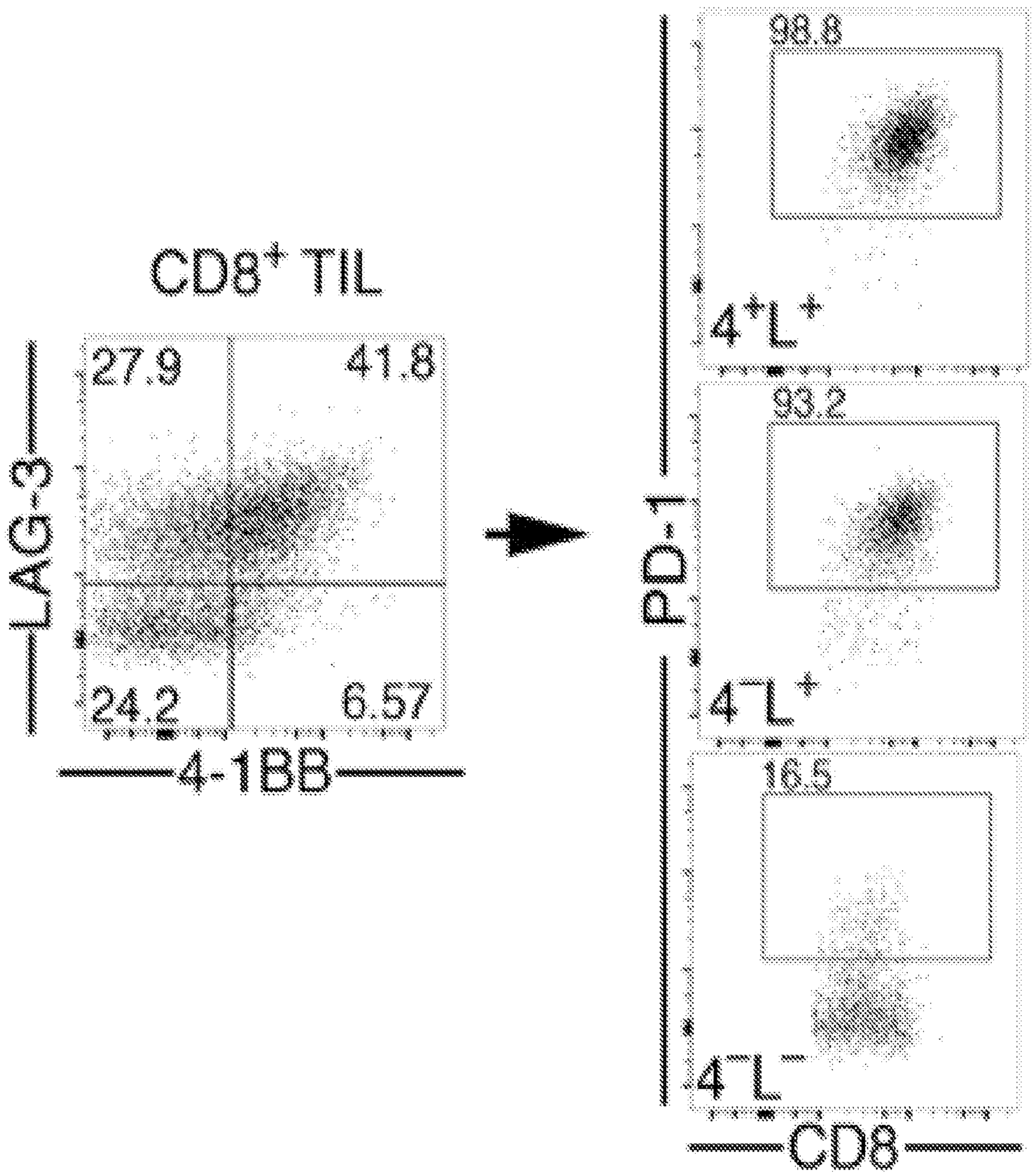


FIG. 4F

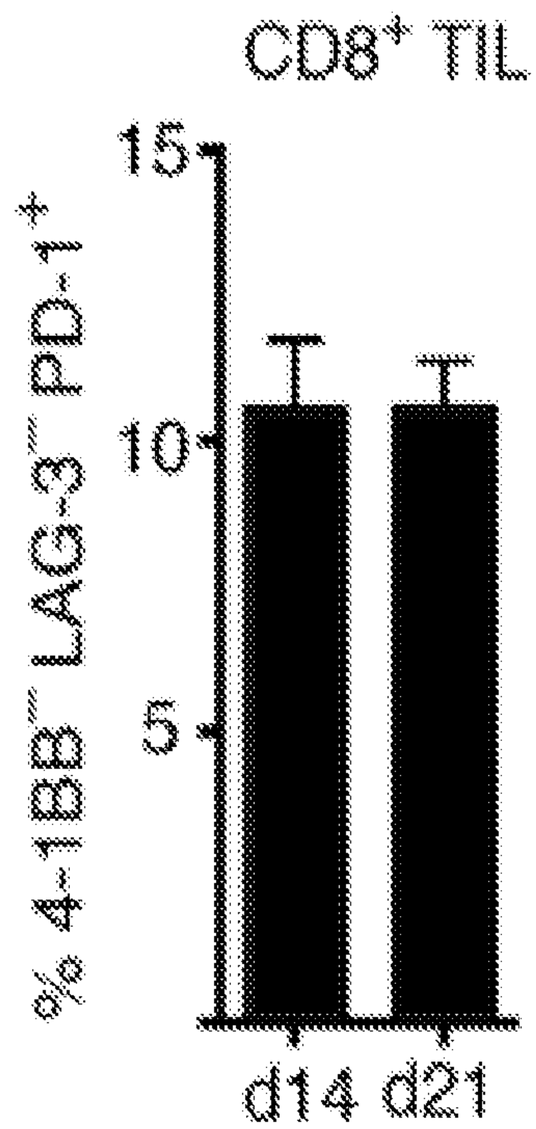

CD8+ TIL
% 4-1BB- LAG-3- PD-1+
15
10
5
d14
d21

FIG. 4G

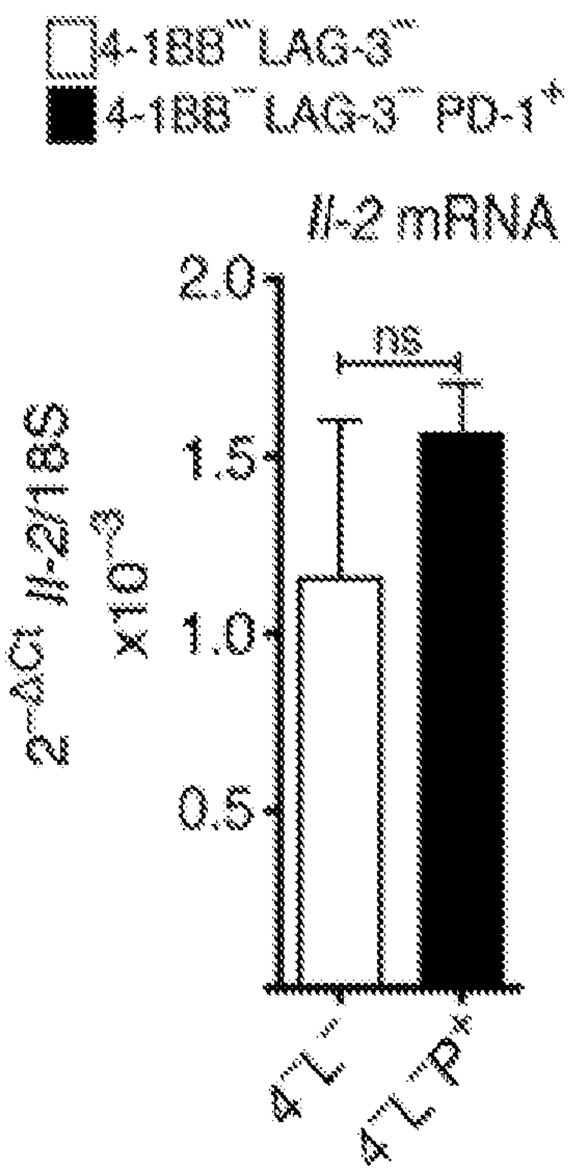

4-1BB- LAG-3-
4-1BB- LAG-3- PD-1+
Il-2 mRNA
2-ΔCt Il-2/18S x10-3
2.0
1.5
1.0
0.5
ns
4-L-
4-L-P+

FIG. 5A

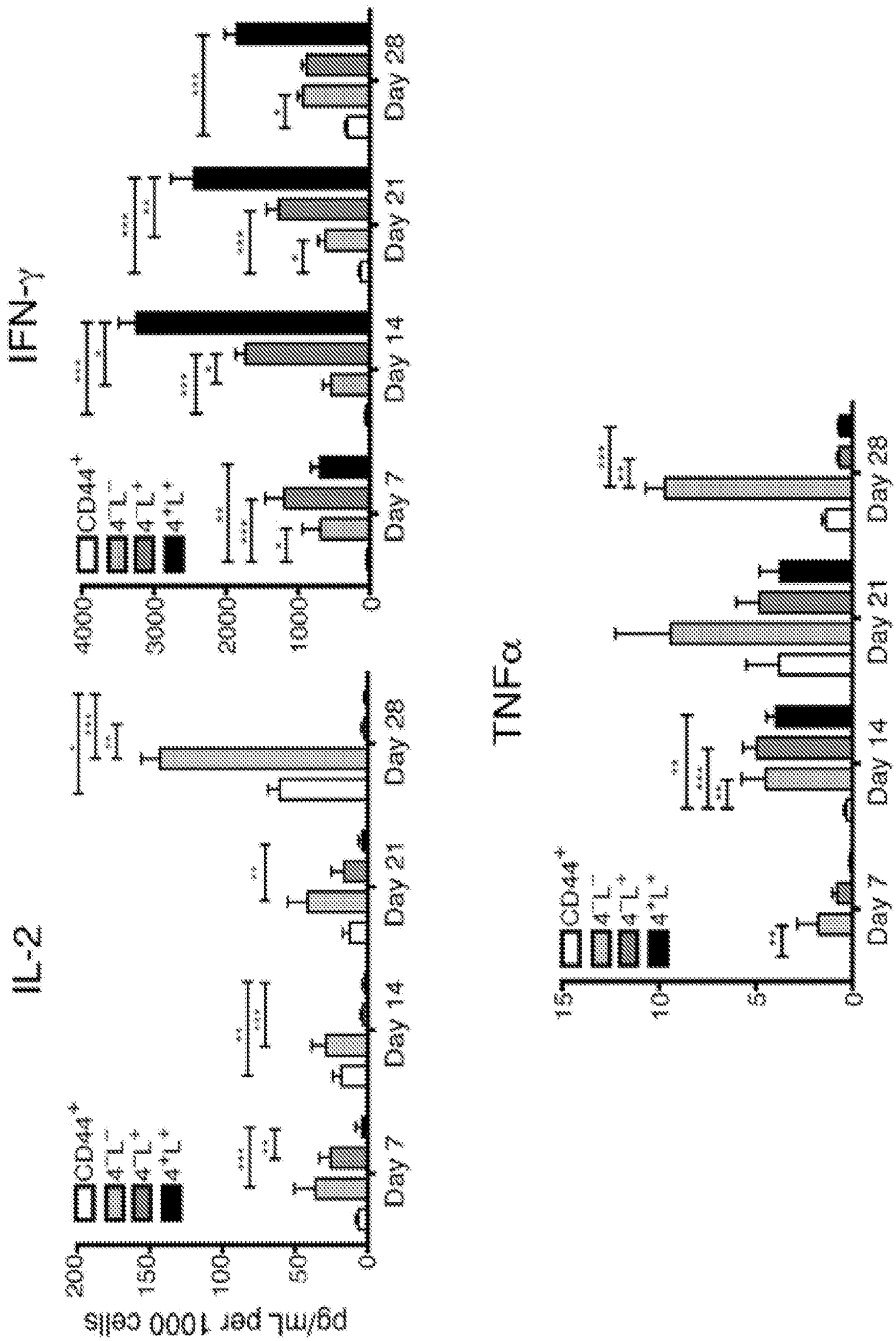

IL-2
pg/mL per 1000 cells
200
150
100
50
0
Day 7
Day 14
Day 21
Day 28
IFN-γ
4000
3000
2000
1000
0
CD44+
4+L-
4-L+
4+L+
TNFα
15
10
5
0

FIG. 5B

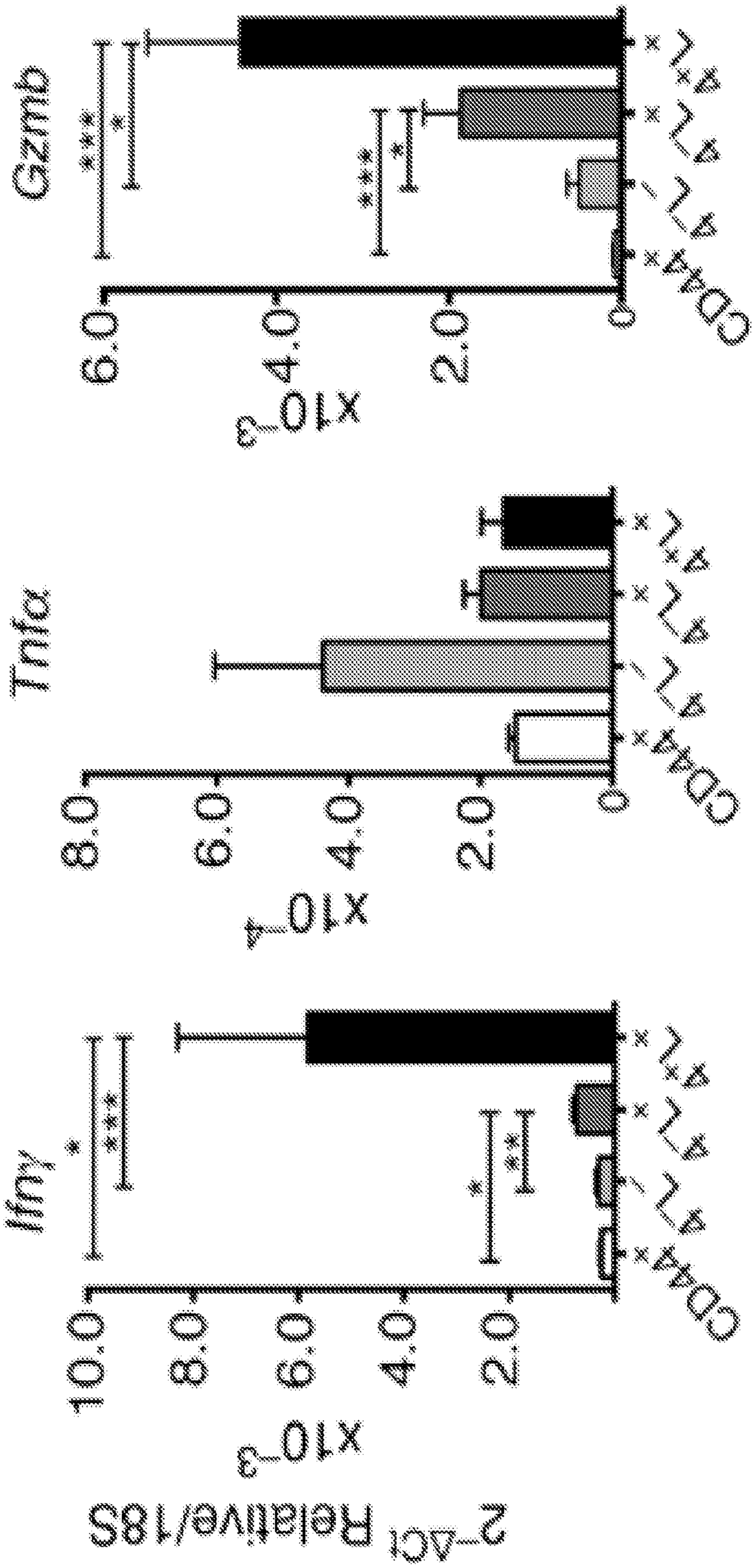

Gzmb
Tnfα
Ifnγ
2^-ΔΔct Relative/18S
x10^-3
x10^-4
x10^-3
Control
Dox
Dox+Ab

FIG. 5C

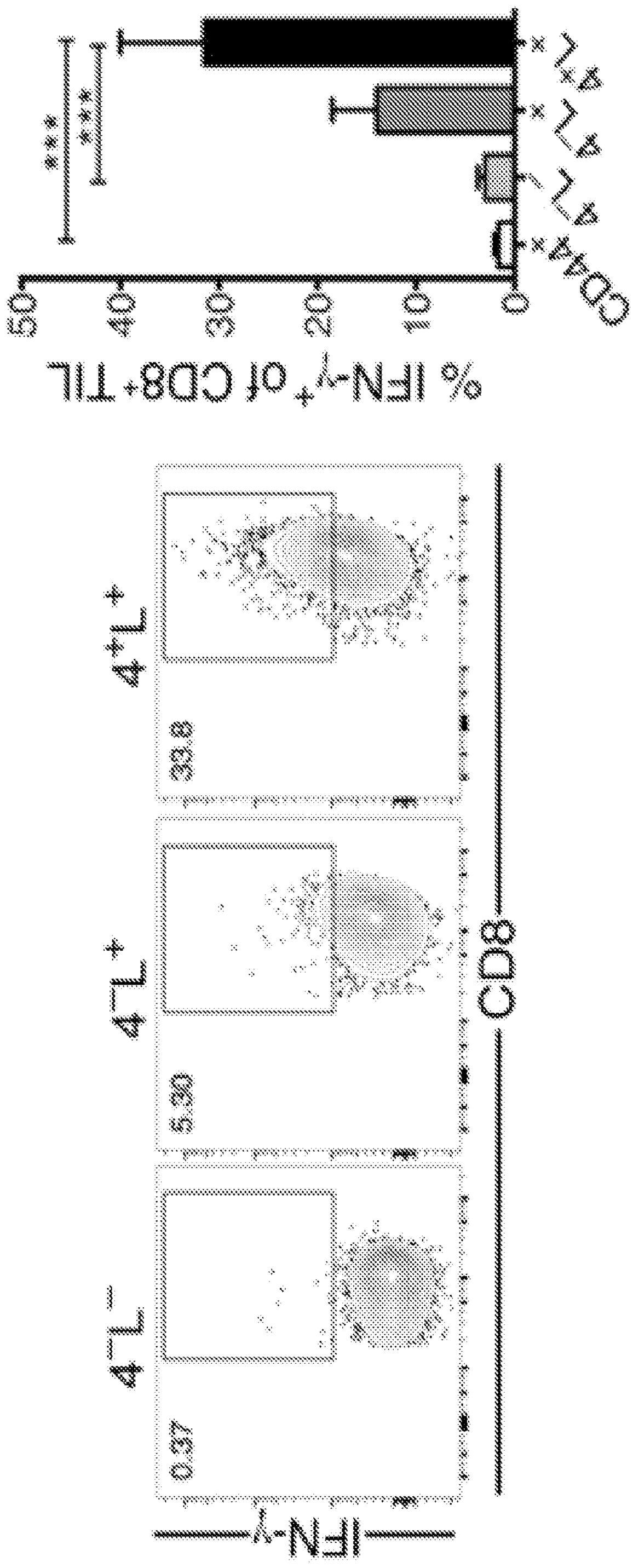

% IFN-γ+ of CD8+ TIL
50
40
30
20
10
0
CD4
CD8
4+L-
4-L-
4+L+
4-L+
0.37
5.90
93.8
IFN-γ

FIG. 5D

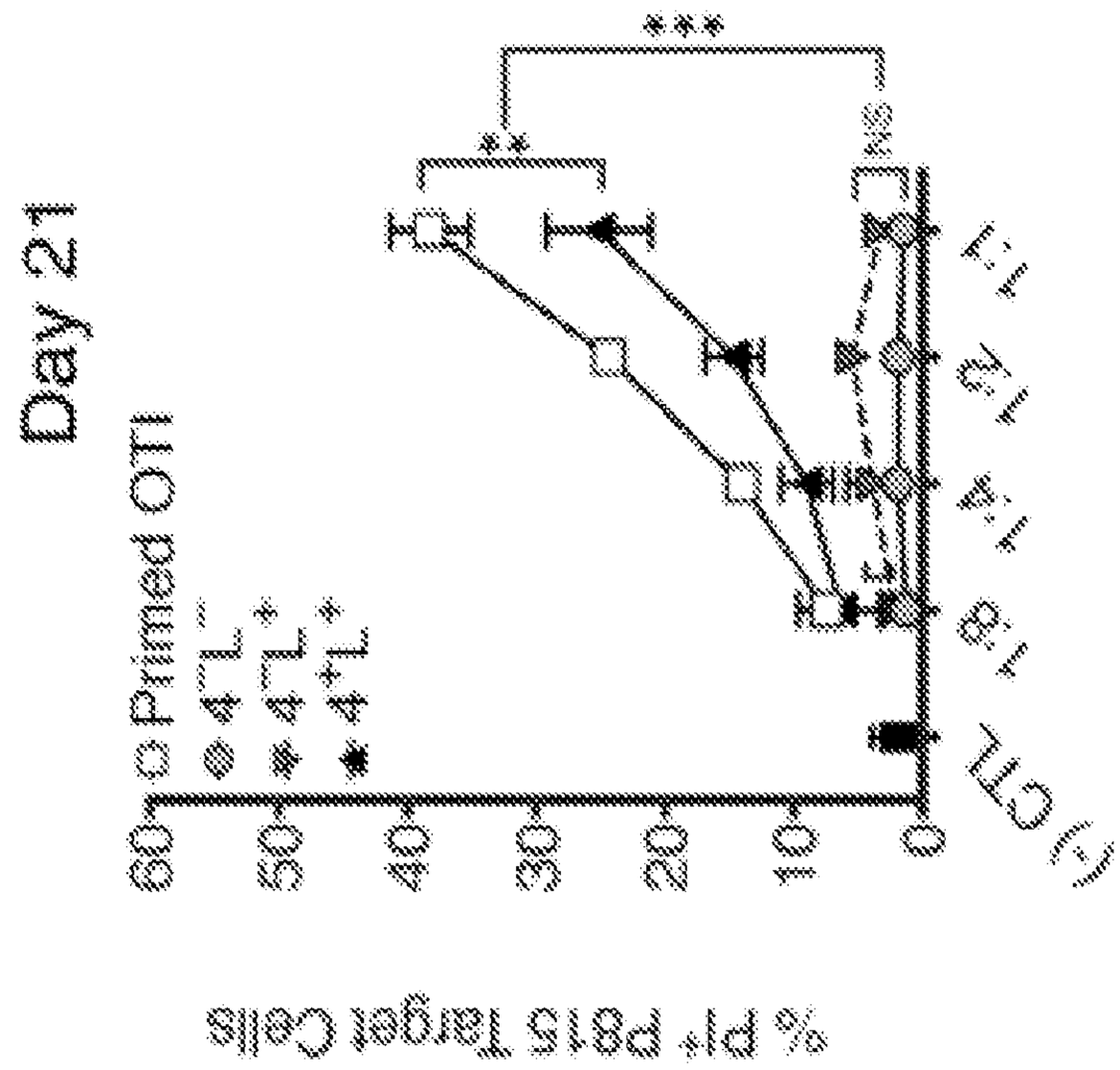

Day 21
% pIr P815 Target Cells
60
50
40
30
20
10
0
Primed OTI
4-L-
4-L+
4+L+
**
**
Day 14
% pIr P815 Target Cells
60
50
40
30
20
10
0
Primed OTI
4-L-
4-L+
4+L+
**

FIG. 5E

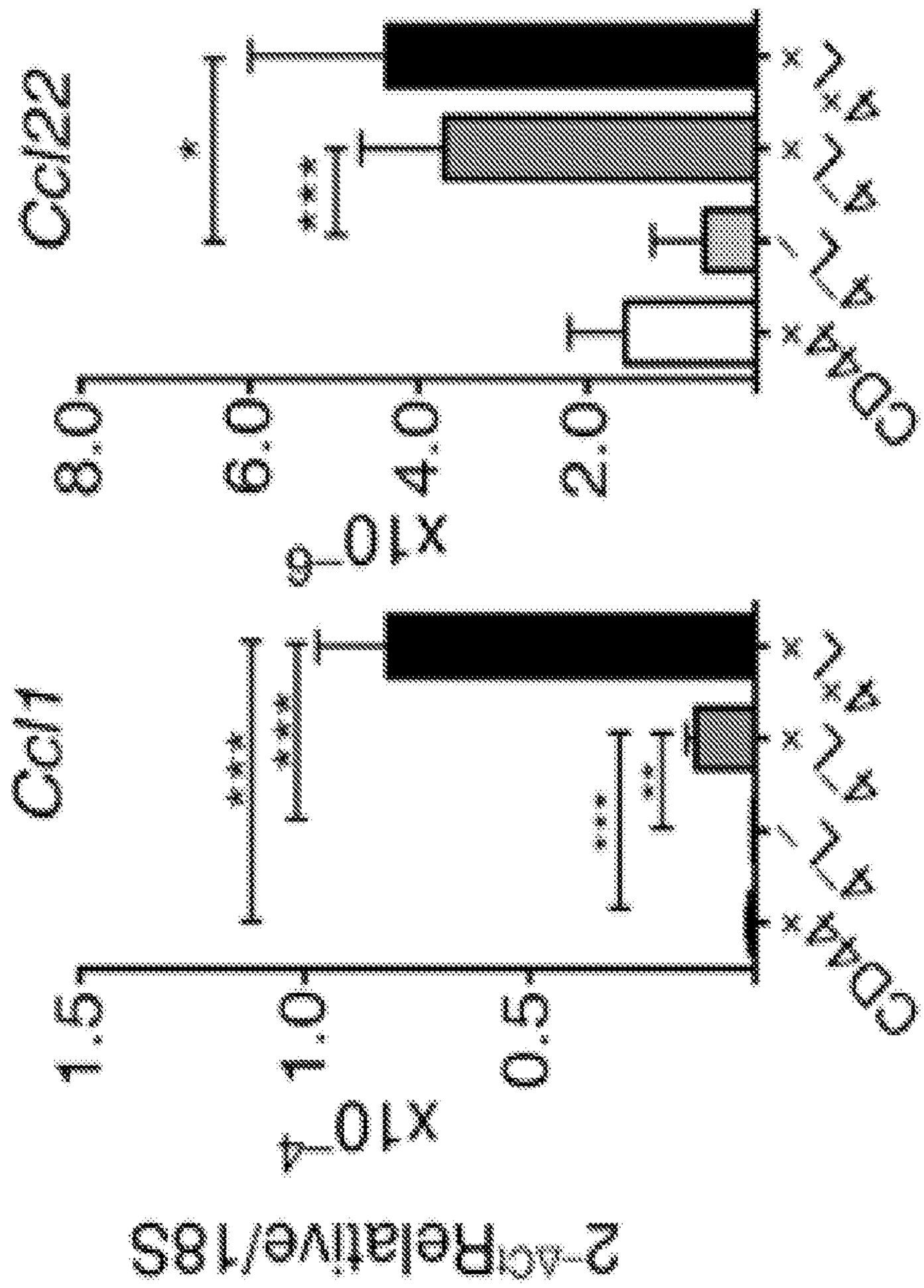


FIG. 6A

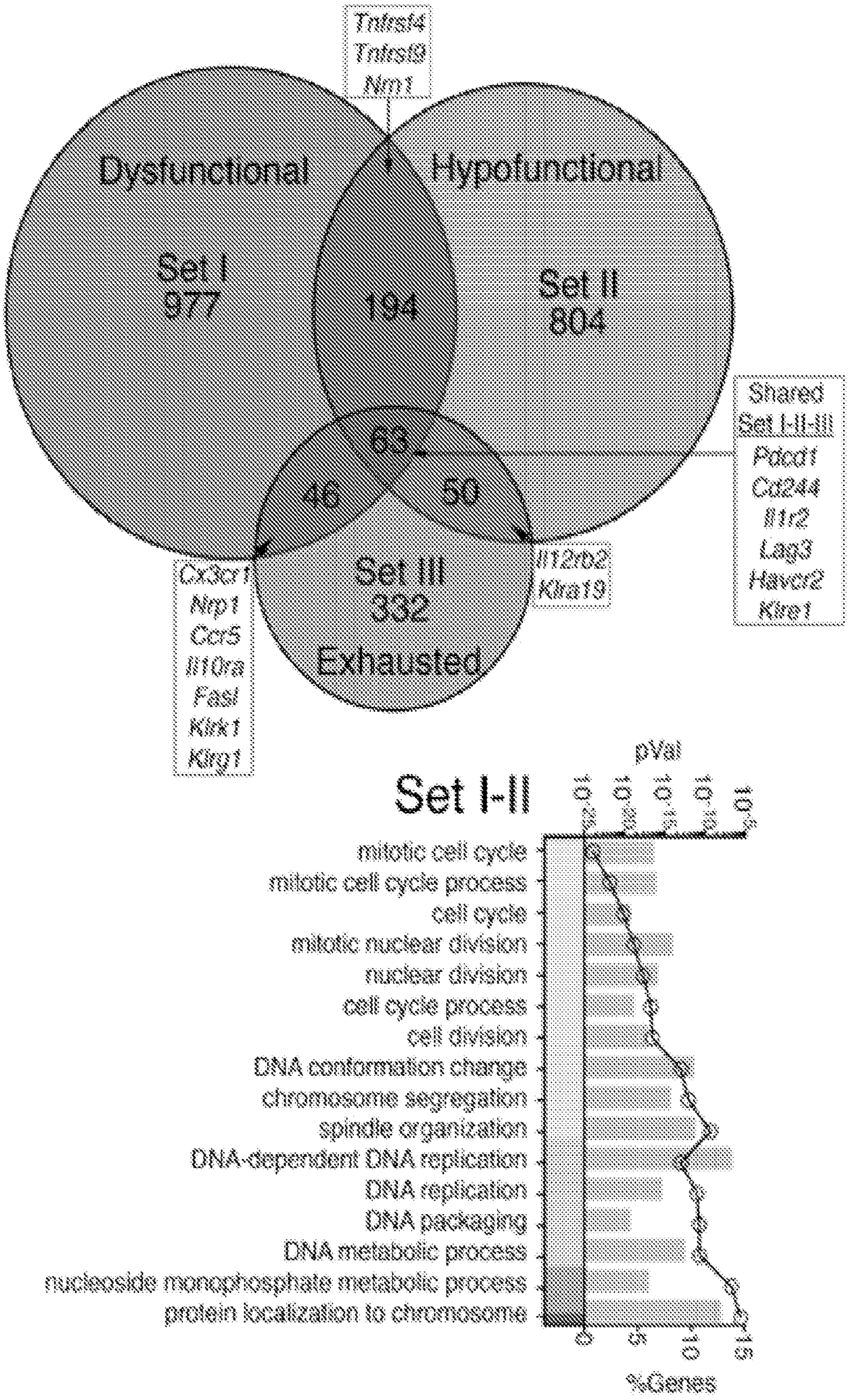

Tnfrsf4
Tnfrsf9
Nm1
Dysfunctional
Hypofunctional
Set I
977
194
Set II
804
63
46
50
Shared
Set I-II-III
Pdcd1
Cd244
Il1r2
Lag3
Havcr2
Klre1
Cx3cr1
Ntp1
Ccr5
Il10ra
Fasl
Klrk1
Klrg1
Il12rb2
Klra19
Set III
332
Exhausted
Set I-II
pVal
mitotic cell cycle
mitotic cell cycle process
cell cycle
mitotic nuclear division
nuclear division
cell cycle process
cell division
DNA conformation change
chromosome segregation
spindle organization
DNA-dependent DNA replication
DNA replication
DNA packaging
DNA metabolic process
nucleoside monophosphate metabolic process
protein localization to chromosome
%Genes

FIG. 6A (cont.)

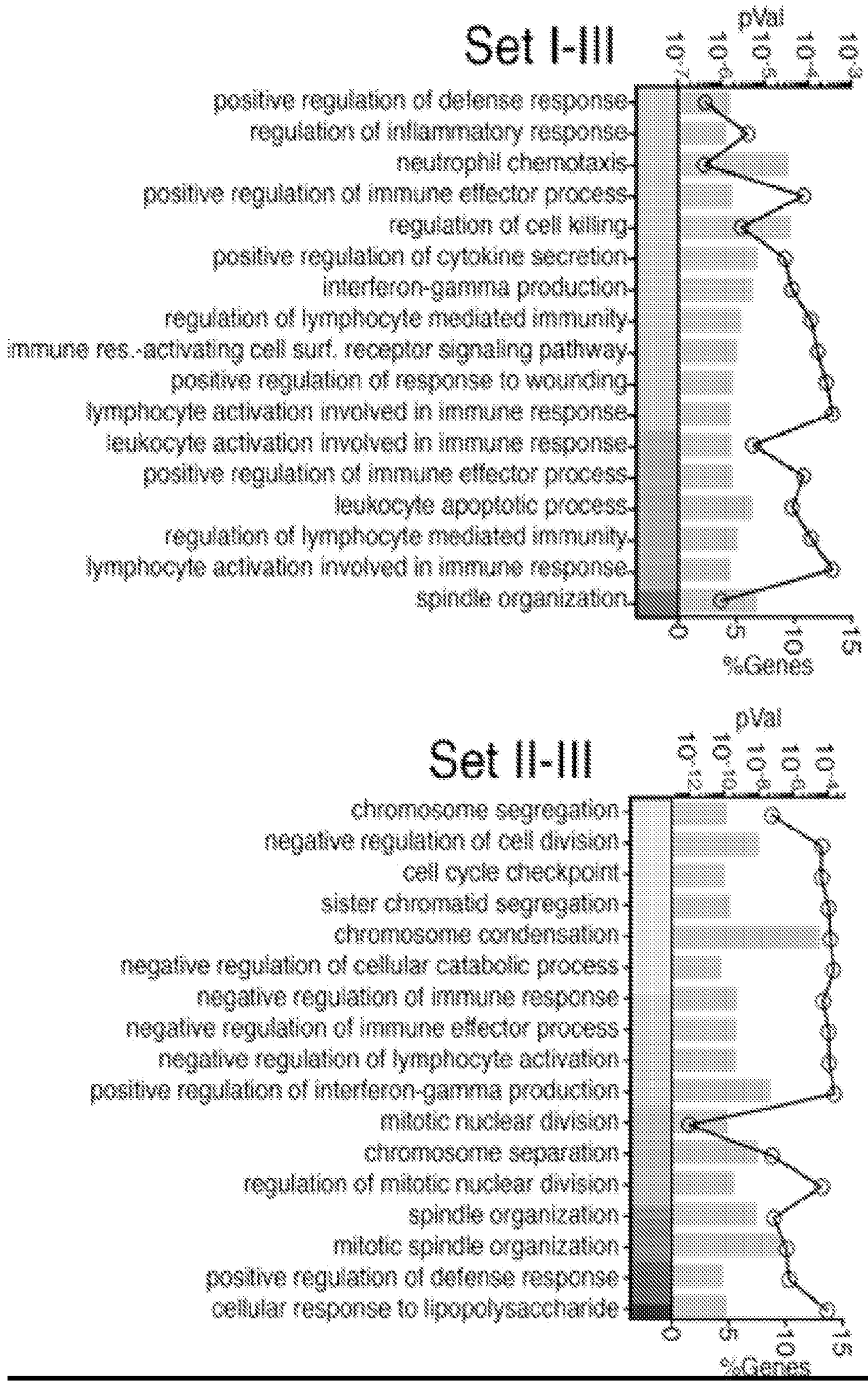

Set I-III
pVal
positive regulation of defense response
regulation of inflammatory response
neutrophil chemotaxis
positive regulation of immune effector process
regulation of cell killing
positive regulation of cytokine secretion
interferon-gamma production
regulation of lymphocyte mediated immunity
immune res.-activating cell surf. receptor signaling pathway
positive regulation of response to wounding
lymphocyte activation involved in immune response
leukocyte activation involved in immune response
positive regulation of immune effector process
leukocyte apoptotic process
regulation of lymphocyte mediated immunity
lymphocyte activation involved in immune response
spindle organization
%Genes
Set II-III
pVal
chromosome segregation
negative regulation of cell division
cell cycle checkpoint
sister chromatid segregation
chromosome condensation
negative regulation of cellular catabolic process
negative regulation of immune response
negative regulation of immune effector process
negative regulation of lymphocyte activation
positive regulation of interferon-gamma production
mitotic nuclear division
chromosome separation
regulation of mitotic nuclear division
spindle organization
mitotic spindle organization
positive regulation of defense response
cellular response to lipopolysaccharide
%Genes

FIG. 6B

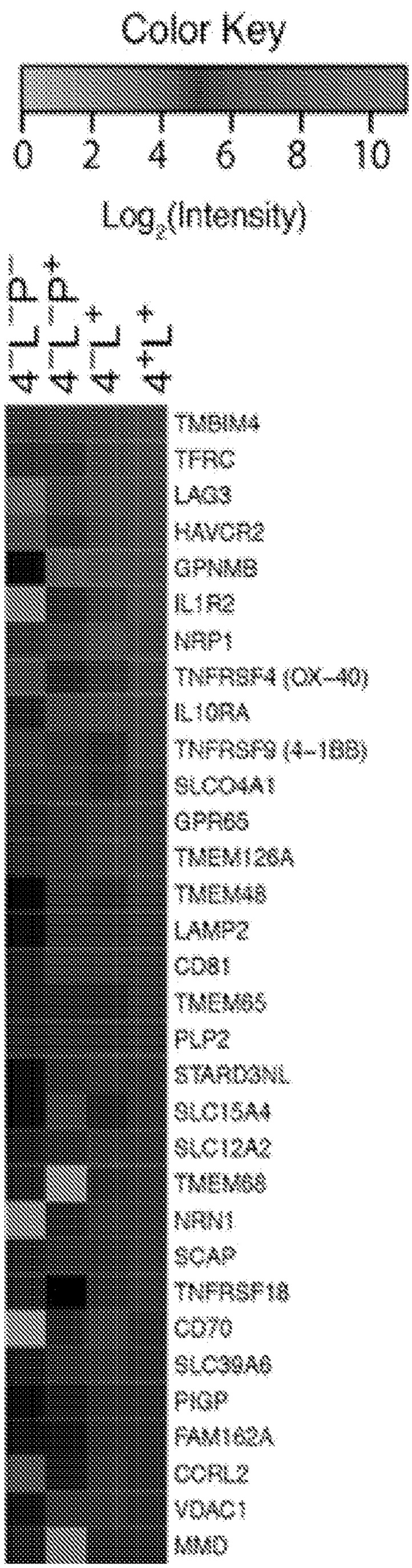

Color Key
0
2
4
6
8
10
Log2(Intensity)
4+L-P-
4+L-P+
4+L+
4+L+
TMBIM4
TFRC
LAG3
HAVCR2
GPNMB
IL1R2
NRP1
TNFRSF4 (OX-40)
IL10RA
TNFRSF9 (4-1BB)
SLCO4A1
GPR65
TMEM128A
TMEM48
LAMP2
CD81
TMEM65
PLP2
STARD3NL
SLC15A4
SLC12A2
TMEM88
NRN1
SCAP
TNFRSF18
CD70
SLC39A8
PIGP
FAM162A
CCRL2
VDAC1
MMD

FIG 6B (cont.)

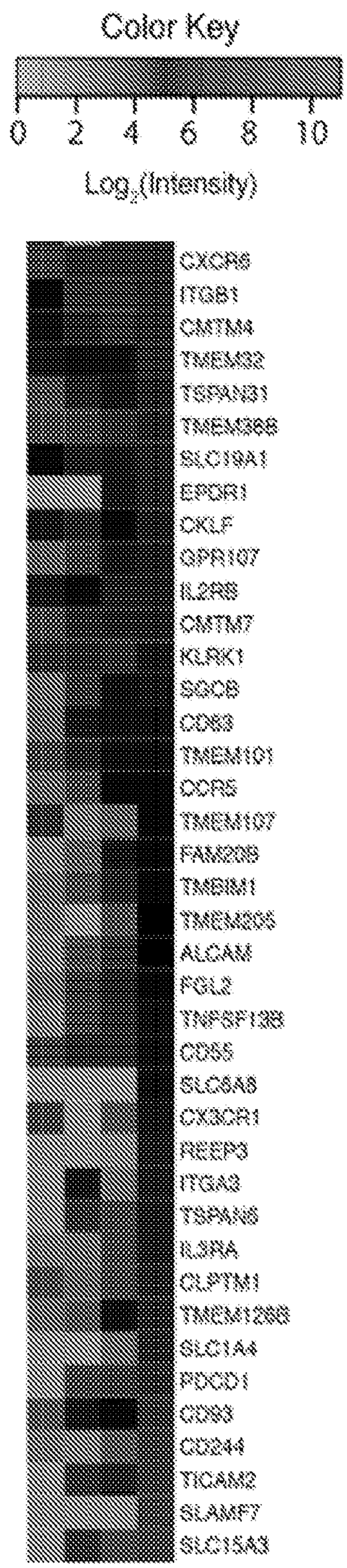

Color Key
0
2
4
6
8
10
Log2(Intensity)
CXCR6
ITGB1
CMTM4
TMEM32
TSPAN31
TMEM368
SLC19A1
EPOR1
CKLF
GPR107
IL2RB
CMTM7
KLRK1
SGCB
CD63
TMEM101
CCR5
TMEM107
FAM208
TMBIM1
TMEM205
ALCAM
FGL2
TNFSF13B
CD55
SLC6A8
CX3CR1
REEP3
ITGA3
TSPAN8
IL3RA
CLPTM1
TMEM286
SLC1A4
PDCD1
CD93
CD244
TICAM2
SLAMF7
SLC15A3

FIG. 6C

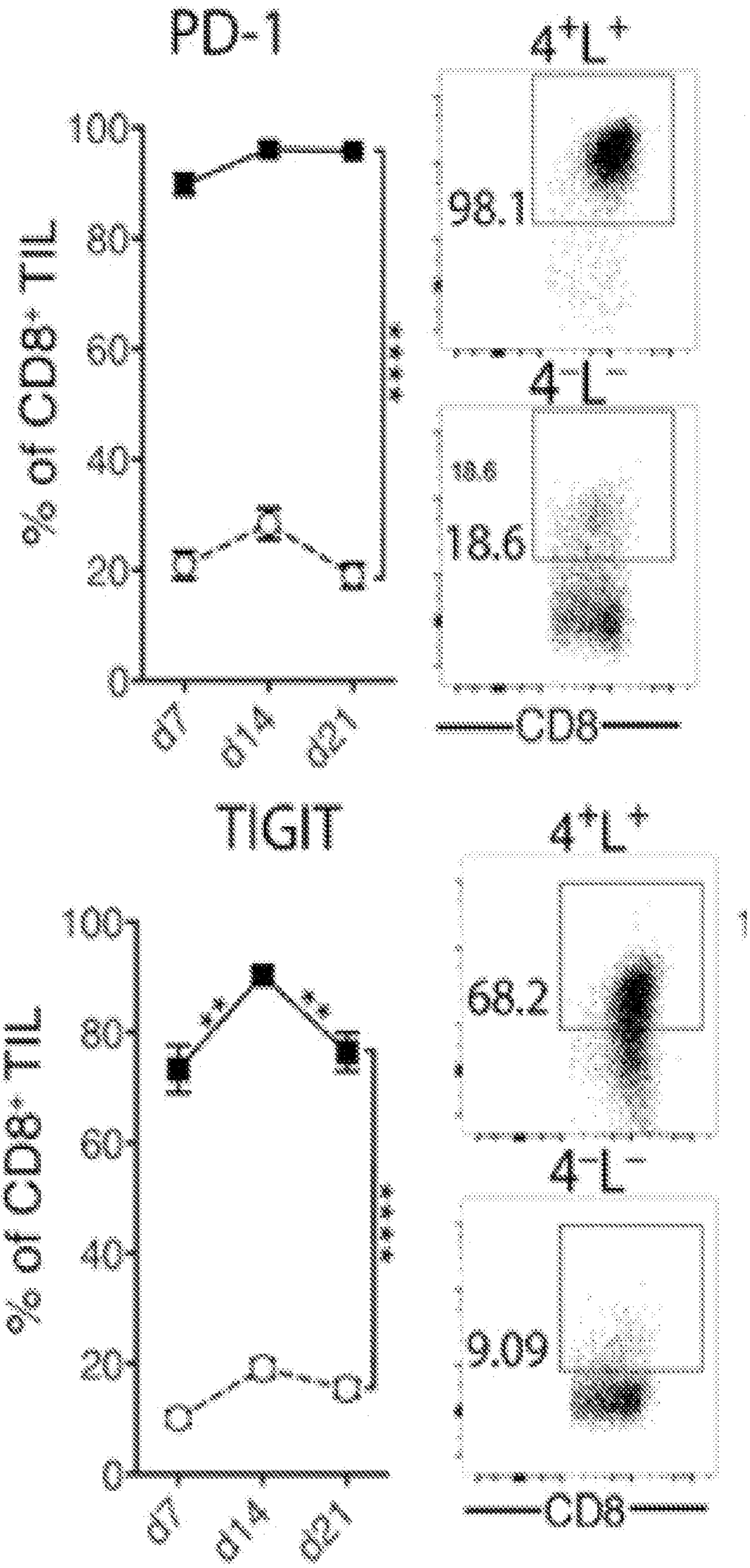

PD-1
% of CD8+ TIL
100
80
60
40
20
0
d7
d14
d21
4+L+
98.1
4-L-
18.6
CD8
TIGIT
% of CD8+ TIL
100
80
60
40
20
0
d7
d14
d21
4+L+
68.2
4-L-
9.09
CD8

FIG. 6C (cont.)

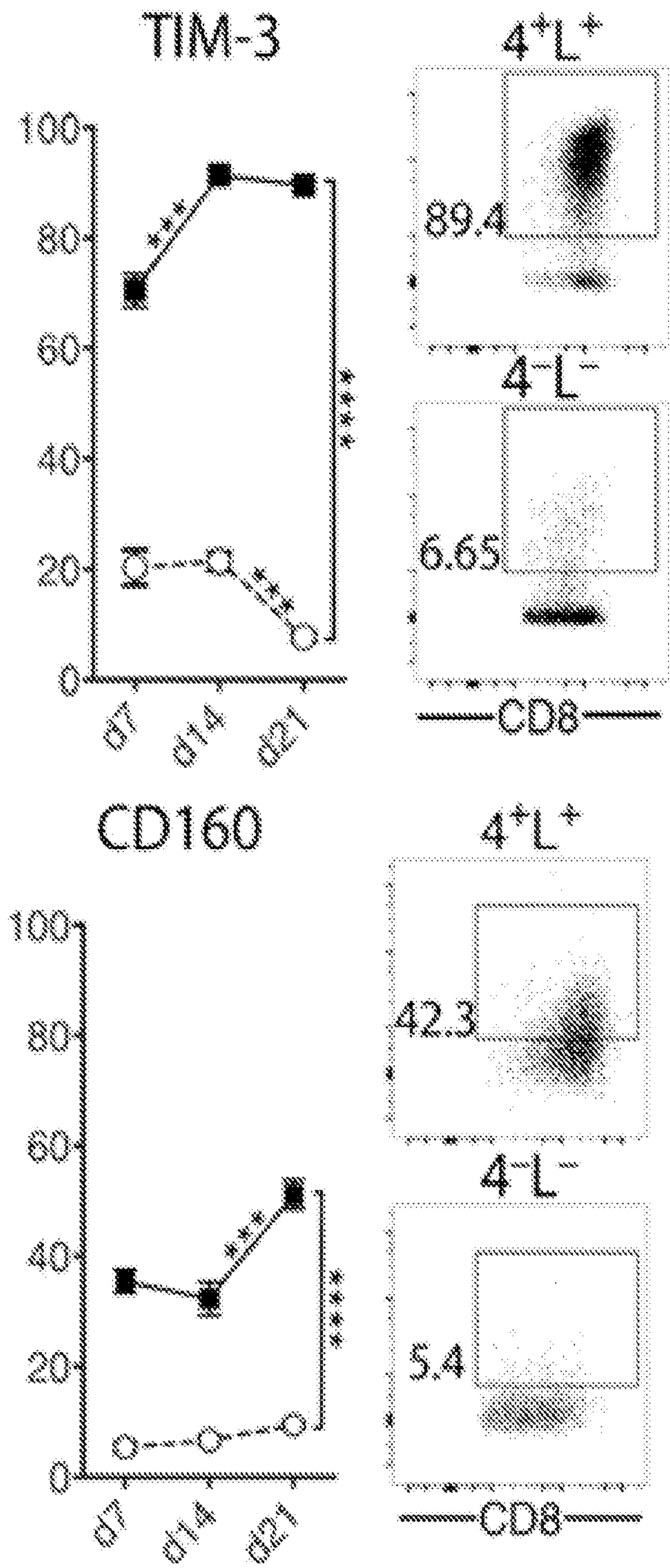

TIM-3
100
80
60
40
20
0
d7
d14
d21
4+L+
89.4
4-L-
6.65
CD8
CD160
100
80
60
40
20
0
d7
d14
d21
4+L+
42.3
4-L-
5.4
CD8

FIG. 6C (cont.)

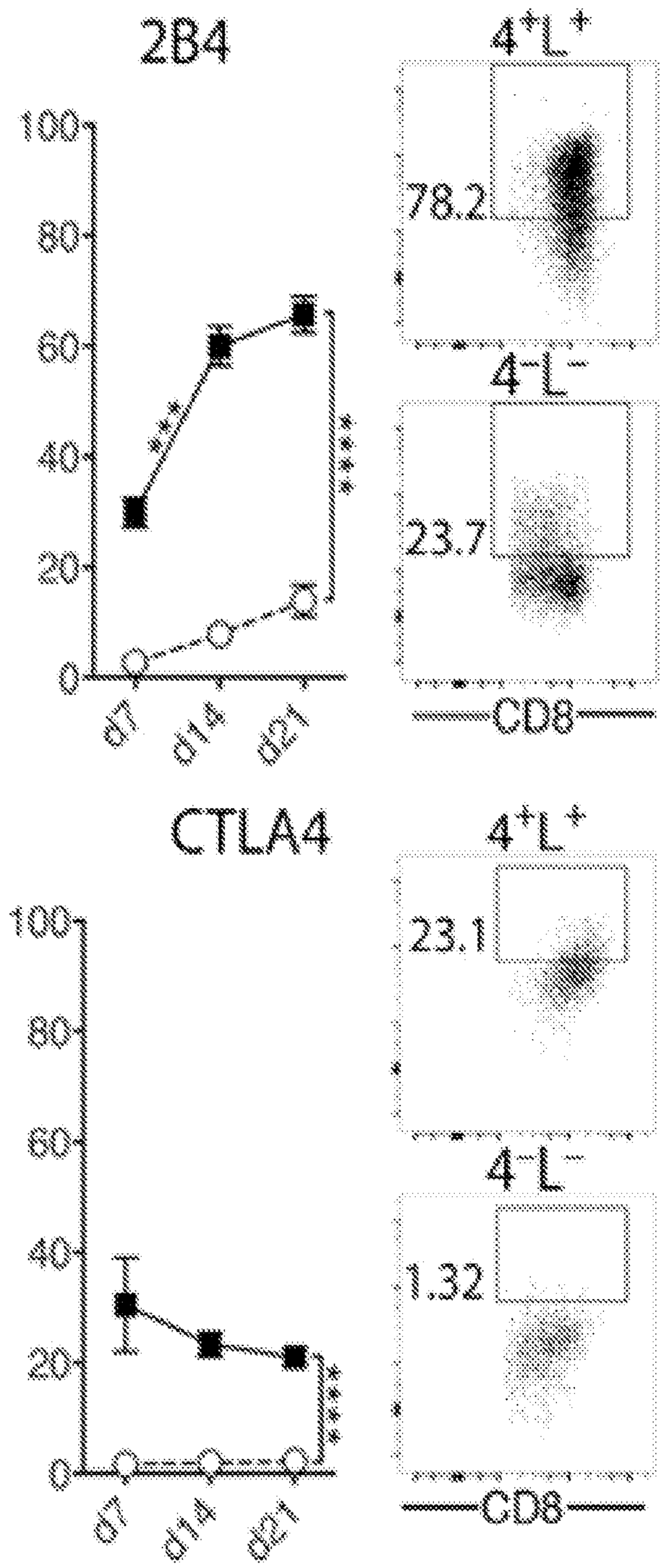
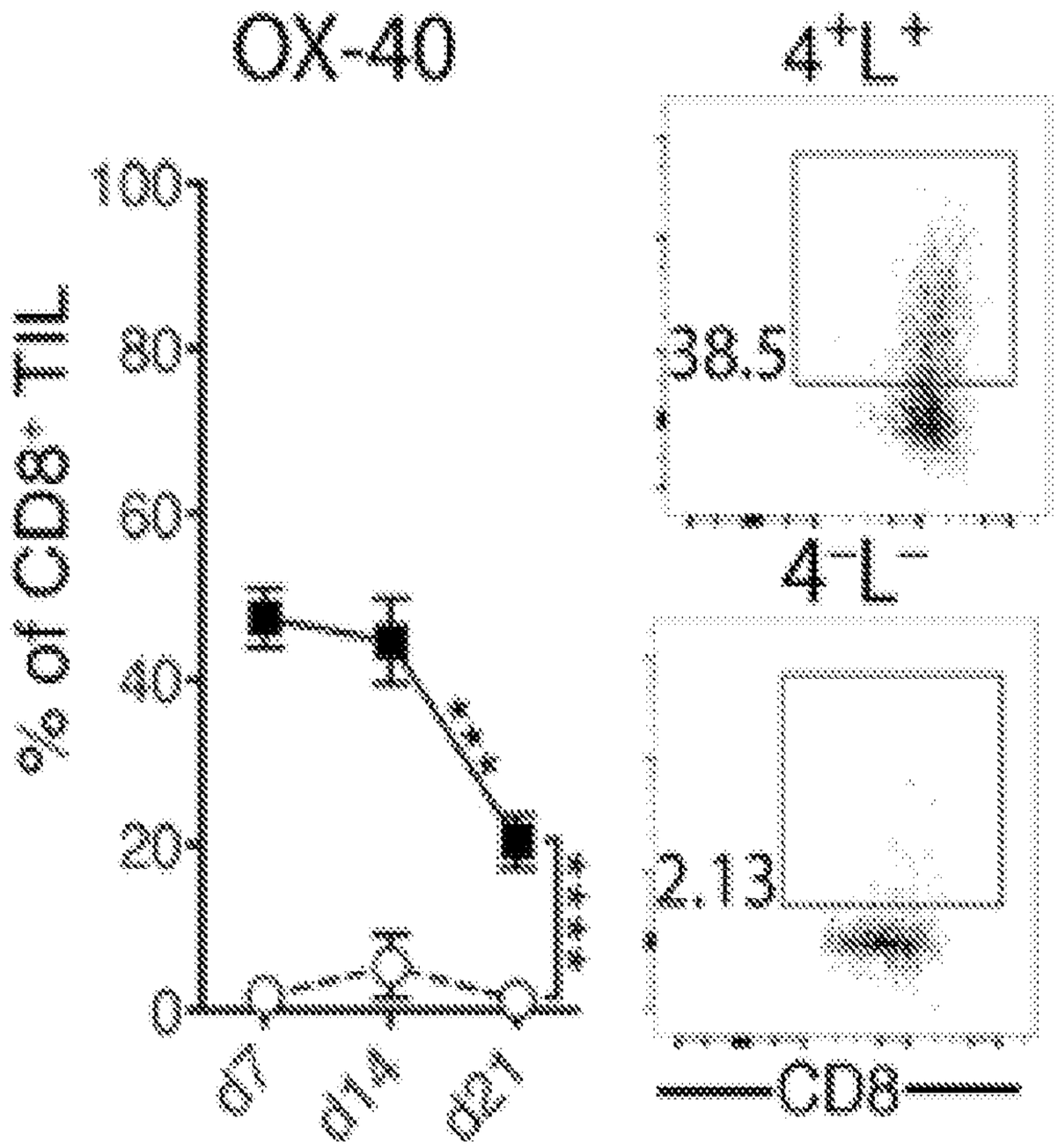

2B4
100
80
60
40
20
0
d7
d14
d21
4+L+
78.2
4-L-
23.7
CD8
CTLA4
4+L+
23.1
4-L-
1.32
CD8

FIG. 6C (cont.)


OX-40
% of CD8+ TIL
100
80
60
40
20
0
d7
d14
d21
4+L+
38.5
4-L-
2.13
CD8

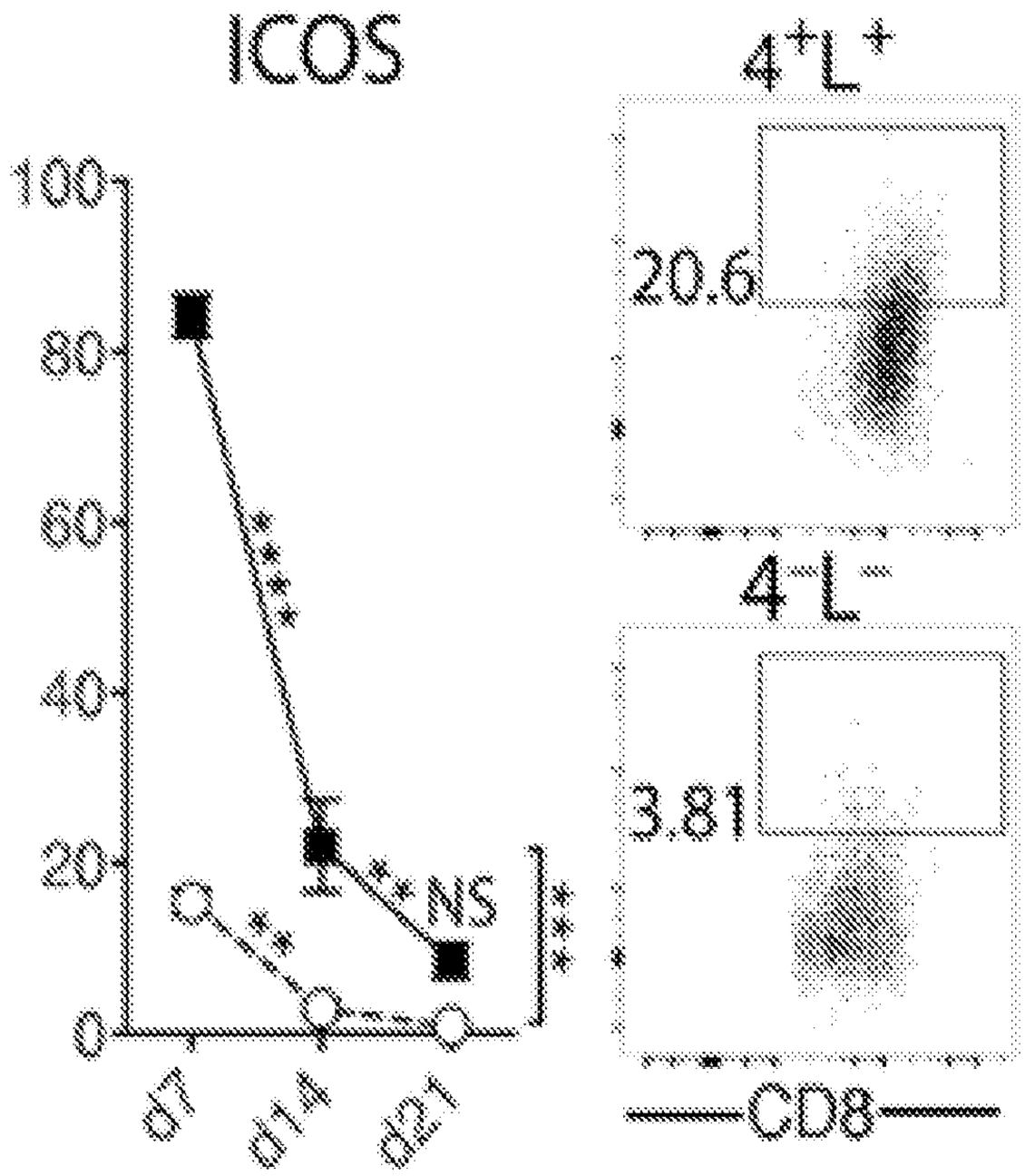

ICOS
100
80
60
40
20
0
NS
d7
d14
d21
4+L+
20.6
4-L-
3.81
CD8

FIG. 6C (cont.)

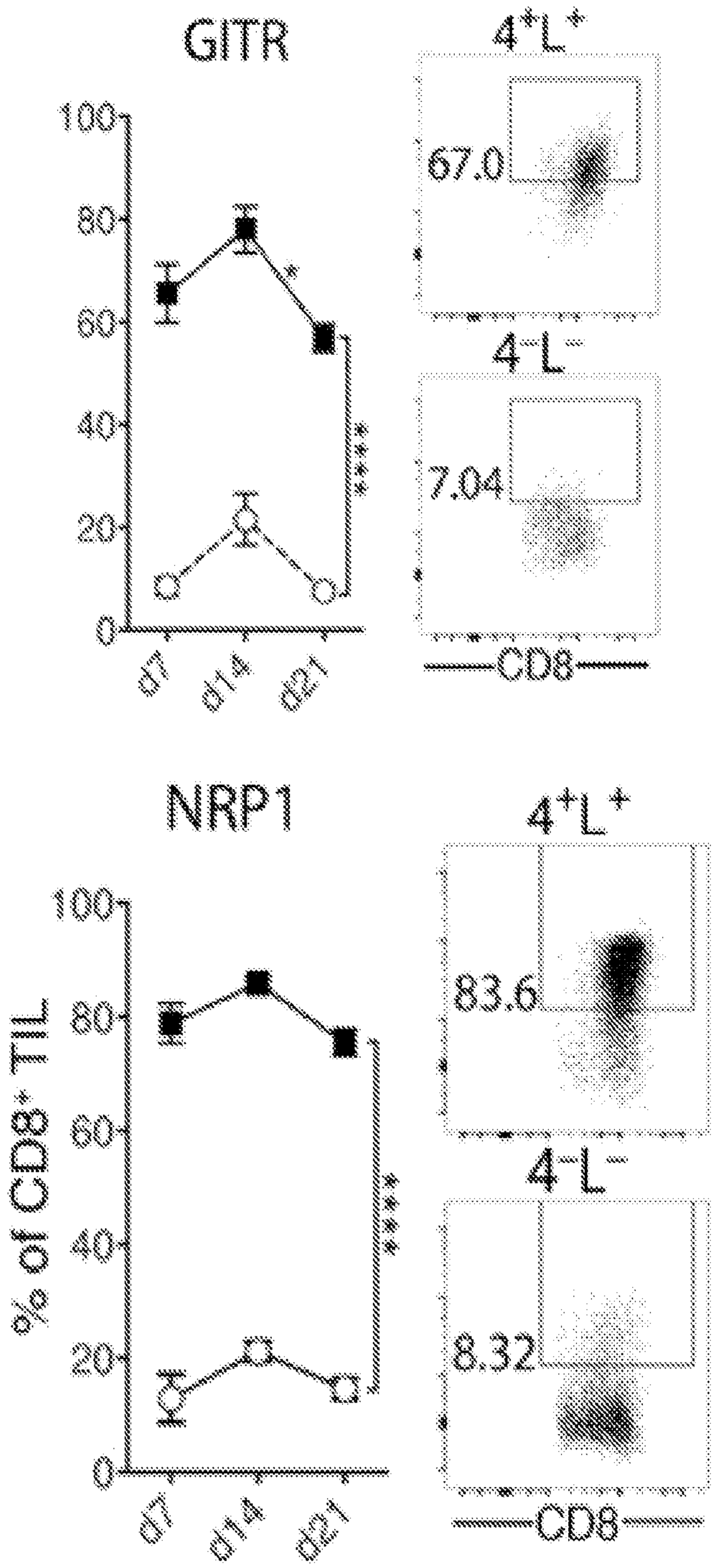

GITR
4+L+
67.0
4-L-
7.04
CD8
100
80
60
40
20
0
d7
d14
d21
NRP1
4+L+
83.6
4-L-
8.32
CD8
% of CD8+ TIL
100
80
60
40
20
0
d7
d14
d21

FIG. 6D

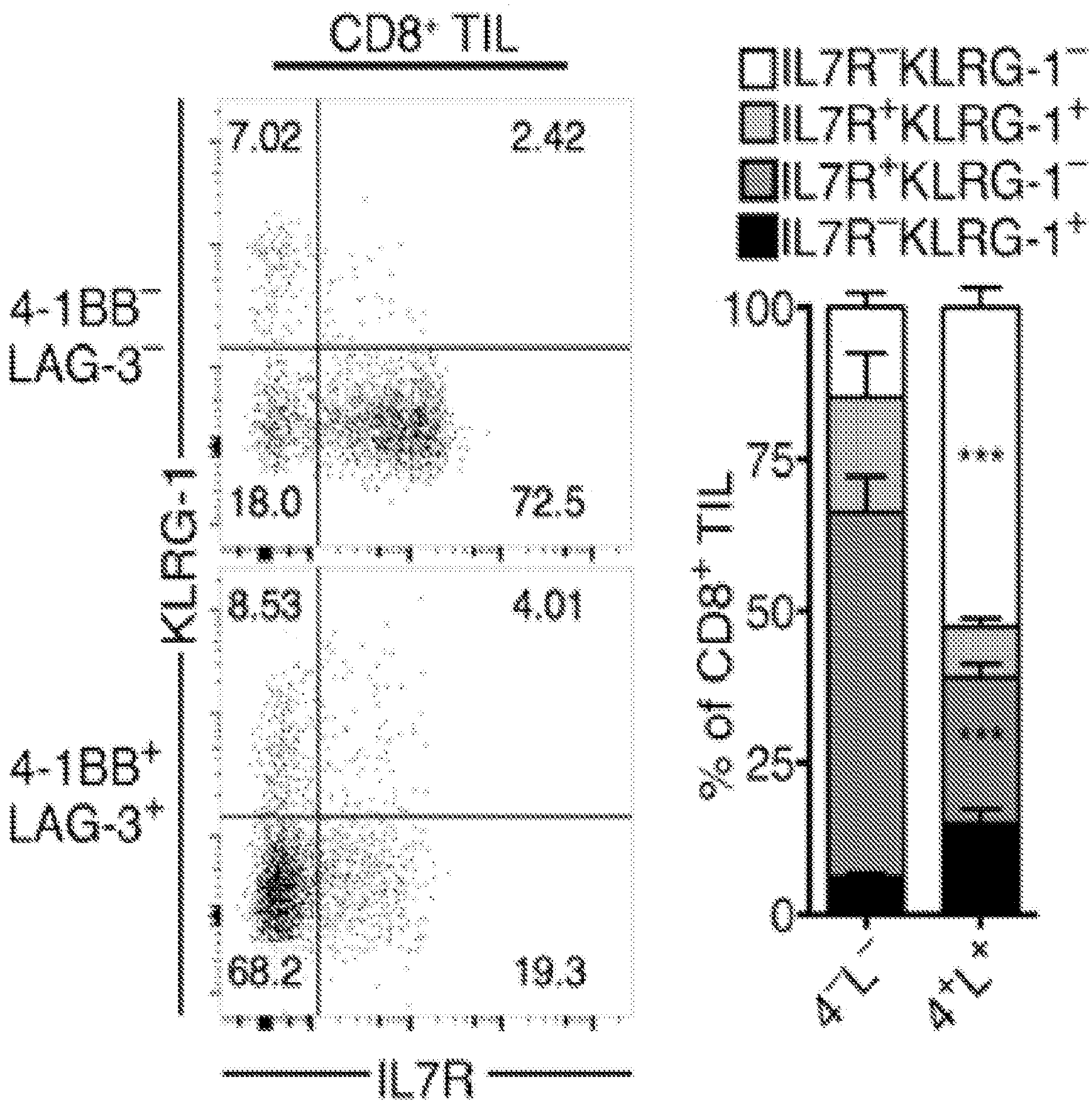

CD8+ TIL
7.02
2.42
18.0
72.5
8.53
4.01
68.2
19.3
4-1BB−
LAG-3−
4-1BB+
LAG-3+
KLRG-1
IL7R
IL7R−KLRG-1−
IL7R+KLRG-1+
IL7R+KLRG-1−
IL7R−KLRG-1+
% of CD8+ TIL
100
75
50
25
0
***
***
4−L−
4+L+

FIG. 7

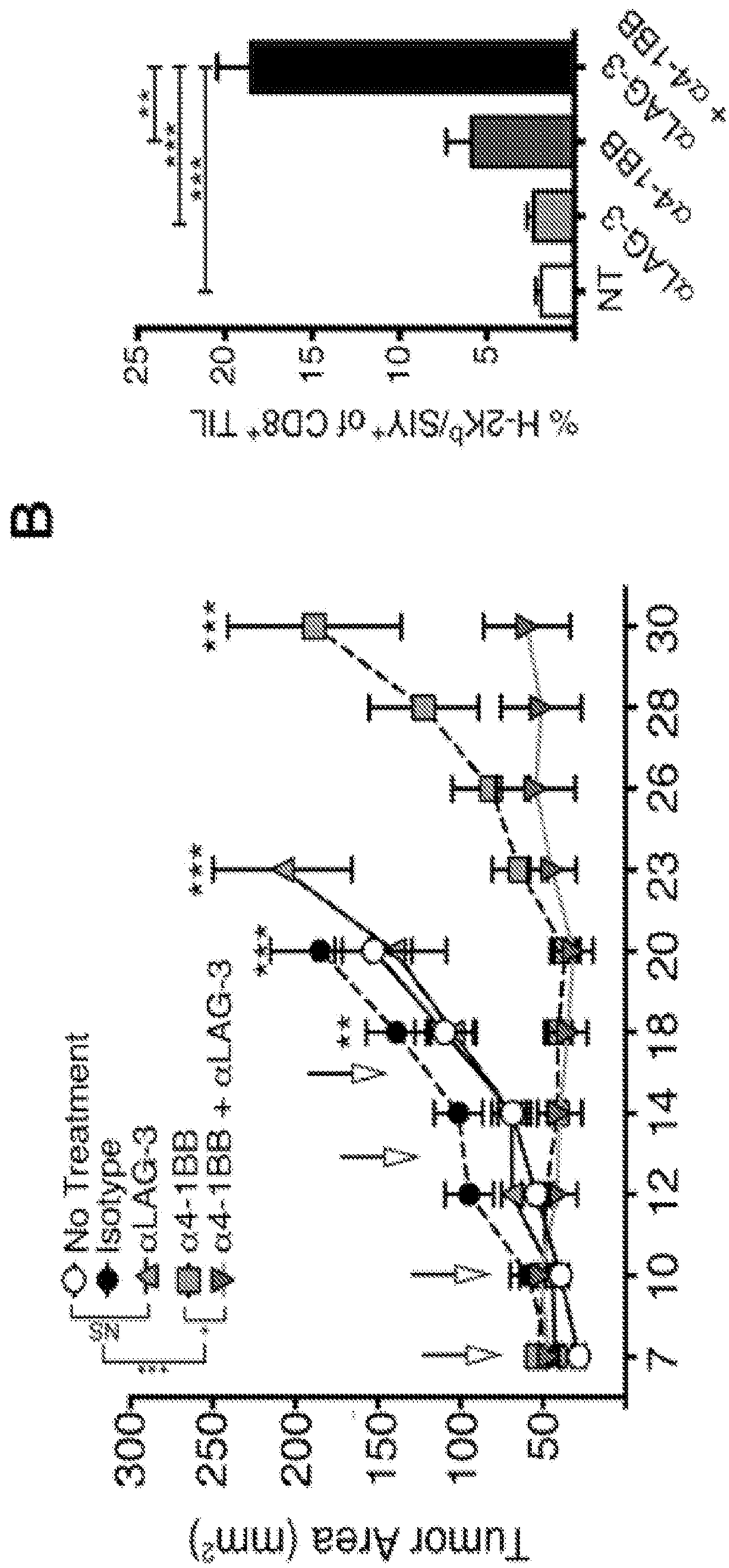

A
Tumor Area (mm²)
300
250
200
150
100
50
7
10
12
14
18
20
23
26
28
30
No Treatment
Isotype
αLAG-3
α4-1BB
α4-1BB + αLAG-3
B
% H-2Kᵇ/SIY⁺ of CD8⁺ TIL
25
20
15
10
5
NT
αLAG-3
α4-1BB
αLAG-3
+ α4-1BB

FIG. 7 (cont.)

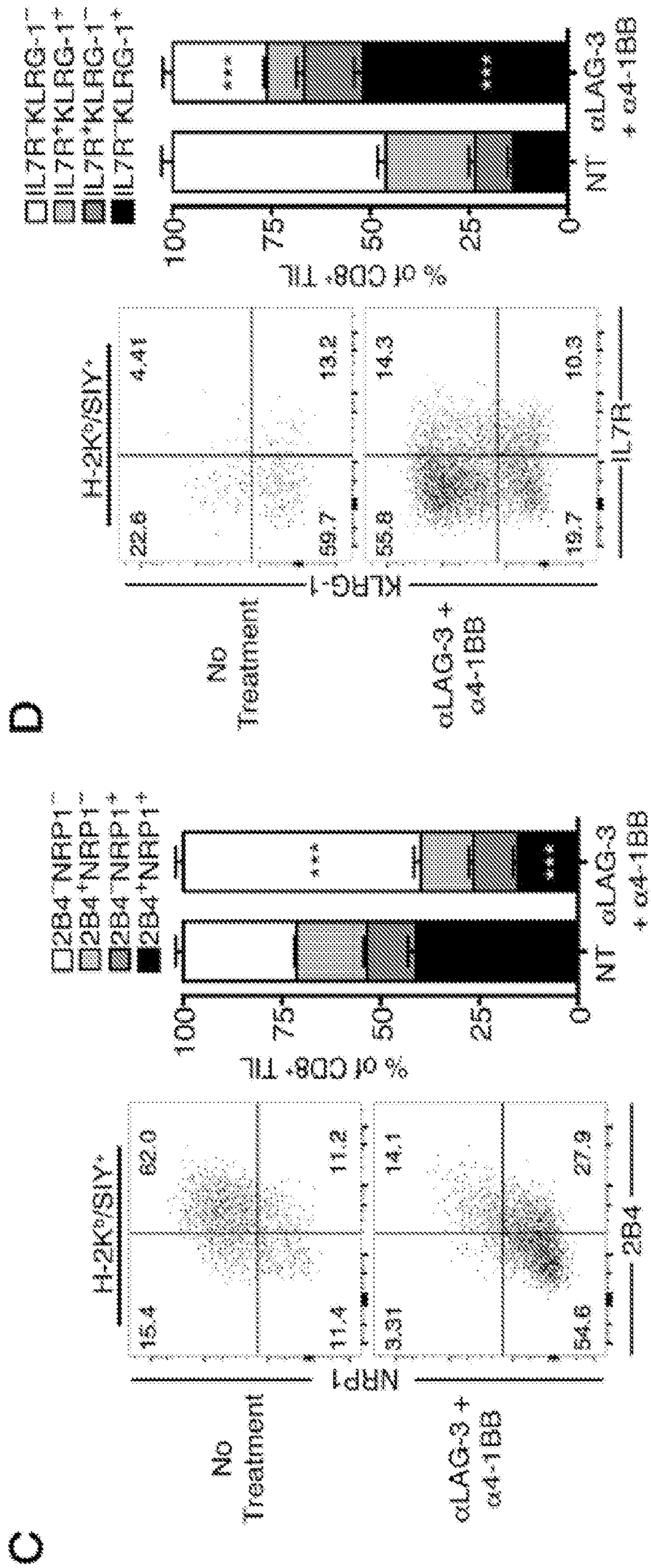

C
No Treatment
αLAG-3 + α4-1BB
NRP1
2B4
H-2Kᵇ/SIY+
15.4
62.0
11.4
11.2
9.91
14.1
54.6
27.9
D
No Treatment
αLAG-3 + α4-1BB
KLRG-1
IL7R
H-2Kᵇ/SIY+
22.6
4.41
59.7
13.2
55.8
14.3
19.7
10.3
% of CD8+ TIL
100
75
50
25
0
NT
αLAG-3
+ α4-1BB
2B4⁻NRP1⁻
2B4⁺NRP1⁻
2B4⁻NRP1⁺
2B4⁺NRP1⁺
IL7R⁻KLRG-1⁻
IL7R⁺KLRG-1⁺
IL7R⁻KLRG-1⁺
IL7R⁺KLRG-1⁻

FIG. 7 (cont.)

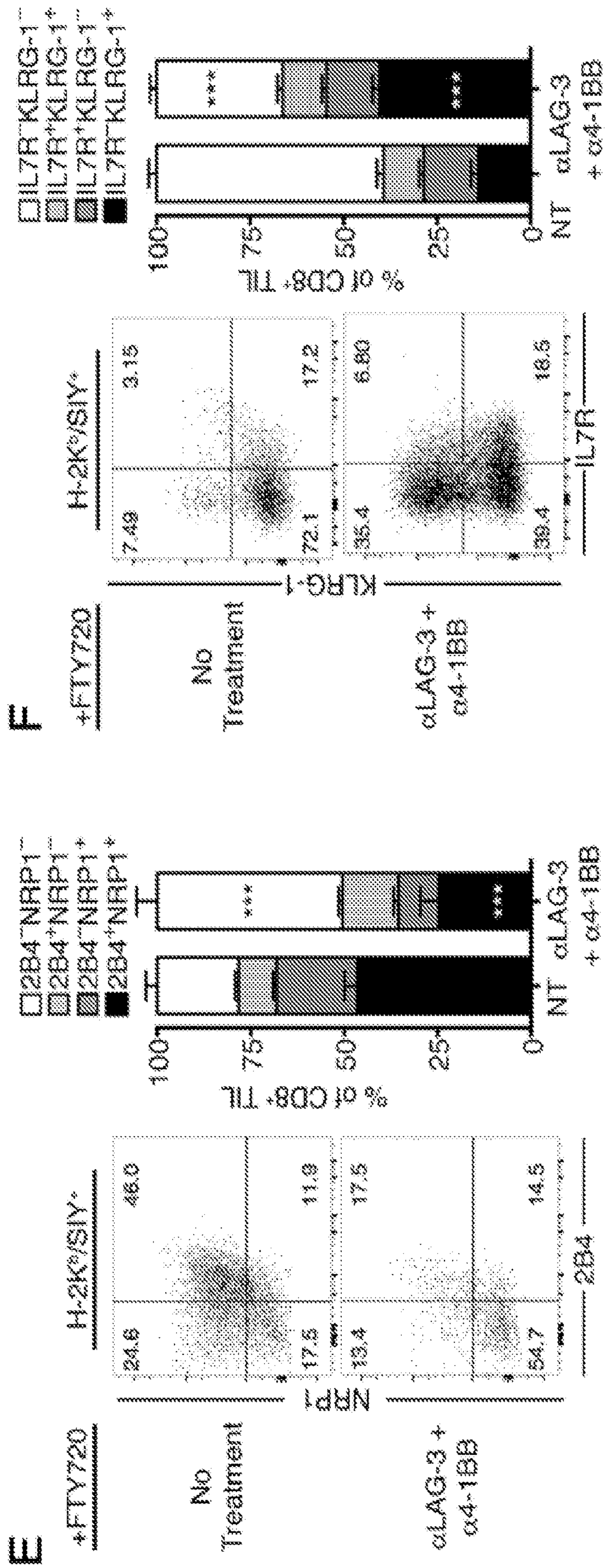

E
+FTY720
No Treatment
αLAG-3 + α4-1BB
H-2Kᵇ/SIY⁺
NRP1
2B4
24.6
17.5
46.0
11.9
13.4
64.7
17.5
14.5
2B4⁻NRP1⁻
2B4⁺NRP1⁻
2B4⁻NRP1⁺
2B4⁺NRP1⁺
% of CD8⁺ TIL
100
75
50
25
0
NT
αLAG-3 + α4-1BB
F
+FTY720
No Treatment
αLAG-3 + α4-1BB
H-2Kᵇ/SIY⁺
KLRG-1
IL7R
7.49
72.1
3.15
17.2
35.4
39.4
6.80
18.3
IL7R⁻KLRG-1⁻
IL7R⁺KLRG-1⁺
IL7R⁺KLRG-1⁻
IL7R⁻KLRG-1⁺
% of CD8⁺ TIL
100
75
50
25
0
NT
αLAG-3 + α4-1BB

FIG. 7 (cont.)

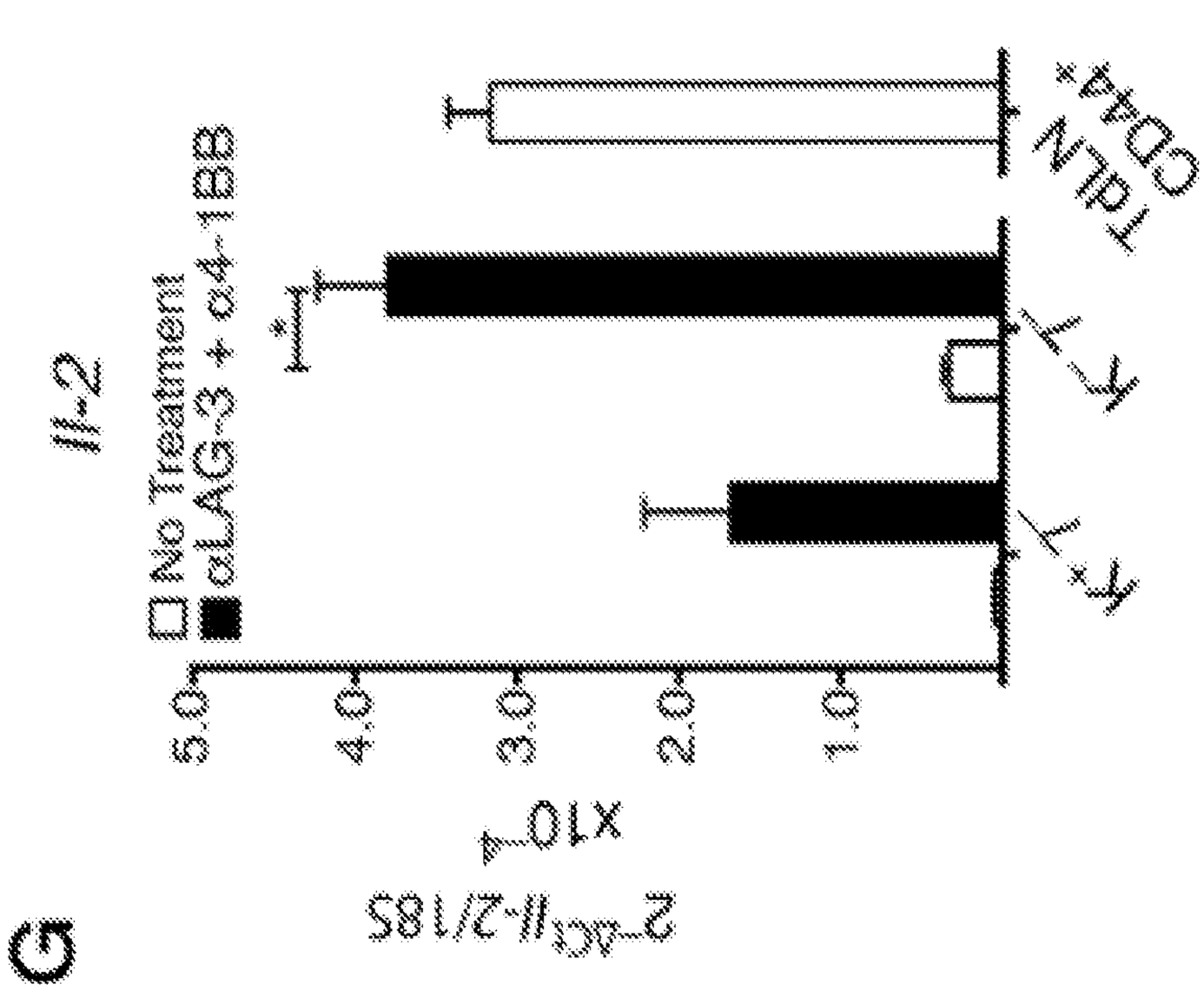

IL-2
IL-2 (pg/mL) per 1000 cells
60
40
20
**
**
T1
T2
IL-2
No Treatment
αLAG-3 + α4-1BB
5.0
4.0
3.0
2.0
1.0
*
*
T1
T2
IL-2/18S
x10⁻⁴

FIG. 8

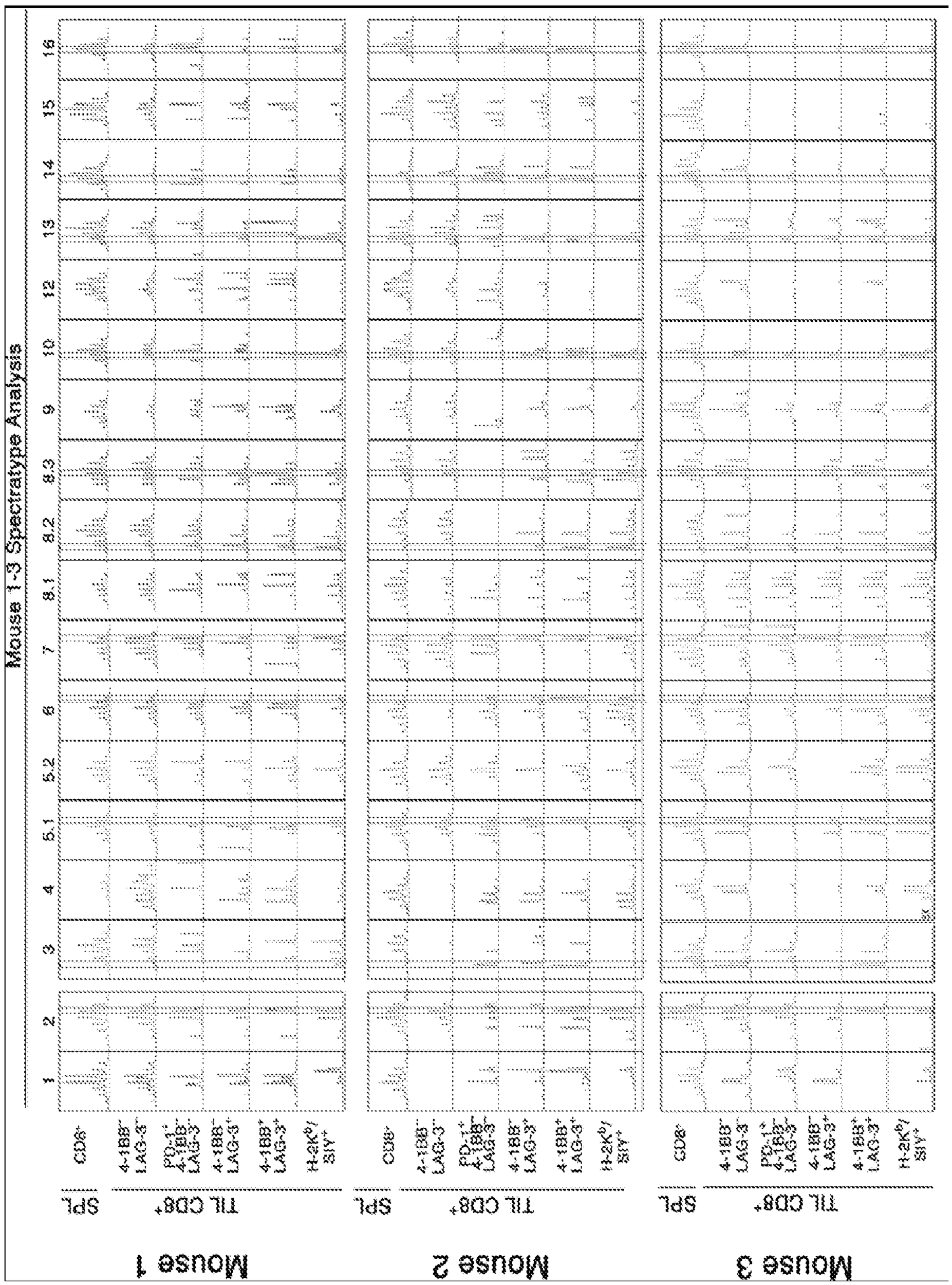

Mouse 1-3 Spectratype Analysis
1
2
3
4
5.1
5.2
6
7
8.1
8.2
8.3
9
10
12
13
14
15
16
Mouse 1
SPL
CD8+
TIL CD8+
4-1BB-
LAG-3-
PD-1+
4-1BB-
LAG-3-
4-1BB+
LAG-3+
4-1BB+
LAG-3+
H-2Kb/
SIY+
Mouse 2
SPL
CD8+
TIL CD8+
4-1BB-
LAG-3-
PD-1+
4-1BB-
LAG-3-
4-1BB-
LAG-3+
4-1BB+
LAG-3+
H-2Kb/
SIY+
Mouse 3
SPL
CD8+
TIL CD8+
4-1BB-
LAG-3-
PD-1+
4-1BB-
LAG-3-
4-1BB-
LAG-3+
4-1BB+
LAG-3+
H-2Kb/
SIY+

FIG. 9

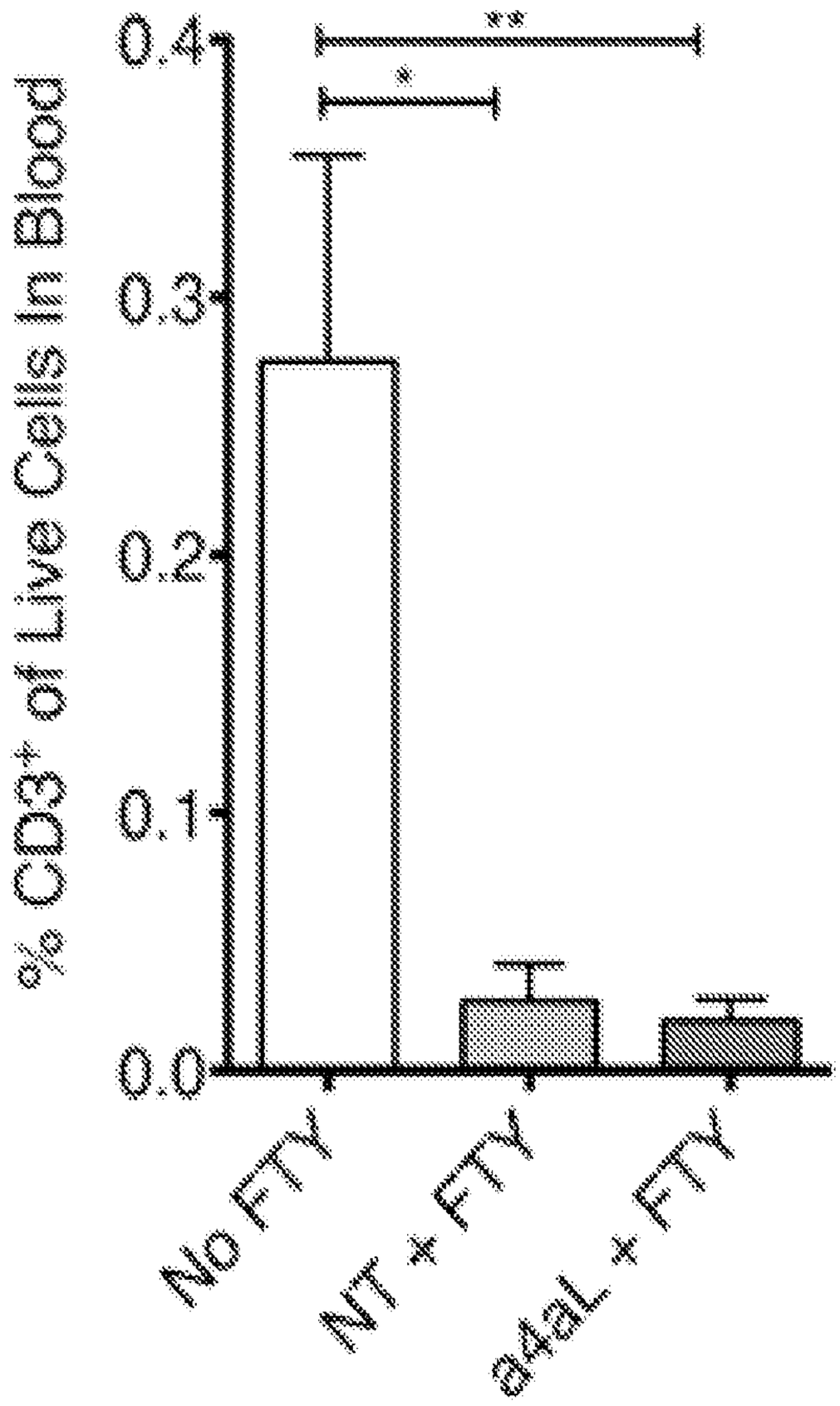


FIG. 10A

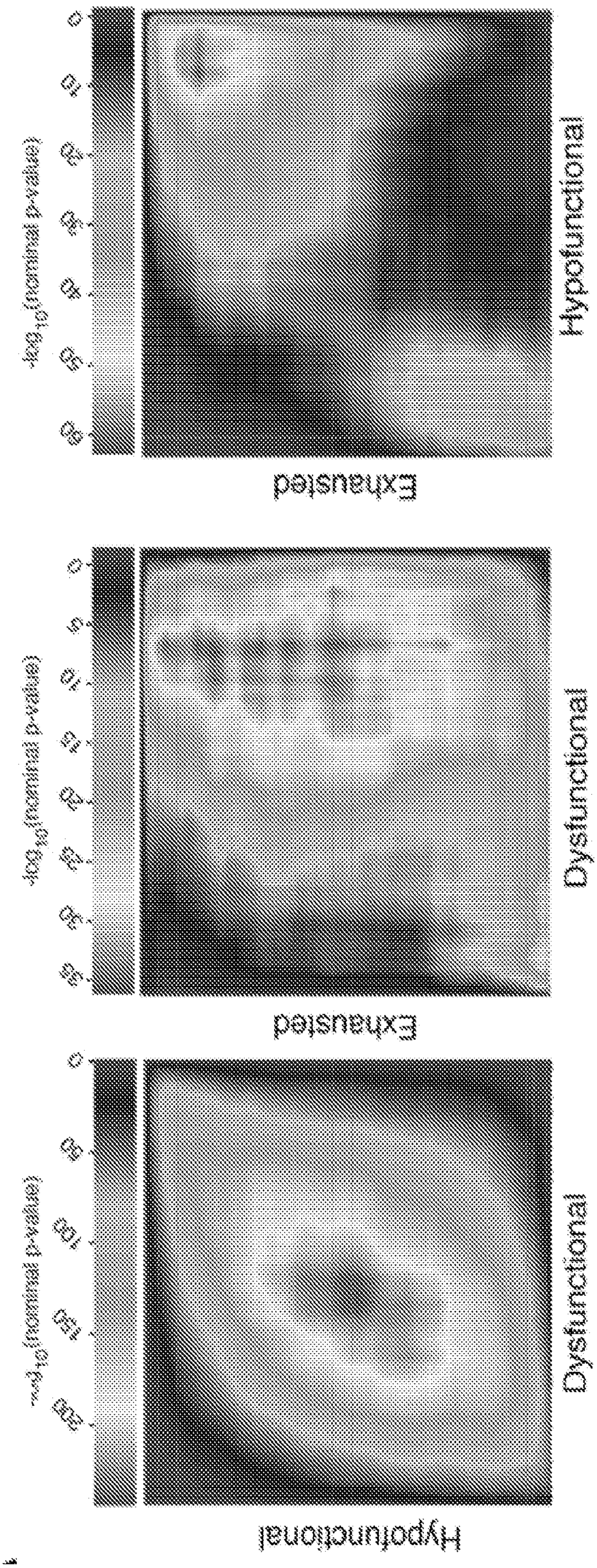

Hypofunctional
Exhausted
Dysfunctional
Exhausted
Dysfunctional
Hypofunctional

FIG. 10A (cont.)

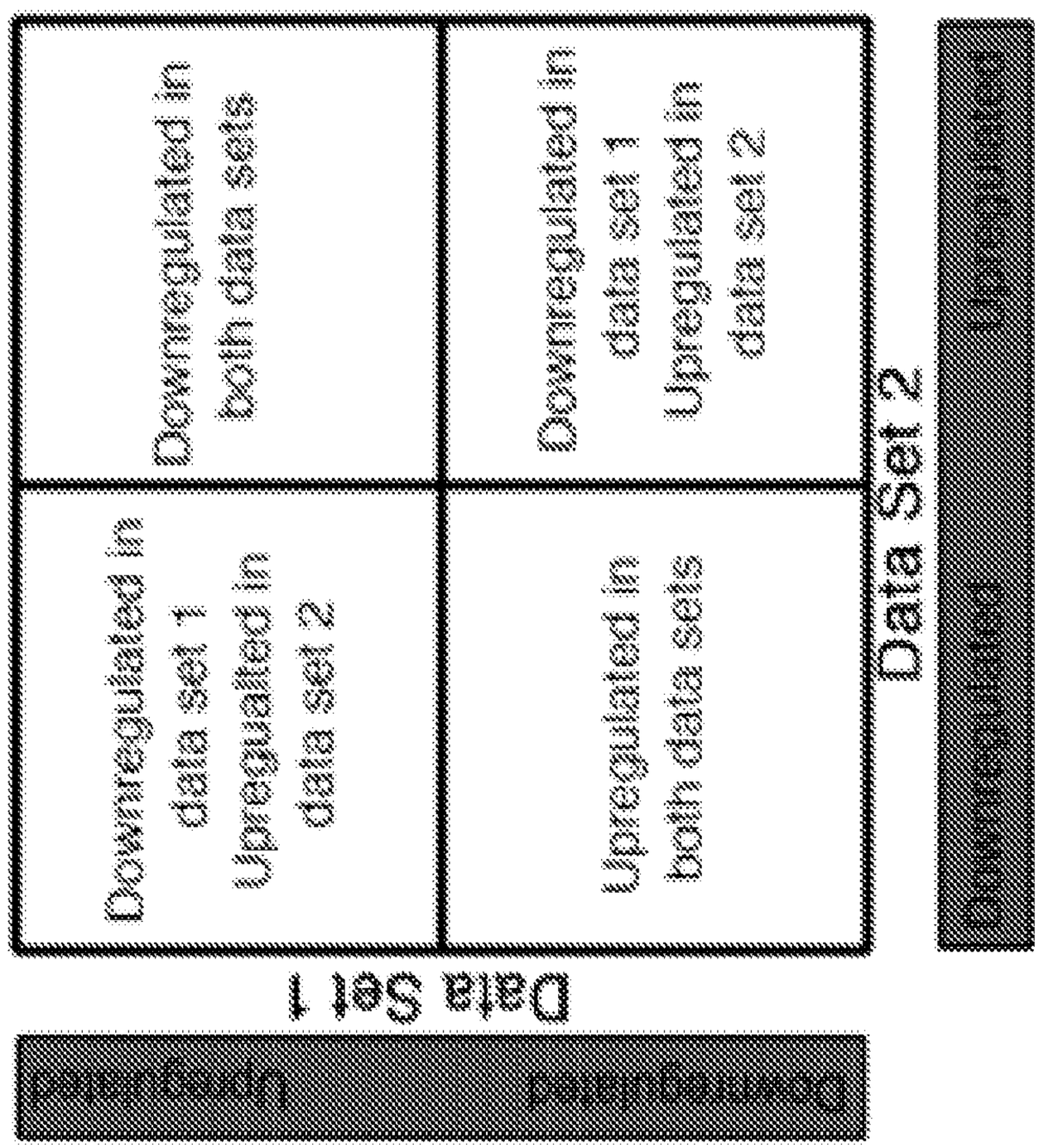

Downregulated
Upregulated
Data Set 1
Downregulated in data set 1 Upregulated in data set 2
Upregulated in both data sets
Downregulated in both data sets
Downregulated in data set 1 Upregulated in data set 2
Data Set 2
Downregulated
Upregulated

FIG. 10B

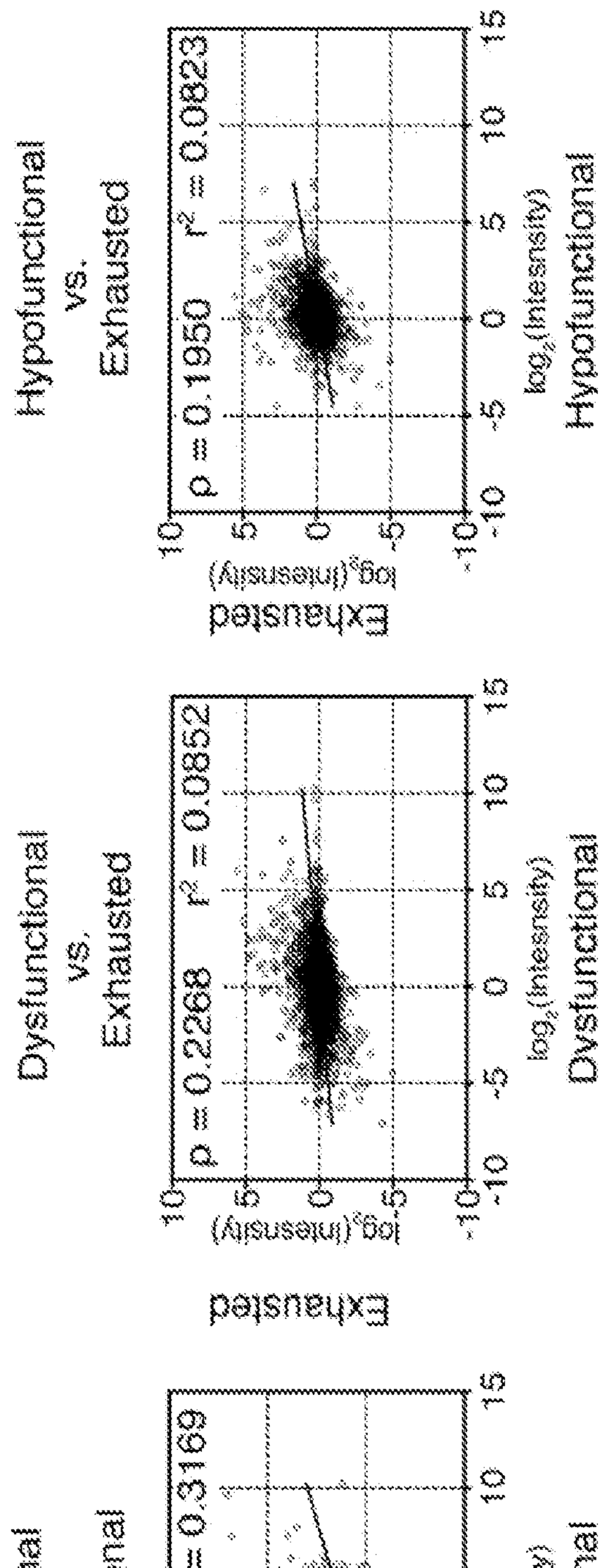

Hypofunctional
vs.
Exhausted
p = 0.1950 r² = 0.0823
Exhausted
log₂(Intensity)
Hypofunctional
log₂(Intensity)
Dysfunctional
vs.
Exhausted
p = 0.2268 r² = 0.0852
Exhausted
log₂(Intensity)
Dysfunctional
log₂(Intensity)
Dysfunctional
vs.
Hypofunctional
p = 0.5691 r² = 0.3169
Hypofunctional
log₂(Intensity)
Dysfunctional
log₂(Intensity)

FIG. 11

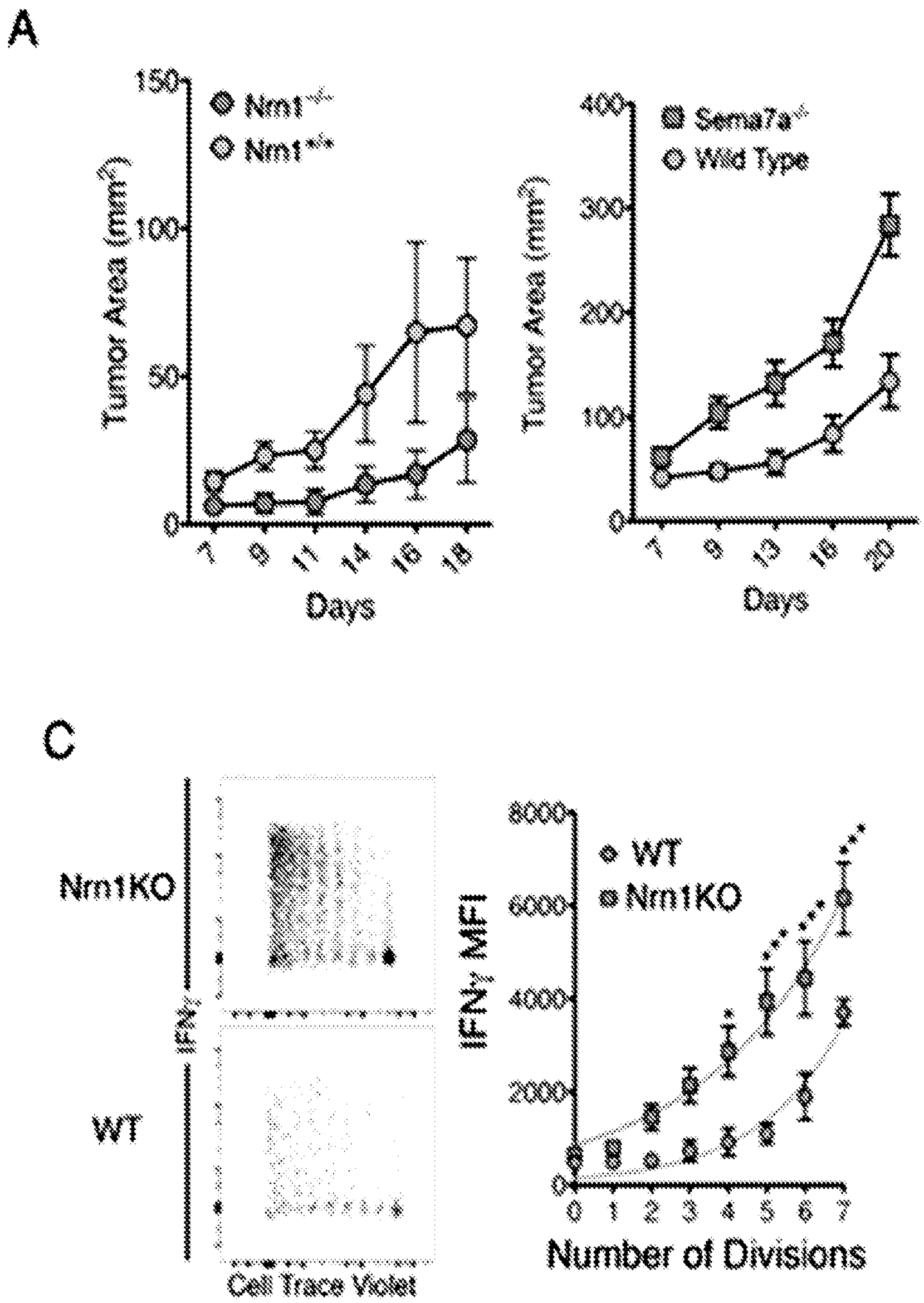
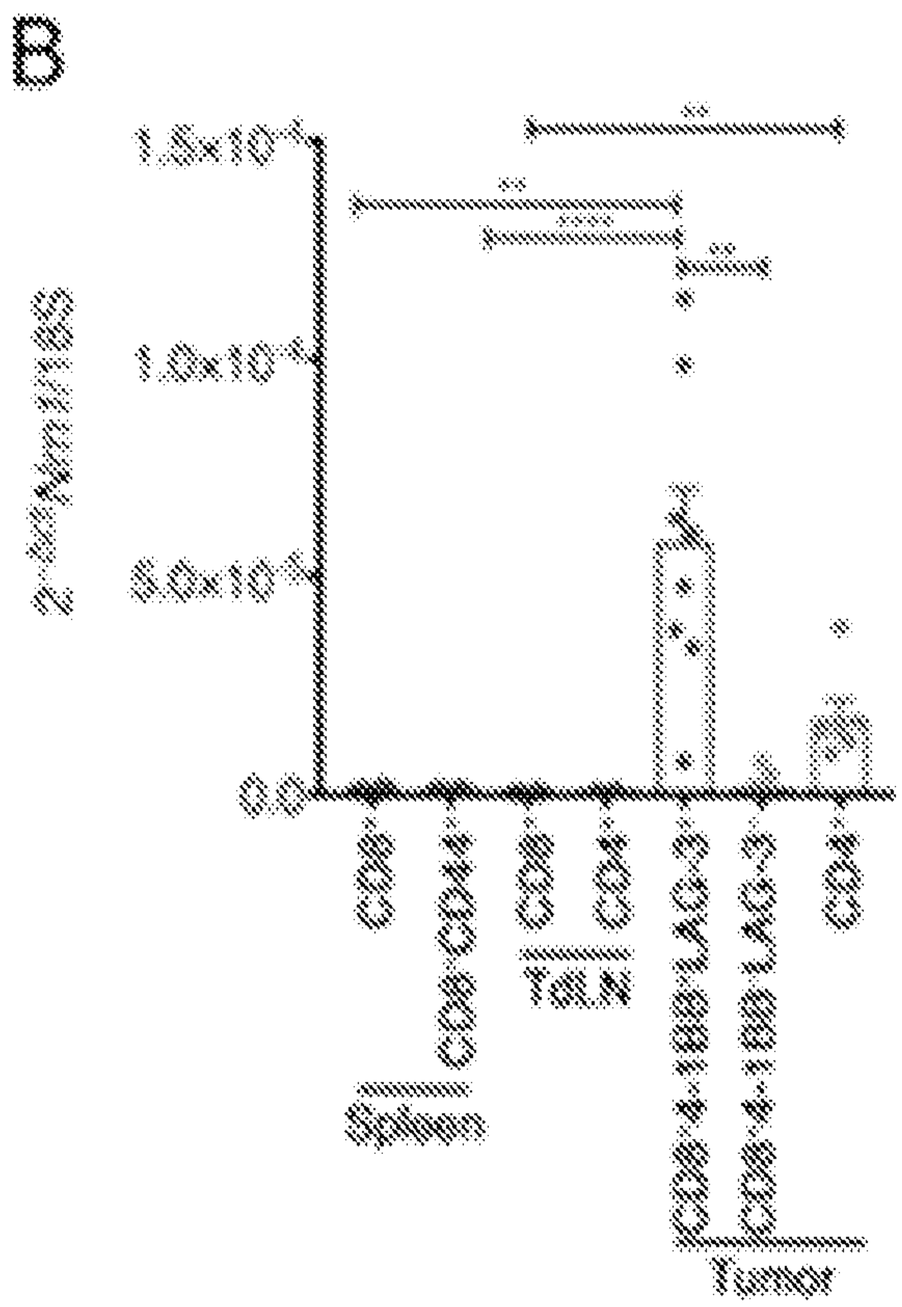

A
Nm1-/-
Nm1+/+
Tumor Area (mm²)
Days
Sema7a-/-
Wild Type
C
Nm1KO
WT
IFNγ
Cell Trace Violet
WT
Nm1KO
IFNγ MFI
Number of Divisions

FIG. 11 (cont.)


B
1.5×10⁴
1.0×10⁴
5.0×10³
0.0
Spleen
Tumor
CD8
CD8+CD44
CD8
CD4
CD8+4-1BB+LAG-3
CD8+4-1BB-LAG-3
CD4

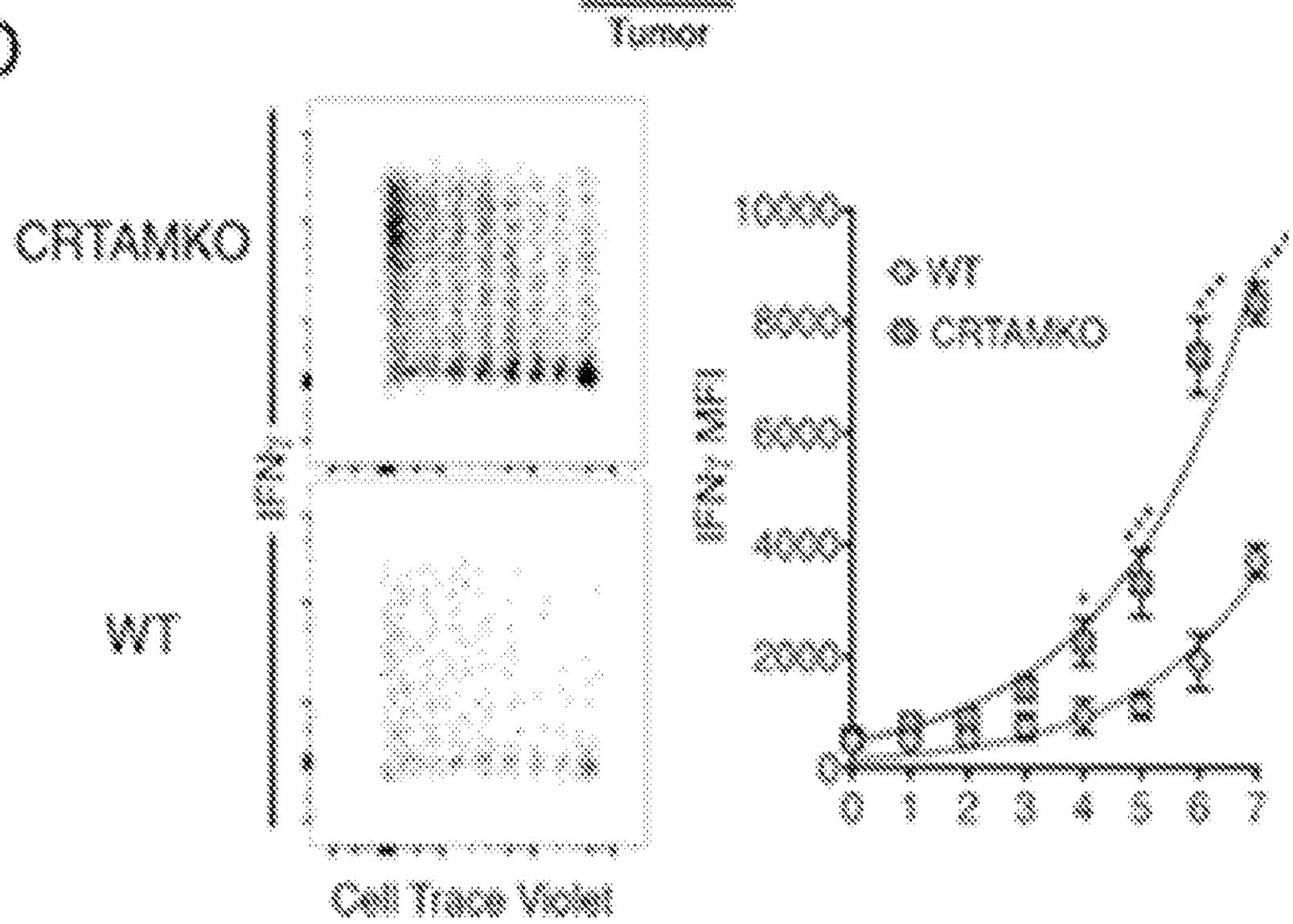

D
CRTAMKO
WT
Cell Trace Violet
10000
8000
6000
4000
2000
0
WT
CRTAMKO
0 1 2 3 4 5 6 7

FIG. 11 (cont.)

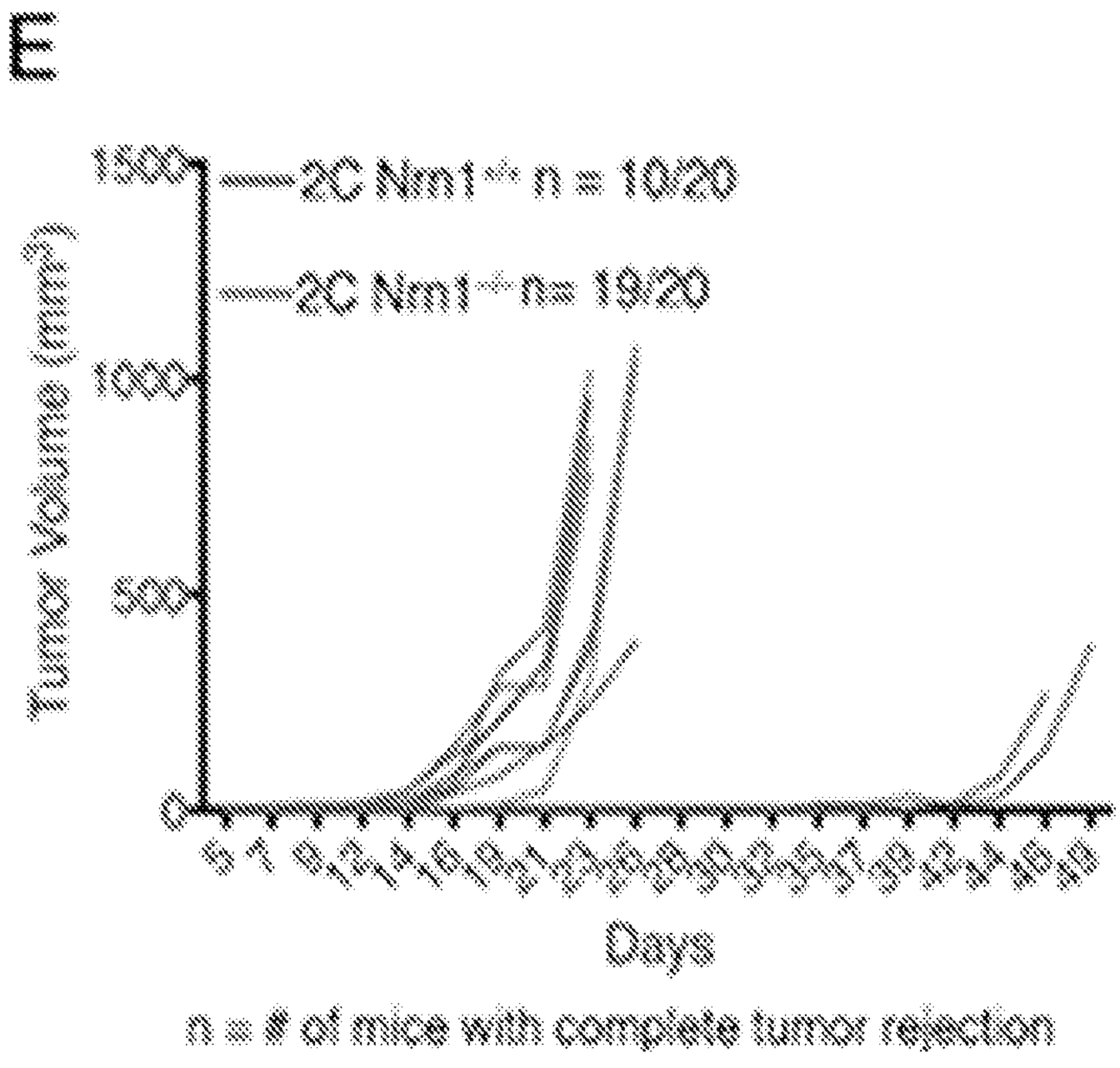

E
2C Nm1 n = 10/20
2C Nm1 n = 19/20
Tumor volume (mm³)
1500
1000
500
0
Days
n = # of mice with complete tumor rejection

FIG. 12

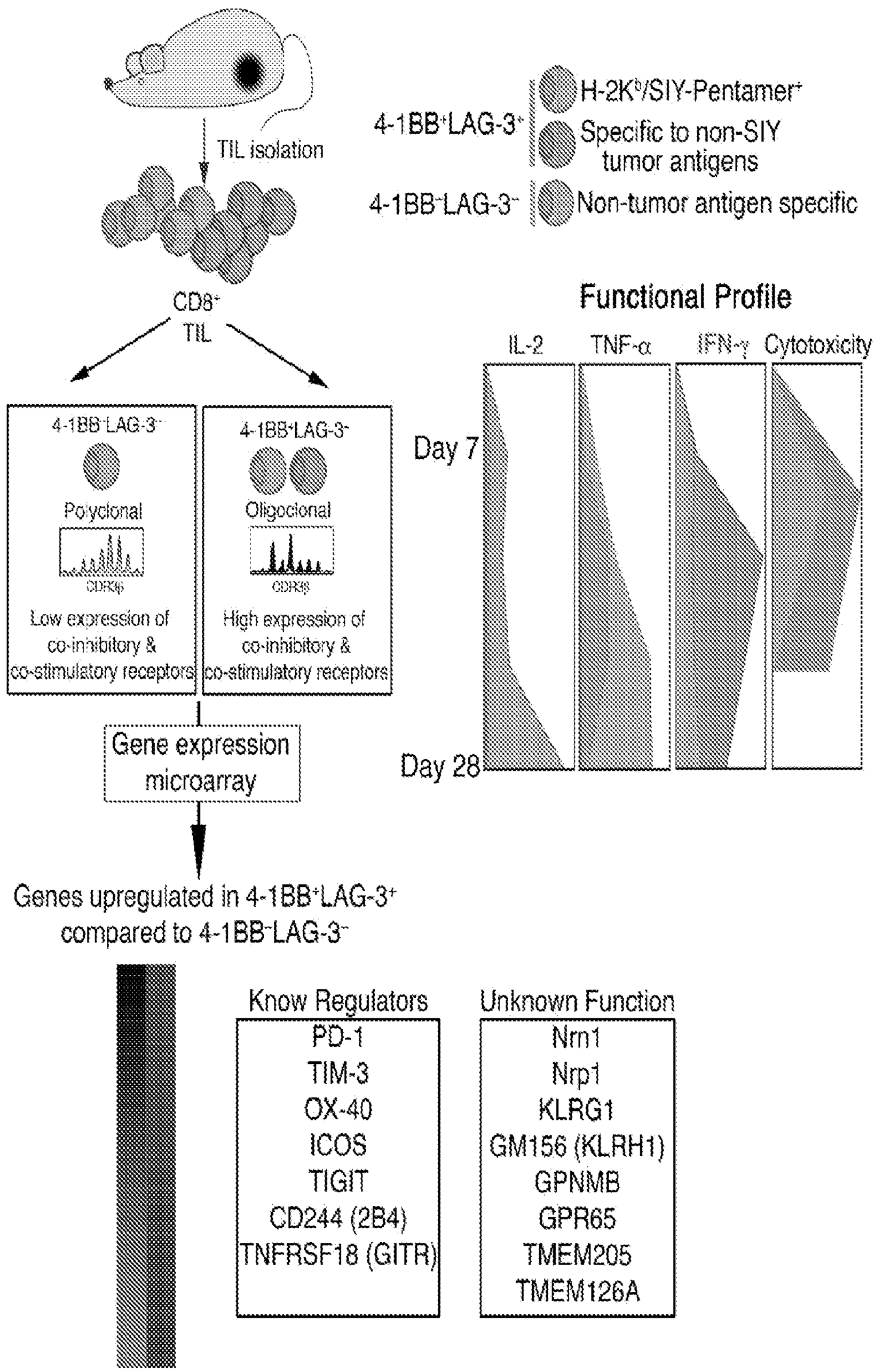
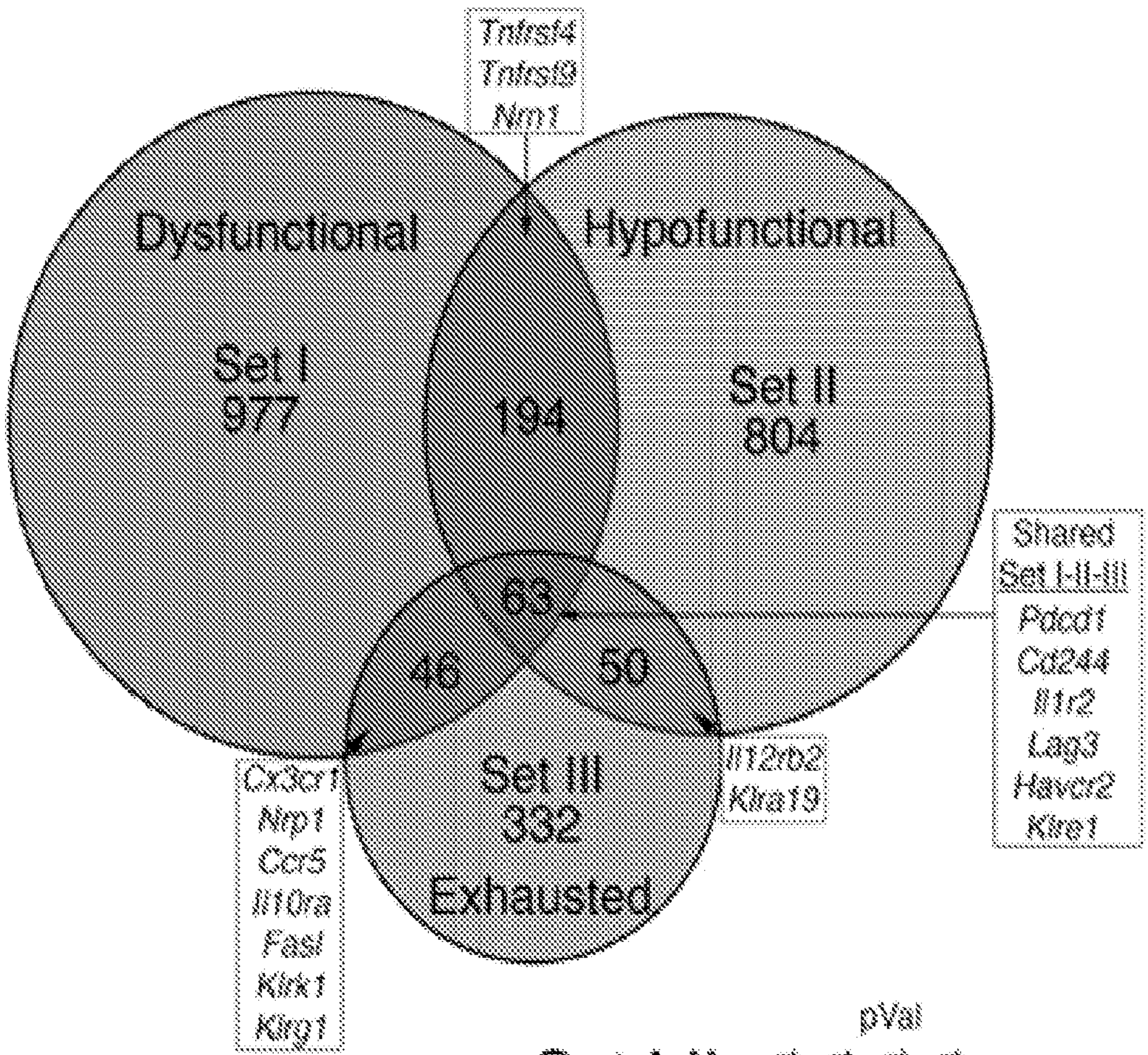

TIL isolation
4-1BB+LAG-3+
H-2Kb/SIY-Pentamer+
Specific to non-SIY tumor antigens
4-1BB-LAG-3-
Non-tumor antigen specific
CD8+ TIL
Functional Profile
IL-2
TNF-α
IFN-γ
Cytotoxicity
Day 7
Day 28
4-1BB-LAG-3-
Polyclonal
CDR3β
Low expression of co-inhibitory & co-stimulatory receptors
4-1BB+LAG-3-
Oligoclonal
CDR3β
High expression of co-inhibitory & co-stimulatory receptors
Gene expression microarray
Genes upregulated in 4-1BB+LAG-3+ compared to 4-1BB-LAG-3-
Know Regulators
PD-1
TIM-3
OX-40
ICOS
TIGIT
CD244 (2B4)
TNFRSF18 (GITR)
Unknown Function
Nrn1
Nrp1
KLRG1
GM156 (KLRH1)
GPNMB
GPR65
TMEM205
TMEM126A

FIG. 6A


Tnfrsf4
Tnfrsf9
Nfil3
Dysfunctional
Hypofunctional
Set I
977
194
Set II
804
63
46
50
Shared
Set I-II-III
Pdcd1
Cd244
Btn2
Lag3
Havcr2
Klrg1
Cx3cr1
Nfp1
Ccr5
Il10ra
Fasl
Klrk1
Klrg1
Set III
332
Exhausted
Il12rb2
Klra19
Set I-II
pVal
mitotic cell cycle
mitotic cell cycle process
cell cycle
mitotic nuclear division
nuclear division
cell cycle process
cell division
DNA conformation change
chromosome segregation
spindle organization
DNA-dependent DNA replication
DNA replication
DNA packaging
DNA metabolic process
nucleoside monophosphate metabolic process
protein localization to chromosome
%Genes