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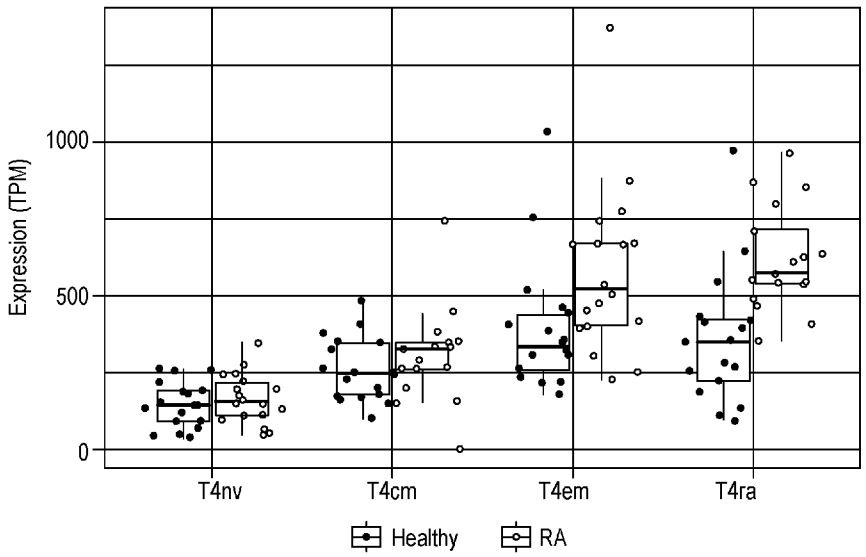


FIG. 1

(57) Abstract: Introduced here are methods of diagnosing, treating, and preventing inflammatory disorders, such as rheumatoid arthritis. The methods comprise receiving biological information from the subject on a memory component comprising computer-executable programs.

[Continued on next page]

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METHODS OF DIAGNOSING AND TREATING RHEUMATOID ARTHRITIS BY IDENTIFYING INFLAMMATORY INITIATORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/612,964, filed on December 20, 2023, the entire contents of which are hereby incorporated by reference it is entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING PROVIDED AS A TEXT FILE

[0002] This application contains an ST.26 compliant Sequence Listing, which is submitted concurrently in xml format via Patent Center and is hereby incorporated by reference in its entirety. The .xml copy, created on December 18, 2024, is named 124824-8129WO01 Sequence Listing.xml and is 5,126 bytes in size.

TECHNICAL FIELD

[0003] Various embodiments concern approaches to diagnose, treat, or determine a prognosis of inflammatory disorders, such as rheumatoid arthritis and inflammatory bowel disease.

BACKGROUND

[0004] Inflammatory disorders, such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), are traditionally treated using therapeutics targeting inflammatory mediators. These "traditional" therapeutics are typically in the modality form of biologics as antibodies or recombinant proteins with inhibitory function. Examples include anti-tumor necrosis factor (TNF) antibodies, anti-interleukin 6 receptor (IL-6R) antibodies, and recombinant interleukin 1 receptor antagonist (IL-1RA) as therapeutic agents targeting TNF, IL-6, and IL-1 proteins, respectively, which have direct inflammatory properties.

[0005] However, traditional therapeutics show benefit for only a subset of autoimmune patients and can often lose effectiveness over time. Because the targets of these therapies are specific mediators of inflammation that lie downstream of initiating and amplifying mechanisms, proinflammatory signaling can still occur. As such,

alternative therapeutics with increased efficacy for the treatment and prevention of inflammatory disorders are needed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 illustrates IL-32 gene expression in effector CD4+ T cell subsets from rheumatoid arthritis (RA) subjects relative to controls.

[0007] FIG. 2 illustrates IL-32 expression in immune cell subsets homozygous for rs4786370 (alternate allele) or heterozygous for rs4786370, relative to controls homozygous for the reference allele. Each dot represents an individual subject. Box plots with mean, interquartile regions, and error bars depict the standard error of the means (SEM).

[0008] FIG. 3 illustrates IL-32 protein levels in plasma samples from subjects having RA (N=18) (right) relative to controls (N=18) (left). Each dot represents an individual subject sample, bar graphs indicate the mean, and error bars depict the SEM.

[0009] FIGS. 4A-4C illustrates supernatant concentration of TNF-α (FIG. 4A), IL-6 (FIG. 4B), and IL-1β (FIG. 4C) in human primary monocyte-derived macrophages following 24-hour stimulation with LPS plus interferon-gamma (single dot), or IL-32**α**, IL-32**β**, IL-32**γ** at various doses.

[0010] FIGS. 5A-5D illustrate effects of *IL-32* knockout on cytokine production by CD4+ T cells. FIGS. 5A and 5B illustrate confirmation of *IL-32* genetic editing in CD4+ T cells. FIGS. 5C and FIG. 5D illustrate TNF-α (FIG. 5C) and IL-6 (FIG. 5D) protein levels in the supernatant of CD4+ cells with IL-32 knockout. Each dot represents an individual subject sample, bar graphs indicate the mean, and error bars depict the SEM. TNF-α (**** $p < 0.001$); IL-6 (** $p < 0.01$).

[0011] FIG. 6 illustrates a mechanistic model of IL-32 involvement as a potential upstream pro-inflammatory amplifying factor and possible points of therapeutic intervention.

[0012] FIG. 7 illustrates a flow diagram for cohort stratification to analyze rheumatoid arthritis (RA) and control (HV) subjects having risk HLAs and PTPN22 variants.

[0013] FIG. 8 illustrates IL-32 expression patterns in immune cell subsets across different cohort types.

[0014] FIG. 9 illustrates IL-32 expression data analysis of immune cell subsets from RA subjects and controls.

[0015] FIGS. 10A and 10B illustrate partial residual plots of IL-32 expression in T cell subsets in RA subjects and controls.

[0016] FIGS. 11A-11C illustrate differentially accessible region (DAR) analysis of immune cell subsets in RA subjects compared to controls.

[0017] FIGS. 12A-12C illustrate analysis of differentially expressed genes (DEGs) with proximal DARS om immune cell subsets in RA subjects compared to controls.

[0018] FIG. 13 illustrates a heatmap of IL-32 transcript isoform expression across immune cell subsets.

[0019] FIGS. 14A and 14B illustrate estimates of IL-32 transcript isoform expression across immune cell subsets in RA subjects compared to controls. FIG. 14C illustrates transcription factor binding prediction for sites proximal to IL-32.

[0020] FIGS. 15A and 15B illustrate IL-32 expression levels between immune cell subsets for major cell types (FIG. 15A) and T cell subtypes (FIG. 15B) in synovial tissue.

[0021] FIGS. 16A-16C illustrate Uniform Manifold Approximation and Projection (UMAP) plots (FIGS. 16A and 16B) and expression analysis (FIG. 16C) of IL-32 in different cell populations of RA synovium (N=4 RA synovial samples).

[0022] FIGS. 17A and 17B illustrate gene detection and mitochondrial read proportion analysis in T cell subtypes.

[0023] FIGS. 18A and 18B illustrate percentage of IL-32 -positive cells across different cell populations for the samples of FIGS. 17A and 17B.

[0024] FIGS. 19A-19F illustrates single-cell analysis of fibroblasts, monocytes, T cells, and B cells in leukocyte-poor RA (N=17), leukocyte-rich RA (N=19), and osteoarthritis (OA) samples.

[0025] FIGS. 20A-20C illustrate expression levels of IL-32, TNF, and IL6 across cell populations of FIGS. 19A-19F. SC-T1: CD4+ CCR7+ T cells; SC-T2: CD4+ FOXP3+ regulatory T cells; SC-T3: CD4+ PDCD1+ T peripheral helper and T follicular

helper; SC-T4: CD8+ GZMK+ T cells; SC-T5: CD8+ GNLY+GZMB+ T cells; SC-T6: CD8+ GZMK+ GZMB+ T cells; SC-B1: naive IGHD+CD27− B cells; SC-F2: HLA-DRAhi sublining fibroblasts).

[0026] FIGS. 21A and 21B illustrate percentage of IL-32 -positive cells across major cell types and cell subsets for the cell populations of FIGS. 19A-19F.

[0027] FIG. 22 illustrates IL-32 expression patterns in T cells from synovial biopsies from RA (N=70), OA (N=9), and repeated RA (N=3) samples.

[0028] FIG. 23 illustrates IL-32 expression patterns in B cells from synovial biopsies from RA (N=70), OA (N=9), and repeated RA (N=3) samples.

[0029] FIG. 24 illustrates IL-32 expression patterns in stromal cells from synovial biopsies from RA (N=70), OA (N=9), and repeated RA (N=3) samples.

[0030] FIGS. 25A-25G illustrate expression levels of various genes across cell populations in OA and RA samples of FIGS. 19A-19F.

[0031] FIGS. 26A-26D illustrate expression levels of additional genes across cell populations in OA and RA samples of FIG. 24; * p values < 0.05, ** p values < 0.01, *** p value < 0.001.

[0032] FIGS. 27A-27F illustrate percentage of IL-32 -positive cells across cell populations in OA and RA samples of FIG. 24; * p values < 0.05, ** p values < 0.01, *** p value < 0.001.

[0033] FIG. 28 illustrates IL-32 expression levels across T cell subtypes for RA and OA samples of FIG. 24.

[0034] FIG. 29 illustrates expression levels of multiple genes across cell types and tissue types in RA Arthrocentesis (RA Athro), OA Arthrocentesis (OA Athro), and RA biopsy samples.

[0035] FIG. 30 illustrates mean IL-32 expression by sample in T cells from OA (N=8) and RA (N=73) subjects.

[0036] FIG. 31. illustrates a correlation heatmap between effect estimate vectors for 15 DEGs comparisons between RA samples and controls.

[0037] FIG. 32 illustrates a correlation heatmap between effect estimate vectors for 15 DEGs comparisons between RA samples and controls, computed on pairwise union of significant genes.

[0038] FIGS. 33A-33C illustrate correlation plots between different DEG comparisons of FIGS. 31 and 32.

[0039] FIGS. 34A and 34B illustrate expression of Triggering Receptor Expressed on Myeloid cells 1 (TREM-1) under different IL-32 conditions.

[0040] FIG. 35 illustrates IL-32 alpha (α), beta (β), and gamma (γ) isoform associations across immune cell subsets in RA subjects.

[0041] FIG. 36 illustrates DARs near IL-32 in different immune cell subsets. Significant peaks are shown in black data point.

[0042] FIG. 37 illustrates motifs from FIG. 36 that match at peaks (positive strand).

[0043] FIG. 38 illustrate transcription factor binding peaks for IL-32 (positive strand).

[0044] FIGS. 39A and 39B illustrate correlation analysis of gene expression across immune cell subsets in RA subjects compared to controls (FIG. 39A) and transcription factor correlations with IL-32 (FIG. 39B) (positive strand).

[0045] FIG. 40 illustrates transcription factor binding predictions for peaks near IL-32.

[0046] FIG. 41 illustrates motifs that match at peaks of FIG. 40.

[0047] FIG. 42 illustrates expression of transcription factors and immune-associated transcripts across different immune cell subsets in RA samples.

[0048] FIG. 43 illustrates transcript and immune cell subset associations within RA subjects compared to controls.

[0049] FIGS. 44A-44D illustrate correlation analysis of gene expression across immune cell populations in RA subjects and controls (FIG. 44A), RA subjects only (FIG. 44B), controls only (FIG. 44C), and in RA subjects compared to controls (FIG. 44D).

[0050] FIG. 45 illustrates transcription factors that correlate with IL-32 differently in RA subjects compared to controls.

[0051] FIGS. 46A-46F illustrate protein level measurements in macrophage-like cells for Myeloid differentiation primary response 88 (MYD88) knockout cells and TIR domain containing adaptor molecule 1 (TICAM1; or TIR-domain-containing adapter-inducing interferon-β (TRIF)) knockout cells compared to wildtype controls when treated with exogenous recombinant IL-32 protein.

[0052] FIG. 47 illustrates TNF protein production in macrophage-like cells following exposure to different IL-32 protein isoforms.

[0053] FIGS. 48A-48E illustrate TNF protein production in macrophage-like cells following exposure to different signaling components.

[0054] FIGS. 49A-49G illustrate toll like receptor (TLR) and interleukin 1 receptor (IL-1R) assessment in the assay of FIGS. 48A-48E.

[0055] FIGS. 50A-50F illustrate cytokine secretion levels from primary CD4+ T cells following IL-32 exposure. Each datapoint represents a mean cytokine expression level from 2 replicates, (n = 5 different donors).

[0056] FIGS. 51A-51F illustrate cytokine secretion levels from proliferating CD4+ T cells following IL-32 exposure. Each datapoint represents a mean cytokine expression level from 2 replicates, (n = 5 different donors).

[0057] FIGS. 52A-52J illustrate cytokine secretion levels from monocytes following IL-32 exposure.

[0058] FIGS 53A-53G illustrate cytokine secretion levels in monocytes and T cells following co-culture with anti-CD3.

[0059] FIGS. 54A-54D illustrate cytokine secretion levels from CD4+ T cells co-cultured with monocytes without anti-CD3 and at increasing amounts of IL-32 exposure.

[0060] Various features of the technology will become more apparent to those skilled in the art from a study of the Detailed Description in conjunction with the drawings. In the drawings, embodiments are illustrated by way of example and not limitation for the purpose of illustration. Those skilled in the art will recognize that alternative embodiments may be employed without departing from the principles of the present disclosure. Accordingly, while specific embodiments are shown in the drawings, the technology is amenable to various modifications.

DETAILED DESCRIPTION

[0061] Traditionally, autoimmune conditions and inflammatory disorders have been treated by targeting inflammatory mediators that lie downstream of initiating and/or amplifying mechanisms. Such treatments include biologic inhibitors of TNF, IL-6, and IL-1. While these treatments may be effective for some subjects, not all subjects prescribed such treatments benefit from their use. For example, some subjects having disease driven by genetic mechanisms (e.g., a single nucleotide polymorphism (SNP) or a haplotype) may not be responsive to any or all of these inhibitors. This is at least partially because these therapies target intermediate steps of an inflammatory signaling pathway. Therefore, proinflammatory signaling upstream of the therapeutic target may still be occurring.

[0062] Inflammatory signaling pathways often possess redundancy or alternative routes, allowing signals to find their way around the disrupted target (e.g., TNF, IL-6, or IL-1). Additionally, compensatory mechanisms may activate, ensuring that the proinflammatory signals still occur, albeit through altered or alternative pathways.

[0063] As such, additional therapeutic approaches for treating or preventing inflammatory disorders are needed.

[0064] Introduced here are approaches to assess inflammatory disorders at the genetic level and treat various conditions by targeting upstream activators or mediators of inflammation. For example, the methods of the present technology may allow more accurate and efficient (e.g., in terms of time and consumption of computational resources) identification of inflammatory disorders and factors associated with disease.

[0065] As further discussed below, the methods could be implemented by a memory component that is either connected to one or more sequencing modules or connected to one or more datastores in sequences or datasets generated by one or more sequencing modules are stored. In operation, an analysis platform may implement the approach through execution of its modules, each of which may be responsible for performing one or more steps to progress the associated methods.

[0066] Embodiments may be described with reference to particular types of clinical conditions, dataset formats, platform architectures, and the like. However, those skilled in the art will recognize that these features are similarly applicable to other types of

clinical conditions, dataset formats, and platform architectures. For example, embodiments may be described in the context of a given disease or disease more generally for the purpose of illustration. However, these embodiments are more generally applicable to clinical conditions unless otherwise specified. The term "condition" may be used to refer to a disease or other anomaly of the body or mind with recognizable, measurable, or describable clinical signs or symptoms. As another example, embodiments may be described in the context of an analysis platform that is responsible for predicting the onset or progression of a disease based on an analysis of health data maintained by a healthcare facility (e.g., in the form of EHRs), insurance facility (e.g., in the form of claims), or another entity. However, the relevant features may be similarly applicable regardless of the source or contents of the health data.

[0067] Moreover, while embodiments may be described in the context of computer-executable instructions, aspects of the technology could be implemented via hardware or firmware instead of, or in addition to, software. For example, the analysis platform may reside on a computer server in the form of a desktop application that is responsible for obtaining, processing, and examining health data to predict the onset or progress of disease in corresponding patients. However, aspects of the platform could alternatively be implemented in hardware or firmware. For example, aspects of the approach described herein may be executed by an application-specific integrated circuit ("ASIC") that is customized to do so. The ASIC could be implemented in a specialized computing device that is provided to the patient, for example, as part of a clinical trial or a treatment regimen.

Terminology

[0068] References in the present disclosure to "an embodiment" or "some embodiments" means that the feature, function, structure, or characteristic being described is included in at least one embodiment. Occurrences of such phrases do not necessarily refer to the same embodiment, nor do they necessarily refer to alternative embodiments that are mutually exclusive of one another.

[0069] The terms "comprise" and "comprising" are to be construed in an inclusive sense rather than an exclusive or exhaustive sense (i.e., in the sense of "including but not limited to").

[0070] The term "based on" is also to be construed in an inclusive sense rather than an exclusive or exhaustive sense. Thus, unless otherwise noted, the term "based on" is intended to mean "based at least in part on."

[0071] The terms "connected," "coupled," and variants thereof are intended to include any connection or coupling between two or more elements, either direct or indirect. The connection or coupling can be physical, logical, or a combination thereof. For example, elements may be electrically or communicatively connected to one another despite not sharing a physical connection.

[0072] The term "module" may refer broadly to software, firmware, hardware, or combinations thereof. Modules are typically functional components that generate one or more outputs based on one or more inputs. A computer program may include or utilize one or more modules. For example, a computer program may utilize multiple modules that are responsible for completing different tasks, or a computer program may utilize a single module that is responsible for completing multiple tasks.

[0073] When used in reference to a list of items, the word "or" is intended to cover all of the following interpretations: any of the items in the list, all of the items in the list, and any combination of items in the list.

[0074] The term "about" means a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by acceptable levels in the art. Typically, such variation may be as much 10% above and below a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length and such variation may be influenced by standard applicable measurement practices. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth.

Overview of the Methods

[0075] Identifying upstream activators and/or mediators of inflammation may bring about more accurate diagnoses or prognoses assessments relative to methods focused on identifying factors downstream of these. Similarly, treating subjects having an inflammatory condition or preventing inflammatory disorders by targeting or inhibiting

upstream activators and/or mediators of inflammation may result in improved therapies that are effective in a greater number of subjects relative to traditional approaches.

[0076] As shown in FIG. 6, there may be a plurality of factors contributing to inflammation that lie upstream of detectable disease markers. Identifying these factors may provide early detection, diagnosis, prevention, or treatment of inflammatory disorders such as IBD and autoimmune disorders (e.g., RA, systemic lupus erythematous (SLE), and Crohn's Disease). The present technology comprises methods of identifying these factors and implementing therapies, diagnostics, or prognostic determination accordingly.

A. Identifying Limitations of Traditional Approach

[0077] A common approach to methods of diagnosing or determining prognosis of inflammatory disorders comprise identifying factors (e.g., biomarkers) which are typically elevated in subjects having established or advanced disease. For example, diagnosing a subject as having RA may comprise evaluating levels of biomarkers (e.g., rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR)), which may not be detectable prior to disease onset nor in the early stages of disease. There may be a plurality of factors upstream of these biomarkers which may indicate the presence of disease with greater efficiency or improve insight into disease prognosis.

B. Motivation

[0078] Consider the general problem of utilizing traditional methods to treat an inflammatory condition or determine a prognosis or diagnose a subject as having an inflammatory condition, such as RA. The resulting methods may provide a later diagnosis or reduced treatment efficacy relative to methods which account for upstream activators and/or mediators of inflammation.

[0079] Consider this problem under the lens of healthcare problems, and in particular health data relating to diagnoses and/or identifying drug targets. In such a scenario, an attempt may be made to predict or identify a disease, yet only a small fraction of detectable factors indicative of inflammation may be observed. This is because traditional methods, while still valuable, are limited in their scope of detection or are downstream of inflammatory initiators.

C. Support for Rationale

[0080] Subjects having inflammatory disorders, such as RA, may comprise features that are indicative of RA prognosis or are useful in methods of diagnosis, which are not accounted for in traditional approaches. Such features may include, genetic variants, haplotypes, and differentially expressed genes and/or protein counterparts thereof, that contribute to inflammatory signaling or act as initiators of inflammation.

i. Identifying Differentially Expressed Genes in RA Subjects

[0081] To identify differentially expressed genes in RA 18 matched control subjects were compared to 19 RA subjects using RNA-seq expression data and human leukocyte antigen (HLA) haplotype identification methods. Genetic risk alleles included the Major Histocompatibility Complex, Class II, DR Beta 1 (HLA-DRB1) autoimmune risk haplotype cluster and a known SNP autoimmune risk variant (rs2476601) within the PTPN22 gene coding region (National Center for Biotechnology Information (NCBI) Gene ID: 26191). The HLA-DRB1 risk haplotype cluster included the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02. Other SNP variants that may be assessed in replacement of or in addition to rs2476601 include rs4786370, rs9788910, and rs55699988.

[0082] IL-32 (NCBI gene ID: 9235) was identified as differentially expressed between control and RA subjects from the described risk allele screen in CD4+ T effector memory (T4em) and CD4+ T CD45RA+ effector memory (T4ra) cell subsets (FIG. 1). IL-32 mRNA expression in RA patient CD4+ T cells increases relative to control expression upon advancing effector stage differentiation, from naive (T4nv), to central memory (T4cm), to T4em and T4ra.

[0083] IL-32 expression was determined in immune cell subsets (Table I) in subjects having the rs4786370 SNP risk allele. Expression was compared between subjects homozygous for the reference allele (TT), heterozygous (CT), or homozygous for the risk allele (CC) (FIG. 2). This demonstrated that the rs4786370 SNP in the IL-32 promoter increases IL-32 expression across multiple immune cell subsets in cells heterozygous and homozygous for the risk allele, relative to cells homozygous for the reference allele.

Myeloid	Dendritic Cells	coDC	Conventional DCs
		pIDC	Plasmacytoid DCs
	Monocytes	MoCl	Classical Monocytes
		MoIn	Intermediate Monocytes
		MoNC	Nonclassical Monocytes
T Cells	$CD4^+$ αβ T Cells	T4nv	Naïve $CD4^+$ T cells
		T4cm	Central Memory $CD4^+$ T cells
		T4em	Effector Memory $CD4^+$ T cells
		T4ra	$CD45RA^+$ Effector memory $CD4^+$ T cells
		Treg	$CD4^+$ T Regulatory cells
	$CD8^+$ αβ T Cells	T8nv	Naïve $CD8^+$ T cells
		T8cm	Central Memory $CD8^+$ T cells
		T8em	Effector Memory $CD8^+$ T cells
		T8ra	$CD45RA^+$ Effector memory $CD8^+$ T cells
	γδ T Cells	gaT	Gamma-delta T cells
NK	NK Cells	NKhi	$CD56^{hi}$ NK cells
		NKlo	$CD56^{low}$ NK cells
B Cells	Naïve B Cells	BnUS	Unswitched Naïve B cells
		BnCS	Class Switched Naïve B cells
		traB	Transitional B cells
	Effector B Cells	cMBc	Class Switched Classical Memory B cells
		MBim	IgM^+ IgD^- Classical Memory B cells
		aMBc	Atypical Memory B cells
		pBcs	Class Switched Plasmablast

Table I: Immune Cell Subsets

[0084] Plasma samples from control subjects (N=18) and RA subjects having rs2476601 PTPN22 SNP and the HLA-DRB1 risk haplotype cluster were then assessed for IL-32 protein levels by ELISA. RA subjects having these genetic risk determinants had increased IL-32 plasma levels relative to control subjects. These data suggest that

s2476601 PTPN22 SNP and the HLA-DRB1 risk haplotype cluster may increase IL-32 gene expression and/or IL-32 protein levels in immune cells, which may contribute to RA manifestation.

ii. Identifying Upstream Inflammatory Mediators and Activators

[0085] To identify whether IL-32 acts as an activator of inflammation, human primary monocyte-derived macrophages (derived from donors that do not have RA) were stimulated for 24 hours with LPS plus interferon-gamma (single dot), or IL-32 alpha (α) (FIG. 4A), beta (β) (FIG. 4B), or gamma (γ) (FIG. 4C) isoforms at indicated doses (multiple point curves). Supernatants were collected and Luminex multiplex cytokine assay used to measure levels of TNF-α (NCBI Accession: CAA78745.1), Interleukin-6 (IL-6) (NCBI Accession: P05231.1), and Interleukin-1beta (IL-1β) protein levels.

[0086] This demonstrated that IL-32 β and γ isoforms, but not α, may act as activators of the proinflammatory cytokines, TNF-α, IL-6, and IL-1β (NCBI Accession: P01584.2), and signaling downstream of these cytokines (e.g., Nuclear Factor-kappa B signaling, apoptotic signaling, endothelial activation, immune cell activation, acute phase protein activation, and cellular proliferation).

[0087] IL-32 β and γ isoforms, but not α, have a shared exon 8 domain amino acid sequence (SEQ ID NO: 1, VMRWFQAMLQRLQTWWHGVLAWVKEKVVALVHAVQALWKQFQSFCCSLSELFMS SFQ). This suggests that isoforms comprising an exon 8 domain may have increased inflammatory signaling relative to isoforms lacking an exon 8 domain.

[0088] In some embodiments, the exon 8 domain comprises an amino acid sequence that is about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0089] In some embodiments, the exon 8 domain comprises an amino acid sequence that is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0090] In some embodiments, the exon 8 domain comprises an amino acid sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1. Therefore, targeting Exon 8 or isoforms having Exon 8 may be a potential method of reducing inflammatory signaling.

[0091] To determine whether these proinflammatory cytokines are generated in the absence of IL-32, cells from non-Treg CD4+ T cells (Tresp) from 7 control individuals were deleted of IL-32 using CRISPR-Cas9 gene editing to generate IL-32 knockout (KO) cells (FIG. 5A). IL-32 KO was verified by amplicon sequencing and comparing IL-32 protein levels in wildtype (WT) and KO Tresp lysates measured by ELISA (FIG. 5B).

[0092] Tresp IL-32 WT and IL-32 KO cells were next stimulated in culture using beads coated with activating anti-CD3 and anti-CD28 antibodies for 7 days. Supernatants were collected, and TNF-α and IL-6 levels were measured. Both TNF-α and IL-6 were reduced in the supernatant of IL-32 KO cells relative to IL-32 WT cells, as measured by ELISA and/or multiplex cytokine analysis.

iii. Identifying Genes and Genomic Regions Associated with IL-32 Expression

[0093] To identify potential genes implicated in the IL-32 pathway, ribonucleic acid sequencing (RNA-seq) was performed on IL-32 WT Tresp cells and IL-32 KO Tresp cells (N=7 per group). Differentially expressed genes (DEGs) between IL-32 KO and IL-32 WT samples were analyzed, funneled on false discovery rate (FDR) ≤ 0.05, and the top 40 DEGs downregulated in expression listed as displayed in Table II with log2 fold change (log2FC) between KO versus WT. Forty exemplary genes having significantly reduced expression with IL-32 inhibition are shown in Table II. This suggests that these genes may be potential proinflammatory mediators and may be targets of therapeutic intervention in inflammatory disease.

Gene	NCBI Gene ID	False Discovery Rate	log2FC
ABCA4	24	0.000825510187	-4.871721684
HSPA6	3310	0.006752262609	-4.190654322
HSPA1B	3304	0.003193535742	-3.686104728
ARC	23237	0.008376888321	-3.669127365
CRYAB	1410	0.01448080839	-3.53951828
SNAI1	6615	0.006299875473	-3.440258892
BIVM-ERCC5	100533467	0.006761680694	-3.370667688
HSPA1A	3303	0.002921958553	-3.259988778
WFDC5	149708	0.006076488589	-3.204384727
RASD1	51655	0.005782504983	-3.129884416

TREM1	54210	0.003723277439	-2.994567943
DNAJB1	3337	0.003193535742	-2.838655366
SERPINA1	5265	0.0006661647279	-2.83277766
WNT10A	80326	0.002698140551	-2.648409793
PLAC1	10761	0.007566613331	-2.540326152
IL17F	112744	0.003723277439	-2.295609439
RHOV	171177	0.005341942081	-2.202077557
SERPINH1	871	0.008913151508	-2.169642869
ANKRD20A1	84210	0.00450943085	-2.165451078
ADM	133	0.01711083209	-2.100783167
IL1R2	7850	0.001217501867	-2.069846919
ODF1	4956	0.003470991052	-2.027254811
ABCA1	19	0.003193535742	-2.015333444
ZNF662	389114	0.0066719063	-2.014367575
NIPAL1	152519	0.009823689576	-2.011506938
GYS2	2998	0.01118184531	-1.999412569
HEY1	23462	0.008957504392	-1.99929719
MMP16	4325	0.006608993057	-1.989477107
CA9	768	0.01295766137	-1.98071339
TICAM2	353376	0.003470991052	-1.955333238
SCGB2A2	4250	0.008787632583	-1.934632458
OSMR	9180	0.01550061414	-1.930990606
TMPRSS6	164656	0.0006661647279	-1.922739425
CD19	930	0.01253890421	-1.908779119
CA12	771	0.01100992324	-1.894619253
EPHA4	2043	0.009789369947	-1.894459582
CAV1	857	0.01115846703	-1.883680293
RYR1	6261	0.005668333012	-1.882902959
CCDC121	79635	0.01547443957	-1.872168788
ZNF177	7730	0.02450423889	-1.862867893

Table II: Genes Downregulated Under IL-32 Knockout

[0094] Genomic DNA (gDNA) was next extracted from these IL-32 KO Tresp cells and IL-32 WT Tresp cells. Extracted gDNA was subjected to assay for transposase-accessible chromatin with sequencing (ATAC-seq). Differentially accessible regions (DARs) between these IL-32 KO Tresp cells and IL-32 WT Tresp cells were analyzed, funneled on false discovery rate (FDR) ≤ 0.05 and location within 1kb of the transcriptional start site of a protein coding gene (Table III) or within 300 kb of a protein coding gene (Table IV), and either downregulated or upregulated in accessibility listed as displayed in Table III and Table IV with log2 fold change (log2FC) between IL-32 KO Tresp cells versus IL-32 WT Tresp cells. This indicates that these DARs and DEGs associated with IL-32 expression may be targeted as potential inflammatory mediators.

Genomic Location	Nearest Gene	NCBI Gene ID	False Discovery Rate	log2FC
chr6:2081648	VTI1B	10490	0.0003535696201	-1.306922082
chr19:7903694	HSPA6	3310	0.01803578608	-1.287194656
chr1:1659135	GZMH	2999	0.01314670404	-1.19410325
chr22:19191659	PGK1	5230	0.003983144788	-1.112015455
chr19:1103988	MLKL	197259	0.002812517733	-1.106412571
chr15:73911376	UBL4A	8266	0.02654032187	-1.093572932
chr19:3763010	ADCY3	109	0.03377694109	-1.065678334
chr19:4007553	SUCLA2	8803	0.04365621923	-1.060836412
chr12:66777146	ITPKA	3706	0.0009209975179	-1.053583606
chr20:297491	ENKUR	219670	0.01460368263	-1.048344153
chr22:29767375	BTN2A2	10385	0.0320148726	-1.042107376
chr17:81860935	SLC35G2	80723	0.001649726348	-1.039074885
chr16:85055590	SLCO2B1	11309	0.008528012021	-1.030289375
chr2:10448460	SLC22A31	146429	0.01398758301	-1.024792618
chr6:33410565	CTNNAL1	8727	0.04407806043	-1.023993447
chr11:62841552	SCNN1G	6340	0.01869730743	-1.015093842
chr5:170278748	SLC50A1	55974	0.01121476095	-0.994104075
chr13:18212058	DERA	51071	0.01357326309	-0.9837231564
chr5:49661047	C12orf10	60314	0.0142255501	-0.9697074357
chr5:49659887	CD7	924	0.04803322751	-0.9594988727
chr5:49666220	LRGUK	136332	0.03607344257	-0.9564191891

chr5:49601602	SMAD7	4092	0.02648437235	-0.9507099044
chr5:49657754	AMPD3	272	0.001989364267	-0.944332429
chr5:49658685	ZNF703	80139	0.01836227998	-0.9250125923
chr9:70038358	DNASE1L3	1776	0.04407806043	-0.9148880049
chr10:110353643	VNN2	8875	0.04724439685	-0.9143761491
chr11:59171635	SLC9A5	6553	0.03949288521	-0.8986276703
chr20:51531313	TNPO3	23534	0.03531709643	-0.885811249
chr5:49659528	AGAP3	116988	0.04803322751	-0.872012131
chr1:36373975	POLR2H	5437	0.01836227998	-0.8599156582
chr5:49666568	PTPN18	26469	0.01158605779	-0.8492615854
chr5:151087206	TAP1	6890	0.02537289866	-0.8490401533
chr11:10308140	ZBTB43	23099	0.009181937098	-0.846986064
chr10:69066034	PTP4A3	11156	0.03214821436	-0.8274169767
chr6:2988683	GRK6	2870	0.03271091476	-0.8252893998
chr15:90869921	ST6GALNAC3	256435	0.01467342518	-0.8232838035
chr22:37303988	ARL14EP	120534	0.0009685786315	-0.8214019817
chr20:31186558	PM20D2	135293	0.02584525924	-0.8186568135
chr3:122576370	IQUB	154865	0.004156150386	-0.7973253481
chr17:47721383	TRAF2	7186	0.04724439685	-0.7861647337
chr1:163321837	PRKCDBP	112464	0.03619660107	-0.7643846036
chr2:43596105	CDHR2	54825	0.02522851173	-0.7492502401
chr4:77158342	GIPR	2696	0.009778577979	-0.7489097658
chr19:45667851	THADA	63892	0.01325364537	-0.7399901456
chr5:176541645	RGS5	8490	0.005310766952	-0.7363801301
chr1:209884875	NQO2	4835	0.01467342518	-0.7114226258
chr7:139682631	AMPD3	272	0.01940229189	-0.6965520669
chr11:6320551	DTX4	23220	0.03377694109	-0.6464813064
chr13:18212441	WDR74	54663	0.02677471812	0.5852850491
chr15:52559756	PHF1	5252	0.03535793458	0.6723125764
chr14:54565271	ODC1	4953	0.04407806043	0.7458880417
chr16:67174325	P4HB	5034	0.005310766952	0.8752456833

chr6:125919191	UQCR10	29796	0.01314670404	0.9481187454
chr9:136882694	ZCCHC3	85364	0.04892963735	1.022225298
chr7:92642038	PIAS4	51588	0.0267677123	1.046207947
chr1:43582382	MRPL54	116541	0.03927590589	1.051568984
chr7:123534742	GPX4	2879	0.003983144788	1.17740535
chr3:112002639	CDK11B	984	0.01936365737	1.284677367
chr2:157261204	MAP2K7	5609	0.006566682109	1.31484476

Table III: Differentially Accessible Regions (DARs) Associated with Inhibition of IL-32 Expression

DEG/DAR Gene Nae	**NCBI Gene ID**	**False Discovery Rate (RNA-seq)**	**log2FC (RNA-seq)**
HSPA6	3310	0.006752262609	-4.190654322
CPM	1368	0.004032350897	-1.287918818
GZMH	2999	0.01914334578	-1.220672191
ARRDC3	57561	0.01531827287	-1.161255123
PTPRF	5792	0.01950256522	-1.148181665
AMPD3	272	0.002444438149	-1.123373935
CCNG2	901	0.01190368343	-1.112604394
FGF12	2257	0.007515176953	-1.070716803
ST6GALNAC3	256435	0.02325097129	-1.047895142
TRIM2	23321	0.01380801185	-0.9938791589
NOL3	8996	0.03083025159	-0.9450185269
SMAD7	4092	0.01004986134	-0.9046937276
SERINC5	256987	0.005341942081	-0.8373511214
CD28	940	0.007891415093	-0.779239012
ZBTB43	23099	0.007566613331	-0.7678241445
PM20D2	135293	0.027162814	-0.7456767438
NOD2	64127	0.006165326471	-0.7168802264
AHNAK	79026	0.004789454983	-0.6980538881
BTN2A2	10385	0.01535645736	-0.6735375008
PLTP	5360	0.007549778469	-0.6704718818

TBX21	30009	0.03140492425	-0.5764786258
ZCCHC6	ZCCHC6	0.01627632981	-0.5274576406
HINT3	135114	0.01598885351	-0.5252529515
SLC35G2	80723	0.02340032637	-0.4943745301
MDFIC	29969	0.008488442887	-0.468508482
PHF1	5252	0.03433337636	-0.4602848309
SYNE3	161176	0.04327435208	-0.4545456725
TNIP1	10318	0.01090647266	-0.4500642017
TNFRSF1A	7132	0.01950256522	-0.4070044731
KCMF1	56888	0.01796122192	-0.3792944252
MSL3	10943	0.02325187301	-0.3529892298

Table IV: Downregulated Differentially Expressed Genes that are also DAR Proximal Genes Associated with Inhibition of IL-32 Expression

iv. Identifying Proteins Associated with IL-32 Expression

[0095] To identify potential proteins implicated in the IL-32 pathway, RNA-seq was performed on IL-32 WT Tresp cells and IL-32 KO Tresp cells (N=7 per group). Surface protein expression was measured from these IL-32 WT Tresp cells and IL-32 KO Tresp cells using Targeted Protein Estimation by sequencing (TaPE-seq), a technique using antibodies tagged with oligo barcodes followed by sequencing. Differentially expressed proteins (DEPs) between KO and WT samples were analyzed, funneled on false discovery rate (FDR) ≤ 0.05, and DEPs downregulated in expression listed as displayed in Table V with log2 fold change (log2FC) between KO versus WT. This indicates that these DEPs associated with IL-32 expression may be targeted as potential inflammatory mediators.

Protein	**NCBI Accession(s)**	**False Discovery Rate**	**log2FC**
HLAABC	--	0.02917528021	-0.327874478
CD6	NP_006716.3	0.0424273949	-0.3257930345
CD155	P15151.2	0.0424273949	-0.1575892628
CD60a	--	0.0024152313	-0.1551393923
CD31	NP_000433.4; AAA36186.1	0.02599855847	-0.1473123703

CD279	AAH74740.1	0.02599855847	-0.1203279322
CD30	P28908.1	0.02599855847	-0.08698033023
CD98	P08195.3	0.02917528021	-0.08672580515

Table V: Differentially Expressed Proteins Associated with Inhibition of IL-32 Expression

v. IL-32 Expression Cohort Analysis

[0096] To assess IL-32 expression patterns among RA cohorts, cohorts were stratified for reanalysis according to FIG. 7 and Table VI.

Cohort variable	Comparison
cohort_ra_vs_h	RA with genetic determinants (N=20) vs all controls (N=HV) (35)
cohort_ra_vs_m	RA with genetic determinants (N=20) vs. matched controls (HV) (N=19)
cohort_hla_ra_vs_h	RA with risk HLA alleles (N=16) vs Controls (HV) with risk HLA alleles (N=10)

Table VI. Cohort Stratification Groups

[0097] IL-32 expression was assessed among cohorts for different immune cell subsets and cell types, revealing that IL-32 is a differentially expressed gene (DEG) in T Helper 4 Regulatory Cells (T4ra) and T Helper 4 Effector Memory Cells (T4em) (FIGS. 8-10B) in RA subjects, relative to controls.

[0098] Differentially accessible regions (DARs) potentially associated with IL-32 expression were also assessed in the subjects of FIGS. 8-10B for different immune cell subsets (FIGS. 11A-11C and 36). This analysis revealed one DEG having proximal DARs (DEG: LMO4 (NCBI Accession: NP_006760.1); DARs: chr1:87335016, chr1:87404491) (FIGS. 12A-12C). Assessment of the top 1000 DAR motif peaks in RA and controls identified motif enrichment for NFKB2 (NCBI Accession(s): Q00653.4; NP_001309863.1; NP_001275653.1), FOSL1 (NCBI Accession(s): CAG47053.1; NP_001287786.1; NP_001287785.1; NP_001287784.1; NP_001287773.1; NP_005429.1), JDP2 (JUNDM2) (NCBI Accession(s): NP_001128520.1; NP_001128521.1), and CTCF (NCBI Accession(s): NP_001350845.1; NP_006556.1; NP_001177951.1)(Table VII) (FIG. 37).

Top 1000 peaks in RA and top 1000 peaks in HV													
	soPB	MoCl	MoIn	MoNC	coDC	pIDC	BnUS	BnCS	traB	MBim	cMBc	aMBc	pBcs
NFKB2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0
FOSL1	0.9	0.0	1.2	0.0	0.1	0.0	-2.3	-0.7	-1.5	0.0	-0.4	-1.6	0.1
JUN_2	0.7	0.0	0.9	0.0	0.0	0.0	-2.0	-0.8	-1.0	0.0	-0.4	-1.8	0.1
CTCF	0.0	-0.6	-1.5	0.0	-0.9	0.0	0.0	0.0	-0.1	0.0	0.0	0.0	0.0
Top 1000 peaks in RA and top 1000 peaks in HV *(continued)*													
	Treg	T4nv	T4cm	T4em	T4ra	T8nv	T8cm	T8em	T8ra	gadT	NKhi	NKlo	
NFKB2	0.0	3.3	3.0	0.0	3.4	0.0	0.0	0.9	0.0	2.2	0.0	0.0	
FOSL1	1.2	2.6	1.0	0.3	1.0	0.1	0.8	1.1	2.5	0.8	1.0	1.8	
JUN_2	-0.9	-2.6	-0.9	-0.1	-0.0	0.0	-0.5	-0.9	-2.4	-0.8	-0.7	-1.7	
CTCF	0.2	0.5	0.7	0.0	-0.8	0.0	0.0	0.0	-0.9	0.0	0.0	0.0	
Top 1000 proximal peaks in RA and top 1000 proximal peaks in HV													
	soPB	MoCl	MoIn	MoNC	coDC	pIDC	BnUS	BnCS	traB	MBim	cMBc	aMBc	pBcs
NFKB2	-0.4	-0.3	0.0	0.0	0.0	0.0	0.6	0.0	0.3	0.5	0.7	1.7	0.0
CTCF	0.0	-0.3	-1.4	0.0	-0.9	0.0	0.0	0.0	-0.3	0.0	0.0	-0.2	0.0
FOSL1	0.9	0.0	1.4	0.0	0.3	0.0	-1.8	-0.7	-1.0	0.0	-0.3	-1.4	0.0
JUN_2	0.3	0.0	1.6	0.0	0.0	0.0	-1.5	-1.0	-1.1	0.0	-0.3	-1.3	0.0
Top 1000 proximal peaks in RA and top 1000 proximal peaks in HV *(continued)*													
	Treg	T4nv	T4cm	T4em	T4ra	T8nv	T8cm	T8em	T8ra	gadT	NKhi	NKlo	
NFKB2	0.0	1.8	1.5	0.0	2.2	0.0	0.0	0.2	0.1	0.3	0.3	0.3	
CTCF	0.0	0.3	0.0	-0.7	-1.0	0.0	0.0	-1.1	-1.0	0.0	0.1	0.0	
FOSL1	-1.5	-1.8	-0.9	-0.7	-0.4	-0.3	0.0	-0.2	-2.0	-1.3	-0.7	-1.8	
JUN_2	-0.6	-2.1	-0.8	-0.5	-0.8	0.0	-0.2	-0.1	-1.4	-1.2	-0.8	-1.6	

Table VII: Motif Enrichment

[0099] IL-32 transcript isoforms were next assessed between RA subjects and controls (FIGS. 13 and 35). Estimates of IL-32 transcript isoform expression were generated for immune cell subsets in RA subjects compared to controls (FIGS. 14A and 14B). An offset of 0.01 was added to transcripts per million (TPM) values before determining log values.

[0100] Transcription factor binding prediction for sites proximal to IL-32 were next assessed (FIGS. 14C and 38). Transcription factor binding predictions were generated by collecting IL-32 proximal peaks. For each peak, an Assay for Transposase-Accessible Chromatin (ATAC) profile for RA and control subjects were generated. Transcription factor binding predictions for both ATAC profiles (RA and controls) for all motifs that had a good match score at the peak were made. Peaks having no motifs

with a good match score were not assessed for binding predictions. Peaks having multiple motifs with a good match score were considered as being bound to a transcription factor if any of the transcription factor was predicted to be bound. Peaks predicted to be bound in one group (i.e., RA vs. controls) and not bound in another were assessed. Correlation analysis of gene expression across immune cell subsets in RA subjects compared to controls and transcription factor correlations were also assessed on the positive strand (FIGS. 39A-42).

[0101] These analyses revealed that CD8 T cell related transcription factors may bind to IL-32 promoters or regions associated with increasing IL-32 expression, such as IRF4 (NCBI Accession(s): NP_002451.2; NP_001182215.1) and BRD4 (NCBI Accession: AAH35266.1). CTCF, CTCFL (NCBI Accession: Q8NI51.2), and NFYB (NCBI Accession: P25208.2) were shown to have good match scores with peaks that showed differential binding prediction and expression in T subsets and immune cell subtypes (FIGS. 43-45). No transcription factors having good match scores at peaks with differential binding had different expression between RA and control subjects. FOSL1 and JDP2 were also seen to be depleted in Natural Killer Cells with Low Marker Expression Cells (NKlo) and CD8+ Regulatory T Cells (T8ra) in the top 1000 most accessible peaks in RA compared to top 1000 peaks in controls. CTCF appeared depleted in T4ra and T8ra. NFYB expression was not different between RA and control subjects, and NFYB negatively correlated with IL-32 in High Marker Expression Cells (NKhi). CTCFL had low expression in both RA and controls, and was negatively associated with IL-32 in T8ra and Treg. FOSL1 trending to be upregulated in RA in Transitional B Cells (traB), Plasmacytoid Dendritic Cells (pIDC), and Conventional Dendritic Cells (coDC).

vii. IL-32 Expression Between Immune Cell Subtypes

[0102] To further assess IL-32 expression levels between different immune cell subset types, the expression of IL-32 in various immune cell subtypes within synovial tissue samples from patients with rheumatoid arthritis (RA) and osteoarthritis (OA) using publicly available single cell sequencing datasets was assessed Data were sourced from three studies: "Distinct stromal and immune cell interactions shape the pathogenesis of rheumatoid and psoriatic arthritis" (GEO200815), "Fibroblast growth factor receptor 1 as a potential marker of terminal effector peripheral T helper cells in

rheumatoid arthritis patients" (GEO216245), and "Granzyme K+ CD8 T cells form a core population in inflamed human tissue" (GSE202375). Initial cell type annotation was performed using scType, identifying 34 immune system populations, but further refinement with clustering and marker-based approaches was necessary due to scType's limitations with synovial tissue data. The analysis focused on comparing IL-32 expression between T4em/T4ra (effector memory and regulatory T cells) and other T cell subtypes, as well as between T4em/T4ra and other immune cell types (e.g., B cells) within RA samples. Additionally, IL-32 expression was compared between RA and OA samples, and between ACPA- and ACPA+ RA samples if data became available. GEO200815, GEO216245, and GSE202375 were used for analysis, each study incorporated herein by reference in their entireties. The expected outcomes included determining the differential expression of IL-32 in T4em/T4ra cells compared to other T cell subtypes and immune cell types within RA samples, identifying differences in IL-32 expression between RA and osteoarthritis (OA) samples, and highlighting the need for additional data to compare IL-32 expression between ACPA- and ACPA+ RA samples. This study aimed to elucidate the role of IL-32 in the pathogenesis of RA, contributing to a better understanding of the molecular mechanisms underlying RA and potentially identifying new therapeutic targets.

[0103] In RA synovial tissues (N=4), single RNA-seq identified IL-32 expression levels between immune cell subsets for major cell types (FIG. 15A) and T cell subtypes (FIG. 15B). Uniform Manifold Approximation and Projection (UMAP) plots (FIGS. 16A and 16B) and expression analysis (FIG. 16C) of IL-32 in different cell populations of RA synovium (N=4 RA synovial samples; >43,000 cells) were further analyzed using Study #2. As a quality control, gene detection and mitochondrial read proportion analysis in T cell subtypes for the samples of GEO200815 were assessed (FIGS. 16A-16C). Only 1-cells of the T cell subsets had >2,000 genes detected. The median number of genes detected per T cell subtype was approximately 444 genes. The median amount of mitochondrial contamination was about 13% across all T cell subtypes. Gene detection and mitochondrial read proportion analysis in T cell subtypes were assessed using data disclosed in Floudas A, Smith CM, Tynan O, et al Distinct stromal and immune cell interactions shape the pathogenesis of rheumatoid and psoriatic arthritis Annals of the Rheumatic Diseases 2022;81:1224-1242, incorporated herein by reference in its entirety (FIGS. 17A and 17B). Any cells with a mitochondrial read proportion of greater

than 25% of the total reads was removed. The percentage of IL-32 -positive cells across each cell population was then identified (FIGS. 18A and 18B).

[0104] Single cell sequencing datasets from AMP phase I (synovial tissue samples) were analyzed. Samples comprised those described in Zhang F., et al, Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. Nat Immunol. 2019 Jul;20(7):928-942. doi: 10.1038/s41590-019-0378-1; epub 2019 May 6, the entire contents of which are incorporated herein by reference in their entireties. Analysis comprised fibroblasts, monocytes, T cells, and B cells in leukocyte-poor RA (N=17), leukocyte-rich RA (N=19), and osteoarthritis (OA) samples. 18 cell clusters were identified. IL-32, TNF, and IL6 expression levels across cell populations of these samples were assessed (FIGS. 20A-20C) and percentage of IL-32 -positive cells across major cell types and cell subsets were identified (FIG. 21A and 21B).

[0105] Next, IL-32 expression patterns in T cells from synovial biopsies (FIGS 22-30) from RA (N=70), OA (N=9), and repeated RA (N=3) samples were identified from the samples disclosed in Zhang, F., Jonsson, A.H., Nathan, A. et al. Deconstruction of rheumatoid arthritis synovium defines inflammatory subtypes. Nature 623, 616–624 (2023), the disclosure of which is incorporated herein by reference in its entirety.

[0106] This analysis revealed that in synovial tissue, IL-32 was dominantly expressed in T cells. Within T cells, IL-32 was highly expressed in Memory (CD4+ and CD8+) cells and cytotoxic CD8+ cells. There was no significant difference between RA and OA for IL-32 expression level.

viii. IL-32 Pathway Analysis

[0107] Pathway analysis was conducted on IL-32 knockout cells. DEGs, upregulated genes, and downregulated genes were conducted in IL-32 knockout cells, relative to controls. 142 total pathways were identified as having DEG enrichment in IL-32 knockout cells, with Gene Ontology pathways having the highest odds ratio including
HP_CONCENTRIC_HYPERTROPHIC_CARDIOMYOPATHY;
HP_RECURRENT_PANCREATITIS;
MODULE_101;
GO_REGULATION_OF_LYMPHOID_PROGENITOR_CELL_DIFFERENTIATION;

HP_MULTIPLE_GLOMERULAR_CYSTS;
MODULE_132;
HP_ABNORMAL_CIRCULATING_ARGININE_CONCENTRATION;
GO_VENOUS_BLOOD_VESSEL_MORPHOGENESIS;
GO_REGULATION_OF_GLYCOGEN_CATABOLIC_PROCESS;
GO_REGULATION_OF_CARDIAC_MUSCLE_CELL_ACTION_POTENTIAL_INVOLVED_IN_REG;
GO_ENERGY_COUPLED_PROTON_TRANSMEMBRANE_TRANSPORT_AGAINST_ELECTROCH;
GO_CHONDROCYTE_DEVELOPMENT_INVOLVED_IN_ENDOCHONDRAL_BONE_MORPHOGI; and
GO_BONE_MINERALIZATION_INVOLVED_IN_BONE_MATURATION.

[0108] Labeling of upregulated pathways in IL-32 knockout cells included Gene Ontology pathways having a DEG enrichment of log2(fold change) > 1 in a given pathways. This revealed 154 significant pathways, those having the highest odds ratio including
GO_POSITIVE_REGULATION_OF_NATURAL_KILLER_CELL_CHEMOTAXIS,
GO_MHC_CLASS_II_PROTEIN_COMPLEX,
REACTOME_DISEASES_ASSOCIATED_WITH_SURFACTANT_METABOLISM,
GO_EOSINOPHIL_CHEMOTAXIS,
FUNG_IL2_TARGETS_WITH_STATS_BINDING_SITES_T1,
GO_REGULATION_OF_NATURAL_KILLER_CELL_CHEMOTAXIS,
GO_OXYGEN_BINDING,
DEBOSSCHER_NFKB_TARGETS_REPRESSED_BY_GLUCOCORTICOIDS,
GO_CCR_CHEMOKINE_RECEPTOR_BINDING, and
GO_MHC_CLASS_I_BIOSYNTHETIC_PROCESS.

[0109] Labeling of downregulated pathways in IL-32 knockout cells included identifying Gene Ontology pathways having a DEG enrichment with log2(fold change) < -1, which revealed 328 significant pathways. Pathways having the highest odds ratio included GO_NEGATIVE_REGULATION_OF_INCLUSION_BODY_ASSEMBLY,
GO_CELL_MIGRATION_INVOLVED_IN_KIDNEY_DEVELOPMENT,
GO_AUTOCRINE_SIGNALING,
FAN_EMBRYONIC_CTX_IN_6_INTERNEURON,

ELVIDGE_HIFIA_AND_HIFZA_TARGETS_DN,
ELVIDGE_HIFIA_TARGETS_DN,
NOJIMA_SFRP2_TARGETS_UP,
NAISHIRO_CTNNB1_TARGETS_WITH_LEF1_MOTIF,
BLANCO_MELO_COVID19_BRONCHIAL_EPITHELIAL_CELLS_SARS_COV_2_INFECTION_DN, and
REACTOME_ATTENUATION_PHASE.

[0110] Gene Set Enrichment Analysis revealed 395 significant pathway changes in IL-32 knockout cells. The most significant of these included WING_RESPONSE_TO_GSH&_INHIBITOR_88216763_UP,
PILON_KUFT_TARGETS_UP,
MONNIER_POSTRADIATION_TUMOR_ESCAPE_ON,
BENPORATH_LED_TARGETS,
CHARAFE_BREAST_CANCER_LUMINAL_VS_BASAL_ON,
SENESE_HDAC3_TARGETS_UP,
FULCHER_INFLAMMATORY_RESPONSE_LECTIU_VE_UPI_ON,
BLANCO_MELO_COVID19_SARS_COV_2_INFECTION_AB94_AGE2,
BAELDE_DIABETIC_NEPHROPATHY_DIN,
ZWANG_DLA58_1_TRANSIENTLY_INDUCED_BY_ECF,
BENPORATH_SUZ12_TARGETS,
BENPORATH_E8_WITH_H3K27ME3,
ENK_U_RESPONSE_EPIDERMIS_ON,
ZHENG_BOUND_BY_FOXFS,
MABBARWEH_DWUCICIFEN_RESISTANCE_UP,
WONG_ADULT_TISSUE_STEM_MODULE,
NAKAMURA_TUMOR_ZONE_PERIPHERAL_V8_CENTRAL_ON,
BLANDO_MELO_BRONCHIAL_EPITHELIAL_CELLS_INFLUENZA_A,
GOZOIT_EBRI_TARGETS_ON, and
REACTOVERNA_POLYMERASE_JLTRANSCRIPTION.

[0111] Gene Set Variation Analysis of the IL-32 knockout cells revealed 5 significant pathway changes:
MEBARKI_HCC_PROGENITOR_WNT_UP_CTNNB1_DEPENDENT;
SHIRAISHI_PLZF_TARGETS_UP;

BURTON_ADIPOGENESIS_PEAK_AT_0HR;
SMID_BREAST_CANCER_BASAL_UP; and
ROZANOV_MMP14_TARGETS_UP.

ix. IL-32 -Associated Gene Signatures

[0112] To identify the gene signature of IL-32 on its expected cell target, macrophages, IL-32 responsive genes were identified through 15 DEG lists. Additional analyses included assessing the correlation of effect estimates to understand the consistency and relationship of IL-32 effects on gene expression. Pathway analysis was conducted using Gene Set Enrichment Analysis to identify significantly enriched pathways and biological processes, and Over-Representation Analysis (ORA) focused on significantly upregulated and downregulated genes to pinpoint specific pathways and functions affected by IL-32. Motif enrichment analysis was performed to discover regulatory motifs overrepresented in the promoter regions of IL-32 responsive genes, providing insights into potential transcription factors involved. This assessment sought to elucidate the molecular mechanisms by which IL-32 influences macrophage function and identify key genes and pathways involved in this process.

[0113] For early gene signature identification, comparisons between IL-32 b at 0 hours and 6 hours with different concentrations (3, 30, and 300 ng/mL) revealed 4887, 2201, and 5701 significant genes, respectively. Late gene signature identification involved comparisons between IL-32 b at 0 hours and 24 hours with different concentrations (3, 30, and 300 ng/mL), resulting in 3847, 5792, and 6282 significant genes, respectively. To distinguish early versus late gene expression, comparisons between IL-32 b at 6 hours and 24 hours with the same concentrations (3, 30, and 300 ng/mL) showed 5280, 1495, and 4848 significant genes, respectively. Additionally, the potential blocking effect of IL-32 alpha on IL-32 gamma was examined, with comparisons at 6 hours and 24 hours showing 0 and 2 significant genes, respectively. Early and late TNF signature identifications were conducted by comparing IL-32 b at 0 hours with TNF at 6 hours and 24 hours, resulting in 2581 and 2560 significant genes, respectively. Early and late IL6 signature identifications were performed by comparing IL-32 b at 0 hours with IL6 at 6 hours and 24 hours, revealing 66 and 44 significant genes, respectively.

[0114] Correlation of effect estimates for all pairwise correlations (FIG. 31) and the same computer on pairwise union of significant genes (FIG. 32) was conducted for all 15 DEG comparisons. The analysis computed the correlation between effects estimates for the pairwise union of significant genes (FDR < 0.05) for each pairwise comparison. Correlation of effect estimates for TNF (NCBI Accession: UQL51144.1) compared to IL-32 assessed between different DEG comparisons (FIGS. 33A-33C) and Triggering Receptor Expressed on Myeloid cells 1 (TREM-1) (NCBI Accession: Q9NP99.1) under different the IL-32 conditions were also assessed (FIGS. 34A and 34B).

x. Assessing IL-32 Signaling

[0115] To assess cellular changes during IL-32 signaling, CRISPR-edited U937 cell lines that targeted a set of genes thought to be relevant for DAMP signaling were generated. This included TREM1, TYROBP (Transmembrane Immune Signaling Adaptor TYROBP; or DAP12), MYD88, TIR domain containing adaptor molecule 1 (TICAM1; or TIR-domain-containing adapter-inducing interferon-β (TRIF)), and TNF receptor superfamily member 1A (TNFRSF1A). The U937 human monocytic cell lines were differentiated to macrophage-like cells using PMA (5nM, 48 hours) before cells were treated with exogenous recombinant IL-32 proteins. MYD88 was identified as a hit. Each assay was repeated, and cytokine secretion was measured via Luminex (FIGS. 46A-46F). This demonstrated that loss of MyD88 may correlate with a loss of IL-32 induced cytokine secretion.

[0116] To corroborate this MYD88 result, a list of inhibitors that target TLR and IL-1 signaling was compiled to test in a bioassay including: neutralizing antibodies to cell surface expressed TLRs, IL-1Ra to inhibit IL-1 receptor signaling, and inhibitors to TIRAP, MyD88, and IRAK4. The assay was assessed for TNF induction by IL-32 protein isoforms, where the macrophage-like differentiated U937 cells were treated with IL-32α, IL-32**β**, and IL-32**γ** isoforms. Supernatants were collected after overnight treatment and TNF measured by ELISA. Similar to human primary macrophages, IL-32**β** and IL-32**γ** were bioactive protein isoforms for the induction of TNF (FIG. 47). The availability of this cell line bioassay may permit scalable testing of ligands, investigation of signaling pathways, screening of potential drug hits, and a consistent release assay.

[0117] This assay was assessed for TNF induction using extracellular TL4R (FIG. 48A), TLR4- TIRAP/TRAM binding with TAK-242 (FIG. 48B), IRAK using two different

compounds (FIG. 48C and 48D), and murine IgG1 control (FIG. 48E). This showed a dependency on all the immediate TLR4 signaling components during IL-32 signaling, supporting that TLR4 may be the IL-32 receptor. Other TLRs did not score in the bioassay (FIGS. 49A-49G). IL-1R1, TLR1, TLR2, TLR5, and TLR6 were not significant hits, were not different from the positive control (IL-32 treatment alone), and did not differ from the negative, non-targeting controls. This suggests that inhibiting these proteins does not disrupt IL-32 signaling and these proteins may not be the IL-32 receptor.

xi. Assessing IL-32 as a Driver of Inflammation

[0118] To assess the role of IL-32 in inflammation, primary CD4+ T cells were treated with different amounts of IL-32**β** or anti-CD3/CD28 beads and IL-2. Cells were incubated for 24 hours, and secreted cytokines were quantified following this via Luminex. IL-32 did not induce significant amounts of cytokine secretion compared to untreated T cells (FIGS. 50A-50F). This suggests that the loss of TNF and IL-6 in IL-32 knockout T cells may not be due to autocrine or paracrine IL-32 cytokine signaling.

[0119] This experiment was repeated, but cells were allowed to expand for 7 days before secreted cytokines were quantified via Luminex. This showed that IL-32 did not affect cytokine secretion during T cell proliferation, suggesting that IL-32 does not induce signaling in T cells and that the loss of TNF and IL-6 in IL-32 knockout cells may not be due to loss of paracrine or autocrine cytokine signaling.

[0120] IL-32 influence on inflammatory response was also assessed in monocytes, at 0, 3, and 300 ng/mL IL-32β exposure (FIGS. 52A-52J). Each assessed cytokine had increased levels, compared to baseline (i.e., 0 ng/mL). This demonstrated that IL-32 may induce a strong immune response in monocytes.

[0121] Cytokine levels were next assessed in anti-CD3 co-cultures, where cytokine levels secreted from T cells and monocytes were assessed following anti-CD3 exposure. Flow cytometry confirms that monocytes and T cells were both activated by co-culture with anti-CD3, as shown by changes in IL-1β, IL1-α, TNF, IL-6, IL-10, IFN-γ, and IL-17A levels (FIGS. 53A-53G).

[0122] CD4+ T cells were next cultured with donor-matched monocytes with or without anti-CD3 and at increasing amounts of IL-32 (0, 0.3, 3, 30, and 300 ng/mL).

Supernatants were collected after 72 hours of culture and cytokine secretion was assessed via Luminex. Three patterns of cytokine secretion were observed: (i) cytokine secretion dependent on IL-32 (e.g., IL-1β), (ii) cytokine secretion dependent on co-culture (e.g. TNF), (iii) and cytokine secretion dependent on IL-32 and co-culture (e.g., IL-17A and IFN-γ effects starting at 3 ng/mL of IL-32) (FIGS. 54A-54D). Since IL-17A and IFN-γ are primarily T cell associated cytokines and were not induced with IL-32 alone, it is hypothesized that IL-32 hyper-activates monocytes to increase T cell activation and cytokine secretion.

D. Steps of the Methods

[0123] For the purposes of illustration, consider the mechanistic model provided in FIG. 6, which suggests potential points of therapeutic intervention for methods of treating or preventing inflammatory disorders, in addition to molecular factors which may be assessed to help diagnose or determine prognoses of disease. These molecule factors may be assessed using a memory component, which receives information, such as a genetic sequence, of biological molecules. This information can be analyzed and compared to the information of a control sample (e.g., a sample from a subject not having disease, a sample from a subject having disease that has received treatment, a reference genome, a reference transcriptome, or a reference proteome). Diagnostic, prognostic, treatment, and prevention assessments may then be performed based off this comparison.

i. Methods of Diagnosis and Determining Prognosis

[0124] The present technology comprises methods of diagnosing or determining a prognosis of an inflammatory condition (e.g., RA or IBD) in a subject by using memory components comprising computer-executable programs. The memory components may comprise one or more of an operating system, a user-facing application, a device driver, a firmware, a script, or an interpreter. The computer-executable programs may comprise functions such as nucleotide sequencing, nucleotide alignment, amino acid sequencing, amino acid alignment, variant calling, and/or assessments thereof.

[0125] In some embodiments, the methods of diagnosis and determining prognosis comprise assessing loci sequences. In some embodiments, the methods comprise diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of at least one locus by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one locus in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0126] In some embodiments, the methods comprise determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of at least one locus by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one locus in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0127] The at least one locus may comprise or consist of a protein coding sequence, a regulatory sequence (e.g., a promoter, an enhancer, a silencer, an insulator, a transcription factor binding site, a cis-regulatory sequence, a trans-regulatory sequence, a response element), or a noncoding sequence. The at least one locus may comprise a sense strand or an antisense strand. The noncoding sequence may comprise an intron or a sequence distal to a coding region. In some embodiments,

the at least one locus comprises one or more selected from a HLA-DRB1 locus, a PTPN22 locus, or a IL-32 locus.

[0128] The sequence difference in (e) may comprise a genetic variant (e.g., a single nucleotide polymorphism (SNP)), a haplotype difference, an insertion, or a deletion, relative to a reference genome. In some embodiments, the sequence difference is a SNP selected from the group consisting of rs2476601, rs4786370, rs9788910, and rs55699988. In some embodiments, the sequence difference in (e) comprises a haplotype sequence selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02.

[0129] In some embodiments, the methods of diagnosis and determining prognosis comprise assessing a transcript isoform level. In some embodiments, the methods comprise diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of a transcript isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0130] In some embodiments, the present technology comprises a method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of a transcript isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0131] In some embodiments, the transcript isoform is an IL-32 transcript isoform. The IL-32 transcript isoform may comprise an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, or an IL-32 gamma transcript isoform. In some embodiments, the IL-32 gamma transcript isoform is ENST00000396890.6. In some embodiments, the IL-32 alpha transcript isoform is ENST00000396887.7. In some embodiments, the IL-32 beta transcript isoform is ENST00000530538.6.

[0132] In some embodiments, the methods of diagnosis and determining prognosis comprise assessing a protein isoform level. In some embodiments, the methods comprise diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of a protein isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0133] In some embodiments, the present technology comprises a method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of a protein isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0134] In some embodiments, the protein isoform is an IL-32 protein isoform. The IL-32 protein isoform may comprise an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, or an IL-32 gamma protein isoform. In some embodiments, the protein isoform is encoded by a transcript selected from the group consisting of ENST00000396890, ENST00000396887, and ENST00000530538. In some embodiments, the protein

[0135] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0136] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0137] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0138] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 2.

[0139] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 2.

[0140] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 2.

[0141] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 3.

[0142] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 3.

[0143] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 3.

[0144] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 4.

[0145] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 4.

[0146] The IL-32 protein isoform may be an IL-32 isoform comprising a sequence at least about 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 4.

[0147] The methods of the present technology may further comprise a step of performing a batch correction operation using a computer-executable program. Nonlimiting examples of batch correction operations include identifying pairs of mutual nearest neighbors (MNN), canonical correlation analysis (CCA), negative binomial regression, surrogate variable analysis, distance-based correlation, and principal component analysis (PCA) correction.

[0148] The methods may further comprise a step of performing a normalization operation using a computer-executable program. Nonlimiting examples of normalization operations include genetic sequencing-based normalization techniques (e.g., library size normalization, GC content normalization, sequencing depth normalization, sequence length normalization, Reads Per Kilobase Million (RPKM) normalization, Fragments Per Kilobase Million (FPKM) normalization, and Transcripts Per Million (TPM) normalization), ribonucleic acid (RNA) sequencing-based normalization techniques (e.g., DESeq/DESeq2 normalization, housekeeping gene normalization, EdgeR normalization, trimmed mean of M-values normalization, and transcript length or depth normalization), and protein-based normalization (e.g., total protein normalization, loading control normalization, staining control normalization, cell number normalization, and total iron content normalization).

(a) Samples of the Methods

[0149] The methods of the present technology may be performed on biological samples and/or dataset-based samples. In some embodiments, the subject sample is

a biological sample. The biological sample may comprise a urine sample, a saliva sample, a circulatory fluid sample (e.g., blood sample or a lymph sample), a synovial fluid sample (e.g., synovial joint fluid), or a solid tissue sample. Nonlimiting examples of solid tissue samples include an epithelial tissue, a connective tissue, a nervous tissue, an adipose tissue, a cartilage, a bone tissue, a skin tissue, a mucous membrane tissue, a glandular tissue, a vascular tissue, a cardiac tissue, a smooth muscle tissue, a skeletal muscle tissue, a neural tissue, a fibrous tissue, a bone marrow tissue, a liver tissue, a kidney tissue, a pancreatic tissue, a pulmonary tissue, and a brain tissue.

[0150] In some embodiments, the subject sample comprises a sequencing dataset. The sequencing dataset may be generated using one or more methods selected from the group consisting of whole genome sequencing, genome-wide association study, Sanger sequencing, next-generation sequencing, nanopore sequencing, shotgun sequencing, pyrosequencing, single-molecule real-time sequencing, and ribonucleic acid (RNA) sequencing (e.g., bulk RNA-seq, single cell RNA-seq, strand-specific RNA seq, long-read RNA-seq, small RNA-seq, isoform-level RNA-seq, pseudo-bulk RNA-seq, and RNA-seq with ribosomal RNA depletion).

[0151] In some embodiments, the subject sample comprises a protein-level dataset. The protein-level dataset may be generated using one or more methods selected from the group consisting of mass spectrometry (MS)-based proteomics (e.g., shotgun proteomics, liquid chromatography-tandem mass spectrometry, quantitative proteomics, targeted proteomics), protein microarrays, flow cytometry, enzyme-linked immunosorbent assays (ELISA), or single-cell proteomics.

[0152] In some embodiments, the subject sample is derived from an immune cell population. In some embodiments, the immune cell population comprises an immune cell subset. Nonlimiting examples of immune cell subsets include myeloid cell subsets, T cell subsets, B cell subsets. The myeloid cell subset may comprise a dendritic cell (DC) subset (e.g., conventional DC or a plasmacytoid DC) or a monocyte subset (e.g., a classical monocyte, an intermediate monocyte, or a nonclassical monocyte). The T cell subset may comprise a CD4+ αβ T cell subset (e.g, a naïve CD4+ T cell, a central memory CD4+ T cell, an effector memory CD4+ T cell, a CD45RA+ effector memory CD4+ T cell, or a CD4+ T regulatory cell), a CD8+ αβ T cell subset (e.g., comprises a naïve CD8+ T cell, a central memory CD8+ T cell, an effector memory CD8+ T cell, or

a CD45RA+ effector memory CD8+ T cell), a γδ T cell subset (e.g., a gamma-delta T cell), or a natural killer (NK) cell subset (e.g., a CD56hi NK cell or a CD56low NK cell). The B cell subset comprises a naïve B cell (e.g., an unswitched naïve B cell, a class switched naïve B cell, or a transitional B cell) or an effector B cell (e.g., a class switched classical memory B cell, an IgM+ IgD- classical memory B cell, an atypical memory B cell, or a class switched plasmablast).

(b) Treatment Plans and Outcomes:

[0153] The methods of the present technology are useful in treating or preventing an inflammatory condition by administering a therapeutic that targets an activator or mediator of inflammation that is upstream of the therapeutic target of traditional approaches. The inflammatory condition may comprise an autoimmune disease, such as RA, or may comprise other immune diseases such as IBD.

[0154] In some embodiments, the treatment plans of the methods comprise administering one or more therapeutics selected from the group consisting of a biologic (e.g., an antibody), a recombinant protein (e.g., recombinant IL-6R antagonist or a recombinant IL-1R antagonist), a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

[0155] In some embodiments, the biologic is an antibody that recognizes and/or binds to a chemokine (e.g., CCL2, CXCL8, CCL5, CXCL12, CCL20, CXCL10, CCL19, CCL21, or CXCCL1) or a cytokine (e.g., an interleukin, a tumor necrosis factor, an interferon, or a growth factor). In some embodiments, the antibody is selected from the group consisting of an anti-TNF antibody, an anti- IL-6 receptor antibody, an anti-IL-1 receptor antibody, and an anti-IL-32 receptor antibody.

[0156] The one or more therapeutics may reduce a level of tumor necrosis factor (TNF) gene expression or protein, a level of anti-interleukin-6 (IL-6) gene expression or protein, a level of interleukin-1 receptor antibody (IL-1) gene expression or protein, or a level or interleukin-32 (IL-32) gene expression or protein. The one or more therapeutics that reduce a level of IL-32 gene expression or IL-32 protein may target the IL-32 exon 8 domain.

[0157] In some embodiments, the one or more therapeutics comprises an inhibitor of an activator of TNF-α, IL6 (NCBI Accession: P05231.1), IL1α (NCBI Accession: P01583.1), IL-1β (NCBI Accession: P01584.2), or IL-32 gene expression.

[0158] In some embodiments, the one or more therapeutics comprises an inhibitor of an activator of TNF-α, IL-6, IL-1α, IL-1β, or IL-32 protein function.

[0159] In some embodiments, the one or more therapeutics comprises an inhibitor of JUN (NCBI Accession: AAA59197.1), c-Fos (NCBI Accession: CAA24756.1), FOSB (NCBI Accession: P53539.1), FOSL1 (NCBI Accession: CAG47053.1), FOSL2 (NCBI Accession: CAG47058.1), or ATF1 (NCBI Accession: P18846.2) gene expression.

[0160] In some embodiments, the one or more therapeutics comprises an inhibitor of activator protein 1 (AP-1) activity. The inhibitor of AP-1 activity may be selected from the group consisting of a carbachol, a resveratrol, a curcumin, a quercetin, a chlorogenic acid, an anthocyanin, a sulforaphane, a corticosteroid, a tanshinone, a C-Jun N-terminal Kinase (JNK) inhibitor, and a protease inhibitor.

[0161] In some embodiments, one or more therapeutics comprises an inhibitor of expression of one or more genes selected from the group consisting of PTPN22, TICAM1 (NCBI Accession: Q8IUC6.1), PRTN3 (NCBI Accession: P24158.3), F2R1 (NCBI Accession: KAI4021761.1), ABCA4 (NCBI Accession(s): P78363.3; NP_001412253.1; NP_000341.2), HSPA6 (NCBI Accession: NP_002146.2), HSPA1B (NCBI Accession: UQL51172.1), ARC (NCBI Accession: AAF07185.1), CRYAB (NCBI Accession: P02511.2), SNAI1 (NCBI Accession: O95863.2), BIVM-ERCC5 (NCBI Accession(s): NP_001191354.2; KAI4063751.1; KAI4063750.1), HSPA1A (NCBI Accession: UQL51171.1), WFDC5 (NCBI Accession(s): AAQ89181.1; Q8TCV5.1), RASD1 (NCBI Accession: Q9Y272.1; NP_057168.1; NP_001186918.1), TREM1 (NCBI Accession(s): AAL74018.1; Q9NP99.1; NP_061113.1; NP_001229519.1; NP_001229518.1), DNAJB1 (NCBI Accession: CAG38724.1), SERPINA1 (NCBI Accession: P01009.3), WNT10A (NCBI Accession: AAG45153.1), PLAC1 (NCBI Accession: AAG22596.1), IL17F (NCBI Accession: Q96PD4.3), RHOV (NCBI Accession: Q96L33.1), SERPINH1 (NCBI Accession: SERPINH1), ANKRD20A1 (NCBI Accession: Q5TYW2.1), ADM (NCBI Accession: AAC60642.1), IL1R2 (NCBI Accession: P27930.1), ODF1 (NCBI Accession: Q14990.2), ABCA1 (NCBI Accesion: AAF86276.1), ZNF662 (NCBI Accession(s): AAI28086.1; Q6ZS27.1), NIPAL1 (NCBI

Accession: Q6NVV3.1), GYS2 (NCBI Accession: P54840.2), HEY1 (NCBI Accession: CAB75715.1), MMP16 (NCBI Accession: P51512.2), CA9TICAM2 (NCBI Accession: Q96RR4.2), SCGB2A2 (NCBI Accession(s): AAH67220.1; Q13296.1), OSMR (NCBI Accession(s): AAH63468.1; AAH10943.1; Q99650.1), TMPRSS6 (NCBI Accession: AAH39082.1), CD19 (NCBI Accession(s): AAB60697.1; AAA69966.1), CA12 (NCBI Accession(s): AAH01012.1; O43570.1), EPHA4 (NCBI Accession(s): AAI05003.1; AAH26327.1; P54764.1), CAV1 (NCBI Accession(s): Q03135.4; CCQ43147.1; NP_001166368.1; NP_001744.2), RYR1 (NCBI Accession: P21817.3), CCDC121 (NCBI Accession: AAH66969.1), and ZNF177 (NCBI Accession(s): Q13360.4; NP_001371587.1; NP_001166122.1).

[0162] In some embodiments, one or more therapeutics comprises an inhibitor of one or more proteins selected from the group consisting of TRIF (NCBI Accession: Q8IUC6.1), PR3 (NCBI Accession(s): PR3, XP_054177459.1), PAR2 (NCBI Accession: P55085.1), HLAABC, CD6 (NCBI Accession: P30203.3), CD155 (NCBI Accession: P15151.2), CD60a (NCBI Accession: Q92185.1), CD31 (NCBI Accession: AAA36186.1), CD279 (NCBI Accession: AAH74740.1), CD30 (NCBI Accession: P28908.1), and CD98 (NCBI Accession(s): BAA33851.1; NP_003477.4; NP_002385.3; NP_001013269.1; NP_001012682.1; NP_001012680.1; AAH01061.2; AAH03000.2; AAH42600.1).

ii. Methods of Treatment and Prevention

[0163] The present technology comprises methods of treating or preventing an inflammatory condition in a subject. In some embodiments, the inflammatory condition is an autoimmune disease (e.g., RA). In some embodiments, the inflammatory condition is IBD.

[0164] In some embodiments, the methods comprise administering to the subject one or more therapeutics that inhibit an activator of (a) gene expression of one or more genes selected from the group consisting of *TNF* (NCBI Gene ID: 7124), *IL1* (NCBI Gene ID(s): 3553; 3552), and *IL6* (NCBI Gene ID: 3569), or (b) activity of one or more proteins selected from the group consisting of TNF, IL-1 (NCBI Accession(s): AAH08678. Q9NZN1.2; NP_000567.1; XP_054197785. CAA27448.1; Q28579.1) (e.g., IL1α (NCBI Accession: P01583.1), IL-1β (NCBI Accession: P01584.2), and IL-6.

[0165] The activator of *TNF* gene expression or protein function may be encoded by a gene or may be a protein. In some embodiments, the gene is selected from the group consisting of Nuclear Factor-kappa B (NF-κB) (NCBI Gene ID: 4790; 5970), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A) (NCBI Gene ID: 7132), a Toll-like Receptor (NCBI Gene ID(s): 7097; 7099; 10333; 54106; 7098; 7096; 51284; 7100; 51311), IL-1, interleukin-17 (IL-17) (NCBI Gene ID(s): 3605; 112744; 27190; 27189; 53342), a pathogen-associated molecular pattern (PAMP), interferon-gamma (IFN-γ) (NCBI Gene ID: 3458), CD40 ligand (CD40L) (NCBI Gene ID: 959), F2R Like Trypsin Receptor 1 (F2RL1) (NCBI Gene ID: 2150), Proteinase 3 (PRTN3) (NCBI Gene ID: 5657), and a Mitogen-Activated Protein Kinase (MAPK) gene (NCBI Gene ID: 5594; 5595; 5598; 5601; 547616; 5596; 5599; 5601; 5602; 5600; 6300; 5603; 1432; 225689). In some embodiments, the protein is selected from the group consisting of NF-κB, Tumor Necrosis Factor Receptor 1 (TNFR1) (NCBI Accession: AAA61201.1), CD40 (NCBI Accession(s): P25942.1; ABI49511.1; ALQ33425.1; CAC29424.1), a Toll-like Receptor (NCBI Accession(s): KAI4025147.1; AAH33756.1; ABC86910.1; O00206.2; NP_612567.1; NP_003257.1; AAF05316.1; AAC34135.1; AAY82270.1), IL-1, IL-17 (NCBI Accession(s): Q16552.1; AAQ89290.1), IFN-γ (NCBI Accession: P01579.1), CD14 (NCBI Accession: CAG33297.1), TIR Domain-Containing Adapter-Inducing Interferon-β (TRIF) (NCBI Accession(s): Q8IUC6.1; NP_891549.; NP_001372607.1; NP_001372609.1; NP_001372608.1), Myeloid Differentiation Primary Response 88 (MyD88) (NCBI Accession: AAC50954.1), Protease activated receptor 2 (PAR2) (NCBI Accession(s): P55085.1; NP_001098047.1), Proteinase 3 (PRTN3) (NCBI Accession(s): P24158.3; XP_054177459.1; EAW69591.1; EAW69590.1; AAH96186.1), and a MAPK protein (NCBI Accession(s): P_002736.3; P27361.4; 8XU4_L; P31152.2; NP_002739.1; Q13164.2; NP_001310251.; NP_001310250.1; CAG38817.1; AAH51731.1; CAG30400.1; CAG30401.1; CAG38729.1; CAG38743.1; AAH28034.1).

[0166] The activator of *IL6* gene expression or IL-6 protein function may be encoded by a gene or may be a protein. In some embodiments, the gene is selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, Signal Transducer and Activator of Transcription 3 (STAT3), TNF, IL-17, IL-6R (NCBI Gene ID: 3570), F2R1 (NCBI Gene ID: 6581), PRTN3, and a MAPK gene. In some embodiments, the protein is selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, STAT3, TNF,

IL-17, IL-6R (NCBI Accession(s): P08887.1; AAI32687.1), PAR2, PRTN3, and a MAPK protein.

[0167] The activator of *IL1* gene expression or IL-1 protein function may be encoded by a gene or may be a protein. In some embodiments, the gene is selected from the group consisting of NF-κB, a Toll-like Receptor, NOD-like Receptor Family, Pyrin Domain Containing 3 (NLRP3) (NCBI Gene ID: 114548), Apoptosis-Associated Speck-like Protein Containing a CARD (ASC) (NCBI Gene ID: 29108), IL-18R (NCBI Gene ID: 8809), MyD88 (NCBI Gene ID: 4615), F2R1, PRTN3, and Interleukin-1 Receptor-Associated Kinase (IRAK) (NCBI Gene ID: 3654). In some embodiments, the protein is selected from the group consisting of NLRP3 (NCBI Accession(s): AAI43360.1; AAI17212.1), ASC (NCBI Accession(s): (BAA87339.2; NP_037390.2; NP_660183.1), Pro-caspase-1 (NCBI Accession: P29466.1), a Toll-like Receptor, MyD88, Absent in Melanoma 2 (AIM2) (NCBI Accession: XBC19909.1), PAR2, PRTN3, and a MAPK protein.

[0168] In some embodiments, the one or more therapeutics is selected from the group consisting of a biologic, a recombinant protein, a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

[0169] In some embodiments, the one or more therapeutics comprises an IL-32 gene expression inhibitor. In some embodiments, the IL-32 is a β or a γ isoform. In some embodiments, the IL-32 gene expression inhibitor targets an IL-32 exon 8 domain.

[0170] In some embodiments, the one or more therapeutics comprises an IL-32 protein inhibitor. In some embodiments, the IL-32 is a β or a γ isoform. In some embodiments, the IL-32 exon 8 domain is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0171] In some embodiments, the one or more therapeutics comprises an IL-32 protein inhibitor. In some embodiments, the IL-32 is a β or a γ isoform. In some embodiments, the IL-32 exon 8 domain is about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

[0172] In some embodiments, the one or more therapeutics comprises an IL-32 protein inhibitor. In some embodiments, the IL-32 is a β or a γ isoform. In some

embodiments, the IL-32 exon 8 domain is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

Additional Embodiments

[0173] Various embodiments of the present technology are set forth below in paragraphs [0174] to [0271]:

[0174] 1. A method of diagnosing rheumatoid arthritis (RA) in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0175] 2. A method of diagnosing rheumatoid arthritis (RA) in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b).

[0176] 3. Use of a memory component comprising a computer-executable program for diagnosing rheumatoid arthritis (RA) in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by the memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0177] 4. Use of a memory component comprising a computer-executable program for diagnosing rheumatoid arthritis (RA) in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by the memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b).

[0178] 5. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0179] 6. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b).

[0180] 7. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0181] 8. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b).

[0182] 9. The method or the use of any one of embodiments 1-8, wherein the at least one loci comprises a protein coding sequence.

[0183] 10. The method or the use of any one of embodiments 1-9, wherein the at least one loci comprises a regulatory sequence.

[0184] 11. The method or the use of any one of embodiments 1-10, wherein the at least one loci comprises a noncoding sequence.

[0185] 12. The method or the use of embodiment 1 or 5, wherein the at least one loci consists of a protein coding sequence.

[0186] 13. The method or the use of embodiment 1 or 5, wherein the at least one loci consists of a regulatory sequence.

[0187] 14. The method or the use of embodiment 1 or 5, wherein the at least one loci consists of a noncoding sequence.

[0188] 15. The method or the use of any one of embodiments 1-14, wherein the sequence difference in (e) comprises a single nucleotide polymorphism.

[0189] 16. The method or the use of embodiment 15, wherein the single nucleotide polymorphism is selected from the group consisting of rs2476601, rs4786370, rs9788910, and rs55699988.

[0190] 17. The method or the use of any one of embodiments 1-15, wherein the sequence difference in (e) comprises a haplotype sequence selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02.

[0191] 18. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0192] 19. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component.

[0193] 20. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0194] 21. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component.

[0195] 22. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0196] 23. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0197] 24. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component.

[0198] 25. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0199] 26. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

[0200] 27. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0201] 28. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

[0202] 29. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b);

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0203] 30. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b); and

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component.

[0204] 31. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0205] 32. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component.

[0206] 33. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0207] 34. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component.

[0208] 35. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b);

(e) determining the subject as having:

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0209] 36. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01,

and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component.

[0210] 37. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0211] 38. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

[0212] 39. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component.

[0213] 40. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, or an IL-32 gamma transcript isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0214] 41. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

[0215] 42. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0216] 43. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

[0217] 44. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b);

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

[0218] 45. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b); and

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component.

[0219] 46. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

[0220] 47. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component.

[0221] 48. The method of any one of embodiments 1-27 or the use of any one of embodiments 312-340, wherein the sequence received in (a) is determined by sequencing a nucleic acid in a subject sample.

[0222] 49. The method or the use of any one of embodiments 29-32 or 44-34 wherein the level, of the IL-32 protein isoform received in (a) is determined by measuring a protein level in a subject sample.

[0223] 50. The method or the use of any one of embodiments 1-49, wherein the subject sample is a biological sample.

[0224] 51. The method or the use of embodiment 50, wherein the biological sample comprises a urine sample, a saliva sample, a circulatory fluid sample, a synovial fluid sample, or a solid tissue sample.

[0225] 52. The method or the use of embodiment 51, wherein the synovial fluid sample comprises synovial joint fluid.

[0226] 53. The method or the use of embodiment 51, wherein the solid tissue sample comprises one or more tissues selected from the group consisting of an epithelial tissue, a connective tissue, a nervous tissue, an adipose tissue, a cartilage, a bone tissue, a skin tissue, a mucous membrane tissue, a glandular tissue, a vascular tissue, a cardiac tissue, a smooth muscle tissue, a skeletal muscle tissue, a neural tissue, a fibrous tissue, a bone marrow tissue, a liver tissue, a kidney tissue, a pancreatic tissue, a pulmonary tissue, and a brain tissue.

[0227] 54. The method or the use of embodiment 51, wherein the circulatory fluid sample comprises a blood sample or a lymph sample.

[0228] 55. The method or the use of any one of embodiments 1-49, wherein the subject sample is a sequencing dataset.

[0229] 56. The method or the use of embodiment 55, wherein the sequencing dataset is generated using one or more methods selected from the group consisting of whole genome sequencing, genome-wide association study, Sanger sequencing, next-

generation sequencing, nanopore sequencing, shotgun sequencing, pyrosequencing, and single-molecule real-time sequencing.

[0230] 57. The method or the use of any one of embodiments 1-56, wherein the subject sample is derived from an immune cell subset.

[0231] 58. The method or the use of embodiment 57, wherein the immune subset is a myeloid cell subset, a T cell subset, or a B cell subset.

[0232] 59. The method or the use of embodiment 58, wherein the myeloid cell subset comprises a dendritic cell (DC) subset or a monocyte subset.

[0233] 60. The method or the use of embodiment 59, wherein the DC subset comprises a conventional DC or a plasmacytoid DC.

[0234] 61. The method of or the use embodiment 59, wherein the monocyte subset comprises a classical monocyte, an intermediate monocyte, or a nonclassical monocyte.

[0235] 62. The method of or the use embodiment 58, wherein the T cell subset comprises a CD4+ αβ T cell subset, a CD8+ αβ T cell subset, a γδ T cell subset, or a natural killer (NK) cell subset.

[0236] 63. The method or the use of embodiment 62, wherein the CD4+ αβ T cell subset comprises a naïve CD4+ T cell, a central memory CD4+ T cell, an effector memory CD4+ T cell, a CD45RA+ effector memory CD4+ T cell, or a CD4+ T regulatory cell.

[0237] 64. The method or the use of embodiment 62, wherein the CD8+ αβ T cell subset comprises a naïve CD8+ T cell, a central memory CD8+ T cell, an effector memory CD8+ T cell, or a CD45RA+ effector memory CD8+ T cell.

[0238] 65. The method or the use of embodiment 62, wherein the γδ T cell subset comprises a gamma-delta T cell.

[0239] 66. The method or the use of embodiment 62, wherein the NK cell subset comprises a CD56hi NK cell or a CD56low NK cell.

[0240] 67. The method or the use of embodiment 58, wherein the B cell subset comprises a naïve B cell or an effector B cell.

[0241] 68. The method or the use of embodiment 67, wherein the naïve B cell comprises an unswitched naïve B cell, a class switched naïve B cell, or a transitional B cell.

[0242] 69. The method or the use of embodiment 67, wherein the effector B cell comprises a class switched classical memory B cell, an IgM+ IgD- classical memory B cell, an atypical memory B cell, or a class switched plasmablast.

[0243] 70. The method or the use of any one of embodiments 1-69, wherein the treatment plan in (f) comprises administering one or more therapeutics selected from the group consisting of a biologic, a recombinant protein, a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

[0244] 71. The method or the use of embodiment 70, wherein the one or more therapeutics reduces a level of tumor necrosis factor (TNF) gene expression or protein, a level of anti-interleukin-6 (IL-6) gene expression or protein, a level of interleukin-1 receptor antibody (IL-1) gene expression or protein, or a level or interleukin-32 (IL-32) gene expression or protein.

[0245] 72. The method or the use of embodiment 70, wherein the biologic comprises an antibody.

[0246] 73. The method or the use of embodiment 72, wherein the antibody is selected from the group consisting of an anti-TNF antibody, an anti- IL-6 receptor antibody, an anti-IL-1 receptor antibody, and an anti-IL-32 receptor antibody.

[0247] 74. The method or the use of embodiment 70, wherein the one or more recombinant proteins comprise a recombinant IL-6R antagonist or a recombinant IL-1R antagonist.

[0248] 75. The method or the use of embodiment 71, wherein the one or more therapeutics that reduces a level of IL-32 gene expression or protein targets an IL-32 exon 8 domain.

[0249] 76. The method or the use of embodiment 71, wherein the one or more therapeutics comprises an inhibitor of an activator of TNF, IL6, IL1α, IL1β, or IL-32 gene expression.

[0250] 77. The method or the use of embodiment 71, wherein the one or more therapeutics comprises an inhibitor of an activator of TNF, IL6, IL1α, IL1β, or IL-32 protein function.

[0251] 78. The method or the use of embodiment 76 or 77, wherein the one or more therapeutics comprises an inhibitor of JUN, c-Fos, FOSB, FOSL1, FOSL2, or ATF1 gene expression.

[0252] 79. The method or the use of embodiment 76 or 77, wherein the one or more therapeutics comprises an inhibitor of activator protein 1 (AP-1) activity.

[0253] 80. The method or the use of embodiment 79, wherein the inhibitor of AP-1 activity is selected from the group consisting of a carbachol, a resveratrol, a curcumin, a quercetin, a chlorogenic acid, an anthocyanin, a sulforaphane, a corticosteroid, a tanshinone, a C-Jun N-terminal Kinase (JNK) inhibitor, and a protease inhibitor.

[0254] 81. The or the use method of embodiment 70, wherein the one or more therapeutics comprises an inhibitor of expression of one or more genes selected from the group consisting of PTPN22, TICAM1, PRTN3, F2R1, ABCA4, HSPA6, HSPA1B, ARC, CRYAB, SNAI1, BIVM-ERCC5, HSPA1A, WFDC5, RASD1, TREM1, DNAJB1, SERPINA1, WNT10A, PLAC1, IL17F, RHOV, SERPINH1, ANKRD20A1, ADM, IL1R2, ODF1, ABCA1, ZNF662, NIPAL1, GYS2, HEY1, MMP16, CA9TICAM2, SCGB2A2, OSMR, TMPRSS6, CD19, CA12, EPHA4, CAV1, RYR1, CCDC121, and ZNF177.

[0255] 82. The or the use method of embodiment 70, wherein the one or more therapeutics comprises an inhibitor of one or more proteins selected from the group consisting of TRIF, PR3, PAR2, HLAABC, CD6, CD155, CD60a, CD31, CD279, CD30, and CD98.

[0256] 83. A method of treating or preventing RA in a subject in need thereof, the method comprising administering to the subject one or more therapeutics that inhibit an activator of

(a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or

(b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6.

[0257] 84. Use of one or more therapeutics that inhibit an activator of

(a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or

(b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6, for treating or preventing RA in a subject in need thereof.

[0258] 85. The method or the use of embodiment 83, wherein the activator of TNF gene expression or protein function is encoded by a gene selected from the group consisting of Nuclear Factor-kappa B (NF-κB), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), a Toll-like Receptor, IL-1, interleukin-17 (IL-17), a pathogen-associated molecular pattern (PAMP), interferon-gamma (IFN-γ), CD40 ligand (CD40L), F2R Like Trypsin Receptor 1 (F2RL1), Proteinase 3 (PRTN3), and a Mitogen-Activated Protein Kinase (MAPK) gene.

[0259] 86. The method or the use of embodiment 83, wherein the activator of *TNF* gene expression or protein function is a protein selected from the group consisting of NF-κB, Tumor Necrosis Factor Receptor 1 (TNFR1), CD40, a Toll-like Receptor, IL-1, IL-17, IFN-γ, CD14, TIR Domain-Containing Adapter-Inducing Interferon-β (TRIF), Myeloid Differentiation Primary Response 88 (MyD88), Protease activated receptor 2 (PAR2), Proteinase 3 (PRTN3), and a MAPK protein.

[0260] 87. The method or the use of embodiment 83, wherein the activator of *IL6* gene expression or protein function is encoded by a gene selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, Signal Transducer and Activator of Transcription 3 (STAT3), TNF, IL-17, IL-6R, F2R1, PRTN3 and a MAPK gene.

[0261] 88. The method of embodiment 83, wherein the activator of *IL6* gene expression or protein function is a protein selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, STAT3, TNF, IL-17, IL-6R, PAR2, PRTN3, and a MAPK protein.

[0262] 89. The method or the use of embodiment 83, wherein the activator of *IL1* gene expression or protein function is encoded by a gene selected from the group consisting of NF-κB, a Toll-like Receptor, NOD-like Receptor Family, Pyrin Domain Containing 3 (NLRP3), Apoptosis-Associated Speck-like Protein Containing a CARD

(ASC), IL-18R, MyD88, F2R1, PRTN3, and Interleukin-1 Receptor-Associated Kinase (IRAK).

[0263] 90. The method or the use of embodiment 83, wherein the activator of *IL1* gene expression or protein function is a protein selected from the group consisting of NLRP3, ASC, Pro-caspase-1, a Toll-like Receptor, MyD88, Absent in Melanoma 2 (AIM2), PAR2, PRTN3, and a MAPK protein.

[0264] 91. The method or the use of embodiment 83, wherein the one or more therapeutics is selected from the group consisting of a biologic, a recombinant protein, a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

[0265] 92. The method or the use of embodiment 83, wherein the one or more therapeutics comprises an IL-32 gene expression inhibitor.

[0266] 93. The method or the use of embodiment 92, wherein the IL-32 is a β or a γ isoform.

[0267] 94. The method or the use of embodiment 92 or 93, wherein the IL-32 gene expression inhibitor targets an IL-32 exon 8 domain.

[0268] 95. The method or the use of embodiment 83, wherein the one or more therapeutics comprises an IL-32 protein inhibitor.

[0269] 96. The method or the use of embodiment 95, wherein the IL-32 is a β or a γ isoform.

[0270] 97. The method or the use of embodiment 95 or 96, wherein the IL-32 protein inhibitor targets an IL-32 exon 8 domain.

[0271] 98. The method or the use of embodiment 97, wherein the IL-32 exon 8 domain is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

Remarks

[0272] The foregoing description of various embodiments of the claimed subject matter has been provided for the purposes of illustration and description. It is not intended to be exhaustive or to limit the claimed subject matter to the precise forms disclosed. Many modifications and variations will be apparent to one skilled in the art.

Embodiments were chosen and described in order to best describe the principles of the invention and its practical applications, thereby enabling those skilled in the relevant art to understand the claimed subject matter, the various embodiments, and the various modifications that are suited to the particular uses contemplated.

[0273] Although the Detailed Description describes certain embodiments and the best mode contemplated, the technology can be practiced in many ways no matter how detailed the Detailed Description appears. Embodiments may vary considerably in their implementation details, while still being encompassed by the specification. Particular terminology used when describing certain features or aspects of various embodiments should not be taken to imply that the terminology is being redefined herein to be restricted to any specific characteristics, features, or aspects of the technology with which that terminology is associated. In general, the terms used in the following claims should not be construed to limit the technology to the specific embodiments disclosed in the specification, unless those terms are explicitly defined herein. Accordingly, the actual scope of the technology encompasses not only the disclosed embodiments, but also all equivalent ways of practicing or implementing the embodiments.

[0274] The language used in the specification has been principally selected for readability and instructional purposes. It may not have been selected to delineate or circumscribe the subject matter. It is therefore intended that the scope of the technology be limited not by this Detailed Description, but rather by any claims that issue on an application based hereon. Accordingly, the disclosure of various embodiments is intended to be illustrative, but not limiting, of the scope of the technology as set forth in the following claims.

CLAIMS

1. A method of diagnosing rheumatoid arthritis (RA) in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

2. A method of diagnosing rheumatoid arthritis (RA) in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b).

3. Use of a memory component comprising a computer-executable program for diagnosing rheumatoid arthritis (RA) in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by the memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

4. Use of a memory component comprising a computer-executable program for diagnosing rheumatoid arthritis (RA) in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by the memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA if the sequence of (a) is different from the sequence of (b).

5. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the prognosis in (e).

6. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b).

7. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b); and

(f) developing a treatment plan for the subject based on the prognosis in (e).

8. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of at least one of HLA-DRB1, PTPN22, or IL-32 loci by a memory component comprising a computer-executable program;

(b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having:

(i) a good prognosis if the sequence of (a) is the same as the sequence of (b), or

(ii) a worse prognosis relative to (i) if the sequence of (a) is different from the sequence of (b).

9. The method or the use of any one of claims 1-8, wherein the at least one loci comprises a protein coding sequence.

10. The method or the use of any one of claims 1-9, wherein the at least one loci comprises a regulatory sequence.

11. The method or the use of any one of claims 1-10, wherein the at least one loci comprises a noncoding sequence.

12. The method or the use of claim 1 or 5, wherein the at least one loci consists of a protein coding sequence.

13. The method or the use of claim 1 or 5, wherein the at least one loci consists of a regulatory sequence.

14. The method or the use of claim 1 or 5, wherein the at least one loci consists of a noncoding sequence.

15. The method or the use of any one of claims 1-14, wherein the sequence difference in (e) comprises a single nucleotide polymorphism.

16. The method or the use of claim 15, wherein the single nucleotide polymorphism is selected from the group consisting of rs2476601, rs4786370, rs9788910, and rs55699988.

17. The method or the use of any one of claims 1-15, wherein the sequence difference in (e) comprises a haplotype sequence selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02.

18. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

19. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component.

20. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

21. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component.

22. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

23. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

24. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component.

25. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

26. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

27. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

28. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

29. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b);

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

30. A method of diagnosing RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform,

an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b); and

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component.

31. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

32. A method of determining a prognosis of RA in a subject, the method comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component.

33. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

34. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) diagnosing the subject as having RA the presence of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, or HLA-DRB1 type 14:02 in the subject sample sequence received in (a) as compared to the sequence of (b) as determined by the memory component.

35. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b);

(e) determining the subject as having:

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

36. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of HLA-DRB1 from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of HLA-DRB1 in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence of the haplotypes HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis relative to (i) based on the presence of 1 or more haplotypes selected from the group consisting of HLA-DRB1 type 01:01, HLA-DRB1 type 01:02, HLA-DRB1 type 04:01, HLA-DRB1 type 04:04, HLA-DRB1 type 04:05, HLA-DRB1 type 04:08, HLA-DRB1 type 10:01, and HLA-DRB1 type 14:02 in the sequence of (a) as compared to sequence of (b) as determined by the memory component.

37. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) diagnosing the subject as having RA the presence of the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

38. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b);

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis in (e).

39. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a sequence of a PTPN22 locus from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a sequence of a PTPN22 locus in a control sample by the memory component in (a);

(c) comparing the sequence of in (a) to the sequence of (b);

(d) receiving a result from comparing the sequence of (a) and the sequence of (b); and

(e) determining the subject as having

(i) a good prognosis based on the absence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component, or

(ii) a worse prognosis based on the presence the SNP rs2476601 in the sequence of (a) as compared to the sequence of (b) as determined by the memory component.

40. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, or an IL-32 gamma transcript isoform from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

41. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) diagnosing the subject as having RA if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

42. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

43. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 transcript isoform selected from the group consisting of an IL-32 beta transcript isoform, an IL-32 delta transcript isoform, an IL-32 zeta transcript isoform, and IL-32 gamma transcript isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 transcript isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level in (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative to the level in (b) as determined by the memory component.

44. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b);

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the diagnosis in (e).

45. Use of a memory component comprising a computer-executable program for diagnosing RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level of (a) to the level of (b);

(d) receiving a result from comparing the level of (a) and level of (b); and

(e) determining the subject as having RA if the level of (a) is elevated relative to the level of (b) as determined by the memory component.

46. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform,

an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b);

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component; and

(f) developing a treatment plan for the subject based on the prognosis determined in (e).

47. Use of a memory component comprising a computer-executable program for determining a prognosis of RA in a subject, comprising the steps of:

(a) receiving a level of an IL-32 protein isoform selected from the group consisting of an IL-32 beta protein isoform, an IL-32 delta protein isoform, an IL-32 zeta protein isoform, and IL-32 gamma protein isoform, from a subject sample by a memory component comprising a computer-executable program;

(b) receiving a level of the same IL-32 protein isoform in (a) in a control sample by the memory component in (a);

(c) comparing the level in (a) to the level of (b);

(d) receiving a result from comparing the level in (a) and the level in (b); and

(e) determining the subject as a poor prognosis if the level in (a) is elevated relative level in (b) as determined by the memory component.

48. The method of any one of claims 1-27 or the use of any one of claims 312-340, wherein the sequence received in (a) is determined by sequencing a nucleic acid in a subject sample.

49. The method or the use of any one of claims 29-32 or 44-34 wherein the level, of the IL-32 protein isoform received in (a) is determined by measuring a protein level in a subject sample.

50. The method or the use of any one of claims 1-49, wherein the subject sample is a biological sample.

51. The method or the use of claim 50, wherein the biological sample comprises a urine sample, a saliva sample, a circulatory fluid sample, a synovial fluid sample, or a solid tissue sample.

52. The method or the use of claim 51, wherein the synovial fluid sample comprises synovial joint fluid.

53. The method or the use of claim 51, wherein the solid tissue sample comprises one or more tissues selected from the group consisting of an epithelial tissue, a connective tissue, a nervous tissue, an adipose tissue, a cartilage, a bone tissue, a skin tissue, a mucous membrane tissue, a glandular tissue, a vascular tissue, a cardiac tissue, a smooth muscle tissue, a skeletal muscle tissue, a neural tissue, a fibrous tissue, a bone marrow tissue, a liver tissue, a kidney tissue, a pancreatic tissue, a pulmonary tissue, and a brain tissue.

54. The method or the use of claim 51, wherein the circulatory fluid sample comprises a blood sample or a lymph sample.

55. The method or the use of any one of claims 1-49, wherein the subject sample is a sequencing dataset.

56. The method or the use of claim 55, wherein the sequencing dataset is generated using one or more methods selected from the group consisting of whole genome sequencing, genome-wide association study, Sanger sequencing, next-generation sequencing, nanopore sequencing, shotgun sequencing, pyrosequencing, and single-molecule real-time sequencing.

57. The method or the use of any one of claims 1-56, wherein the subject sample is derived from an immune cell subset.

58. The method or the use of claim 57, wherein the immune subset is a myeloid cell subset, a T cell subset, or a B cell subset.

59. The method or the use of claim 58, wherein the myeloid cell subset comprises a dendritic cell (DC) subset or a monocyte subset.

60. The method or the use of claim 59, wherein the DC subset comprises a conventional DC or a plasmacytoid DC.

61. The method of or the use claim 59, wherein the monocyte subset comprises a classical monocyte, an intermediate monocyte, or a nonclassical monocyte.

62. The method of or the use claim 58, wherein the T cell subset comprises a CD4+ αβ T cell subset, a CD8+ αβ T cell subset, a γδ T cell subset, or a natural killer (NK) cell subset.

63. The method or the use of claim 62, wherein the CD4+ αβ T cell subset comprises a naïve CD4+ T cell, a central memory CD4+ T cell, an effector memory CD4+ T cell, a CD45RA+ effector memory CD4+ T cell, or a CD4+ T regulatory cell.

64. The method or the use of claim 62, wherein the CD8+ αβ T cell subset comprises a naïve CD8+ T cell, a central memory CD8+ T cell, an effector memory CD8+ T cell, or a CD45RA+ effector memory CD8+ T cell.

65. The method or the use of claim 62, wherein the γδ T cell subset comprises a gamma-delta T cell.

66. The method or the use of claim 62, wherein the NK cell subset comprises a CD56hi NK cell or a CD56low NK cell.

67. The method or the use of claim 58, wherein the B cell subset comprises a naïve B cell or an effector B cell.

68. The method or the use of claim 67, wherein the naïve B cell comprises an unswitched naïve B cell, a class switched naïve B cell, or a transitional B cell.

69. The method or the use of claim 67, wherein the effector B cell comprises a class switched classical memory B cell, an IgM+ IgD- classical memory B cell, an atypical memory B cell, or a class switched plasmablast.

70. The method or the use of any one of claims 1-69, wherein the treatment plan in (f) comprises administering one or more therapeutics selected from the group consisting of a biologic, a recombinant protein, a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

71. The method or the use of claim 70, wherein the one or more therapeutics reduces a level of tumor necrosis factor (TNF) gene expression or protein, a level of anti-interleukin-6 (IL-6) gene expression or protein, a level of interleukin-1 receptor antibody (IL-1) gene expression or protein, or a level or interleukin-32 (IL-32) gene expression or protein.

72. The method or the use of claim 70, wherein the biologic comprises an antibody.

73. The method or the use of claim 72, wherein the antibody is selected from the group consisting of an anti-TNF antibody, an anti- IL-6 receptor antibody, an anti-IL-1 receptor antibody, and an anti-IL-32 receptor antibody.

74. The method or the use of claim 70, wherein the one or more recombinant proteins comprise a recombinant IL-6R antagonist or a recombinant IL-1R antagonist.

75. The method or the use of claim 71, wherein the one or more therapeutics that reduces a level of IL-32 gene expression or protein targets an IL-32 exon 8 domain.

76. The method or the use of claim 71, wherein the one or more therapeutics comprises an inhibitor of an activator of TNF, IL6, IL1α, IL1β, or IL-32 gene expression.

77. The method or the use of claim 71, wherein the one or more therapeutics comprises an inhibitor of an activator of TNF, IL6, IL1α, IL1β, or IL-32 protein function.

78. The method or the use of claim 76 or 77, wherein the one or more therapeutics comprises an inhibitor of JUN, c-Fos, FOSB, FOSL1, FOSL2, or ATF1 gene expression.

79. The method or the use of claim 76 or 77, wherein the one or more therapeutics comprises an inhibitor of activator protein 1 (AP-1) activity.

80. The method or the use of claim 79, wherein the inhibitor of AP-1 activity is selected from the group consisting of a carbachol, a resveratrol, a curcumin, a quercetin, a chlorogenic acid, an anthocyanin, a sulforaphane, a corticosteroid, a tanshinone, a C-Jun N-terminal Kinase (JNK) inhibitor, and a protease inhibitor.

81. The or the use method of claim 70, wherein the one or more therapeutics comprises an inhibitor of expression of one or more genes selected from the group consisting of PTPN22, TICAM1, PRTN3, F2R1, ABCA4, HSPA6, HSPA1B, ARC, CRYAB, SNAI1, BIVM-ERCC5, HSPA1A, WFDC5, RASD1, TREM1, DNAJB1, SERPINA1, WNT10A, PLAC1, IL17F, RHOV, SERPINH1, ANKRD20A1, ADM, IL1R2, ODF1, ABCA1, ZNF662, NIPAL1, GYS2, HEY1, MMP16, CA9TICAM2, SCGB2A2, OSMR, TMPRSS6, CD19, CA12, EPHA4, CAV1, RYR1, CCDC121, and ZNF177.

82. The or the use method of claim 70, wherein the one or more therapeutics comprises an inhibitor of one or more proteins selected from the group consisting of TRIF, PR3, PAR2, HLAABC, CD6, CD155, CD60a, CD31, CD279, CD30, and CD98.

83. A method of treating or preventing RA in a subject in need thereof, the method comprising administering to the subject one or more therapeutics that inhibit an activator of

(a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or

(b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6.

84. Use of one or more therapeutics that inhibit an activator of

(a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or

(b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6, for treating or preventing RA in a subject in need thereof.

85. The method or the use of claim 83, wherein the activator of TNF gene expression or protein function is encoded by a gene selected from the group consisting of Nuclear Factor-kappa B (NF-κB), Tumor Necrosis Factor Receptor Superfamily Member 1A (TNFRSF1A), a Toll-like Receptor, IL-1, interleukin-17 (IL-17), a pathogen-associated molecular pattern (PAMP), interferon-gamma (IFN-γ), CD40 ligand (CD40L), F2R Like Trypsin Receptor 1 (F2RL1), Proteinase 3 (PRTN3), and a Mitogen-Activated Protein Kinase (MAPK) gene.

86. The method or the use of claim 83, wherein the activator of *TNF* gene expression or protein function is a protein selected from the group consisting of NF-κB, Tumor Necrosis Factor Receptor 1 (TNFR1), CD40, a Toll-like Receptor, IL-1, IL-17, IFN-γ, CD14, TIR Domain-Containing Adapter-Inducing Interferon-β (TRIF), Myeloid Differentiation Primary Response 88 (MyD88), Protease activated receptor 2 (PAR2), Proteinase 3 (PRTN3), and a MAPK protein.

87. The method or the use of claim 83, wherein the activator of *IL6* gene expression or protein function is encoded by a gene selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, Signal Transducer and Activator of Transcription 3 (STAT3), TNF, IL-17, IL-6R, F2R1, PRTN3 and a MAPK gene.

88. The method of claim 83, wherein the activator of *IL6* gene expression or protein function is a protein selected from the group consisting of NF-κB, IL-1, a Toll-like Receptor, STAT3, TNF, IL-17, IL-6R, PAR2, PRTN3, and a MAPK protein.

89. The method or the use of claim 83, wherein the activator of *IL1* gene expression or protein function is encoded by a gene selected from the group consisting of NF-κB, a Toll-like Receptor, NOD-like Receptor Family, Pyrin Domain Containing 3 (NLRP3), Apoptosis-Associated Speck-like Protein Containing a CARD (ASC), IL-18R, MyD88, F2R1, PRTN3, and Interleukin-1 Receptor-Associated Kinase (IRAK).

90. The method or the use of claim 83, wherein the activator of *IL1* gene expression or protein function is a protein selected from the group consisting of NLRP3, ASC, Pro-caspase-1, a Toll-like Receptor, MyD88, Absent in Melanoma 2 (AIM2), PAR2, PRTN3, and a MAPK protein.

91. The method or the use of claim 83, wherein the one or more therapeutics is selected from the group consisting of a biologic, a recombinant protein, a small molecule, an oligonucleotide, an RNA interference (RNAi) therapeutic, and a clustered regularly interspaced short palindromic repeats (CRISPR) therapeutic.

92. The method or the use of claim 83, wherein the one or more therapeutics comprises an IL-32 gene expression inhibitor.

93. The method or the use of claim 92, wherein the IL-32 is a β or a γ isoform.

94. The method or the use of claim 92 or 93, wherein the IL-32 gene expression inhibitor targets an IL-32 exon 8 domain.

95. The method or the use of claim 83, wherein the one or more therapeutics comprises an IL-32 protein inhibitor.

96. The method or the use of claim 95, wherein the IL-32 is a β or a γ isoform.

97. The method or the use of claim 95 or 96, wherein the IL-32 protein inhibitor targets an IL-32 exon 8 domain.

98. The method or the use of claim 97, wherein the IL-32 exon 8 domain is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to SEQ ID NO: 1.

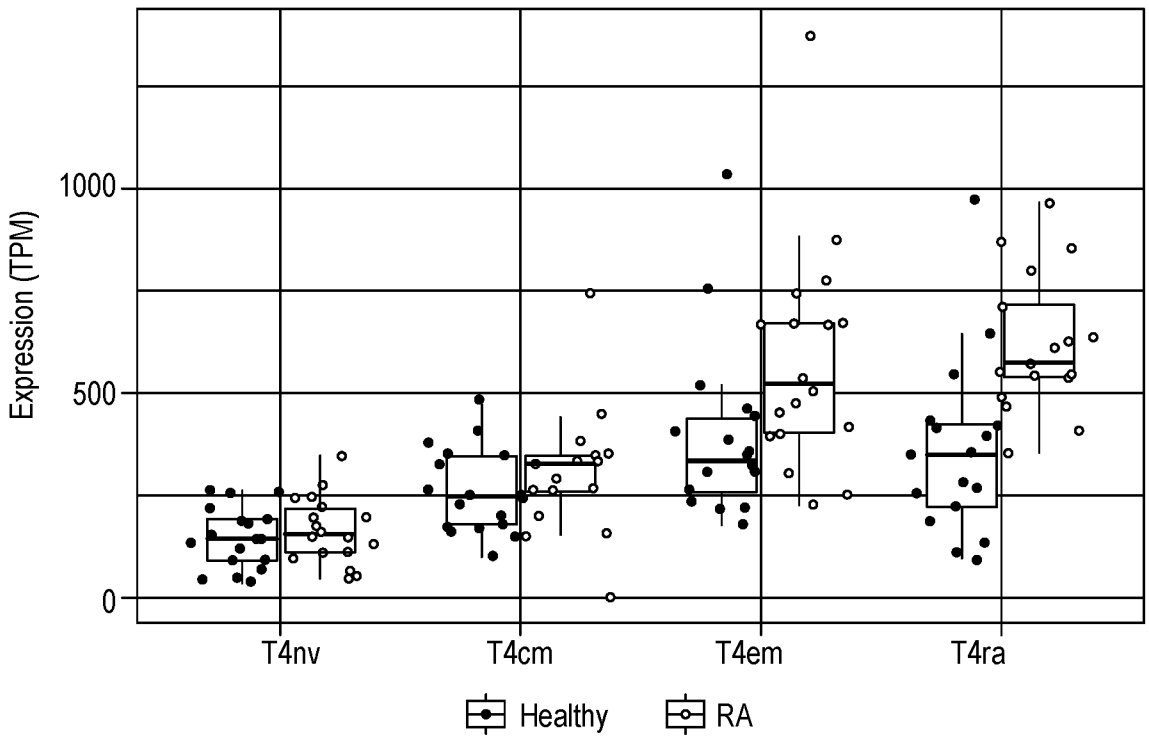


FIG. 1

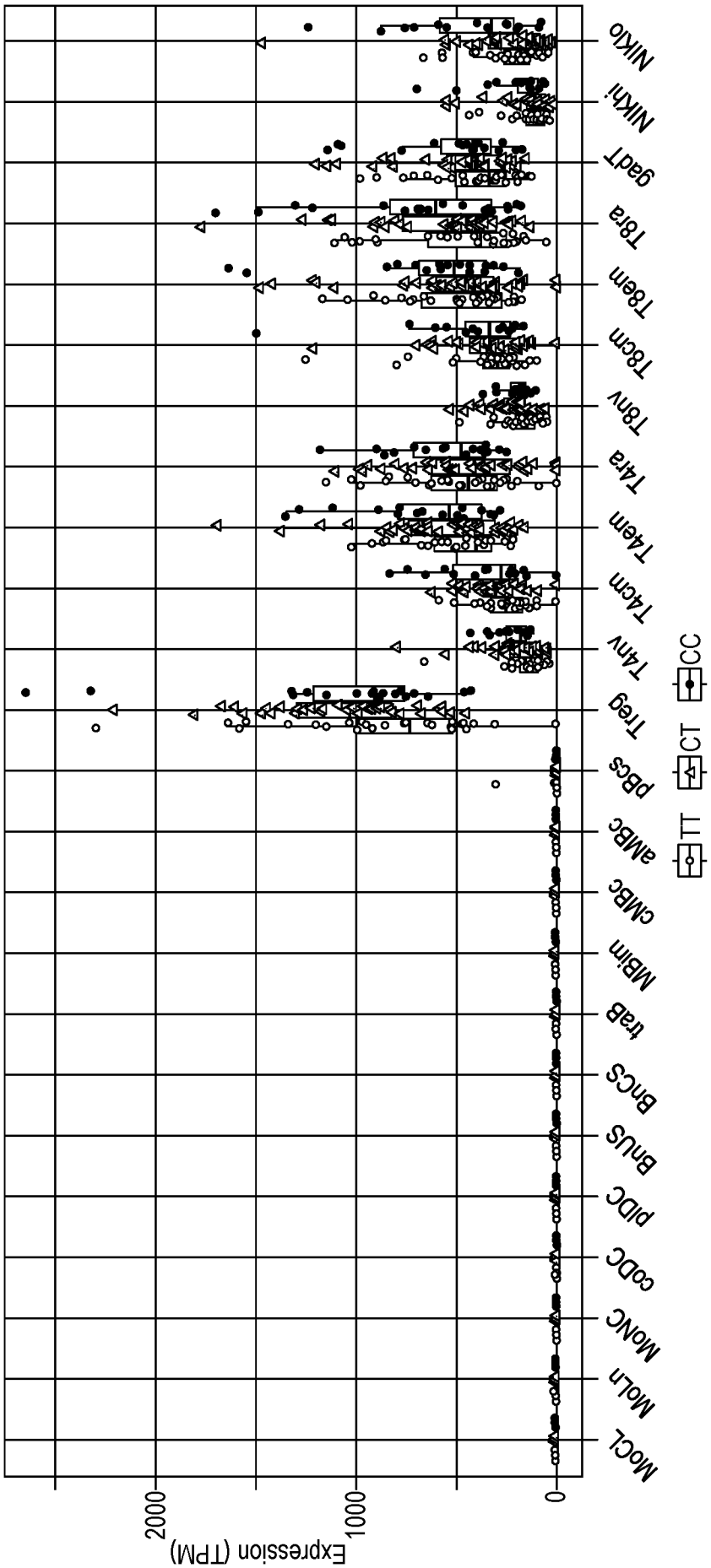

Nlkio
Nlkhi
gadT
Tbra
Tbem
Tbcm
Tbnv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
pIDC
coDC
MoNC
MoLn
MoCL
2000
1000
0
Expression (TPM)
TT
CT
CC

FIG. 2

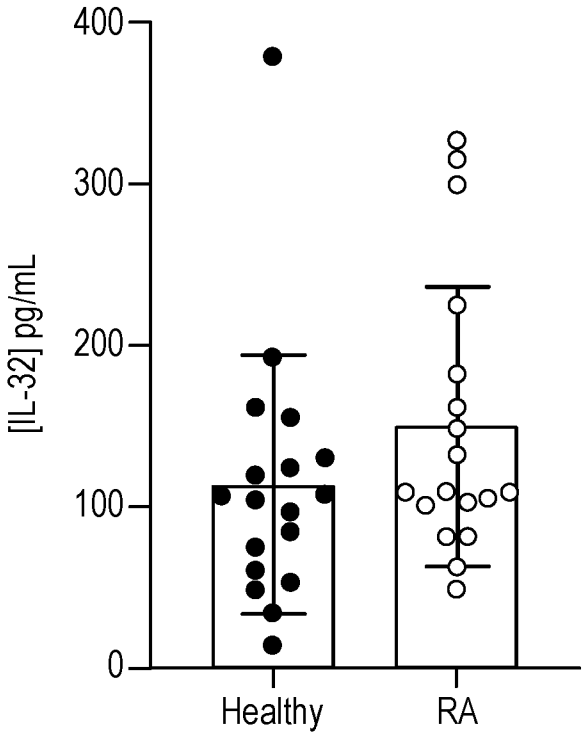

400
300
200
100
0
[IL-32] pg/mL
Healthy
RA

FIG. 3

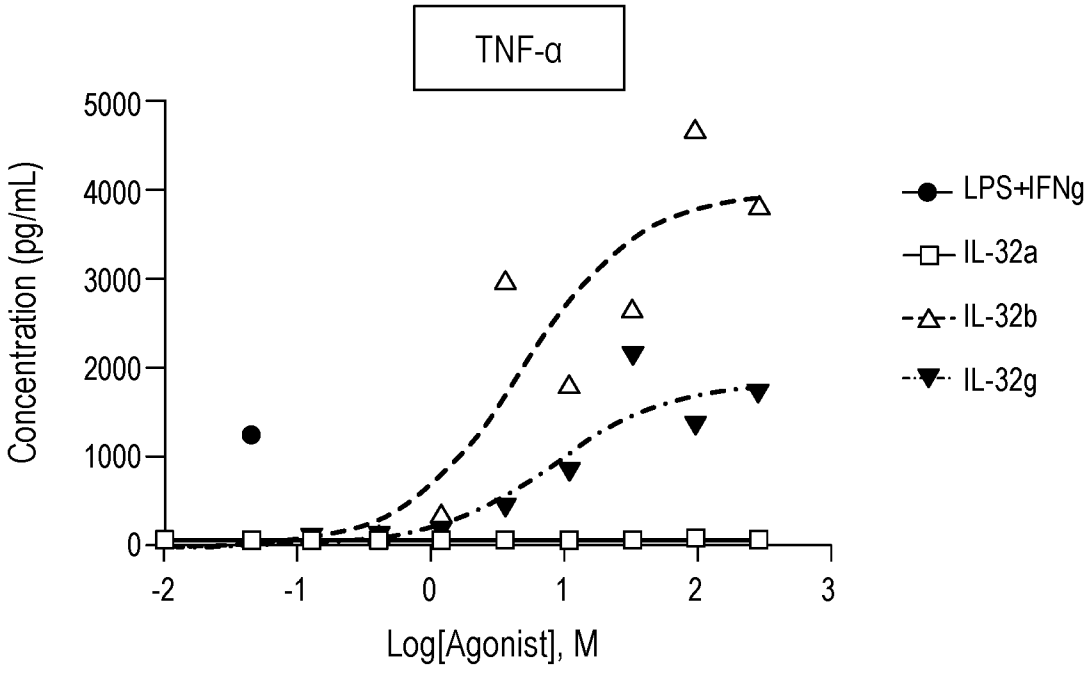

TNF-α
5000
4000
3000
2000
1000
0
Concentration (pg/mL)
-2
-1
0
1
2
3
Log[Agonist], M
LPS+IFNg
IL-32a
IL-32b
IL-32g

FIG. 4A

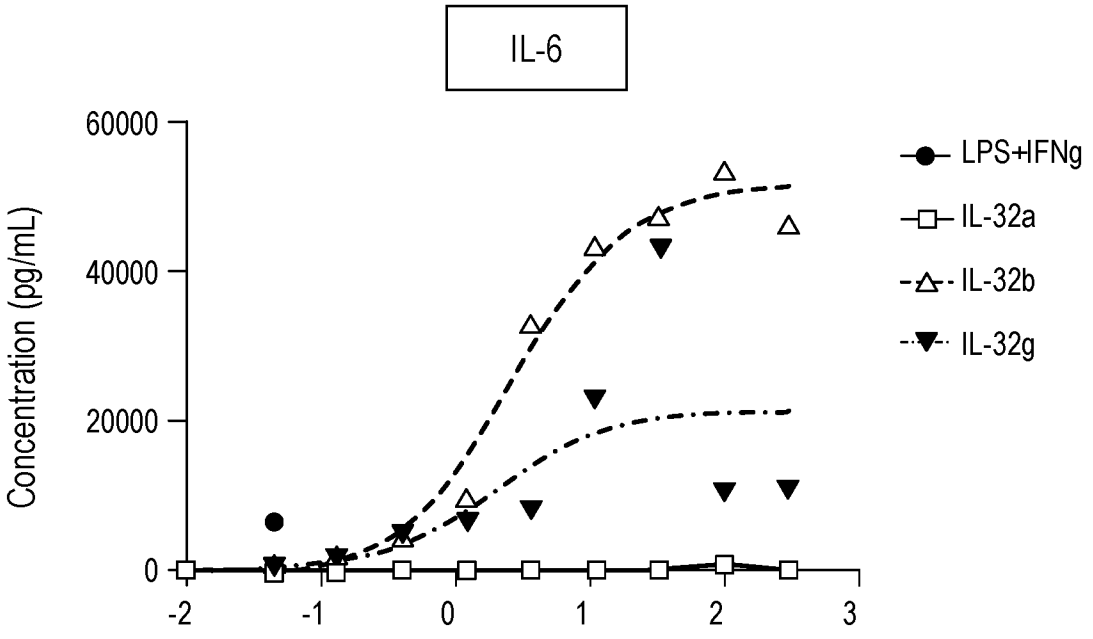

IL-6
60000
40000
20000
0
Concentration (pg/mL)
-2
-1
0
1
2
3
LPS+IFNg
IL-32a
IL-32b
IL-32g

FIG. 4B

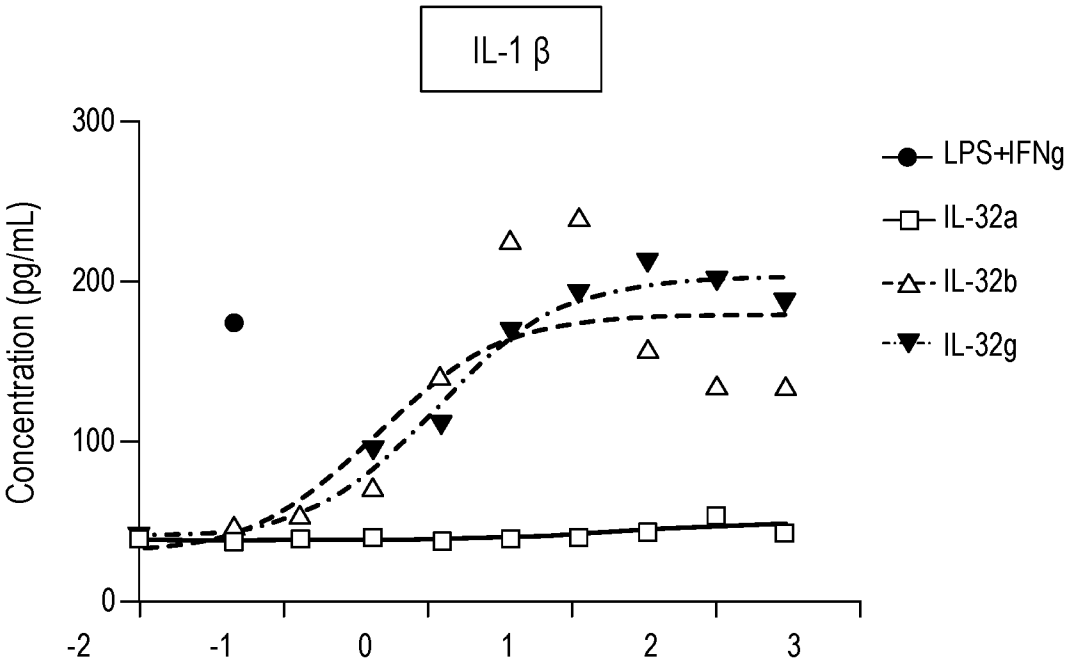

IL-1 β
300
200
100
0
Concentration (pg/mL)
-2
-1
0
1
2
3
LPS+IFNg
IL-32a
IL-32b
IL-32g

FIG. 4C

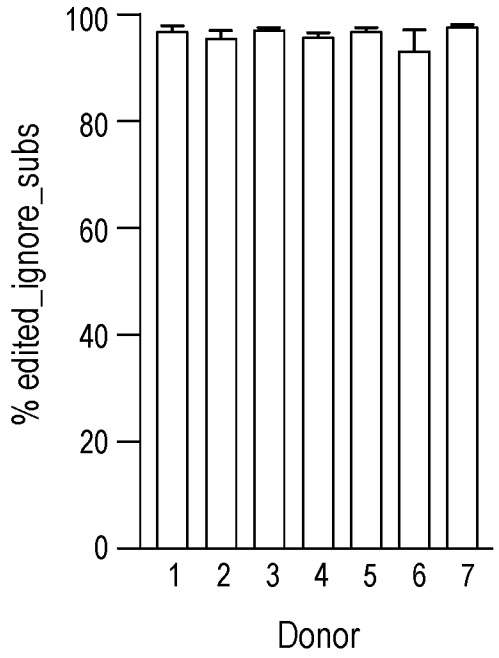

100
80
60
40
20
0
% edited_ignore_subs
1 2 3 4 5 6 7
Donor

FIG. 5A

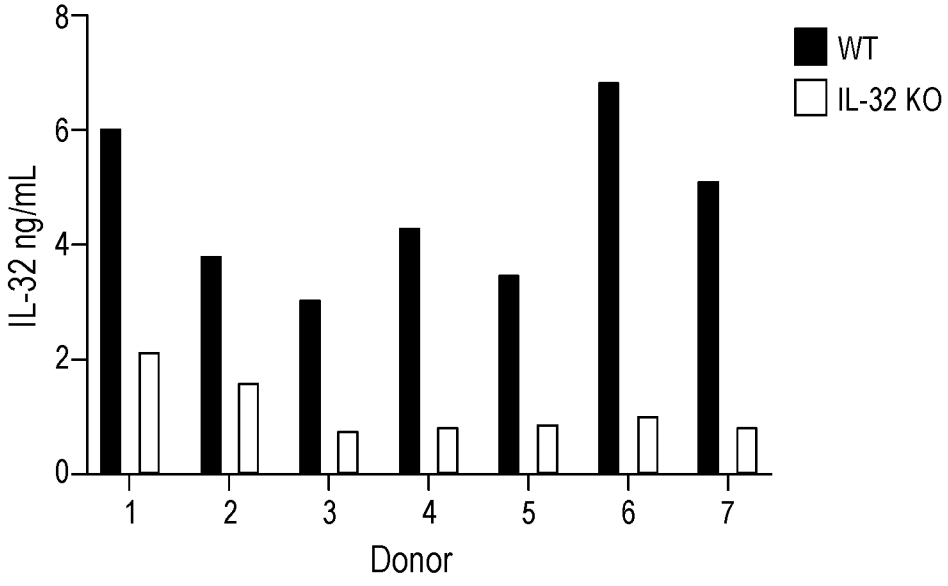

8
6
4
2
0
IL-32 ng/mL
WT
IL-32 KO
1 2 3 4 5 6 7
Donor

FIG. 5B

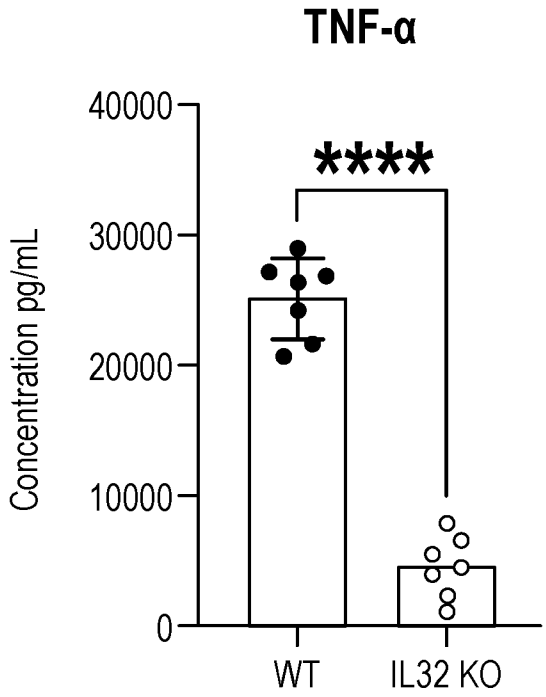

TNF-α
40000
30000
20000
10000
0
Concentration pg/mL
****
WT
IL32 KO

FIG. 5C

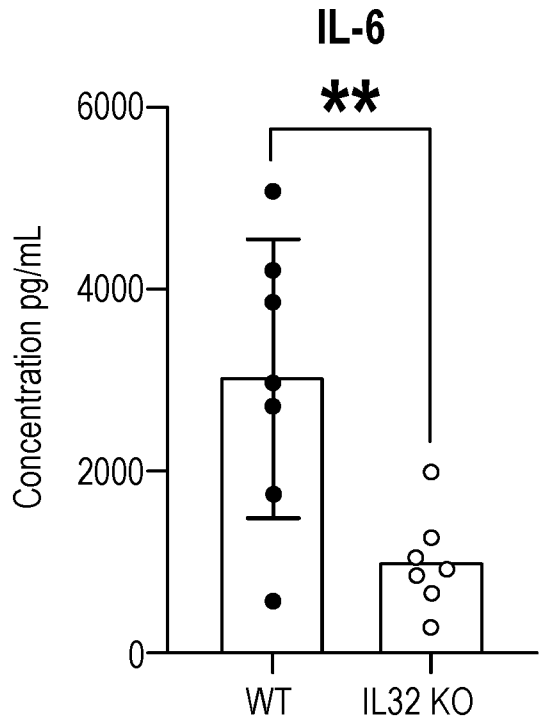

IL-6
6000
4000
2000
0
Concentration pg/mL
**
WT
IL32 KO

FIG. 5D

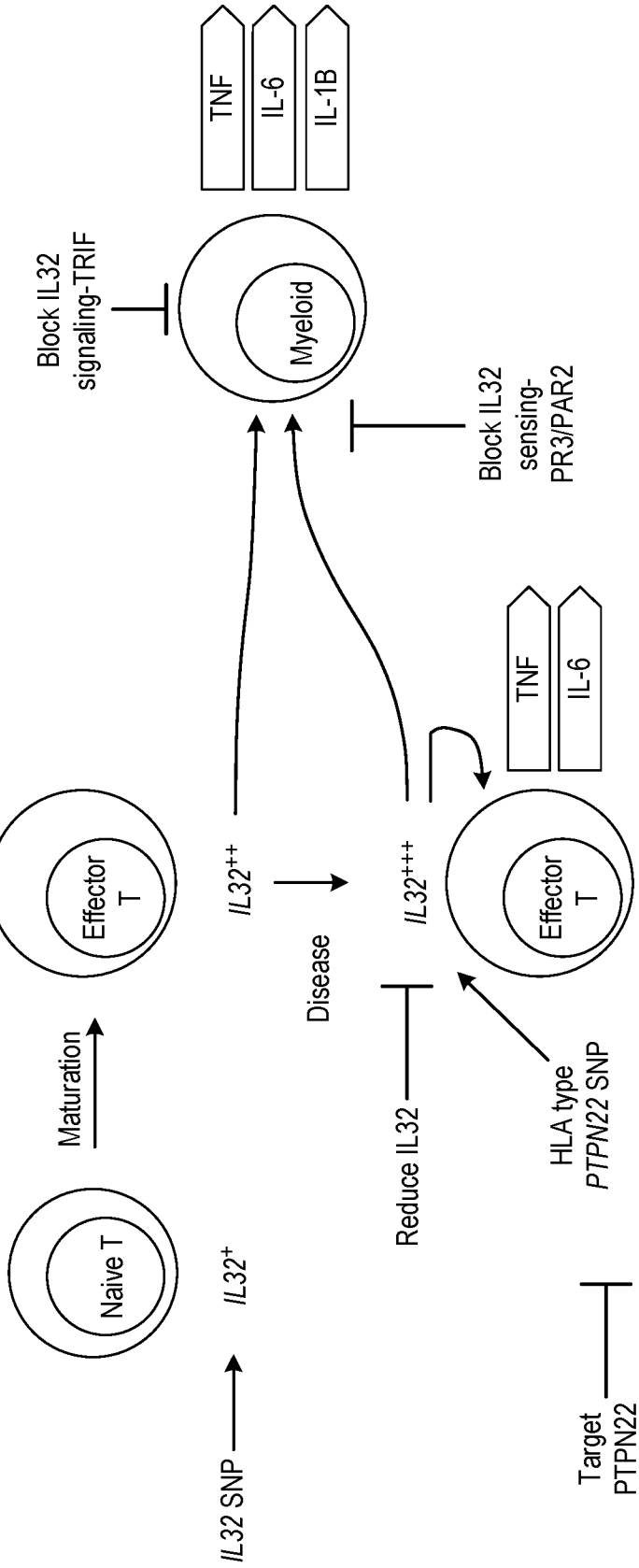

TNF
IL-6
IL-1B
Block IL32 signaling-TRIF
Myeloid
Block IL32 sensing-PR3/PAR2
TNF
IL-6
Effector T
IL32++
Disease
IL32+++
Effector T
Maturation
Naive T
IL32+
Reduce IL32
HLA type PTPN22 SNP
IL32 SNP
Target PTPN22

FIG. 6

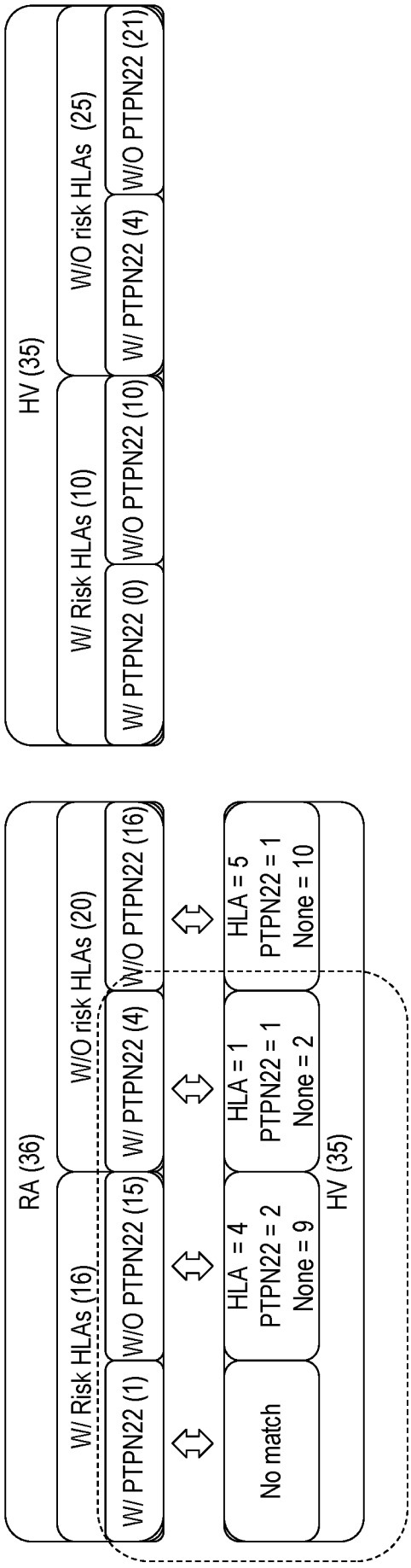

HV (35)
W/ Risk HLAs (10)
W/O risk HLAs (25)
W/ PTPN22 (0)
W/O PTPN22 (10)
W/ PTPN22 (4)
W/O PTPN22 (21)
RA (36)
W/ Risk HLAs (16)
W/O risk HLAs (20)
W/ PTPN22 (1)
W/O PTPN22 (15)
W/ PTPN22 (4)
W/O PTPN22 (16)
No match
HLA = 4
PTPN22 = 2
None = 9
HLA = 1
PTPN22 = 1
None = 2
HLA = 5
PTPN22 = 1
None = 10
HV (35)

FIG. 7

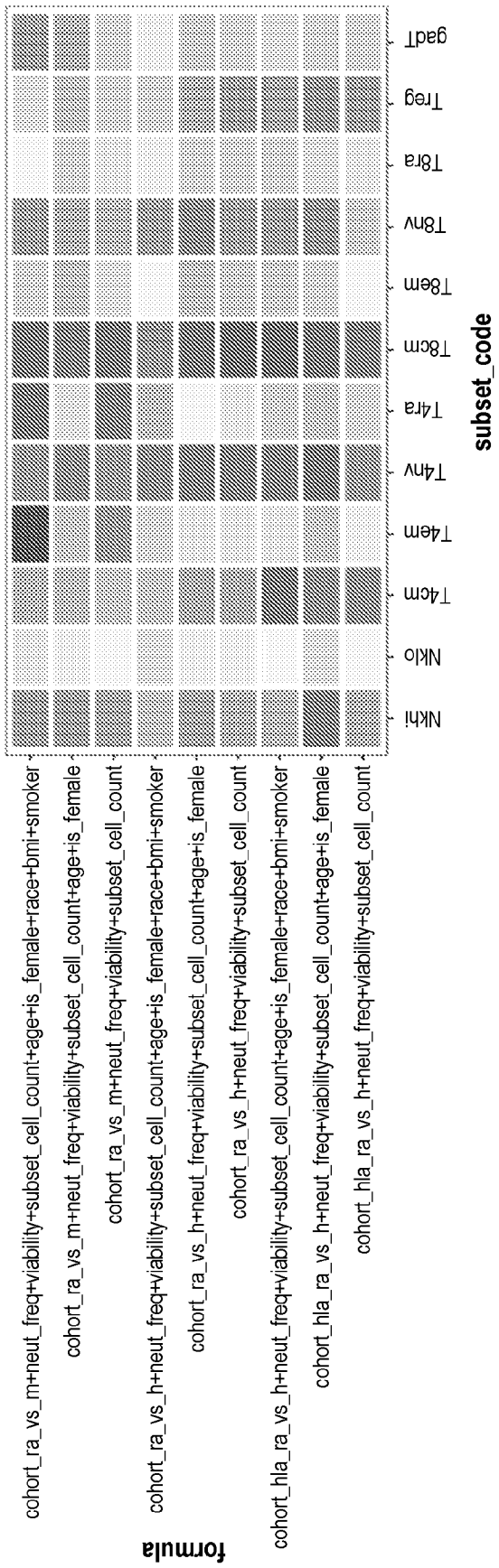

FDR
0.9
0.7
0.5
0.3
0.1
formula
cohort_ra_vs_m+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker
cohort_ra_vs_m+neut_freq+viability+subset_cell_count+age+is_female
cohort_ra_vs_m+neut_freq+viability+subset_cell_count
cohort_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker
cohort_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female
cohort_ra_vs_h+neut_freq+viability+subset_cell_count
cohort_hla_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker
cohort_hla_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female
cohort_hla_ra_vs_h+neut_freq+viability+subset_cell_count
NkHi
NkLo
T4cm
T4em
T4nv
T4ra
T8cm
T8em
T8nv
T8ra
Treg
gadT
subset_code

FIG. 8

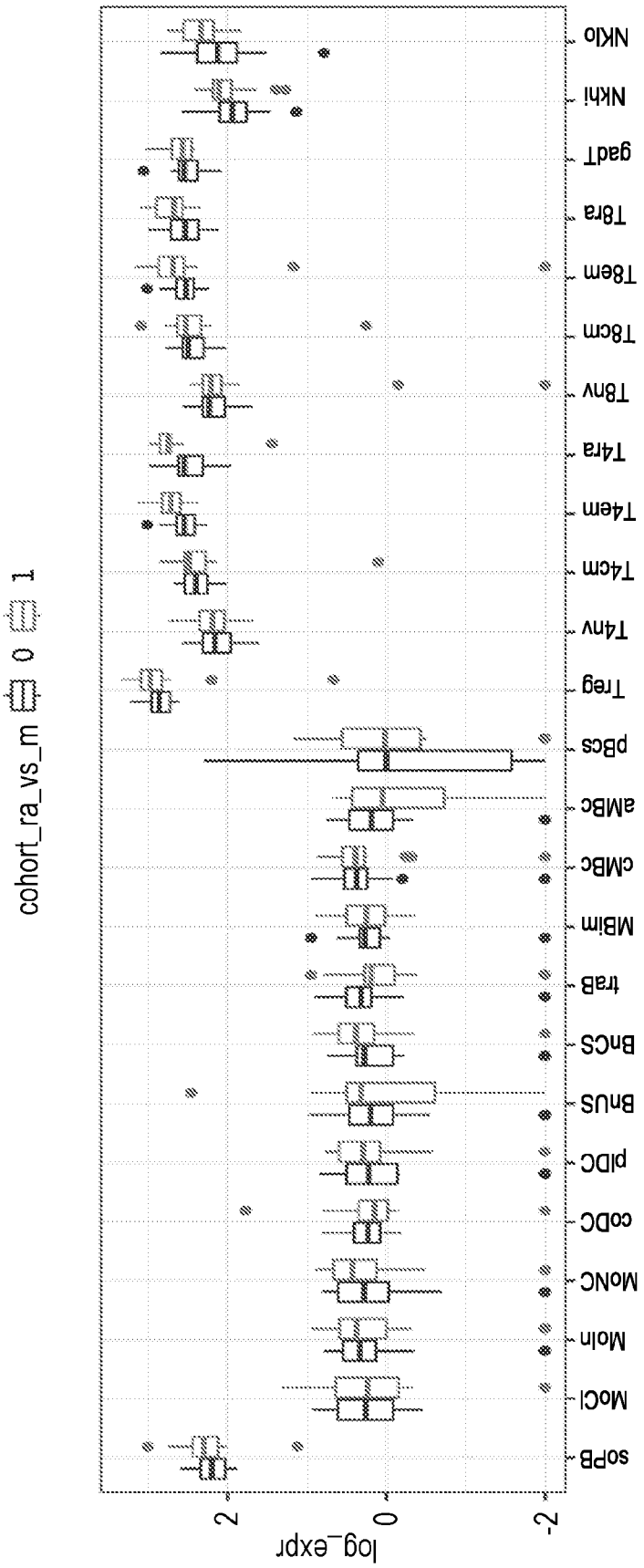

cohort_ra_vs_m 0 1
log_expr
2
0
-2
soPB
MoCl
Moln
MoNC
coDC
pIDC
BnUS
BnCS
traB
MBlm
cMBc
aMBc
pBcs
Treg
T4nv
T4cm
T4em
T4ra
T8nv
T8cm
T8em
T8ra
gadT
Nkhi
Nklo

FIG. 9

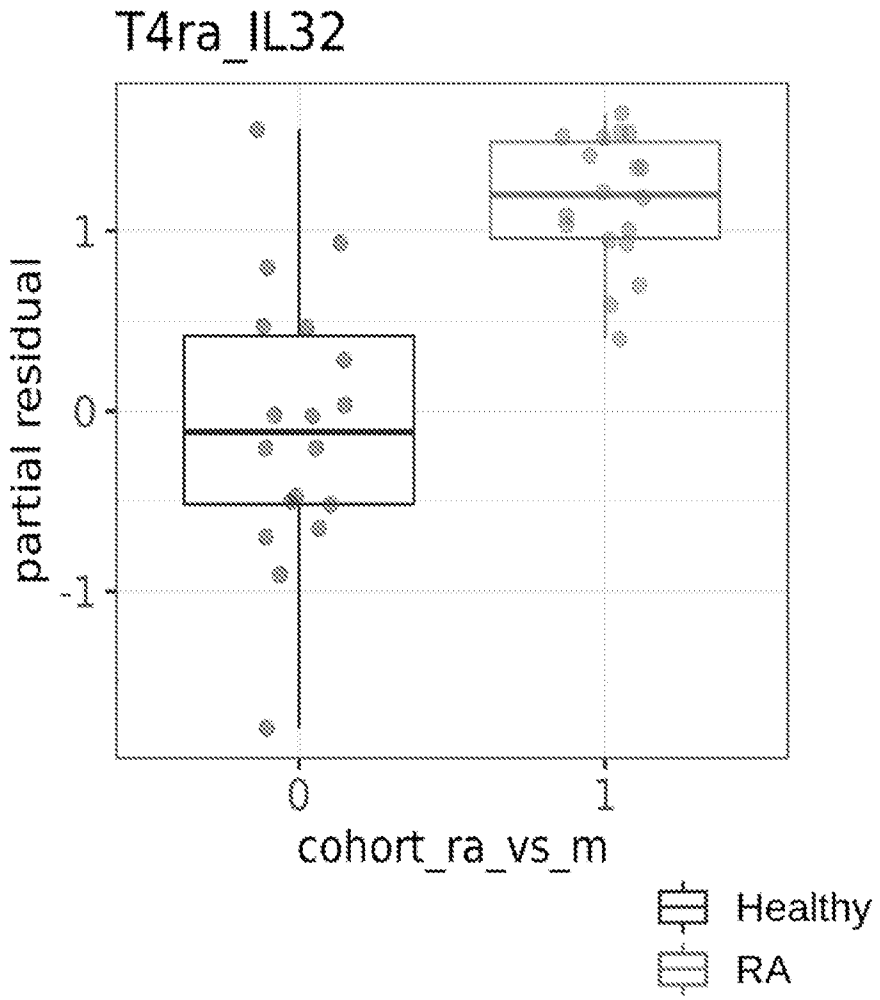
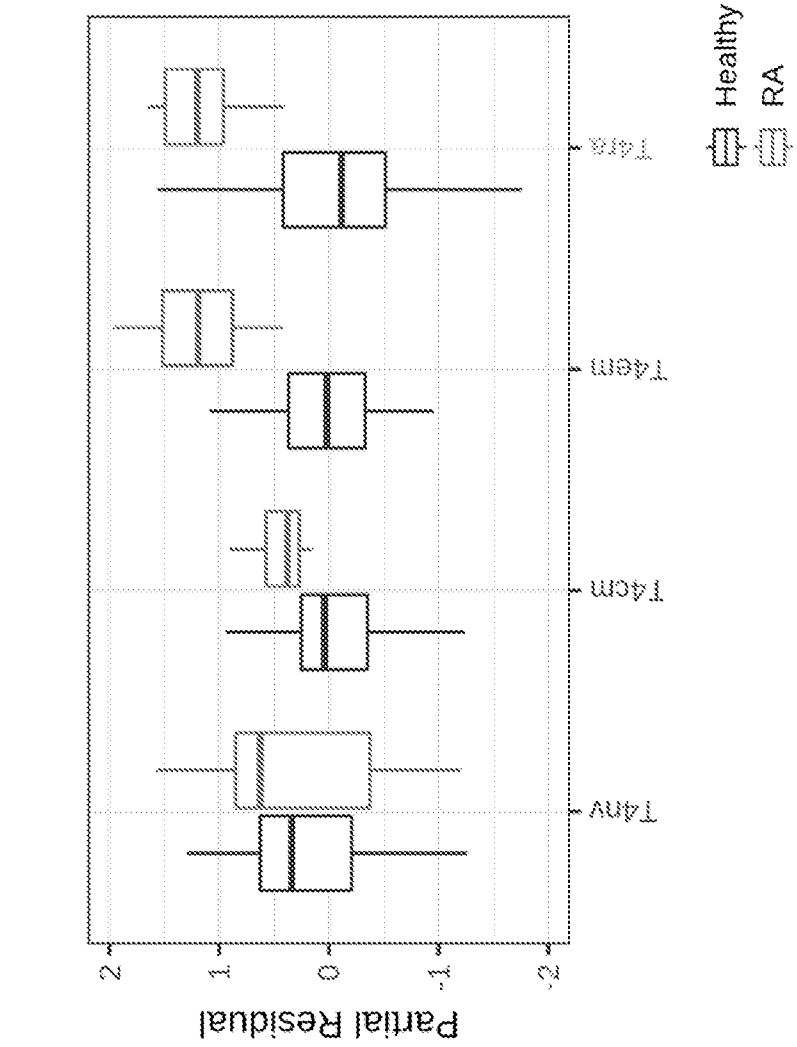


FIG. 10A


Healthy
RA
T4ra
T4em
T4cm
T4nv
Partial Residual
2
1
0
-1
-2

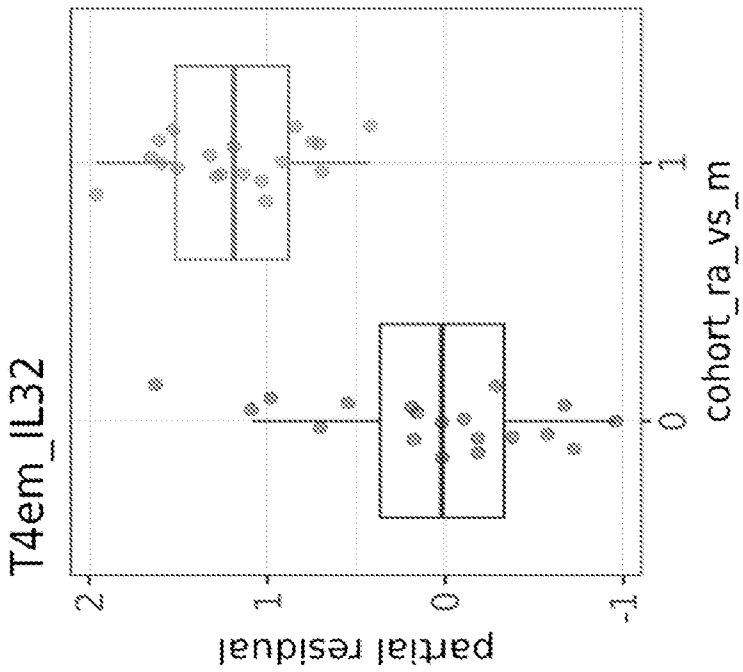

T4em_IL32
partial residual
2
1
0
-1
cohort_ra_vs_m
1
0

FIG. 10B

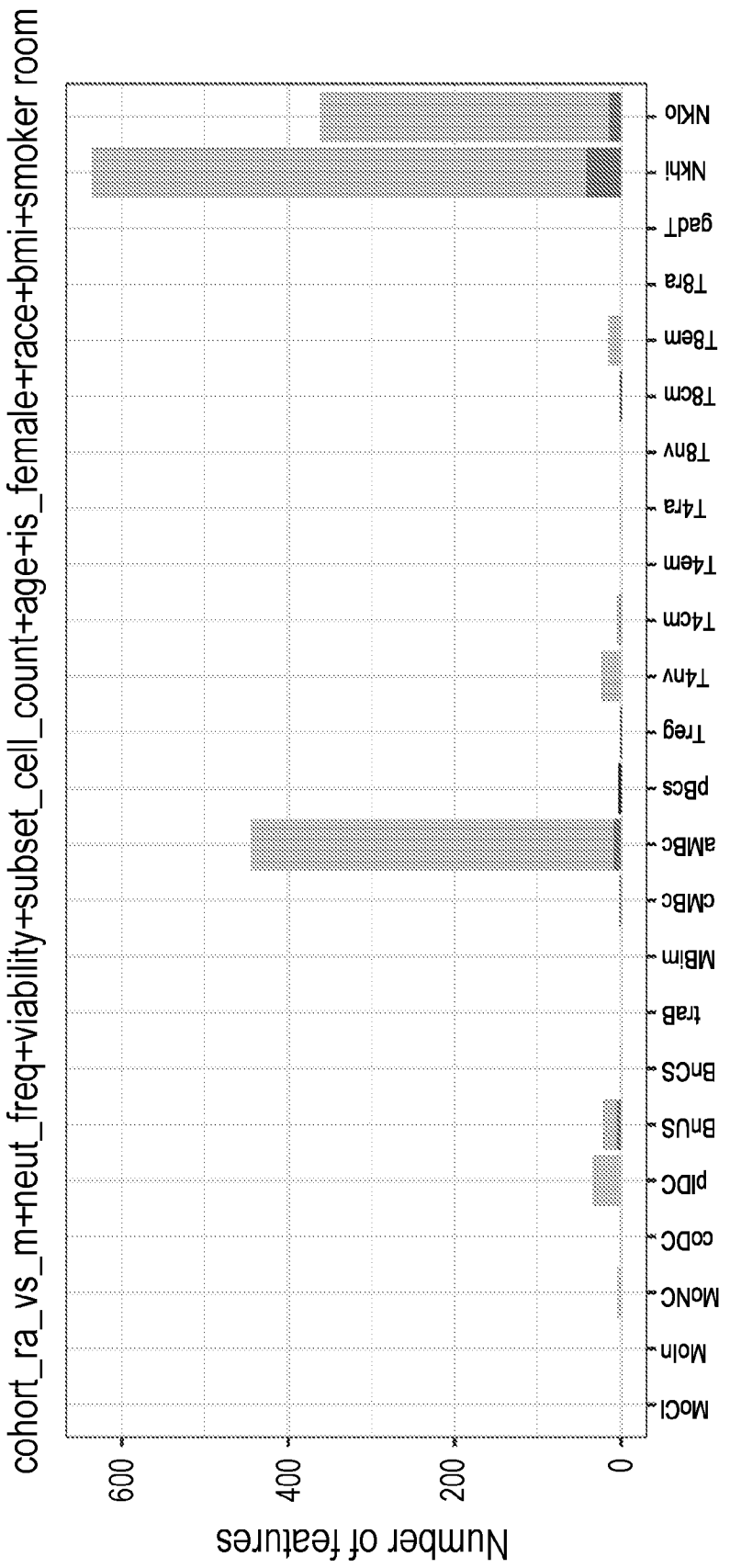

cohort_ra_vs_m+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker room
Number of features
0
200
400
600
MoCl
Moln
MoNC
coDC
pIDC
BnUS
BnCS
traB
MBim
cMBc
aMBc
pBcs
Treg
T4nv
T4cm
T4em
T4ra
T8nv
T8cm
T8em
T8ra
gadT
Nkhi
Nklo

FIG. 11A

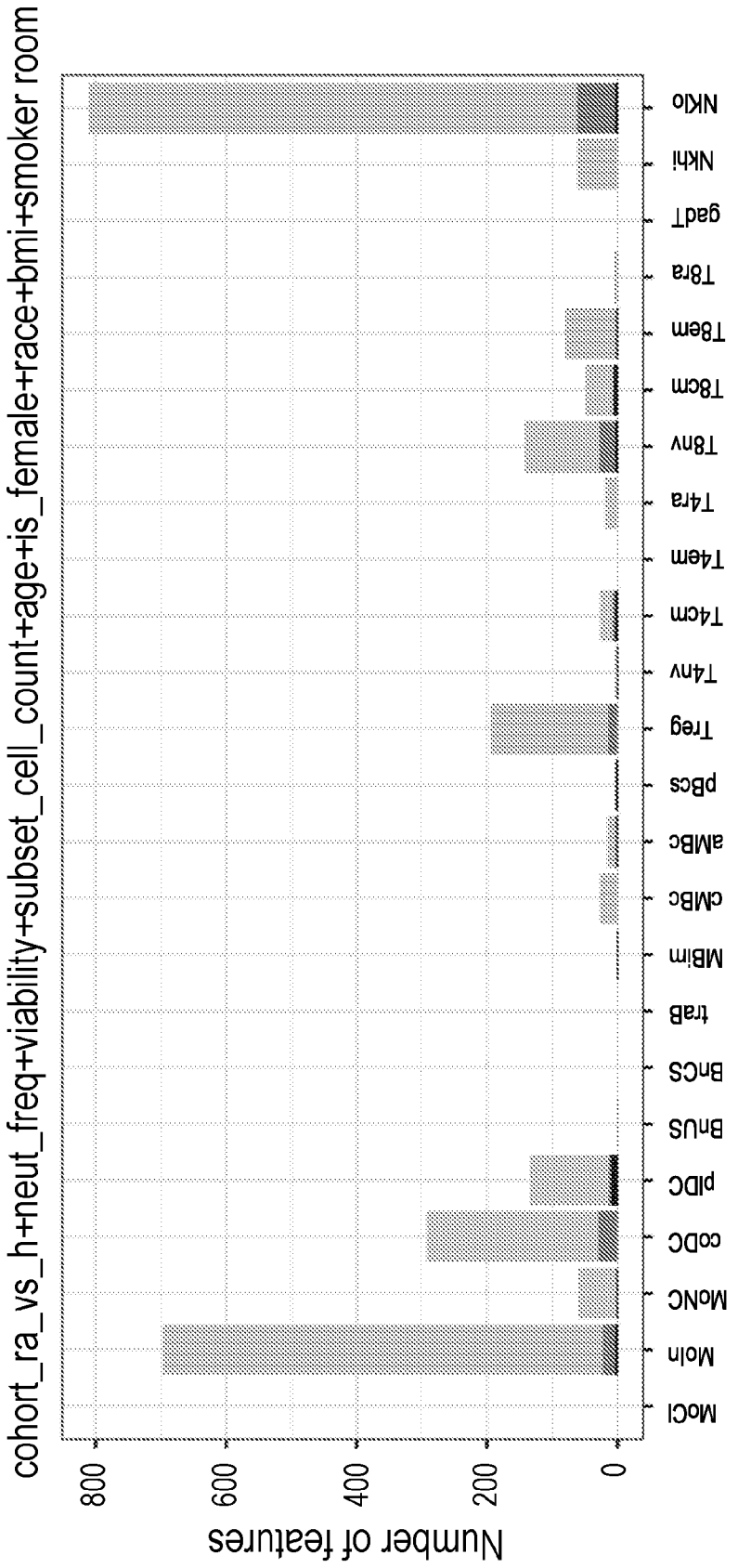

cohort_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker room
Number of features
0
200
400
600
800
MoCl
Moln
MoNC
coDC
pIDC
BnUS
BnCS
traB
MBim
cMBc
aMBc
pBcs
Treg
T4nv
T4cm
T4em
T4ra
T8nv
T8cm
T8em
T8ra
gadT
NKhi
NKlo

FIG. 11B

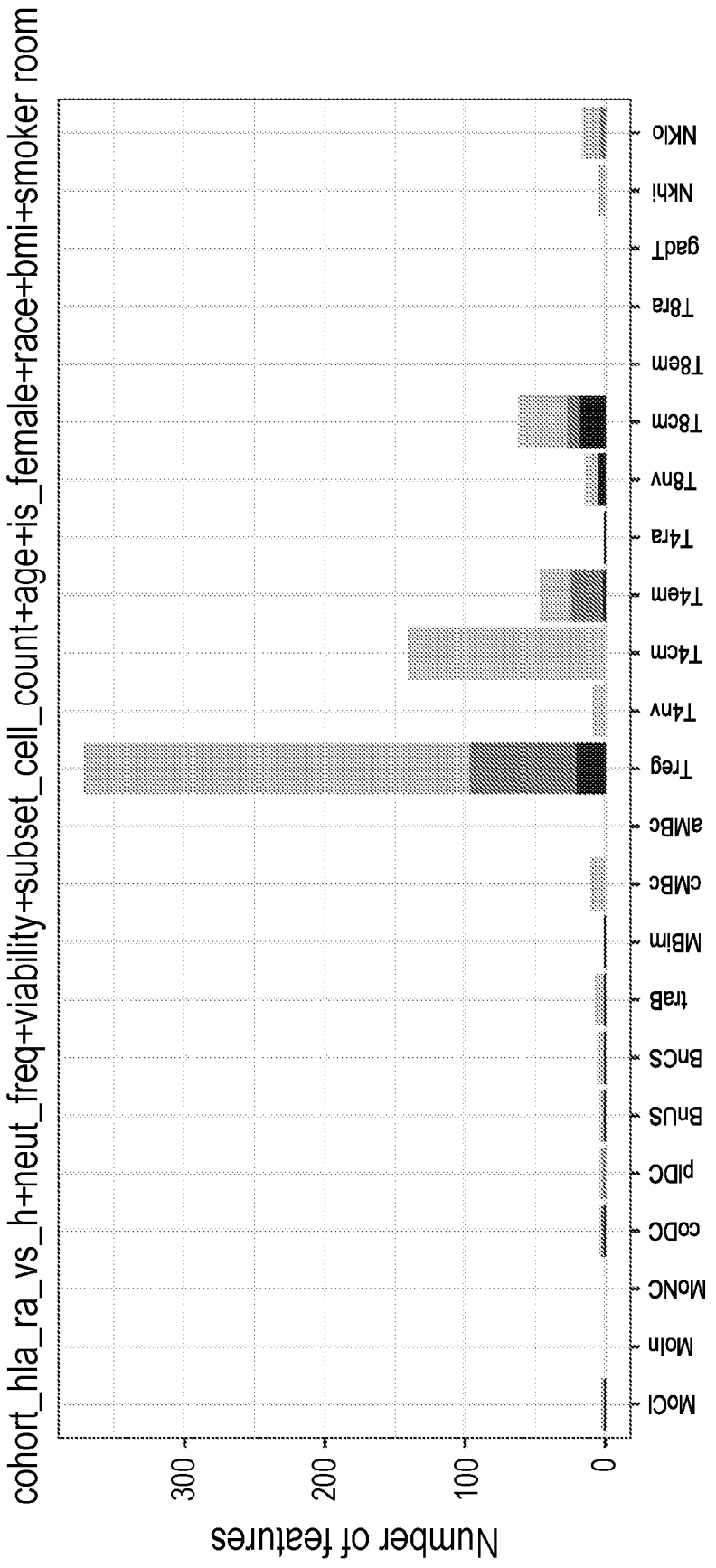

cohort_hla_ra_vs_h+neut_freq+viability+subset_cell_count+age+is_female+race+bmi+smoker room
Number of features
0
100
200
300
MoCl
Moln
MoNC
coDC
pIDC
BnUS
BnCS
traB
MBlm
cMBc
aMBc
Treg
T4nv
T4cm
T4em
T4ra
T8nv
T8cm
T8em
T8ra
gadT
Nkhi
Nklo

FIG. 11C

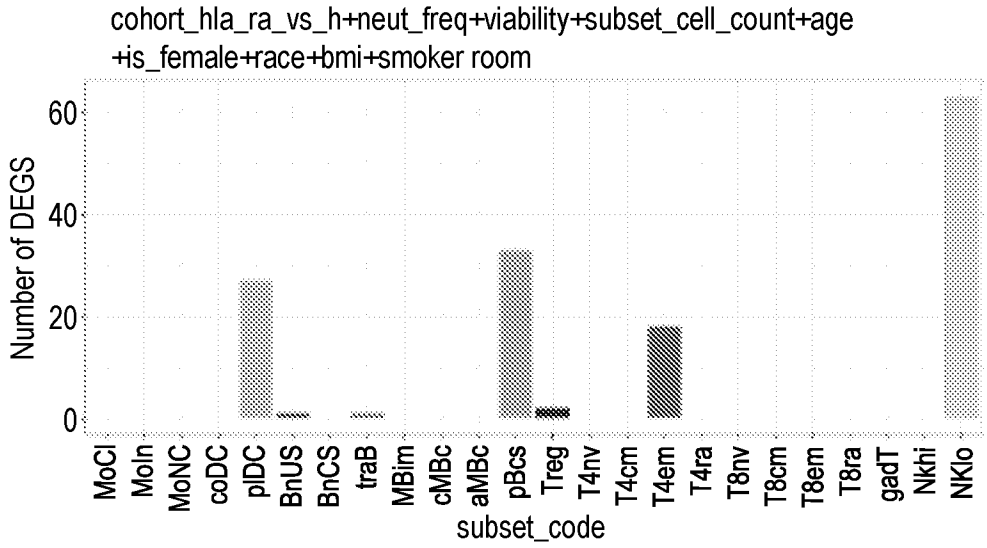


FIG. 12A

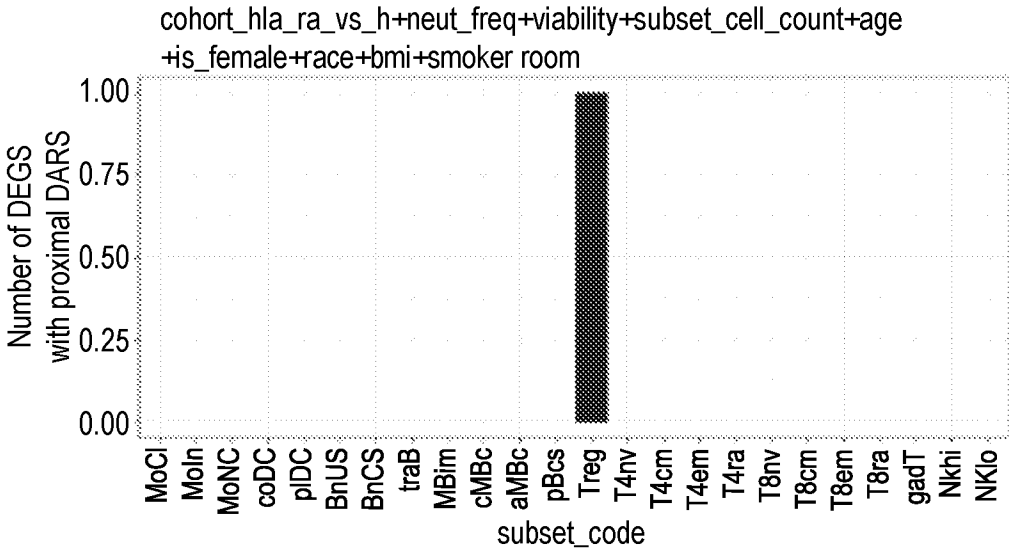


FIG. 12B

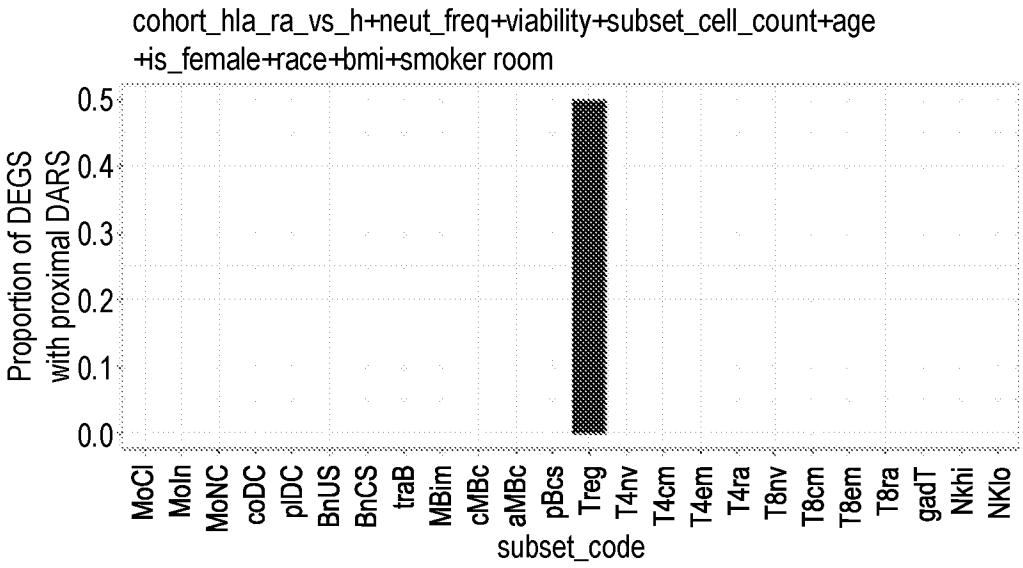


FIG. 12C

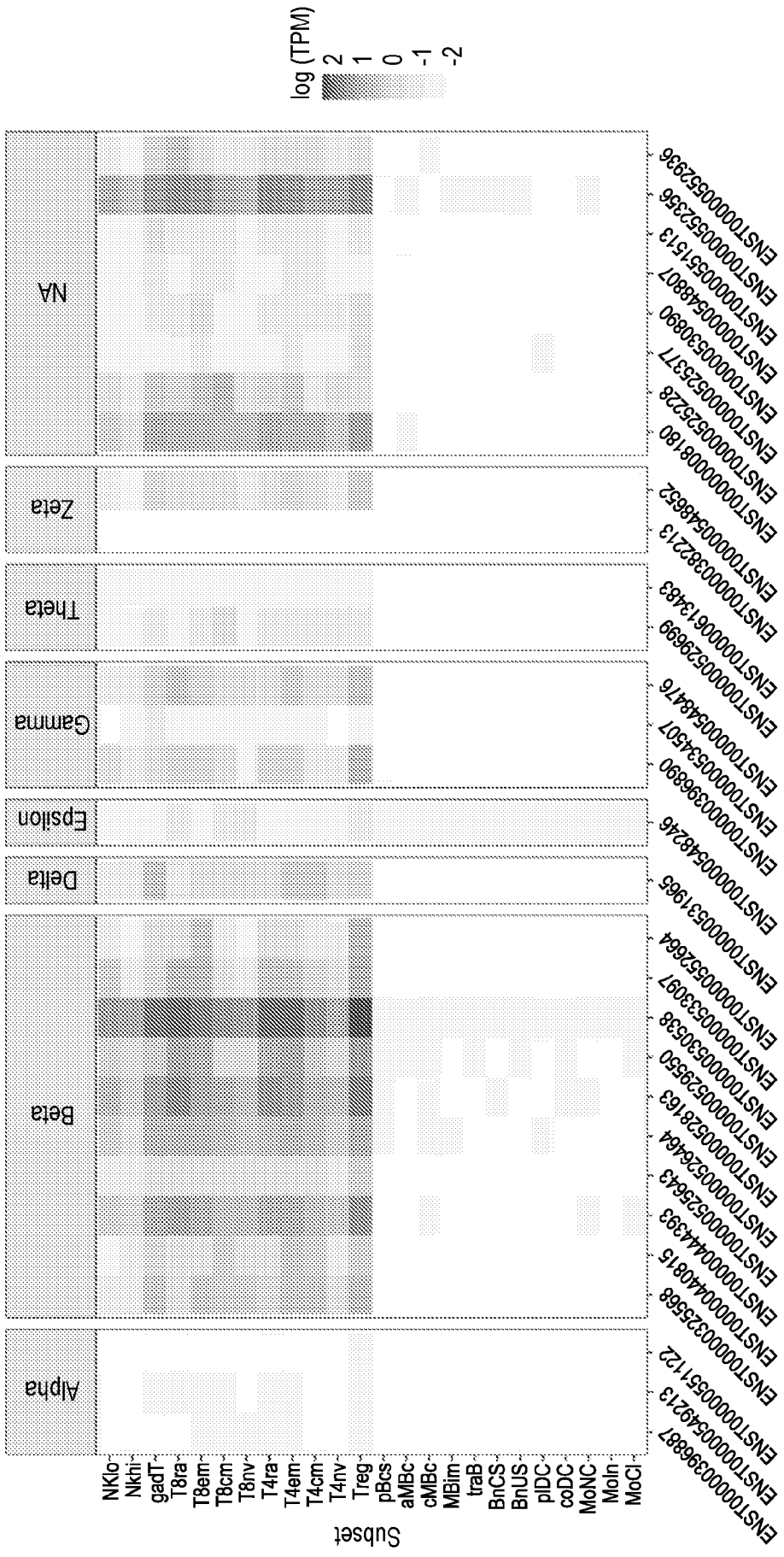

log (TPM)
2
1
0
-1
-2
Alpha
Beta
Delta
Epsilon
Gamma
Theta
Zeta
NA
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl
Transcript ID
ENST00000396887
ENST00000542913
ENST00000551122
ENST00000325568
ENST00000440815
ENST00000544393
ENST00000525643
ENST00000526464
ENST00000528163
ENST00000529550
ENST00000530538
ENST00000533097
ENST00000526664
ENST00000531965
ENST00000548246
ENST00000396890
ENST00000534507
ENST00000548476
ENST00000529699
ENST00000613483
ENST00000382213
ENST00000548652
ENST00000008180
ENST00000525228
ENST00000525377
ENST00000530890
ENST00000548807
ENST00000551513
ENST00000552356
ENST00000529356

FIG. 13

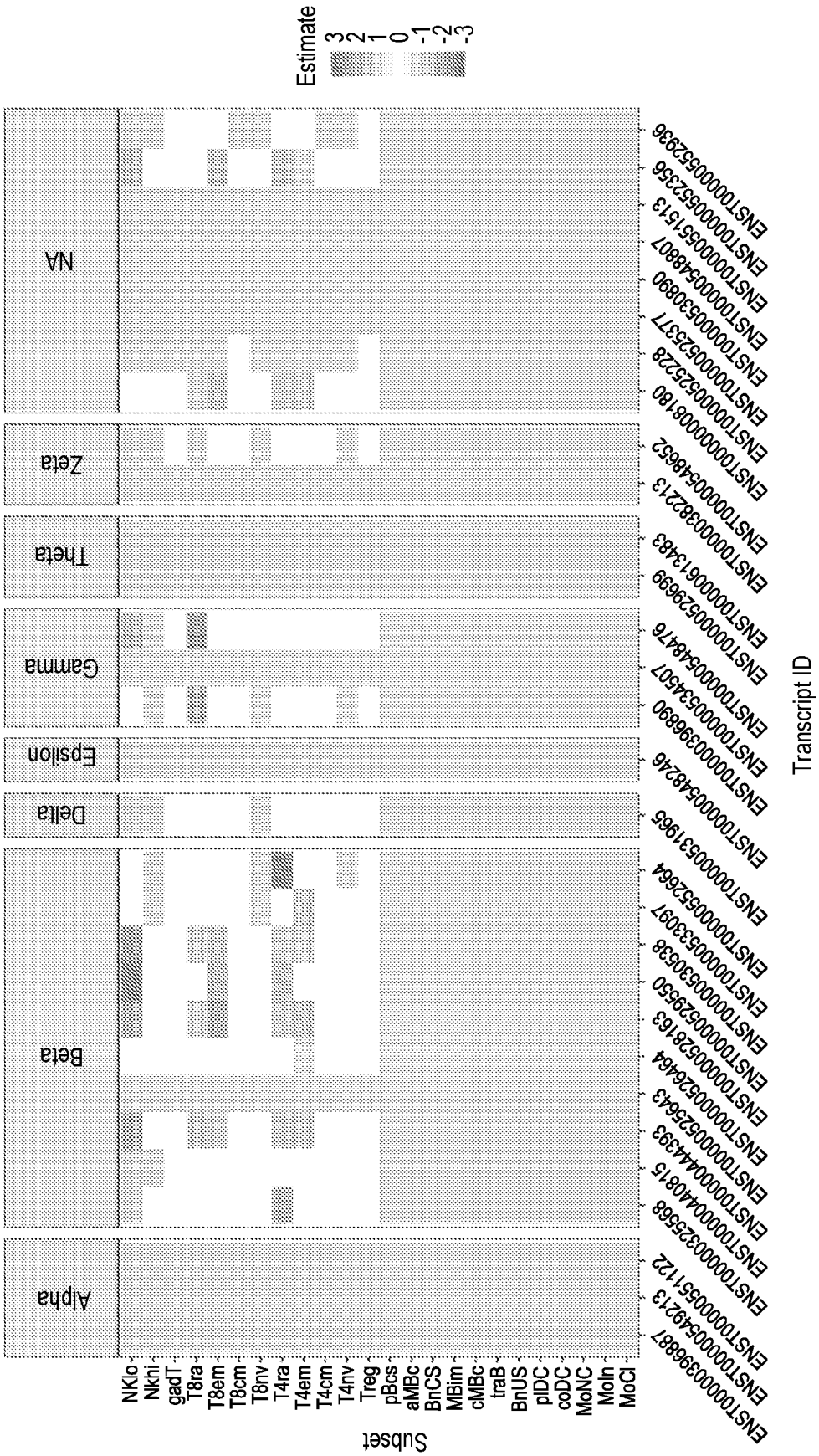

Estimate
3
2
1
0
-1
-2
-3
Alpha
Beta
Delta
Epsilon
Gamma
Theta
Zeta
NA
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
plDC
coDC
MoNC
MoIn
MoCl
Subset
ENST00000396887
ENST00000549213
ENST00000551122
ENST00000325568
ENST00000440815
ENST00000444393
ENST00000523643
ENST00000526464
ENST00000528163
ENST00000529550
ENST00000530538
ENST00000533097
ENST00000526664
ENST00000531965
ENST00000548246
ENST00000539890
ENST00000534507
ENST00000548476
ENST00000529699
ENST00000613483
ENST00000382213
ENST00000548652
ENST00000008180
ENST00000525228
ENST00000525377
ENST00000530890
ENST00000548807
ENST00000551513
ENST00000552356
ENST00000552938
Transcript ID

FIG. 14A

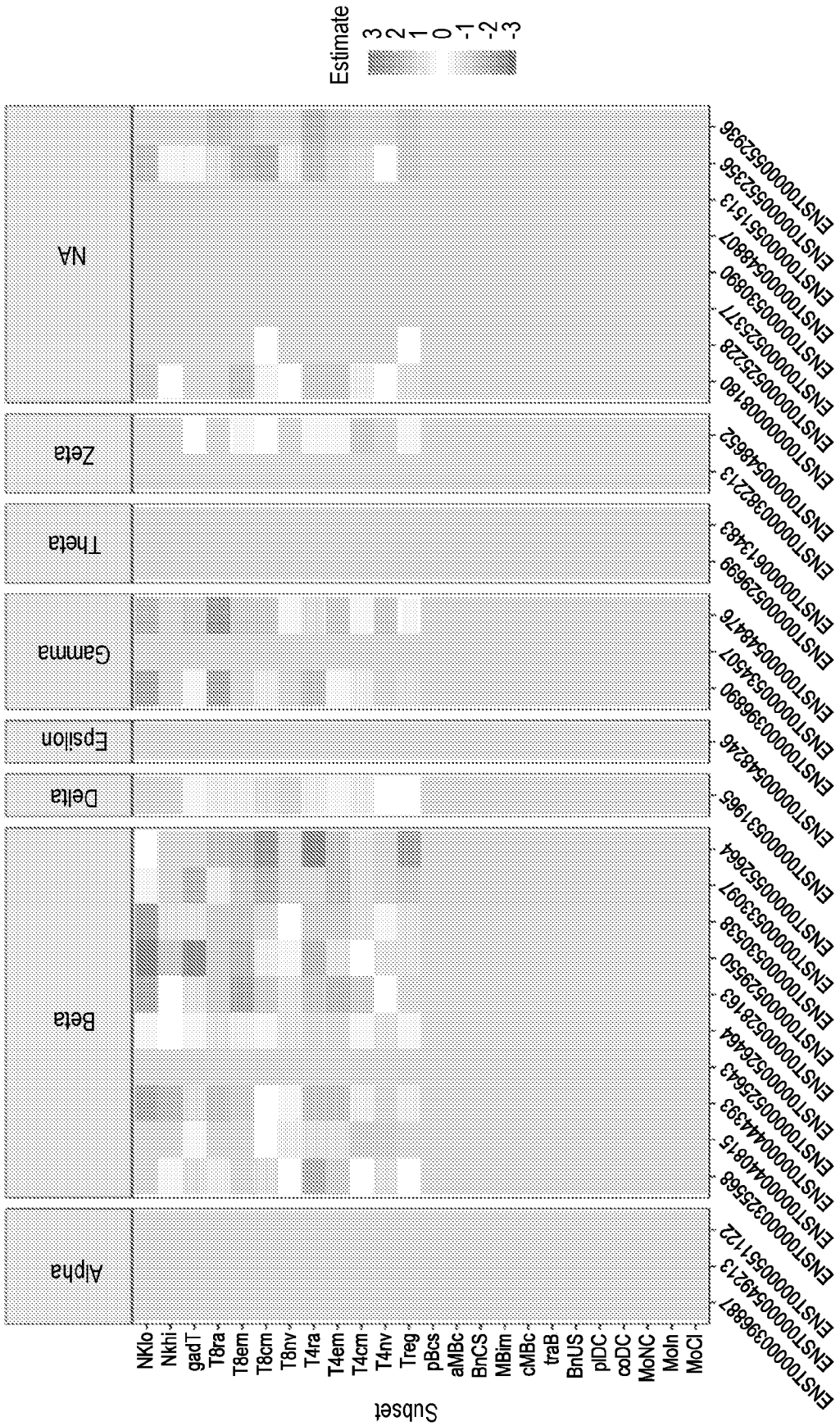

Estimate
3
2
1
0
-1
-2
-3
Alpha
Beta
Delta
Epsilon
Gamma
Theta
Zeta
NA
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
pIDC
coDC
MoNC
MoIn
MoCl
Subset
ENST00000398687
ENST00000549213
ENST00000551122
ENST00000325568
ENST00000440815
ENST00000442393
ENST00000525643
ENST00000526464
ENST00000528163
ENST00000529550
ENST00000530538
ENST00000533097
ENST00000552664
ENST00000531965
ENST00000548246
ENST00000396890
ENST00000534507
ENST00000548476
ENST00000529699
ENST00000613483
ENST00000382213
ENST00000548652
ENST00000008180
ENST00000525228
ENST00000525377
ENST00000530890
ENST00000548807
ENST00000551513
ENST00000552356
ENST00000552936
Transcript ID

FIG. 14B

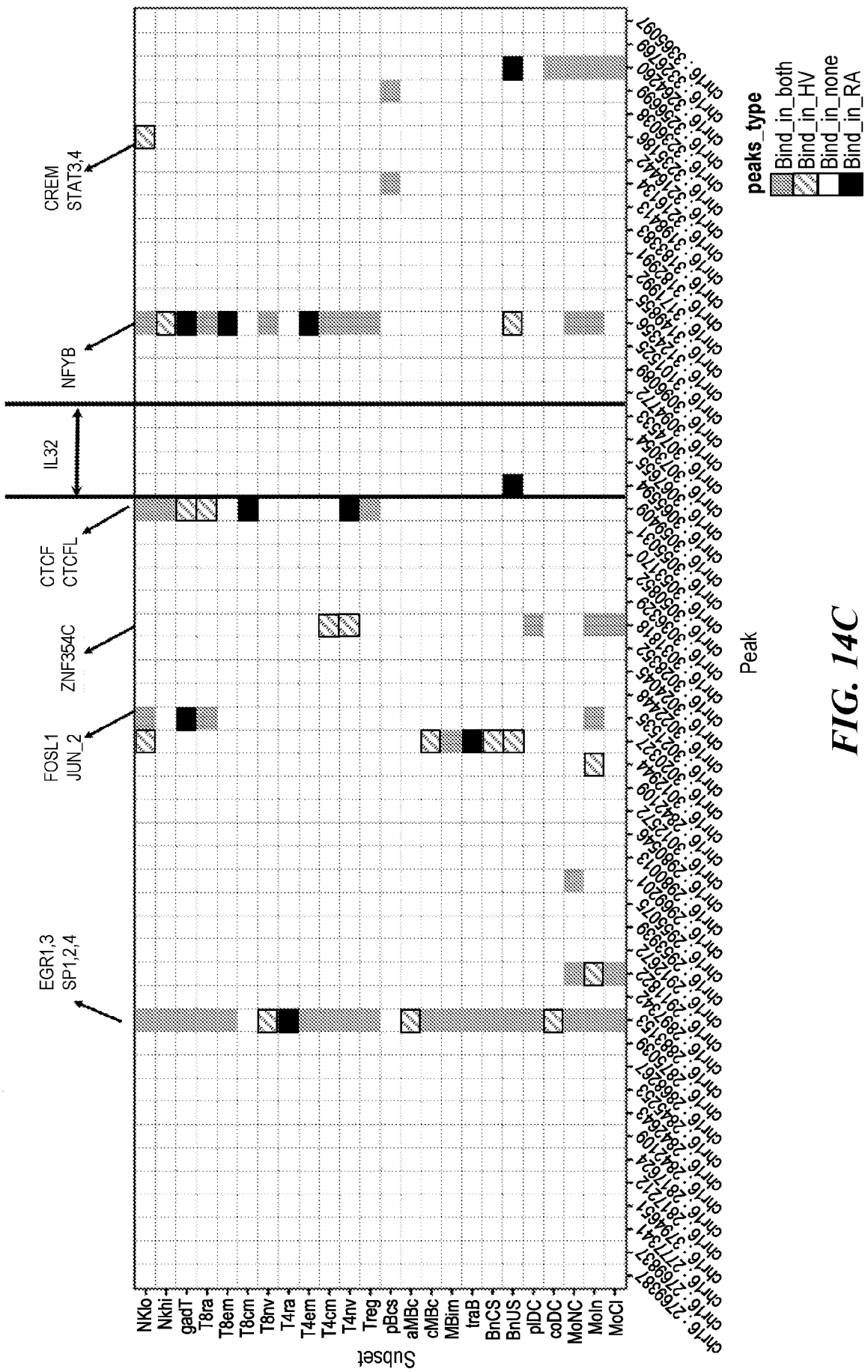

CREM
STAT3,4
NFYB
IL32
CTCF
CTCFL
ZNF354C
FOSL1
JUN_2
EGR1,3
SP1,2,4
peaks_type
Bind_in_both
Bind_in_HV
Bind_in_none
Bind_in_RA
Peak
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl

FIG. 14C

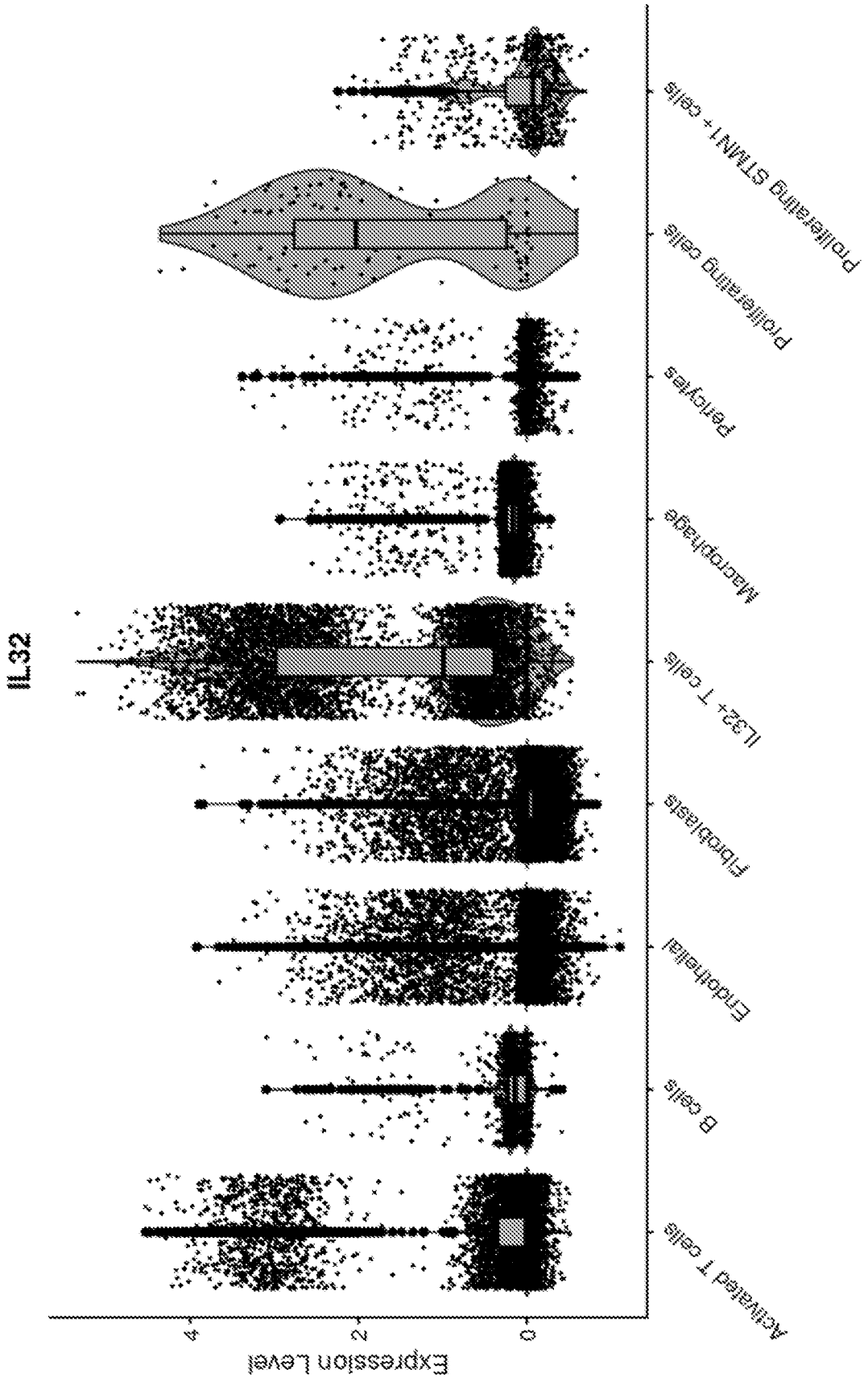

IL32
Expression Level
4
2
0
Activated T cells
B cells
Endothelial
Fibroblasts
IL32+ T cells
Macrophage
Pericytes
Proliferating cells
Proliferating STMN1+ cells

FIG. 15A

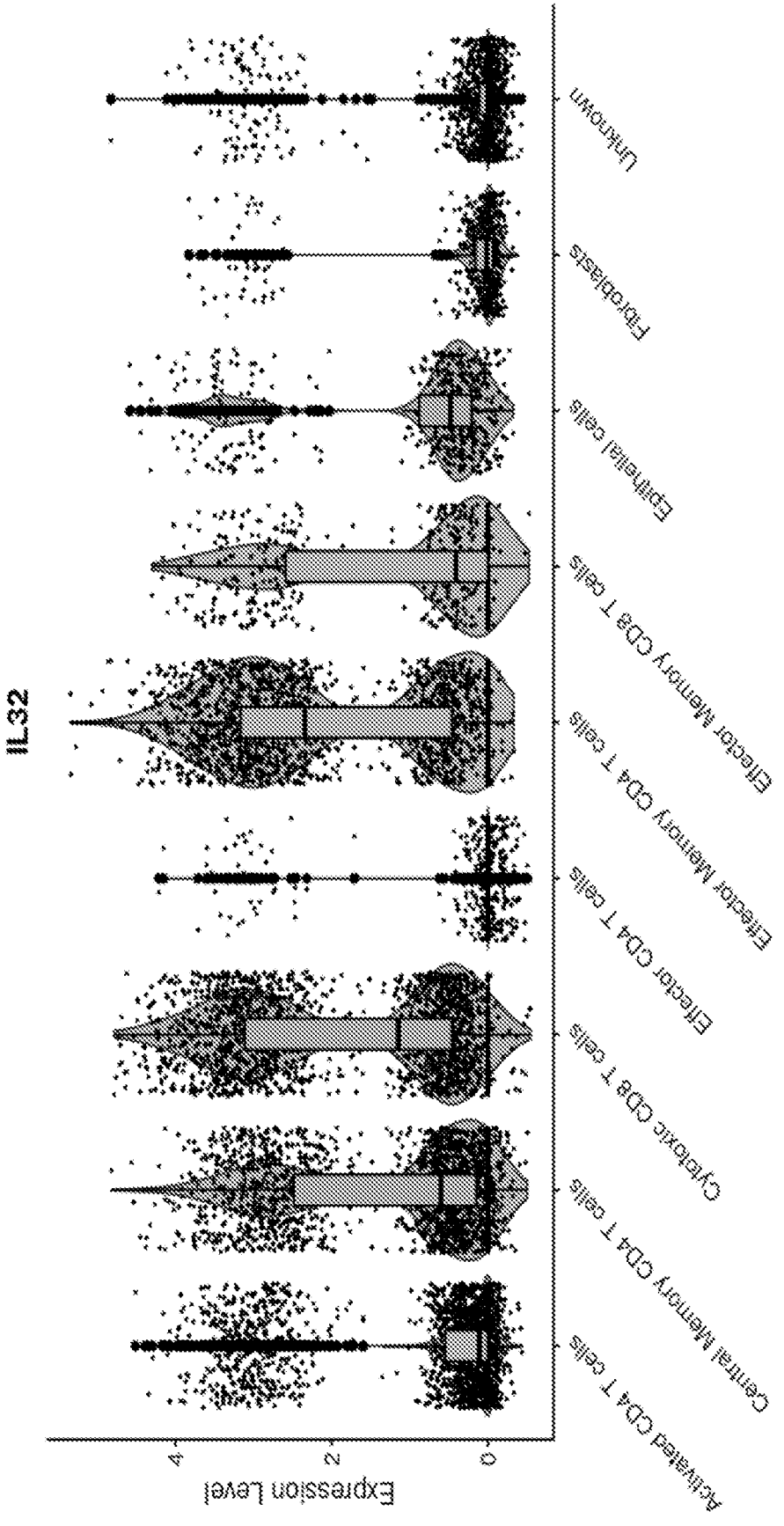

IL32
Expression Level
0
2
4
Activated CD4 T cells
Central Memory CD4 T cells
Cytotoxic CD8 T cells
Effector CD4 T cells
Effector Memory CD4 T cells
Effector Memory CD8 T cells
Epithelial cells
Fibroblasts
Unknown

FIG. 15B

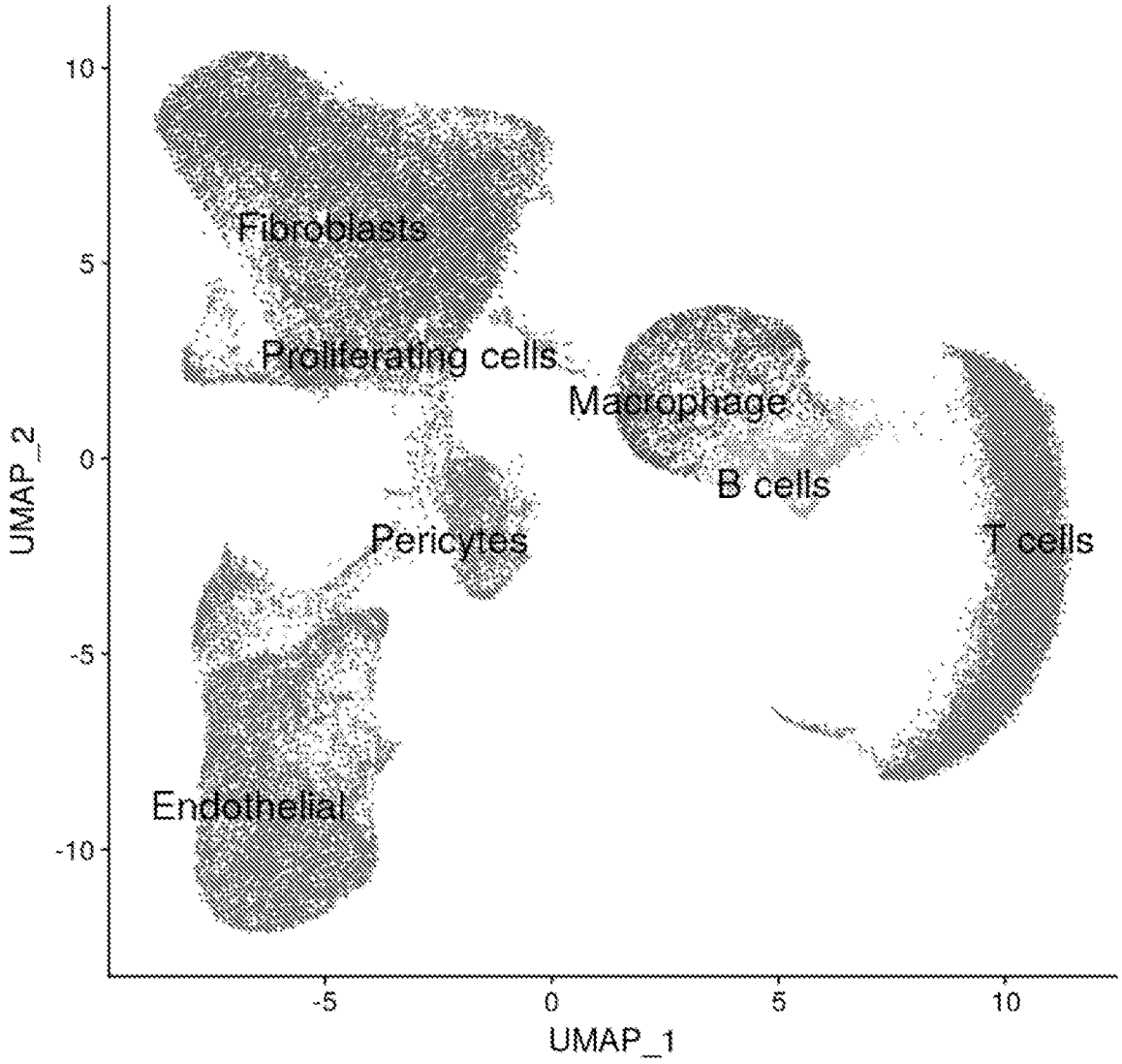

Fibroblasts
Proliferating cells
Macrophage
B cells
T cells
Pericytes
Endothelial
UMAP_2
UMAP_1
10
5
0
-5
-10
-5
0
5
10

FIG. 16A

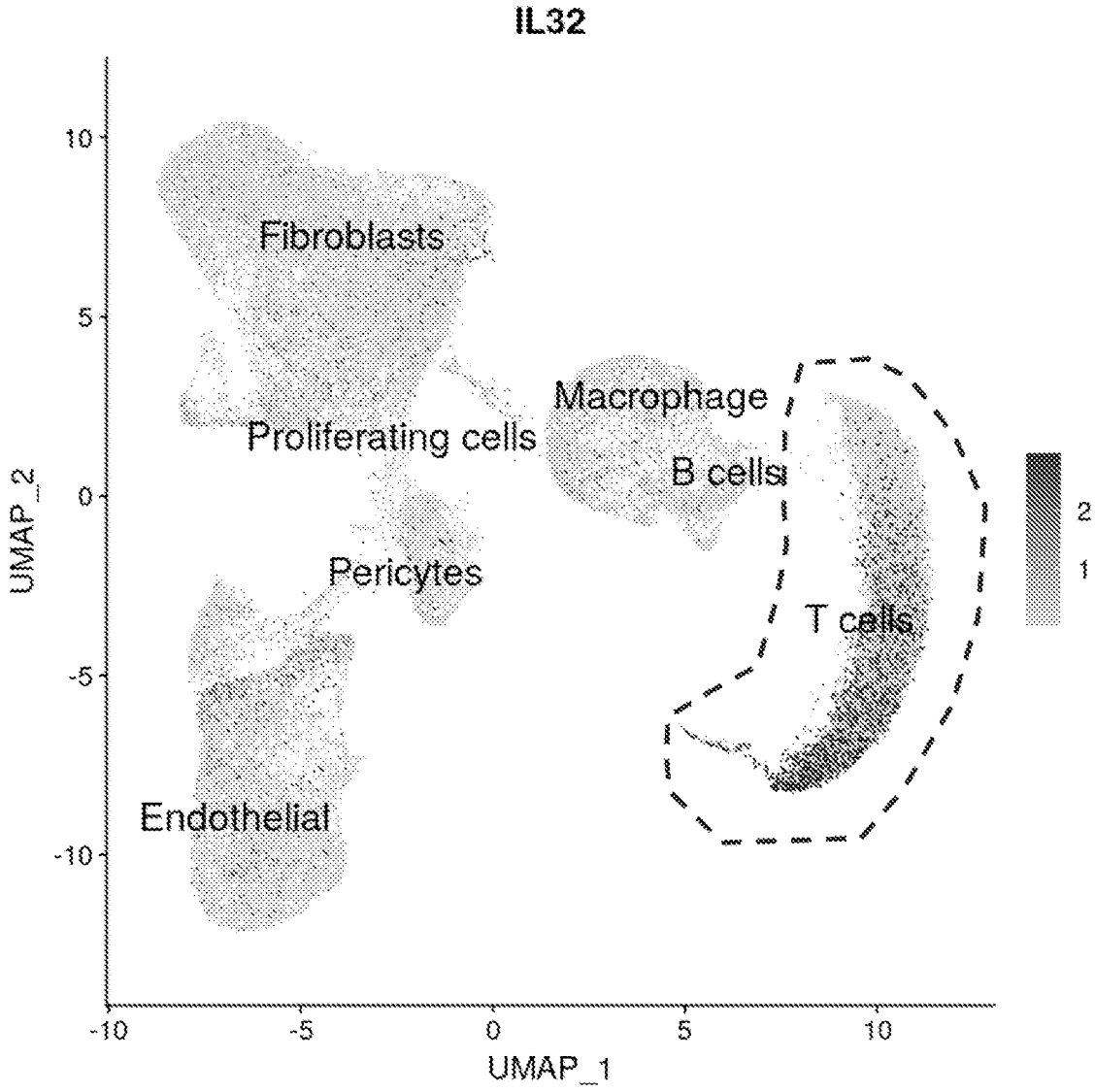

IL32
Fibroblasts
Proliferating cells
Pericytes
Endothelial
Macrophage
B cells
T cells
UMAP_2
UMAP_1
10
5
0
-5
-10
-10
-5
0
5
10
2
1

FIG. 16B

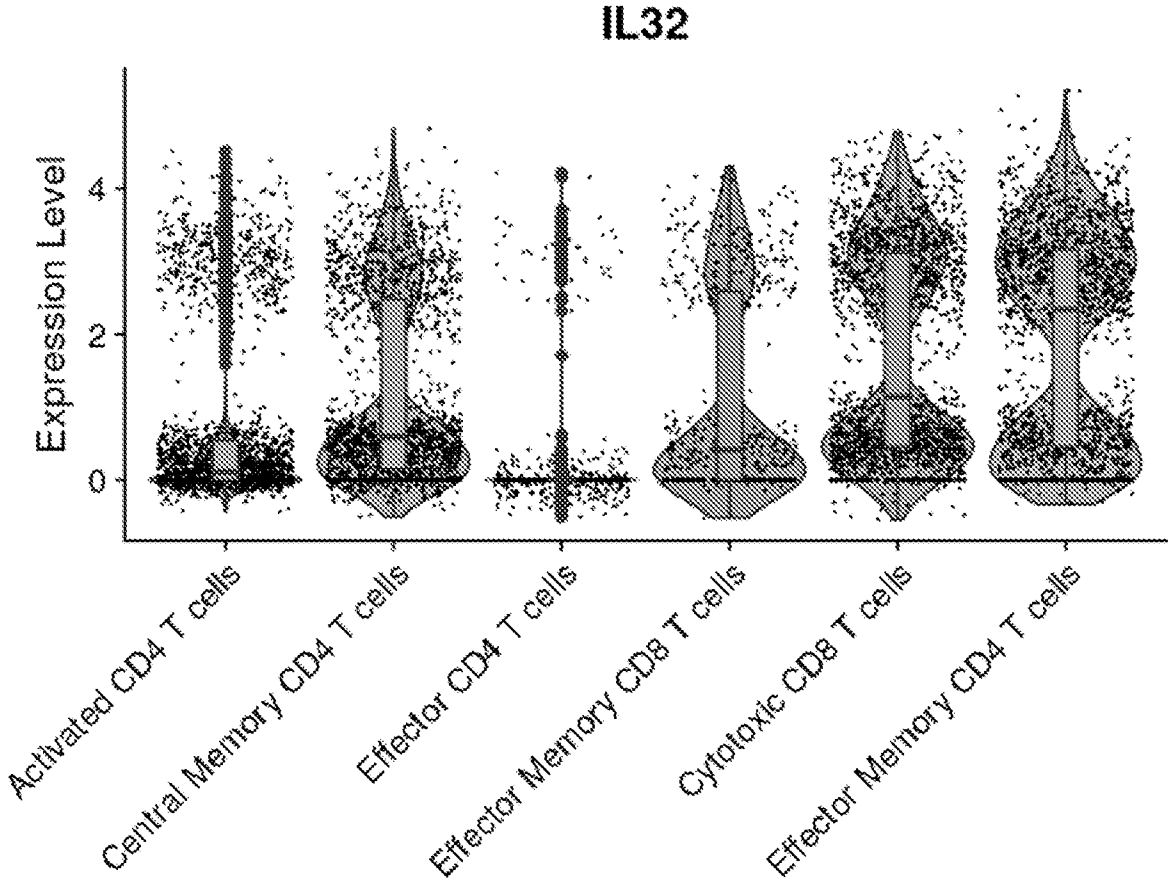

IL32
Expression Level
0
2
4
Activated CD4 T cells
Central Memory CD4 T cells
Effector CD4 T cells
Effector Memory CD8 T cells
Cytotoxic CD8 T cells
Effector Memory CD4 T cells

FIG. 16C

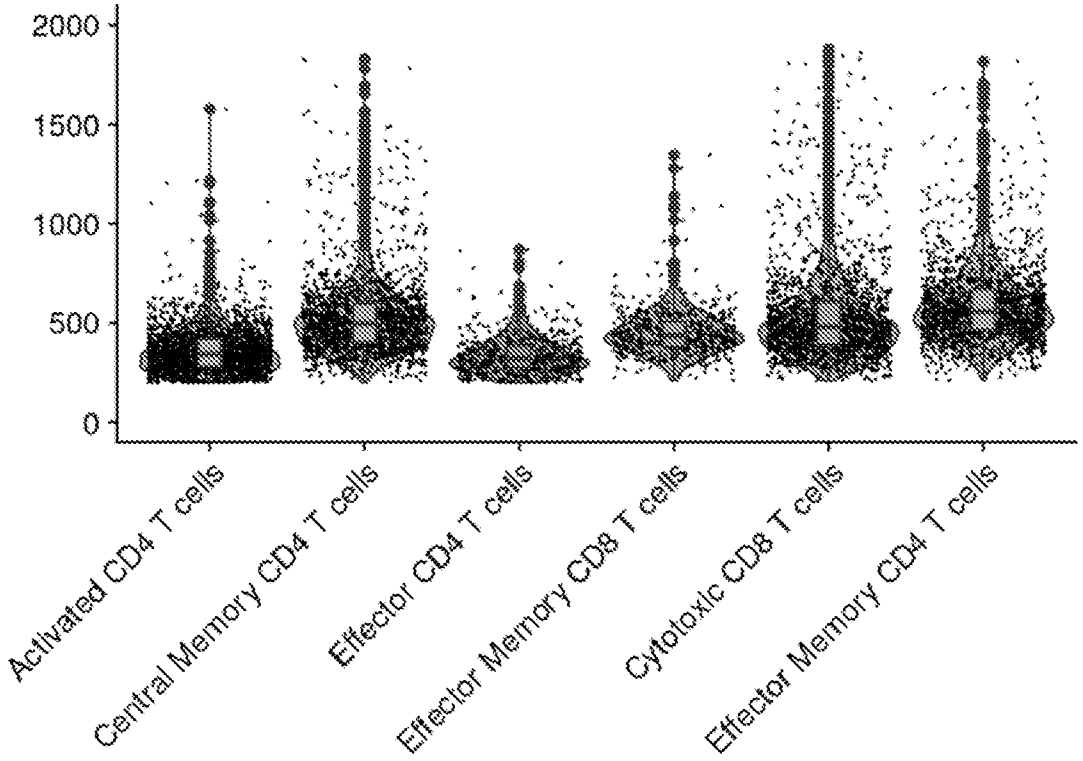


FIG. 17A

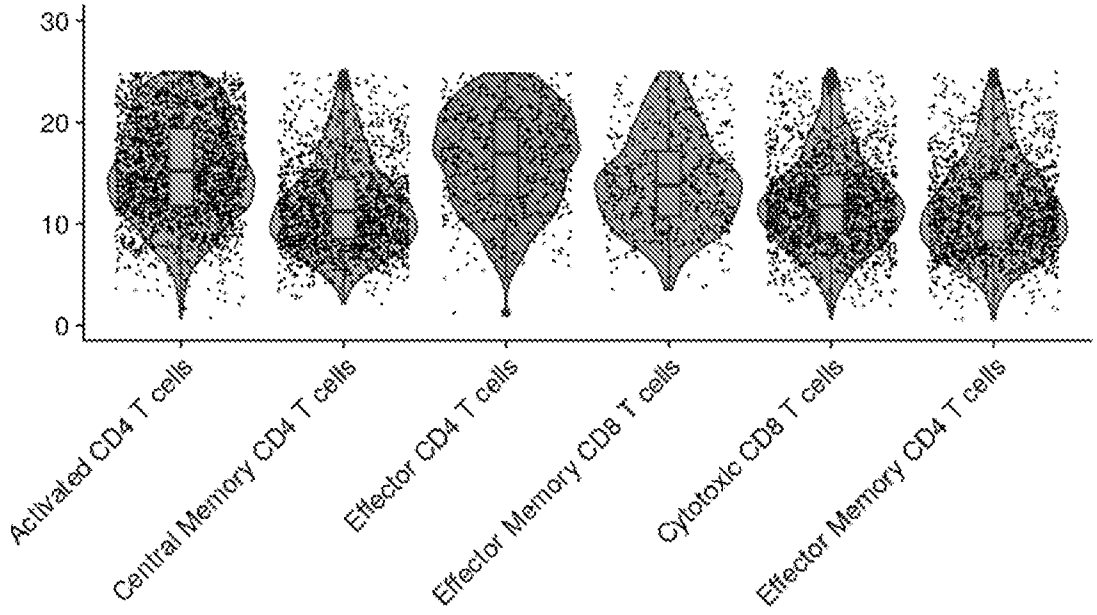


FIG. 17B

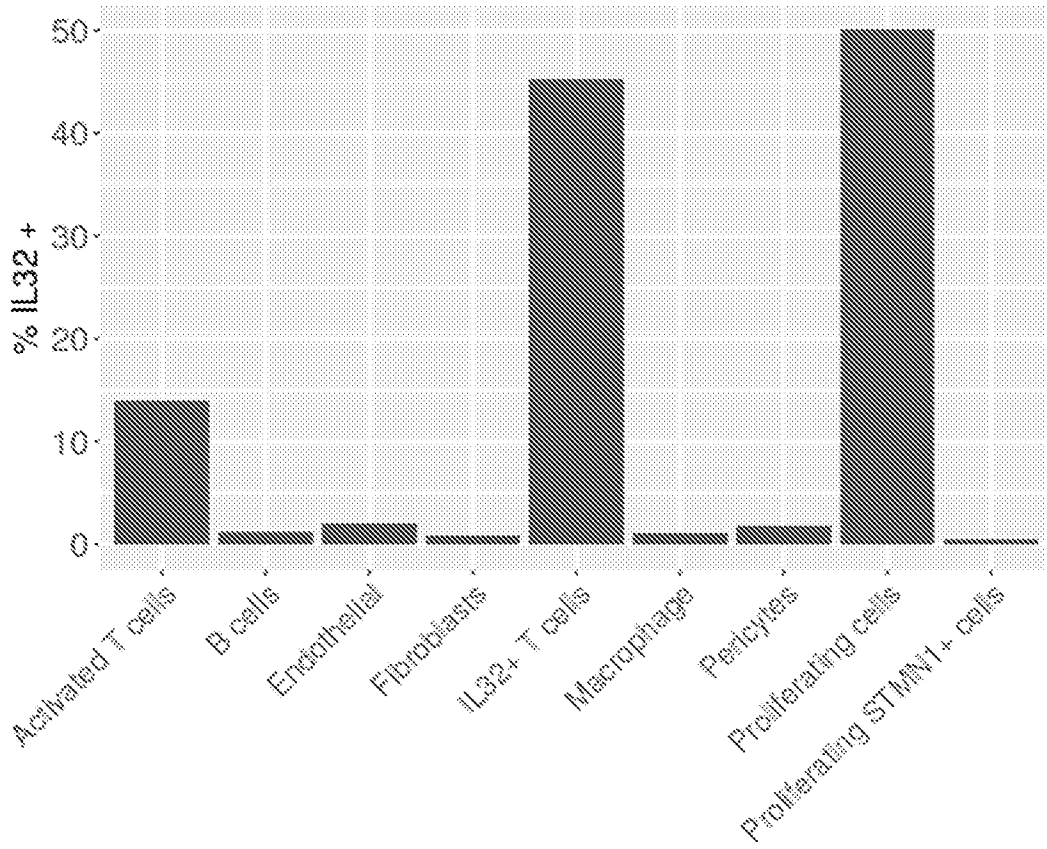


FIG. 18A

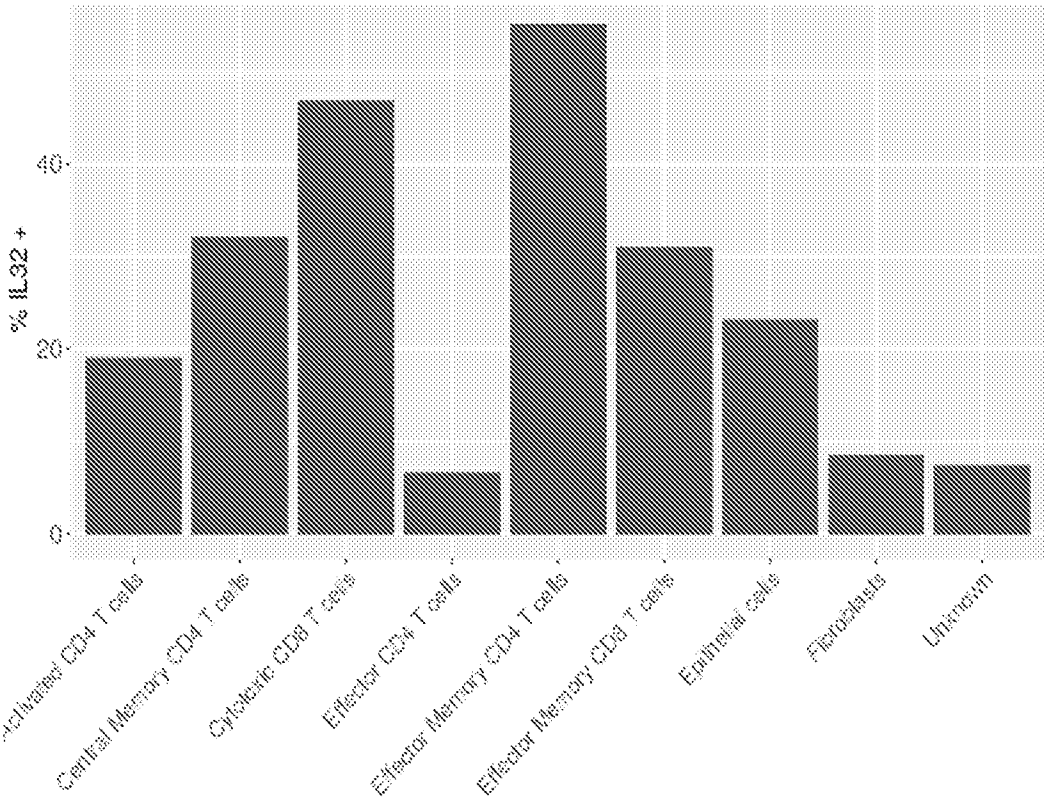


FIG. 18B

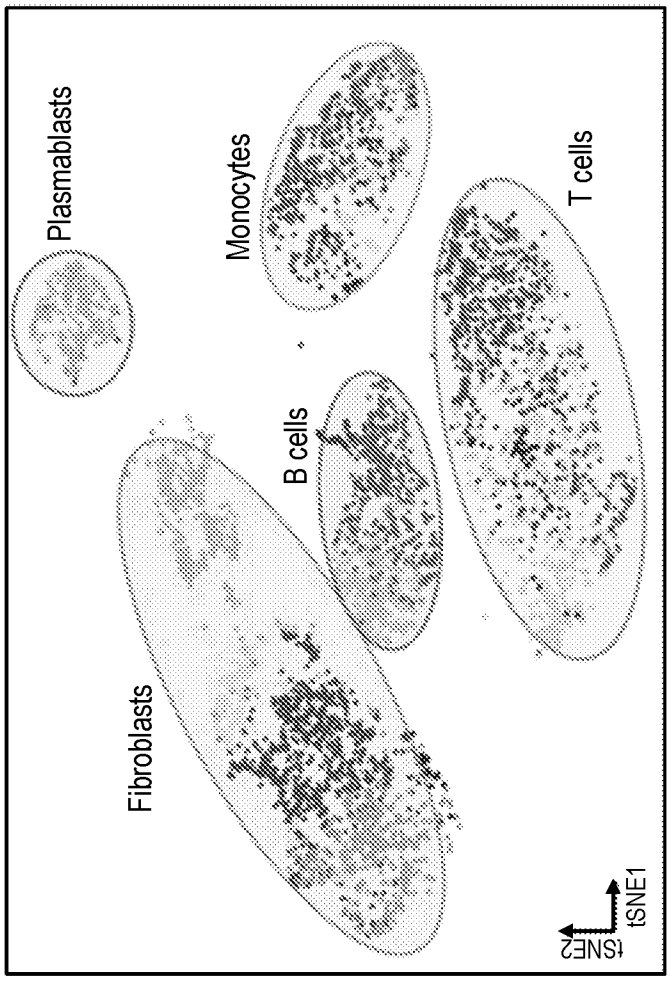


FIG. 19A

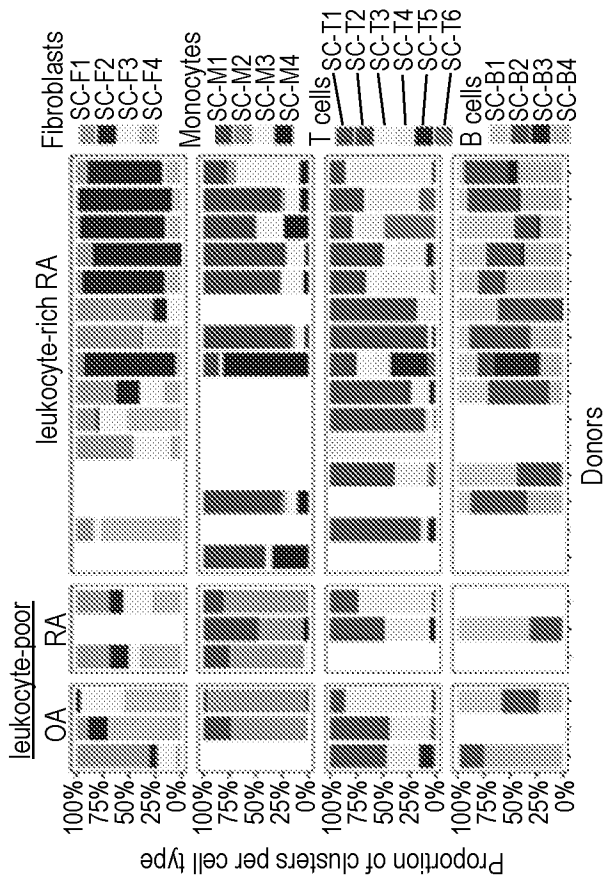


FIG. 19B

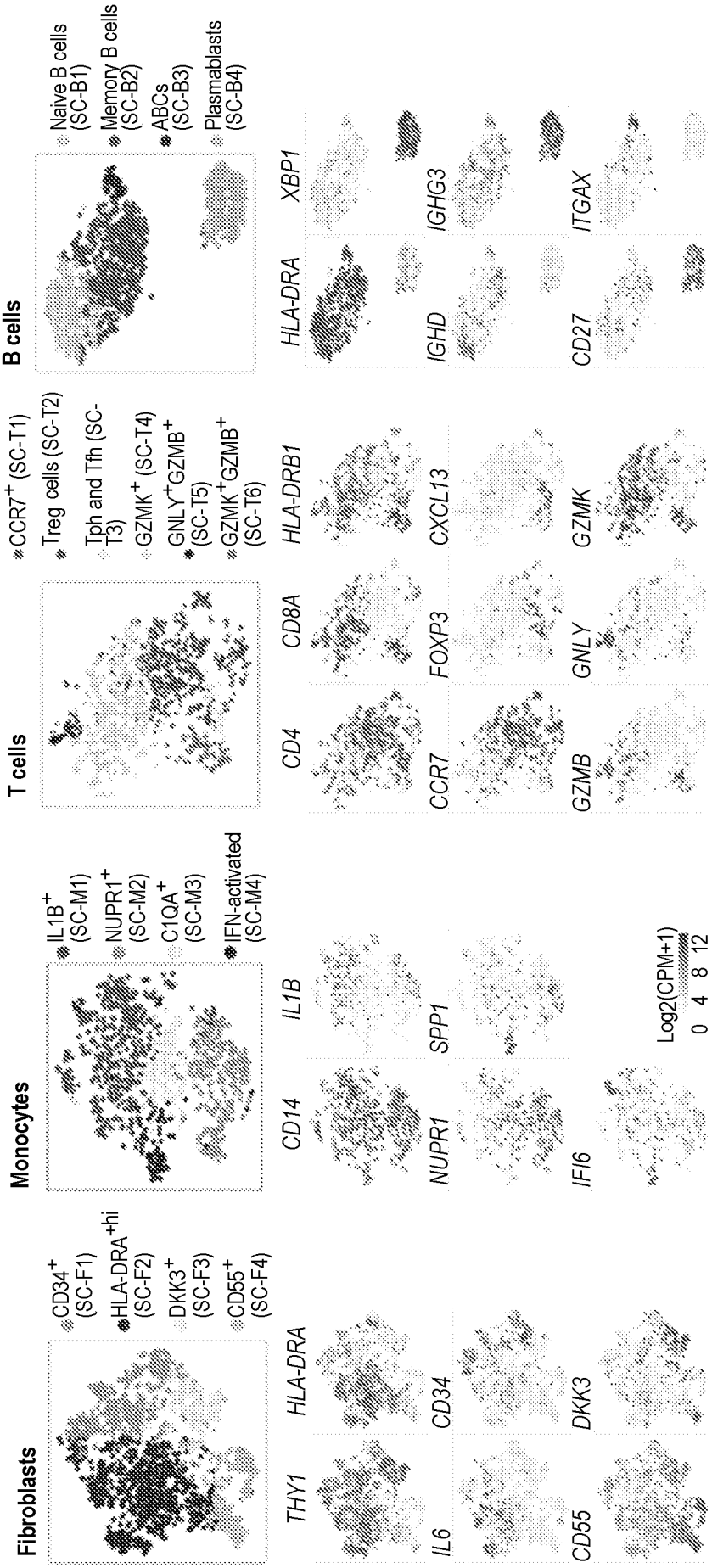


FIG. 19C FIG. 19D FIG. 19E FIG. 19F

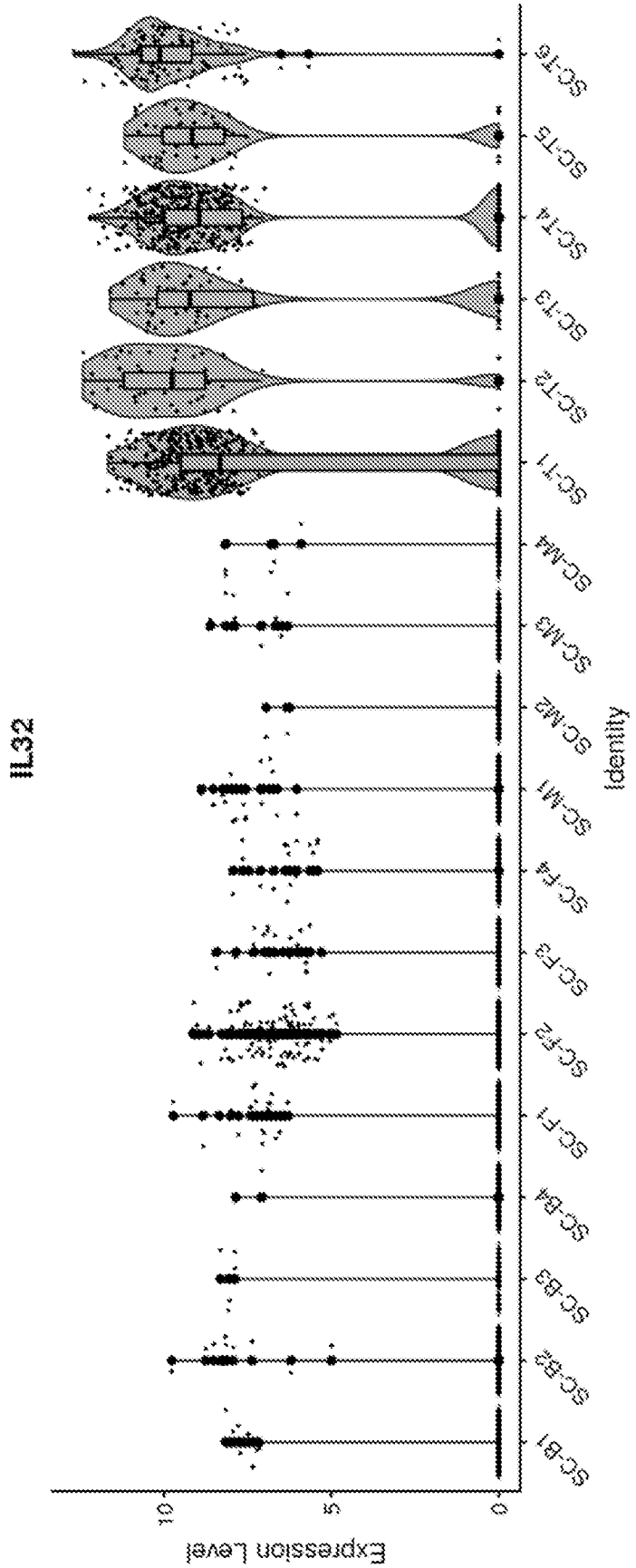

IL32
Expression Level
10
5
0
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 20A

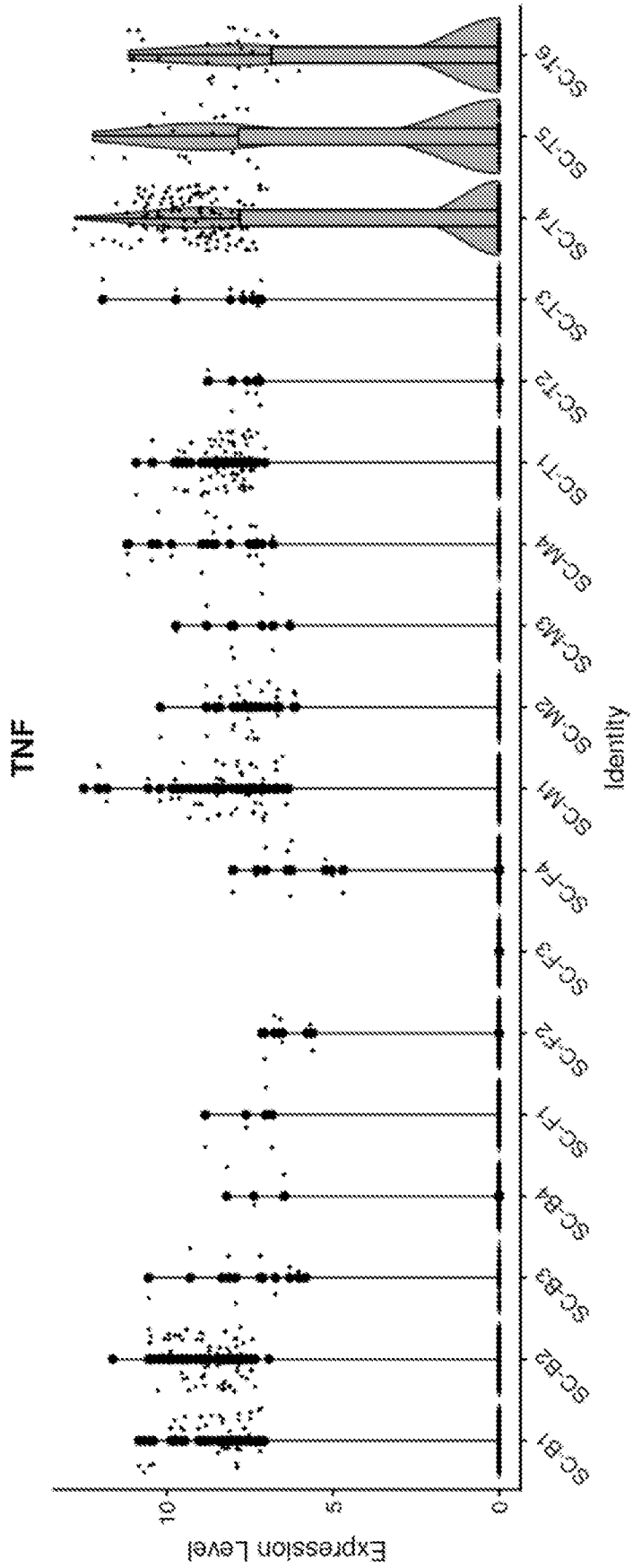

TNF
Identity
Expression Level
0
5
10
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 20B

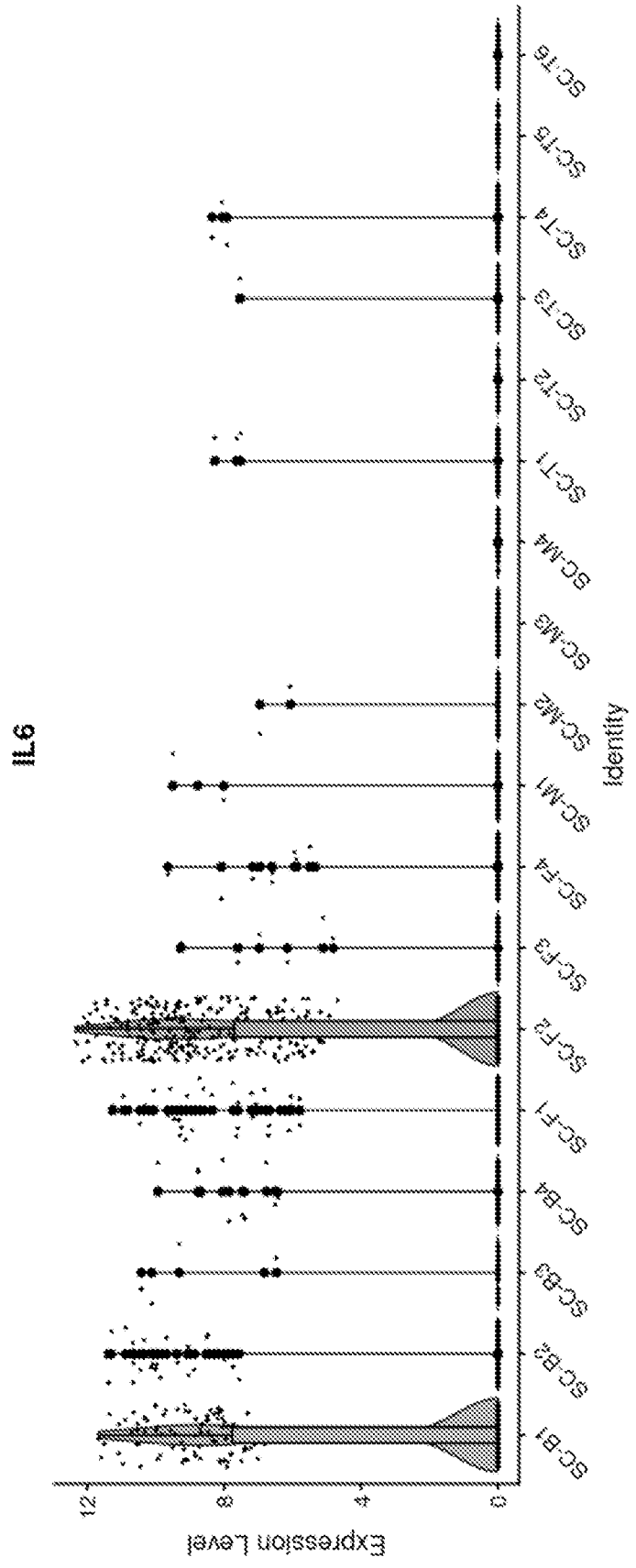

IL6
Expression Level
0
4
8
12
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 20C

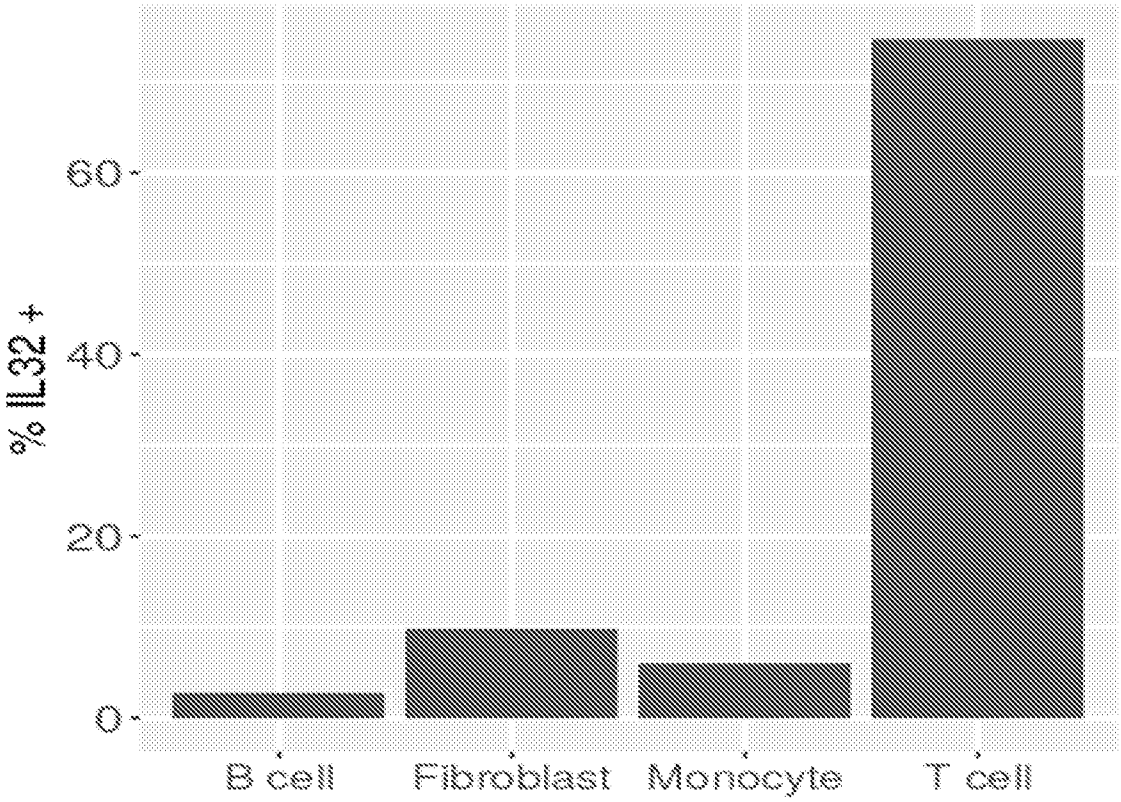


FIG. 21A

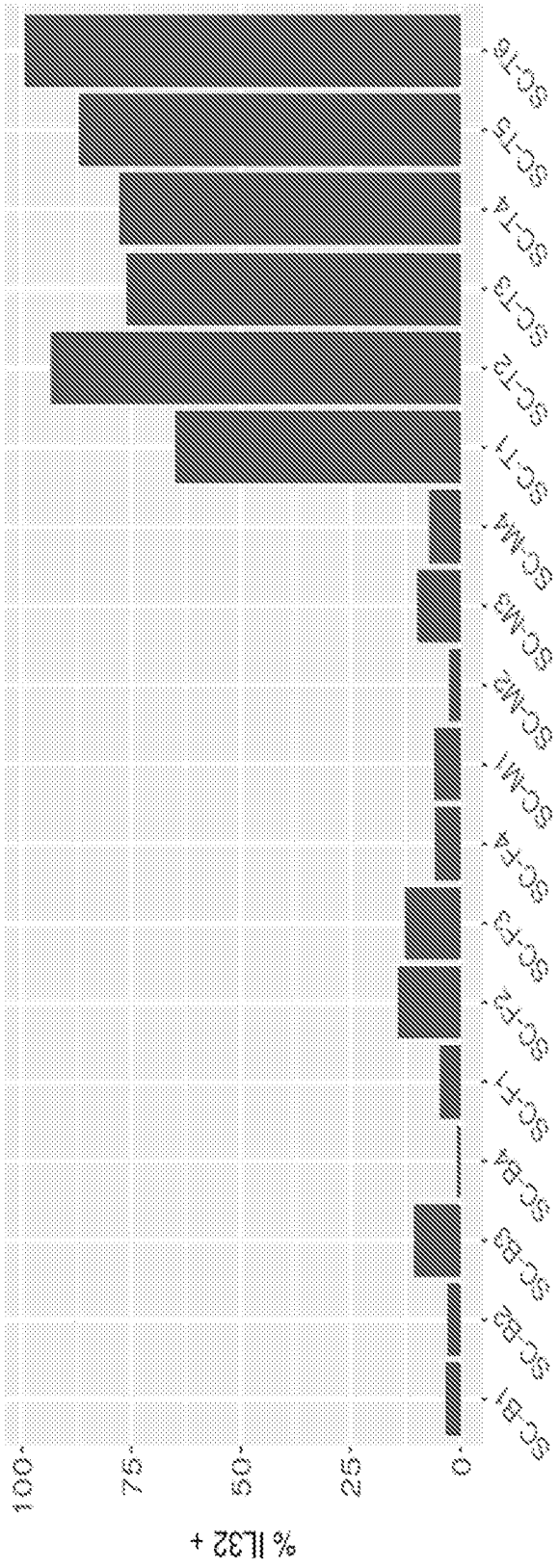

% IL32 +
100
75
50
25
0
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 21B

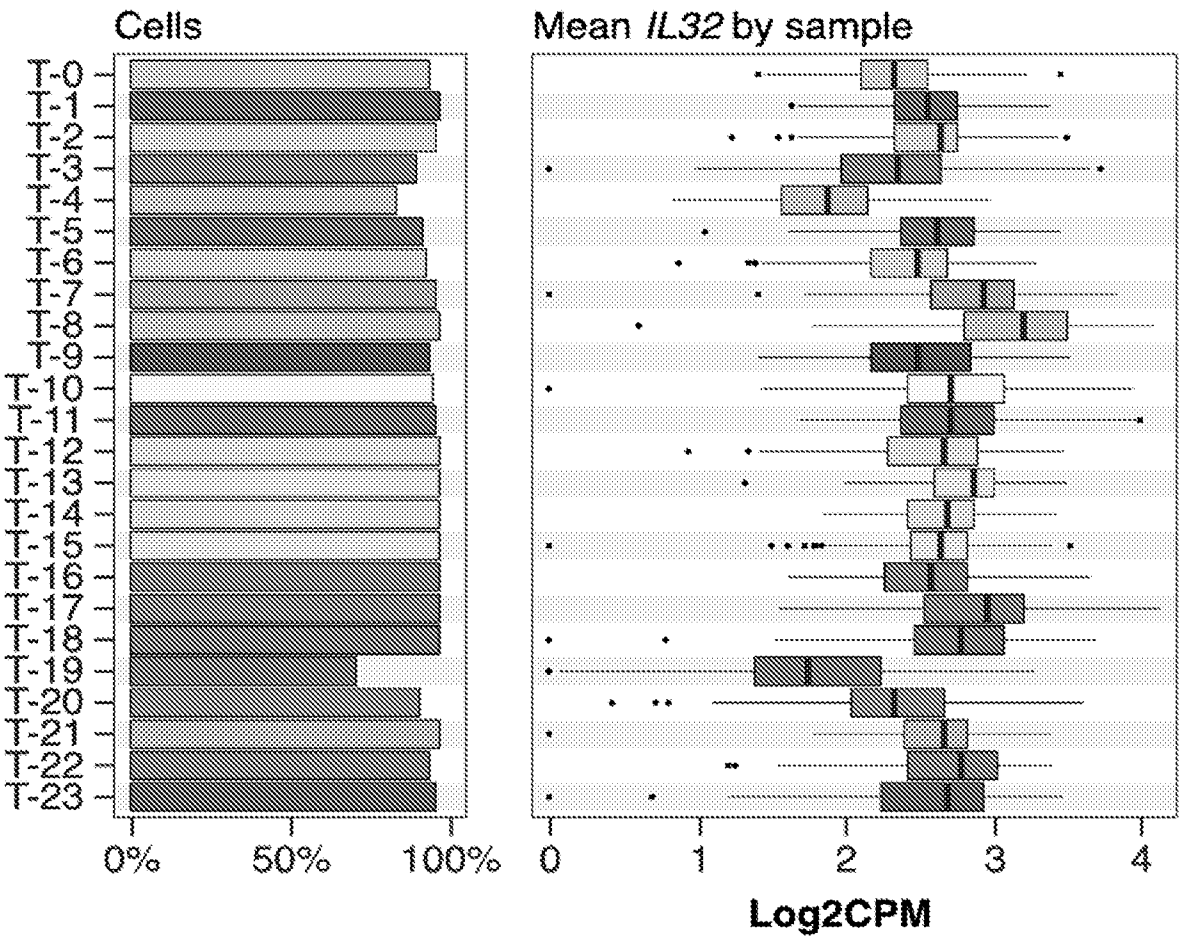

Cells
T-0
T-1
T-2
T-3
T-4
T-5
T-6
T-7
T-8
T-9
T-10
T-11
T-12
T-13
T-14
T-15
T-16
T-17
T-18
T-19
T-20
T-21
T-22
T-23
0%
50%
100%
Mean IL32 by sample
0
1
2
3
4
Log2CPM

FIG. 22

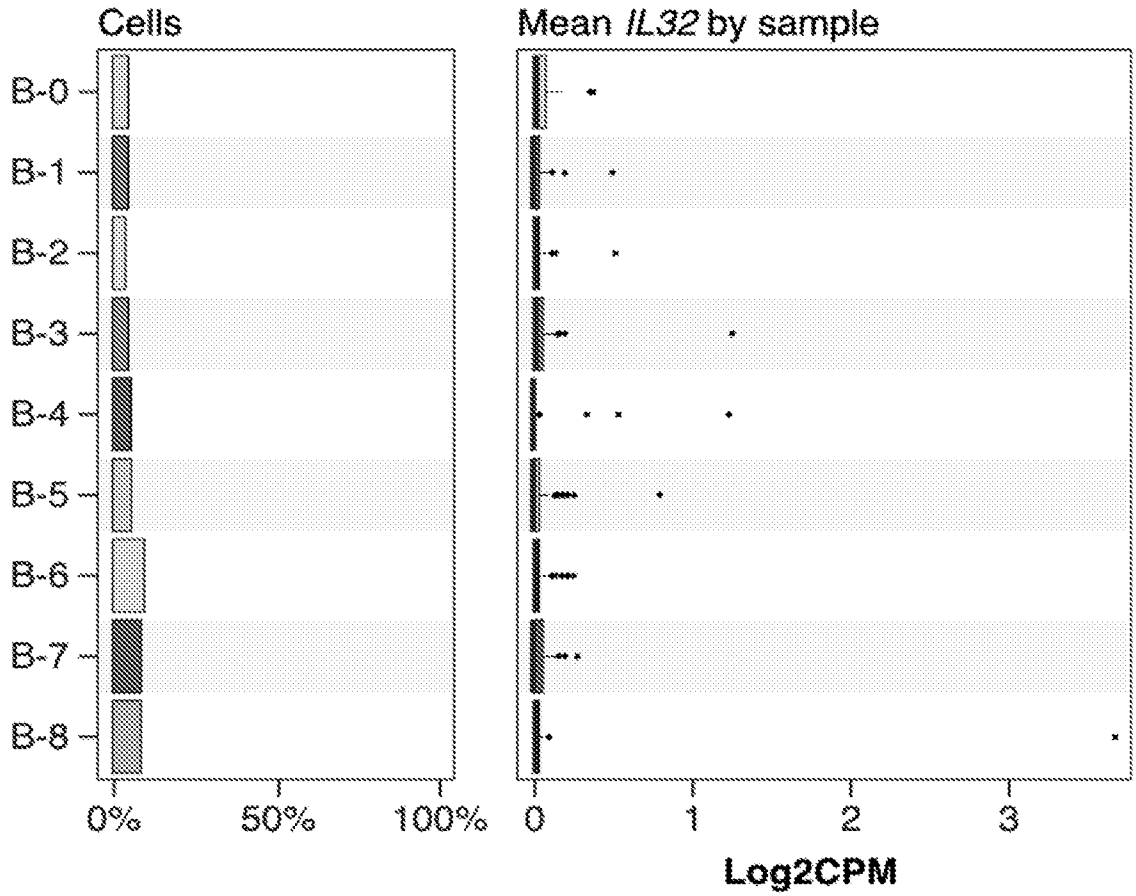

Cells
Mean IL32 by sample
B-0
B-1
B-2
B-3
B-4
B-5
B-6
B-7
B-8
0%
50%
100%
0
1
2
3
Log2CPM

FIG. 23

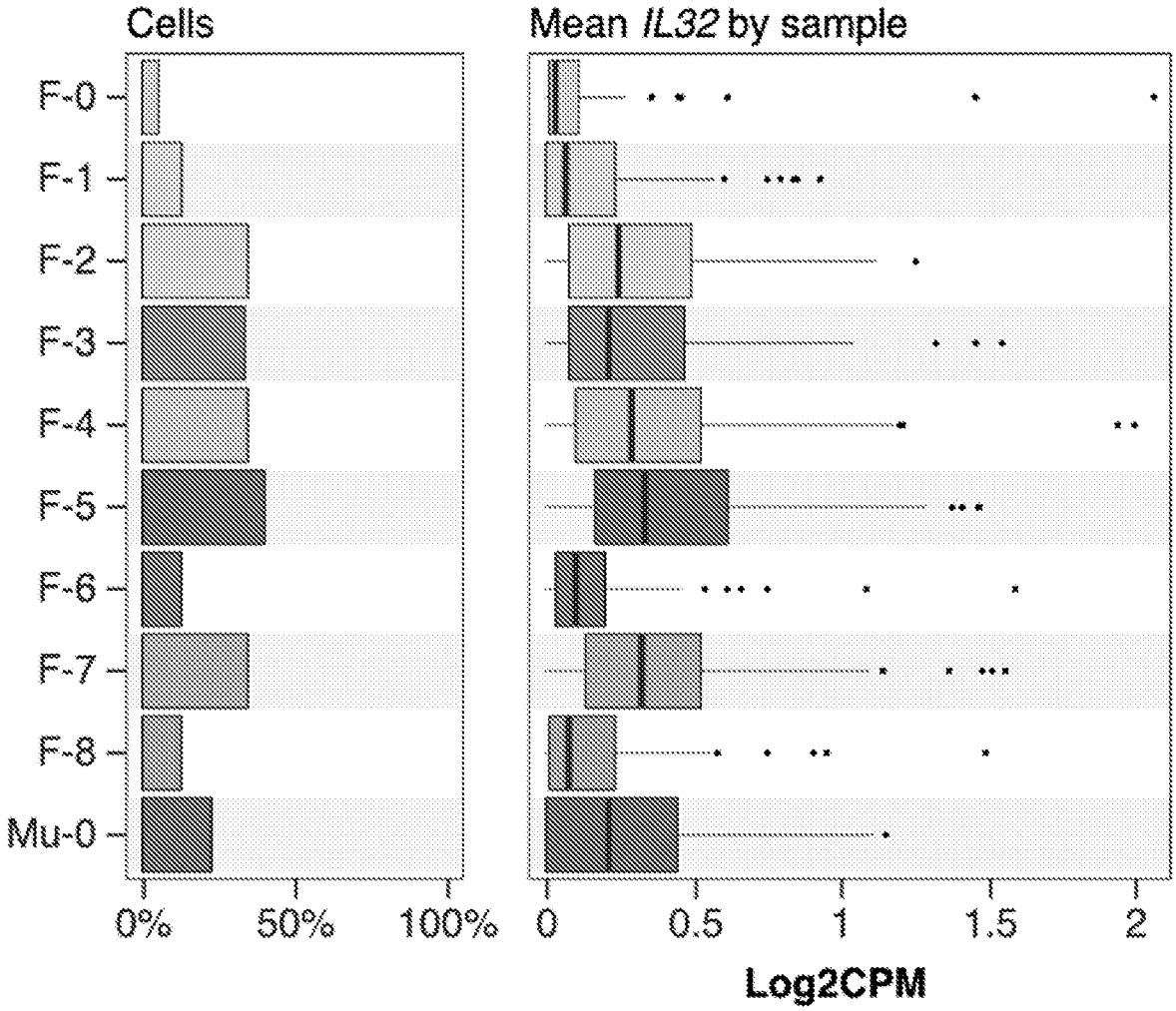

Cells
Mean IL32 by sample
F-0
F-1
F-2
F-3
F-4
F-5
F-6
F-7
F-8
Mu-0
0%
50%
100%
0
0.5
1
1.5
2
Log2CPM

FIG. 24

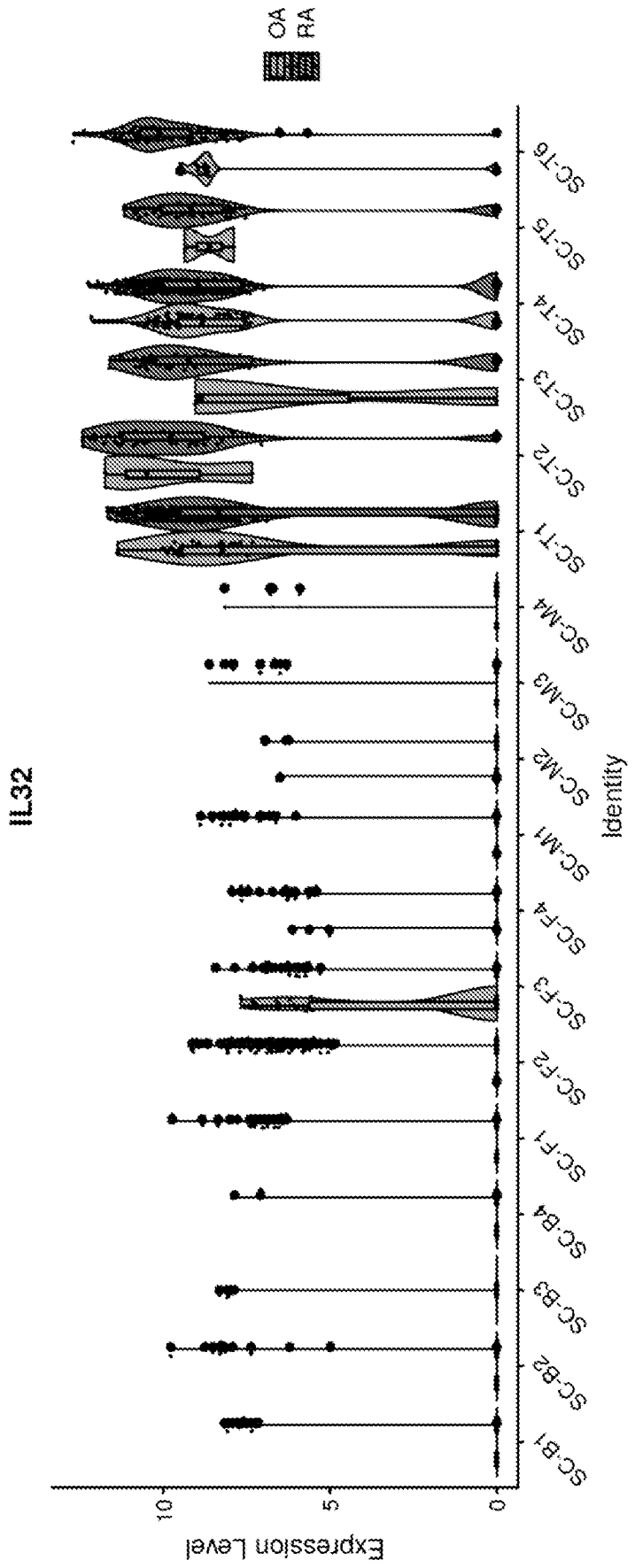

IL32
OA
RA
Expression Level
0
5
10
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25A

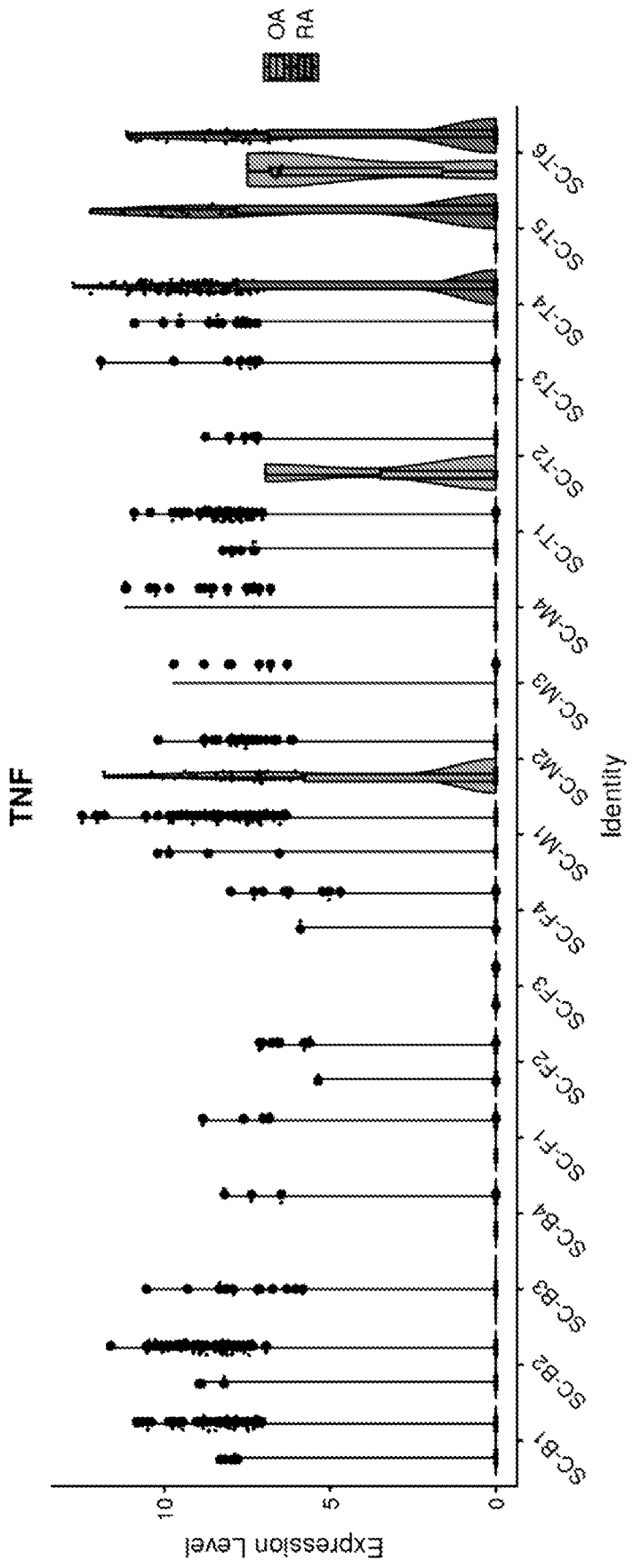

TNF
OA
RA
Expression Level
0
5
10
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25B

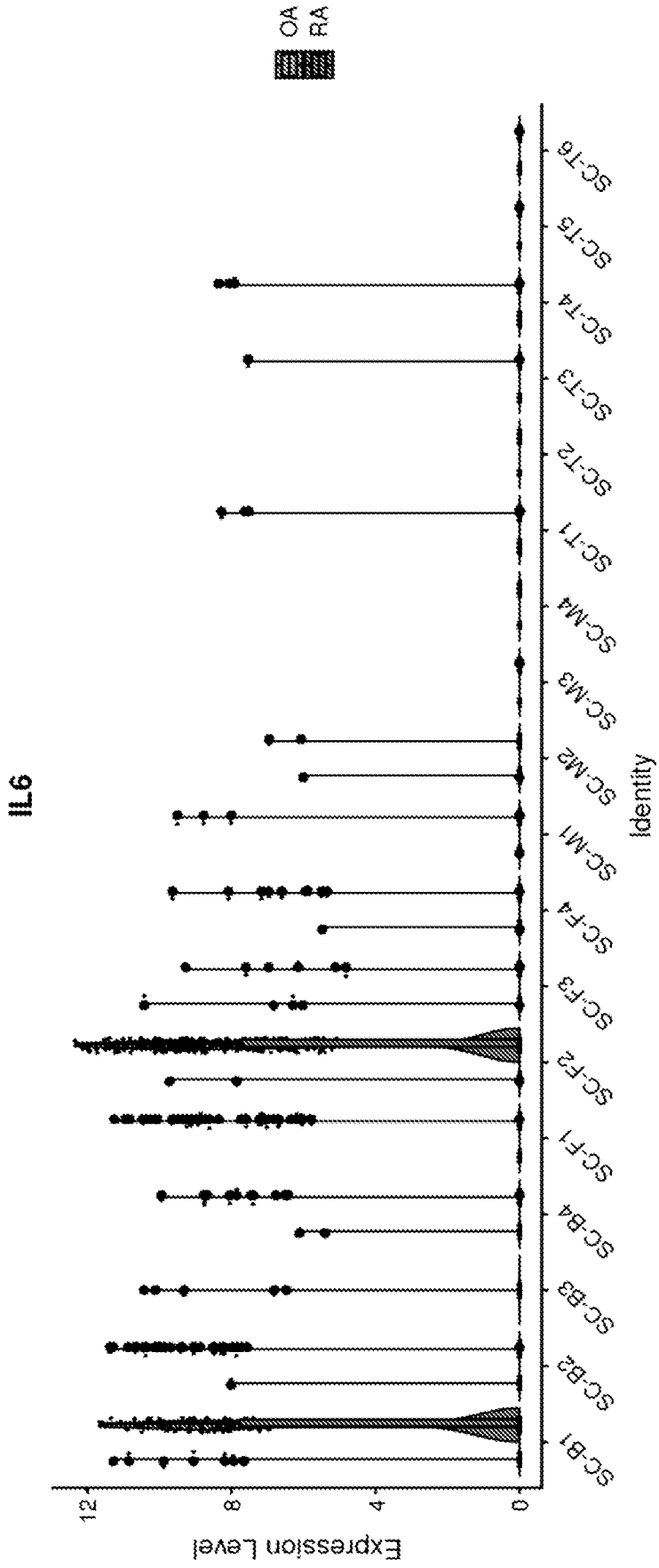

IL6
OA
RA
Expression Level
0
4
8
12
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25C

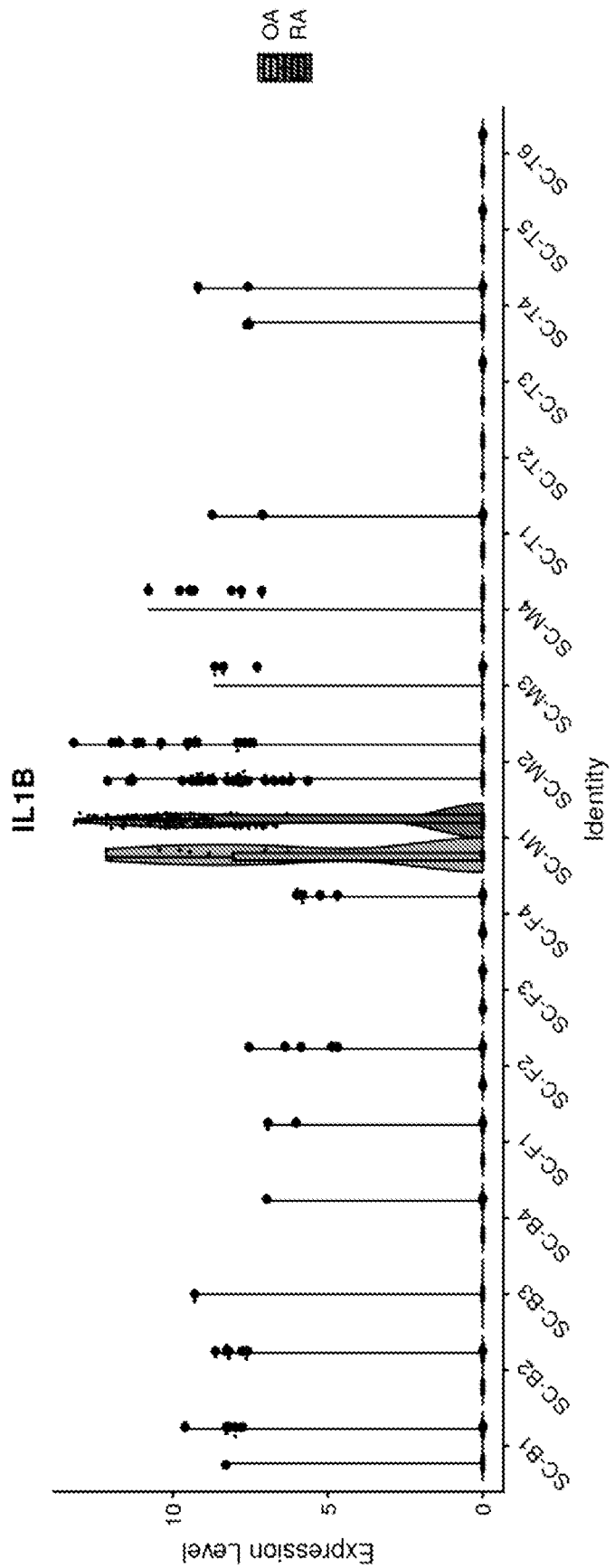

OA
RA
IL1B
Expression Level
10
5
0
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25D

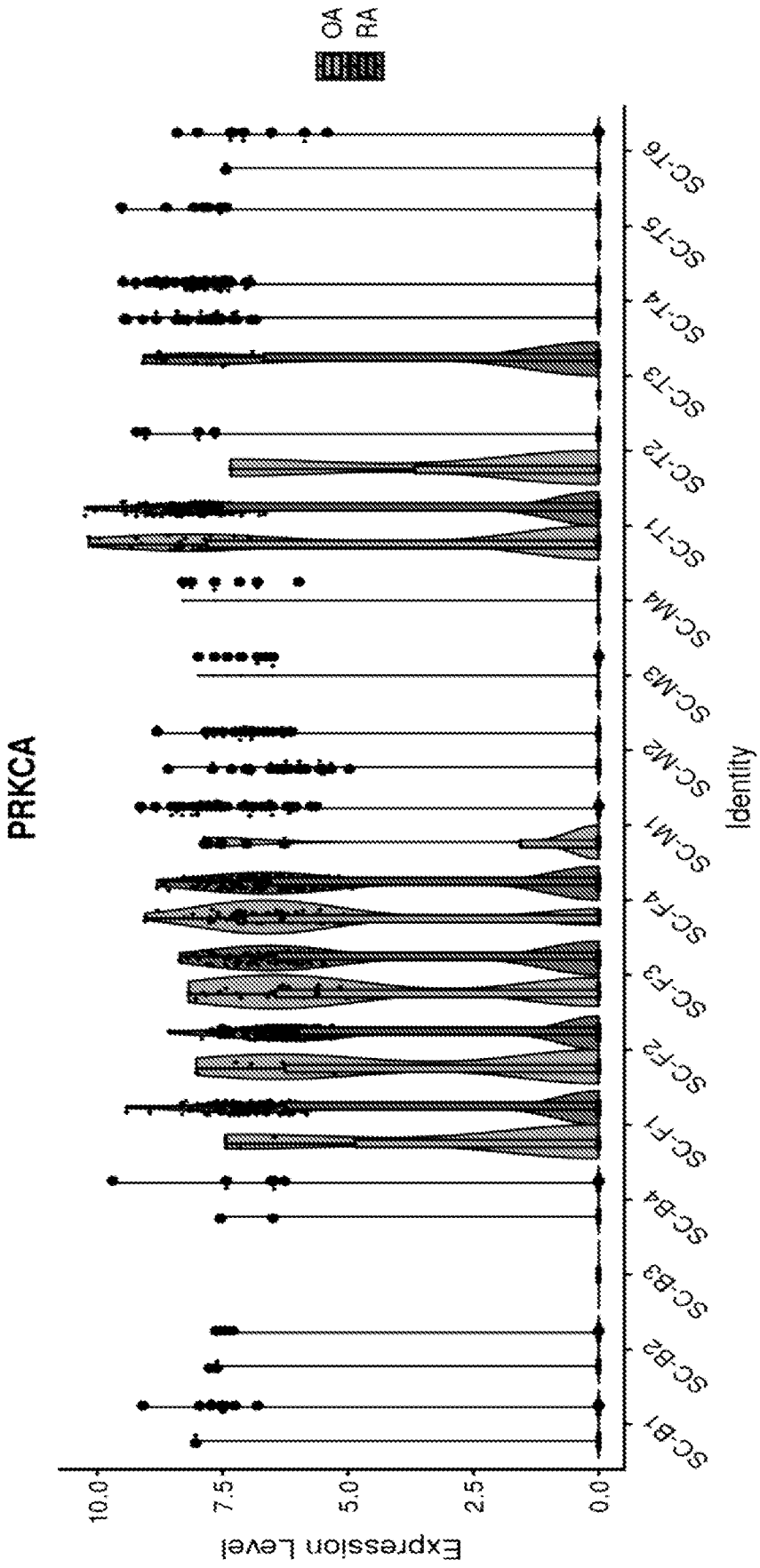

OA
RA
PRKCA
Expression Level
10.0
7.5
5.0
2.5
0.0
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6
Identity

FIG. 25E

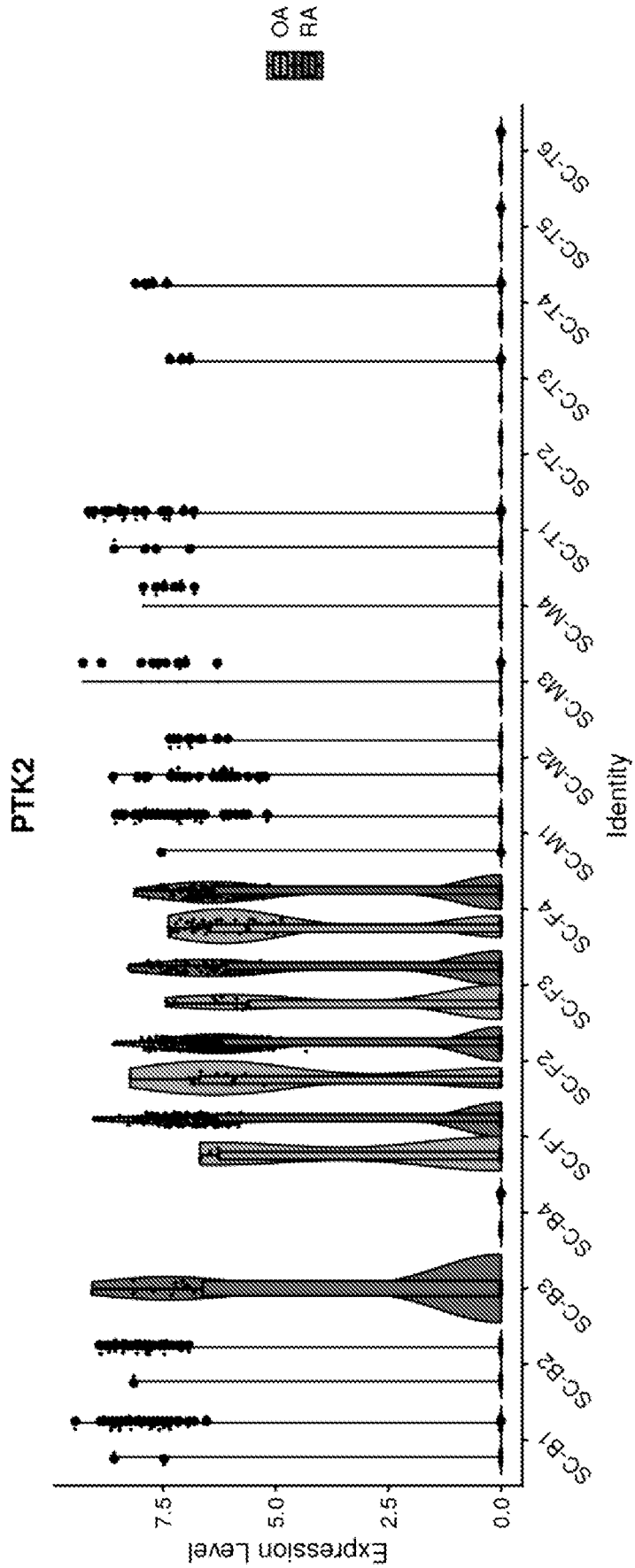

OA
RA
PTK2
Expression Level
7.5
5.0
2.5
0.0
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25F

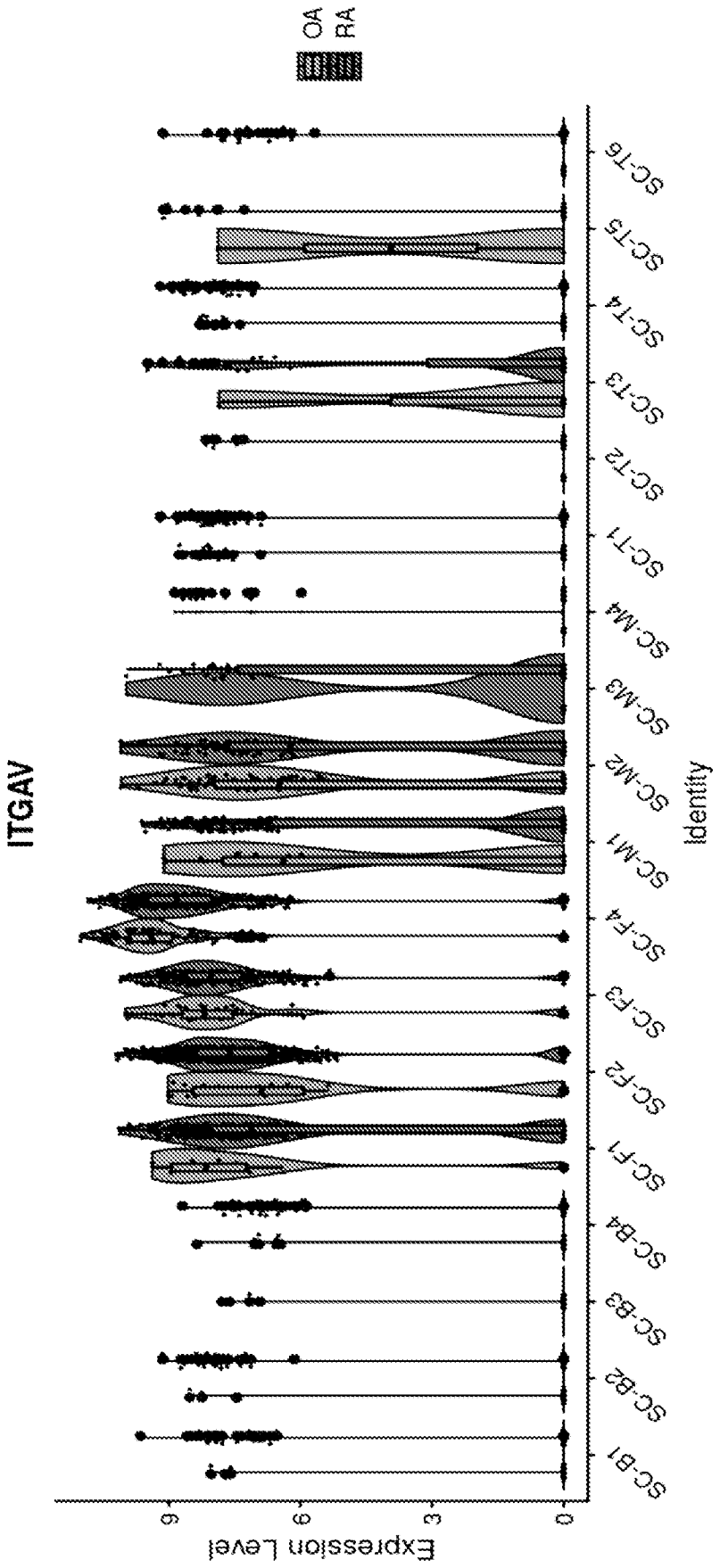

OA
RA
ITGAV
Expression Level
0
3
6
9
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25G

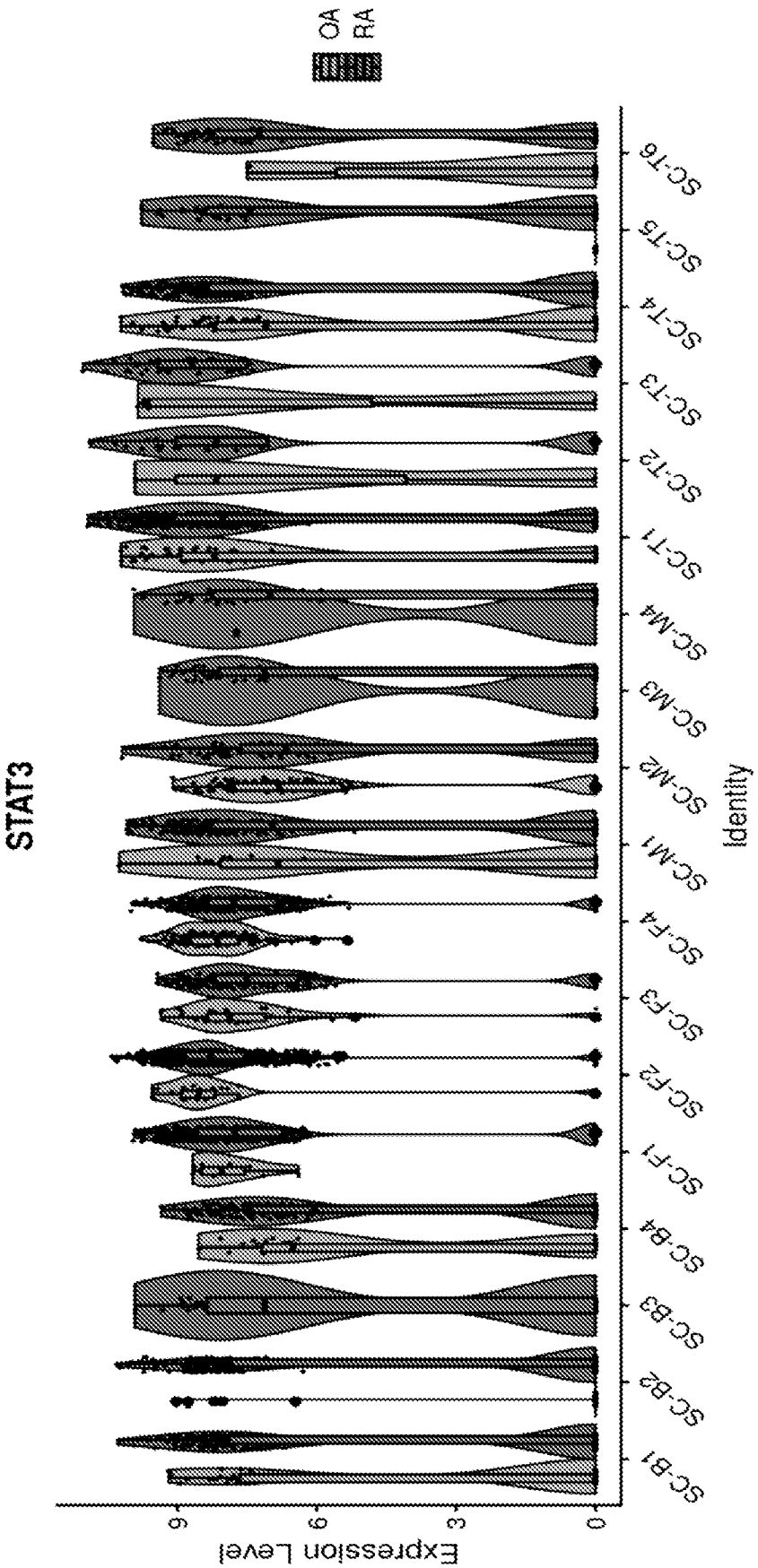

OA
RA
STAT3
Expression Level
9
6
3
0
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 25H

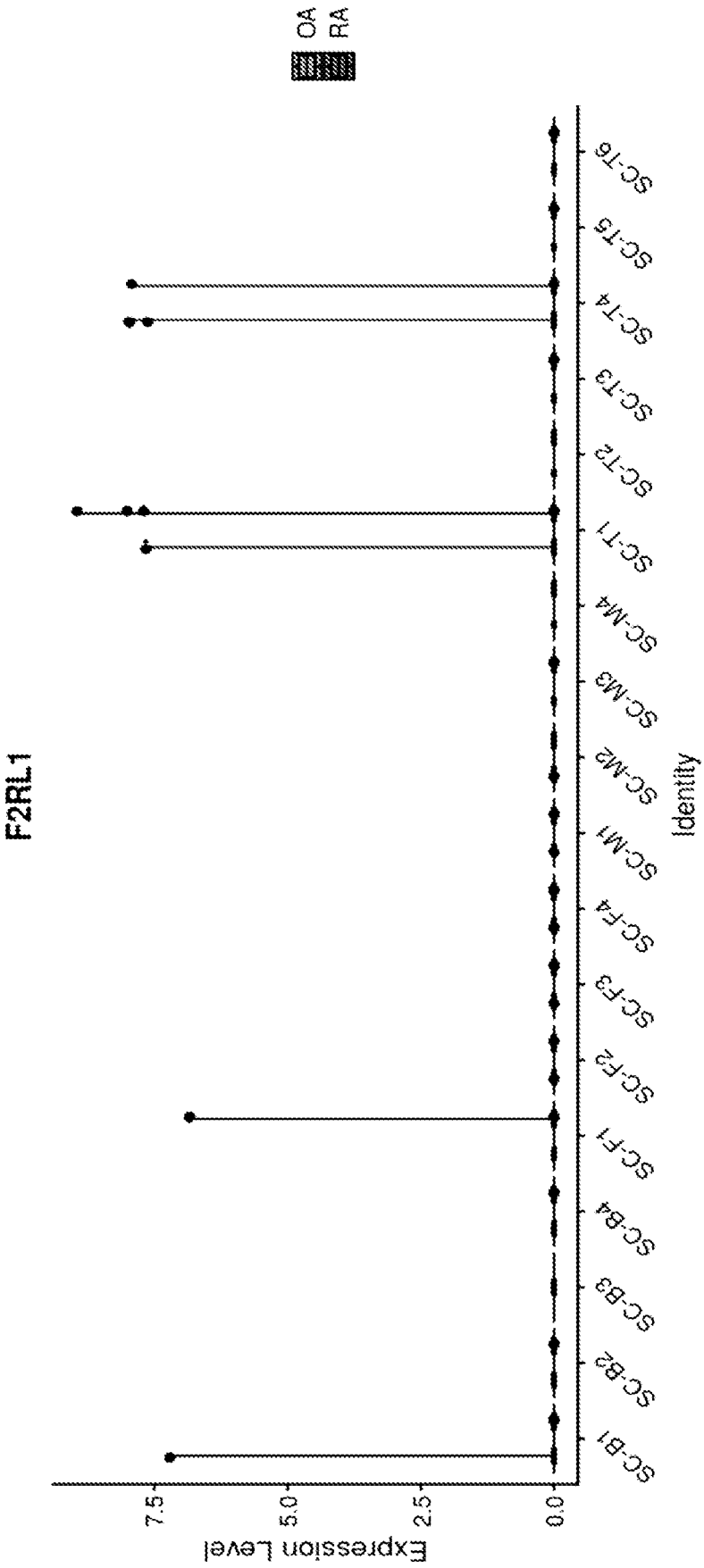

OA
RA
F2RL1
Expression Level
7.5
5.0
2.5
0.0
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 26A

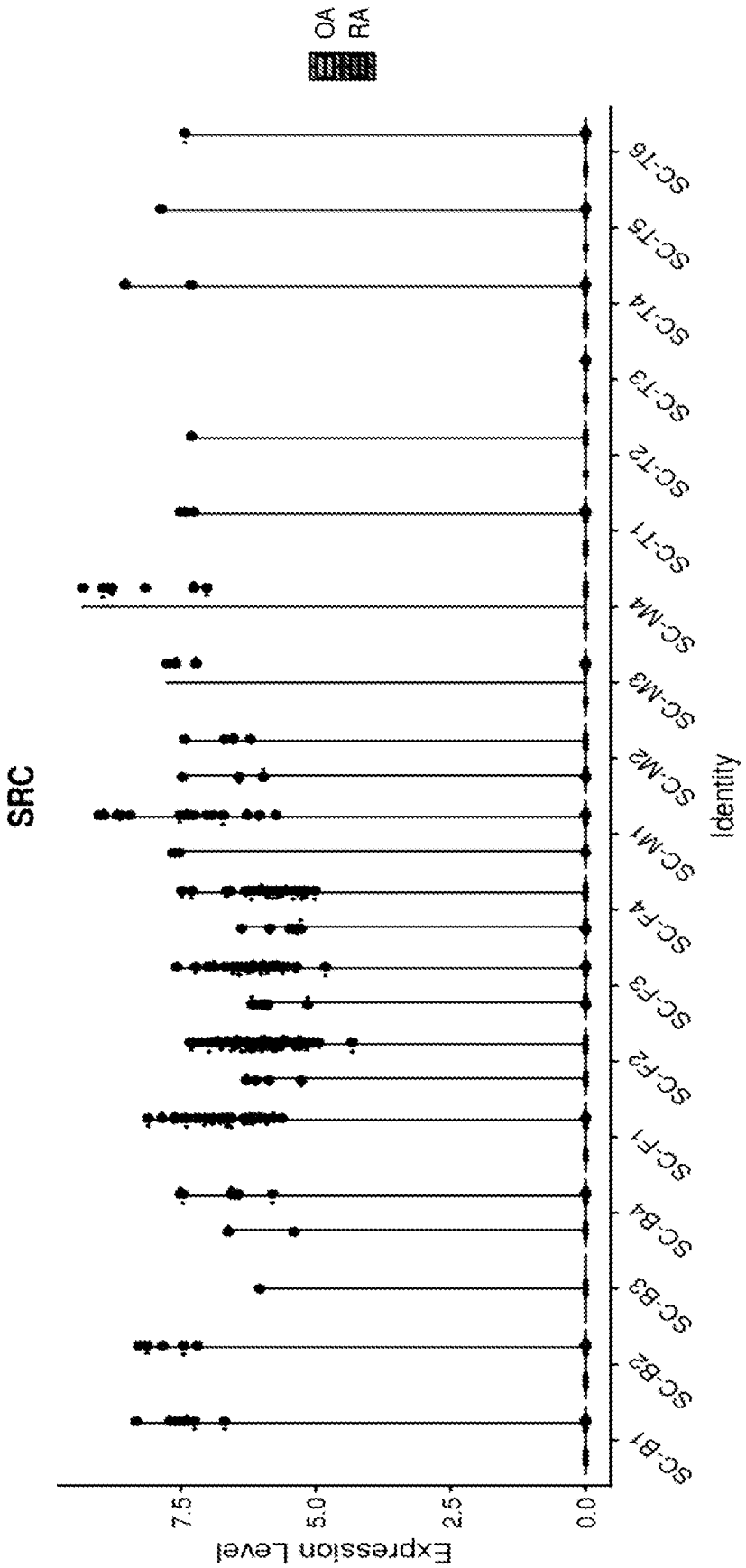

OA
RA
SRC
Identity
SC-T6
SC-T5
SC-T4
SC-T3
SC-T2
SC-T1
SC-M4
SC-M3
SC-M2
SC-M1
SC-F4
SC-F3
SC-F2
SC-F1
SC-B4
SC-B3
SC-B2
SC-B1
Expression Level
7.5
5.0
2.5
0.0

FIG. 26B

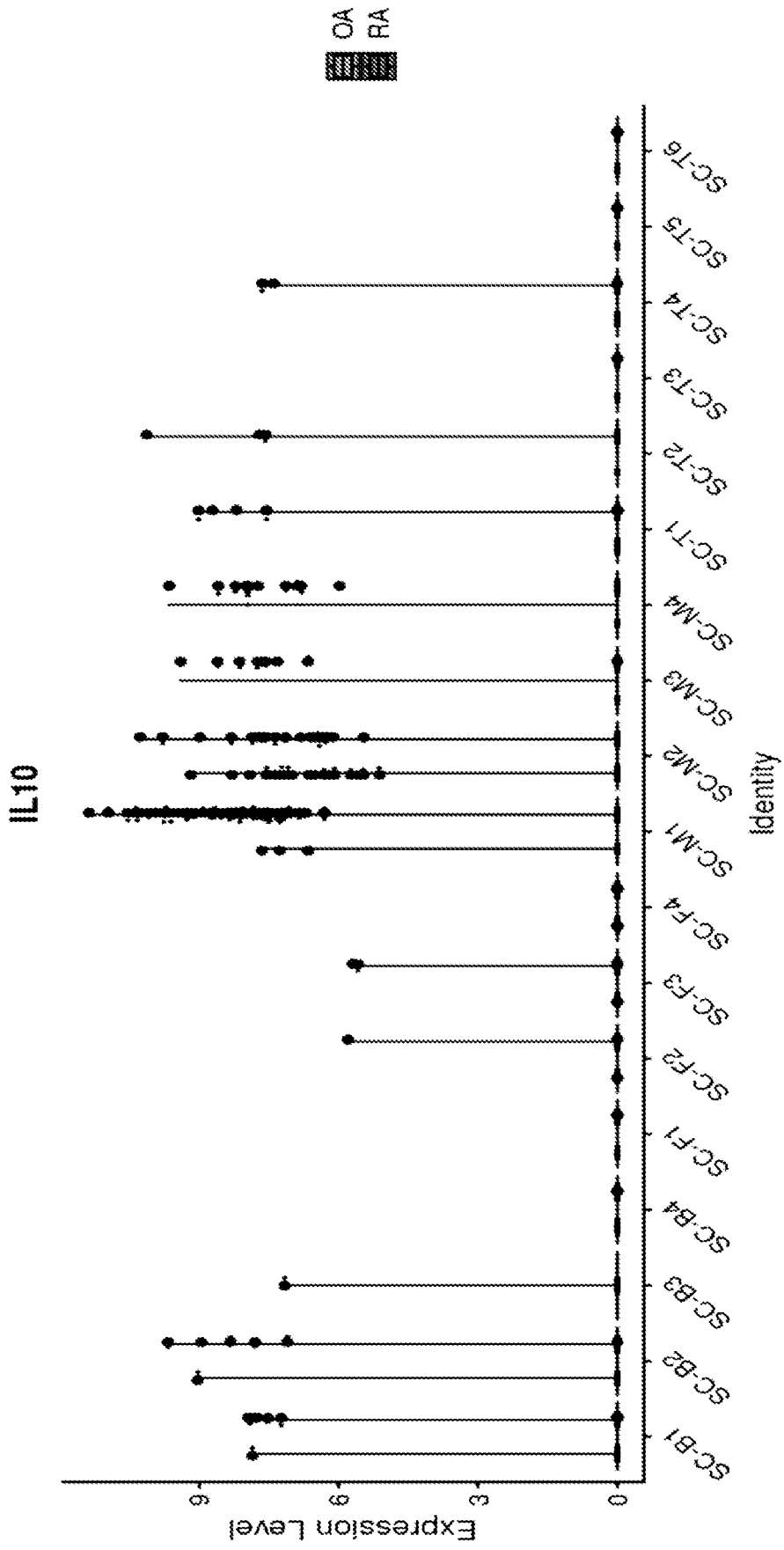

IL10
OA
RA
Expression Level
0
3
6
9
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 26C

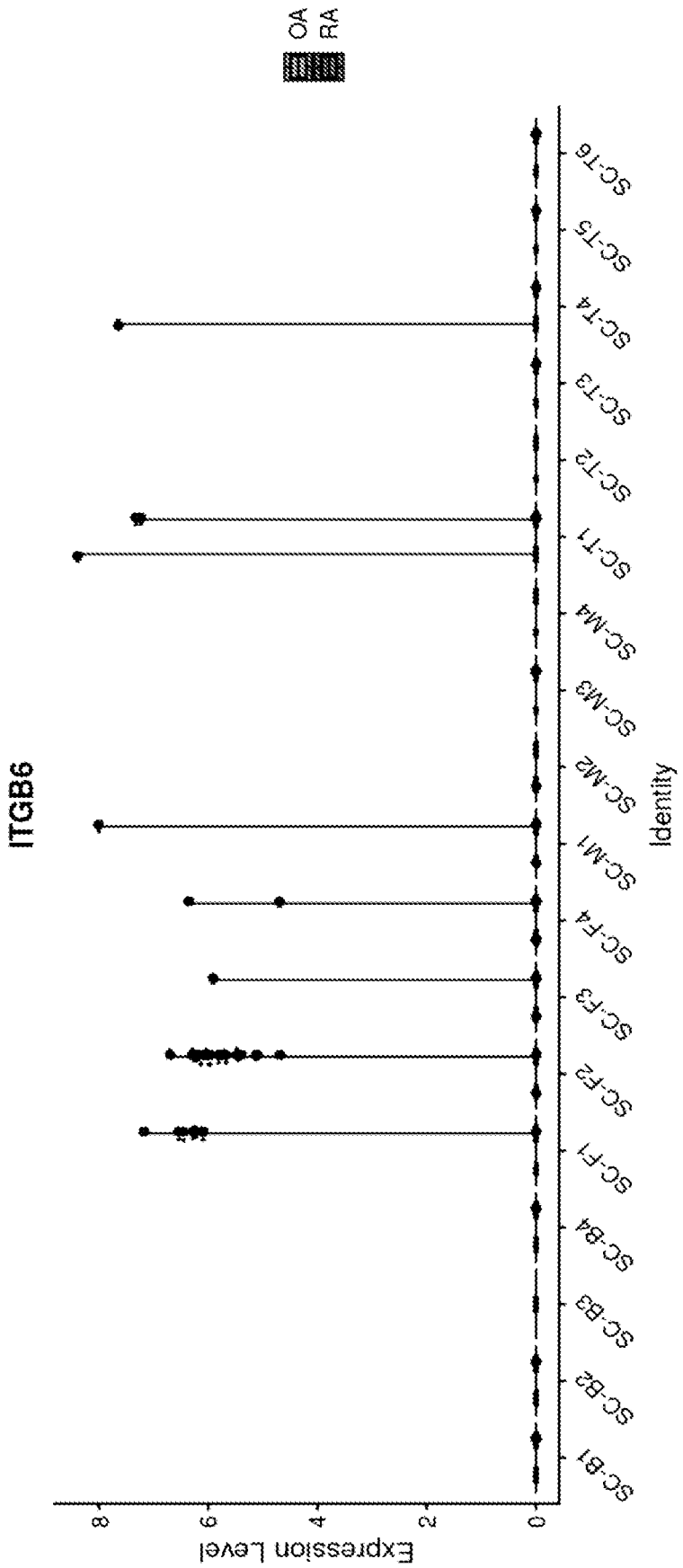

OA
RA
ITGB6
Expression Level
0
2
4
6
8
Identity
SC-B1
SC-B2
SC-B3
SC-B4
SC-F1
SC-F2
SC-F3
SC-F4
SC-M1
SC-M2
SC-M3
SC-M4
SC-T1
SC-T2
SC-T3
SC-T4
SC-T5
SC-T6

FIG. 26D

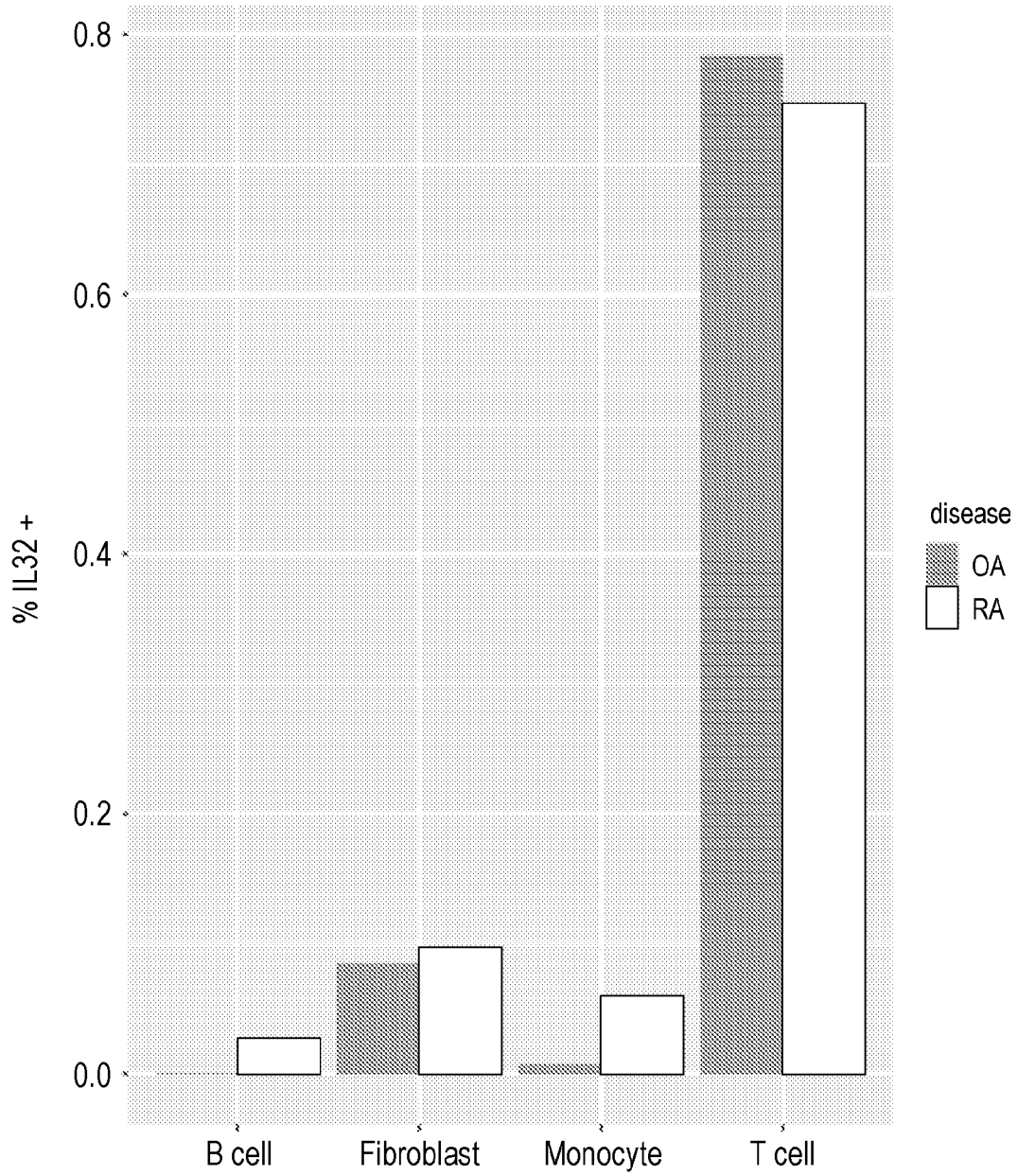

0.8
0.6
0.4
0.2
0.0
% IL32 +
B cell
Fibroblast
Monocyte
T cell
disease
OA
RA

FIG. 27A


disease
OA
RA
SC-T6
SC-T5
SC-T4
SC-T3
SC-T2
SC-T1
SC-M4
SC-M3
SC-M2
SC-M1
SC-F4
SC-F3
SC-F2
SC-F1
SC-B4
SC-B3
SC-B2
SC-B1
1.00
0.75
0.50
0.25
0.00
% IL32 +

FIG. 27B

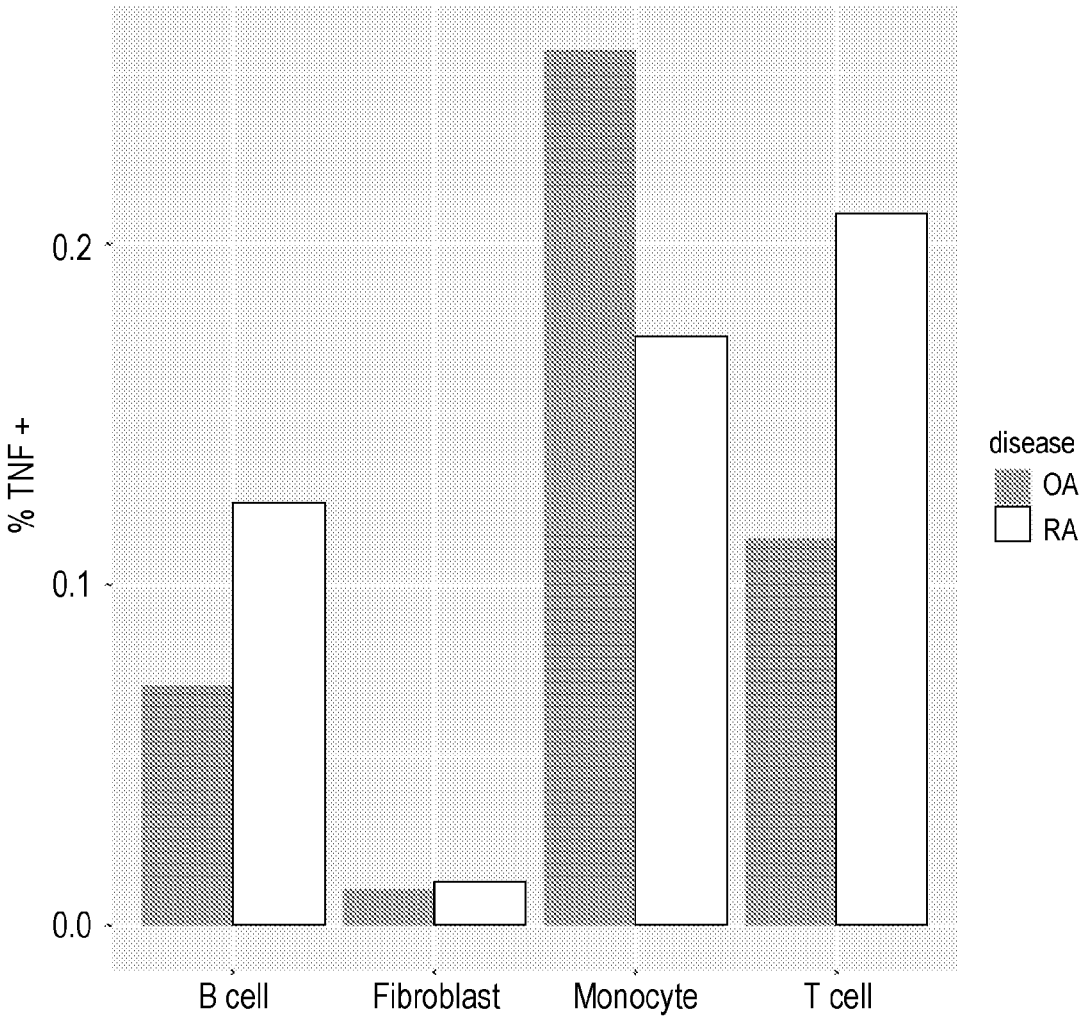


FIG. 27C

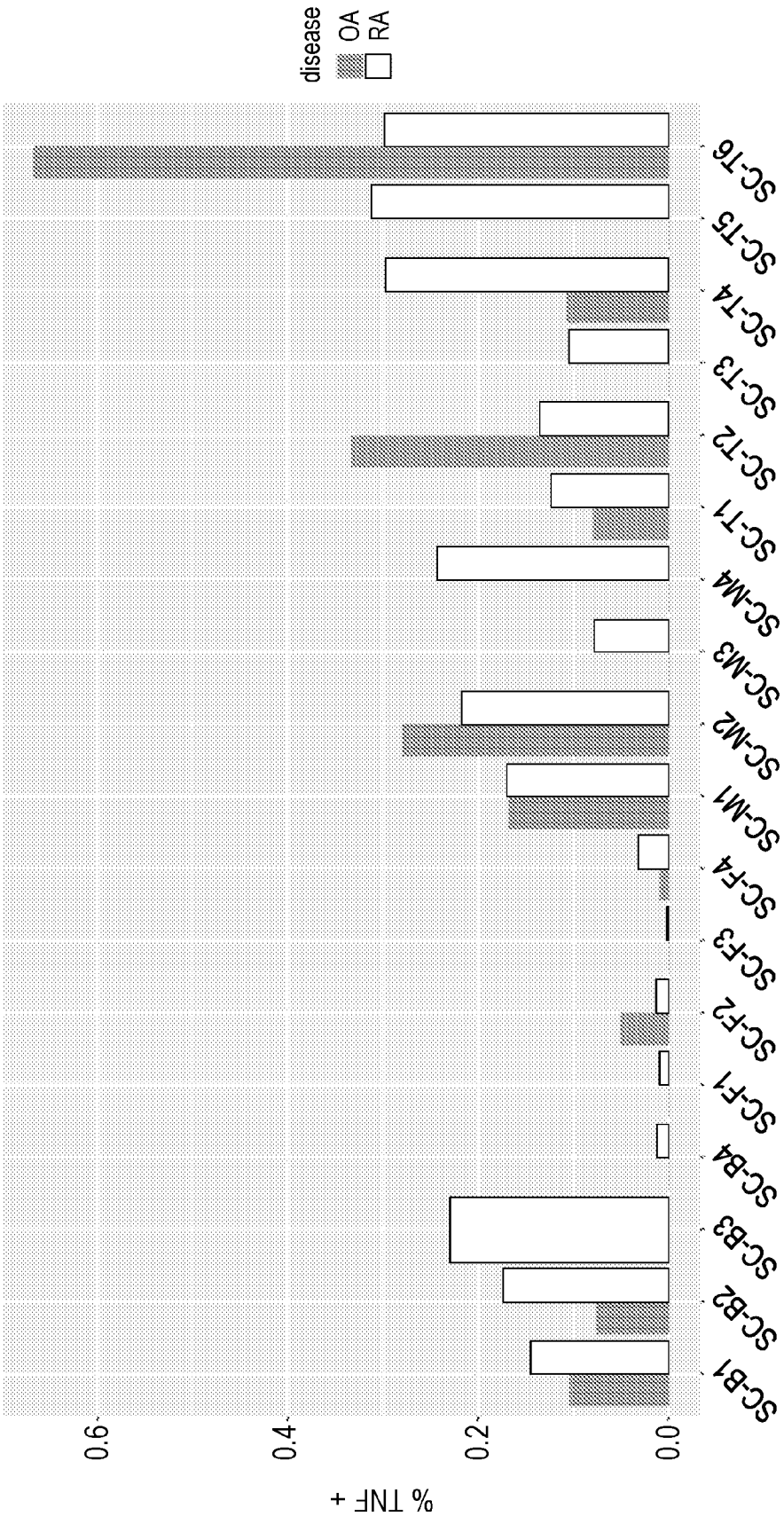

disease
OA
RA
SC-T6
SC-T5
SC-T4
SC-T3
SC-T2
SC-T1
SC-M4
SC-M3
SC-M2
SC-M1
SC-F4
SC-F3
SC-F2
SC-F1
SC-B4
SC-B3
SC-B2
SC-B1
0.0
0.2
0.4
0.6
% TNF +

FIG. 27D

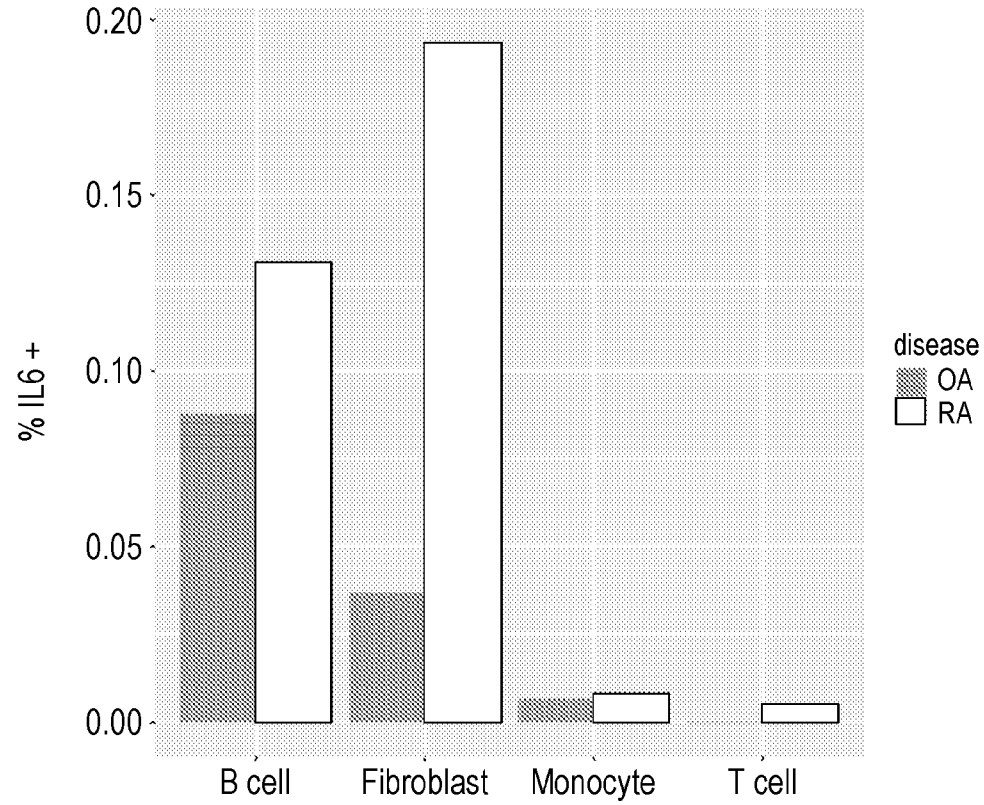


FIG. 27E

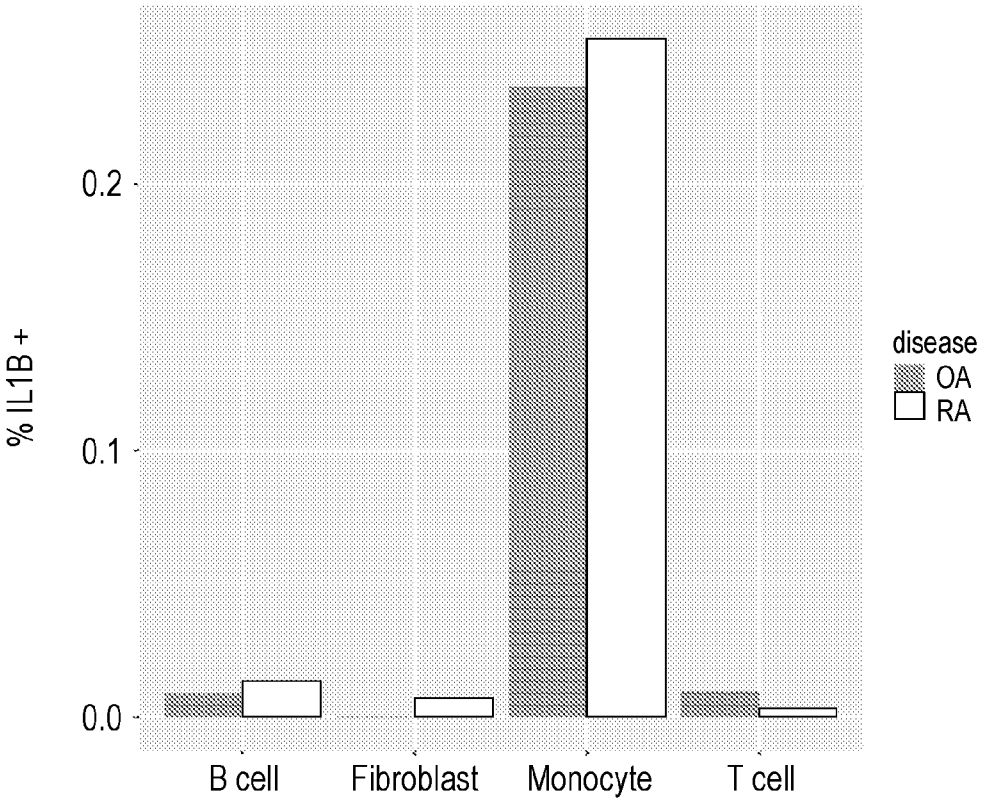


FIG. 27F

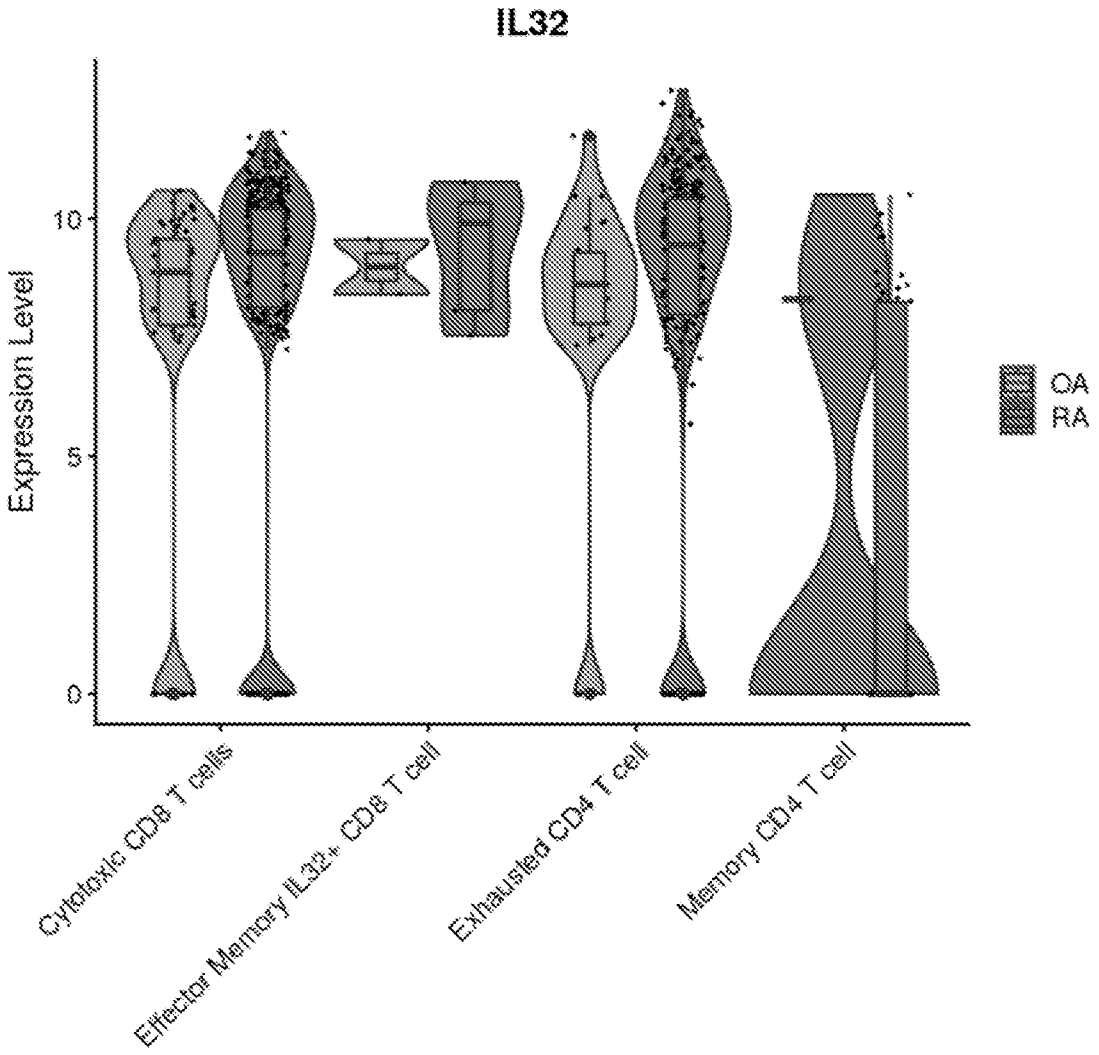

IL32
Expression Level
10
5
0
OA
RA
Cytotoxic CD8 T cells
Effector Memory IL32+ CD8 T cell
Exhausted CD4 T cell
Memory CD4 T cell

FIG. 28

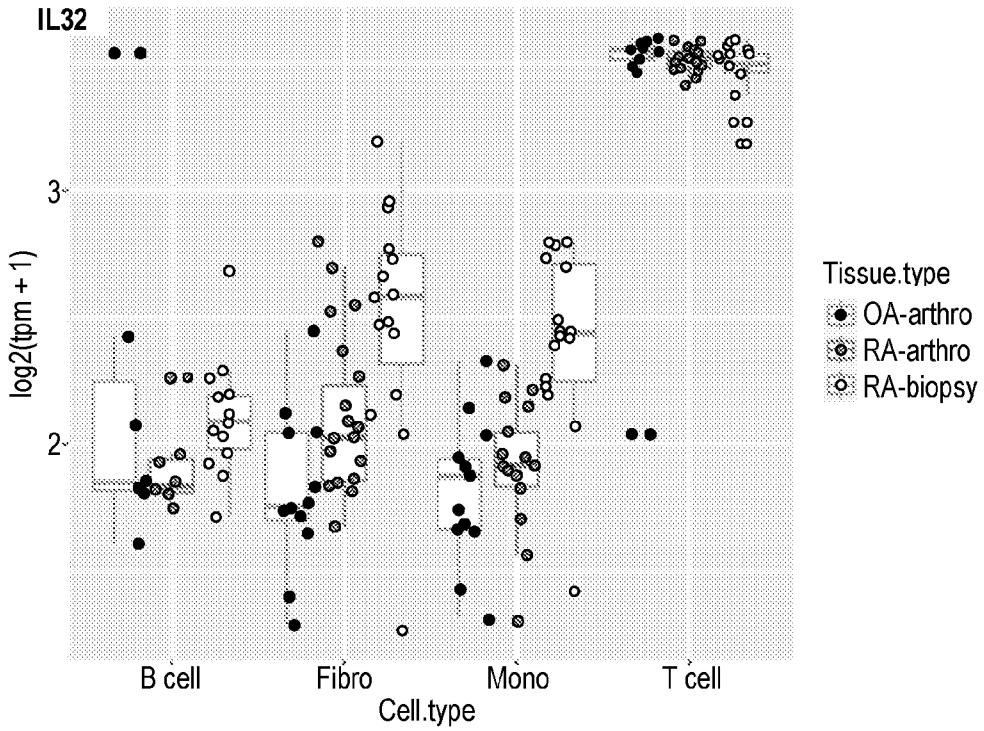


FIG. 29A

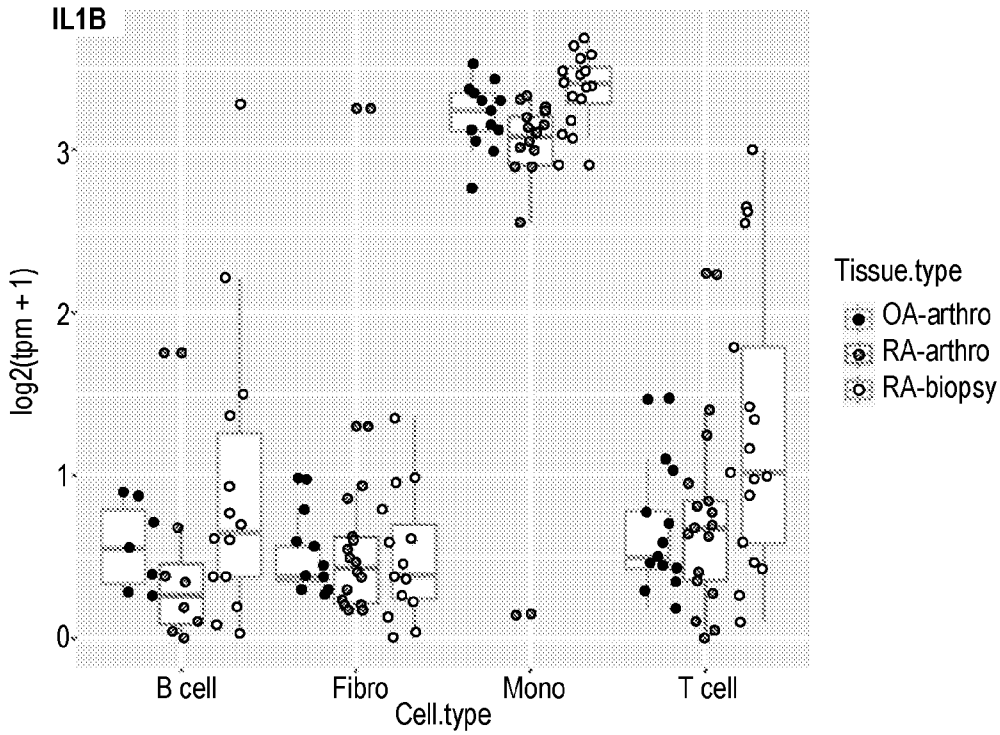


FIG. 29B

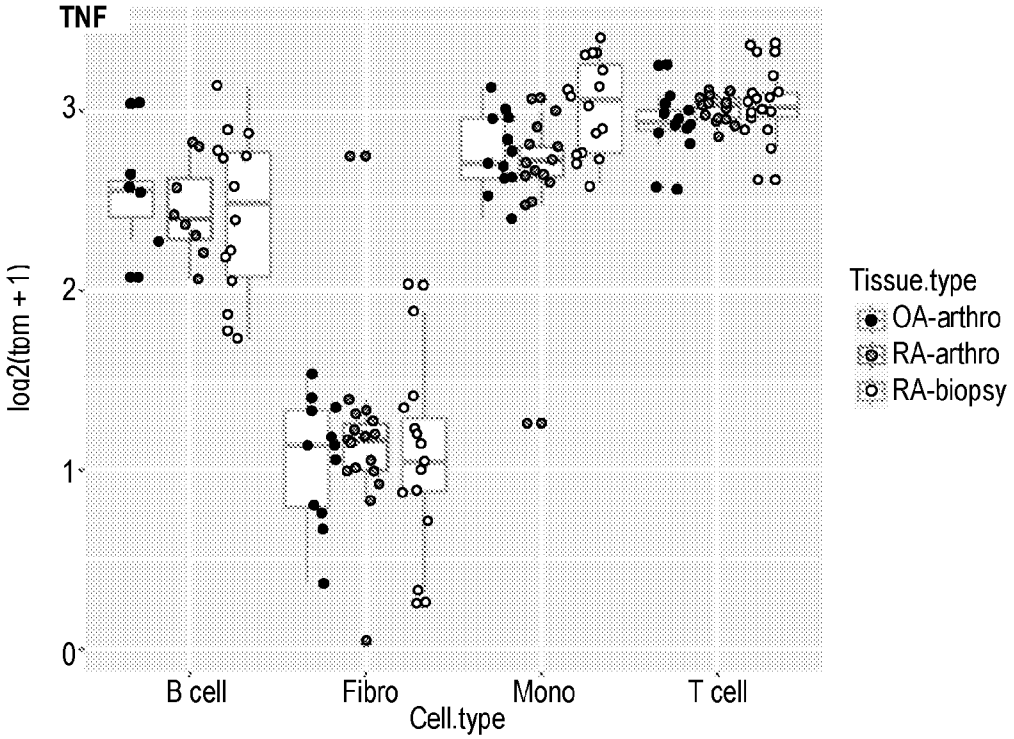


FIG. 29C

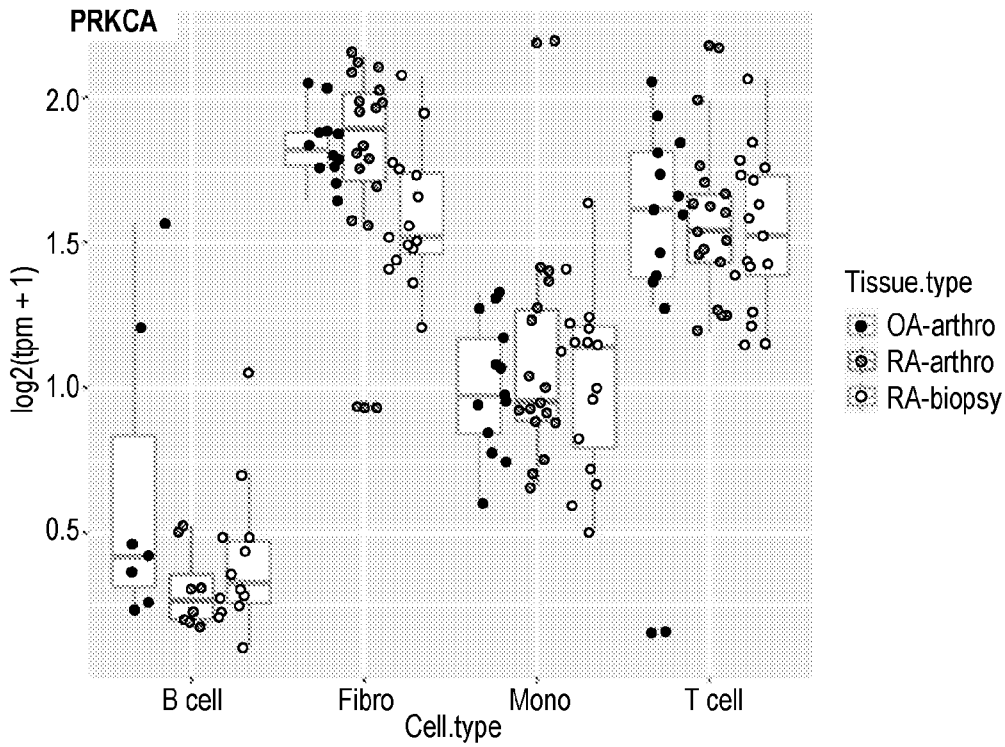


FIG. 29D

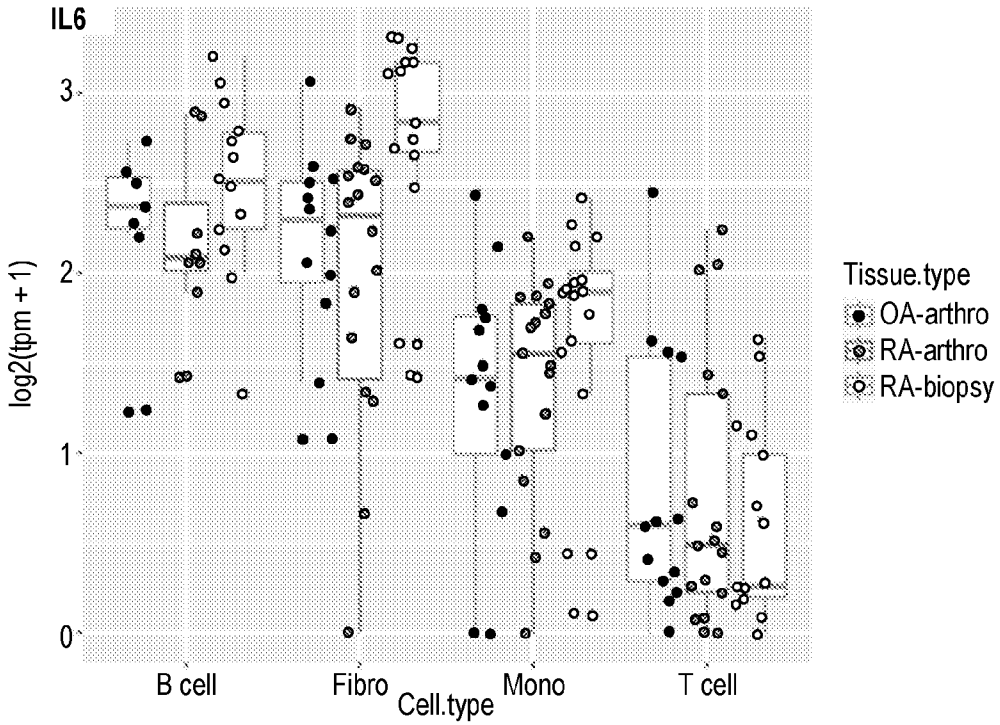


FIG. 29E

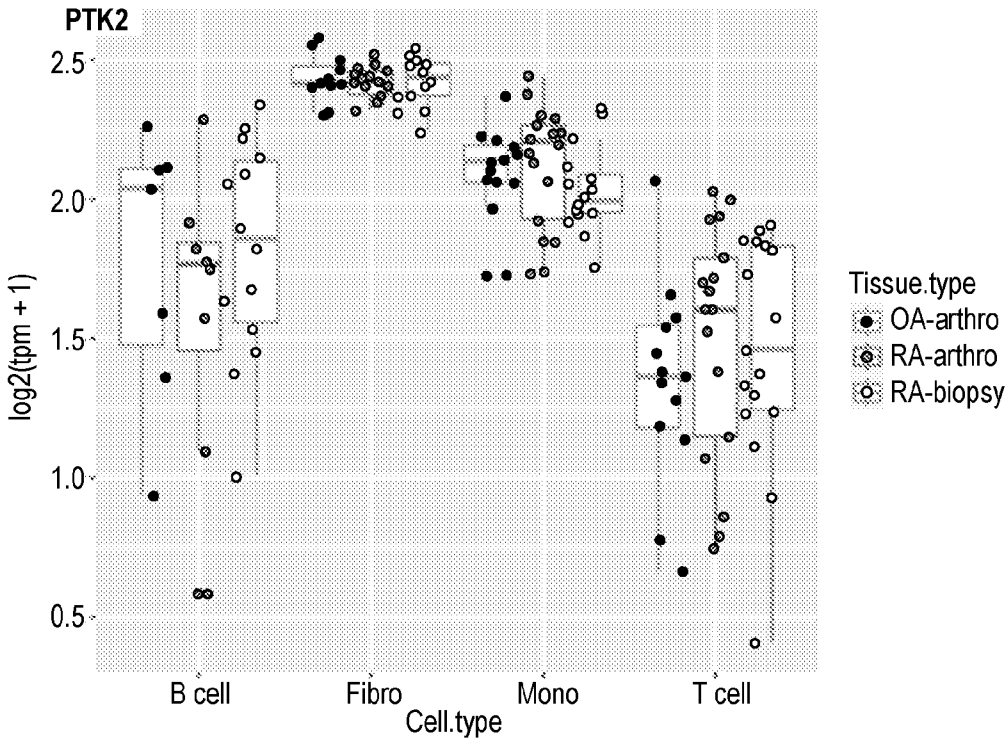


FIG. 29F

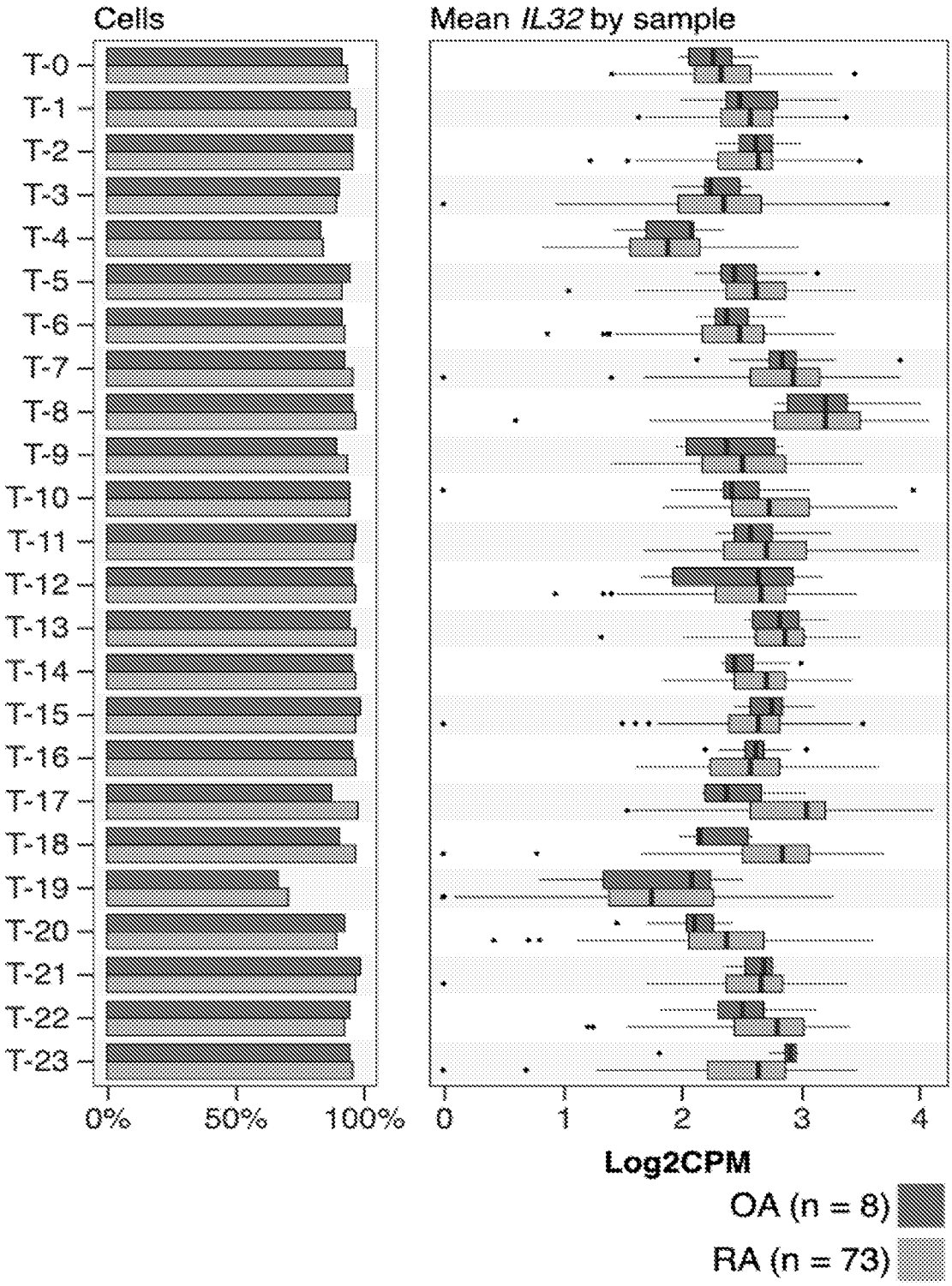

Cells
Mean IL32 by sample
T-0
T-1
T-2
T-3
T-4
T-5
T-6
T-7
T-8
T-9
T-10
T-11
T-12
T-13
T-14
T-15
T-16
T-17
T-18
T-19
T-20
T-21
T-22
T-23
0%
50%
100%
0
1
2
3
4
Log2CPM
OA (n = 8)
RA (n = 73)

FIG. 30

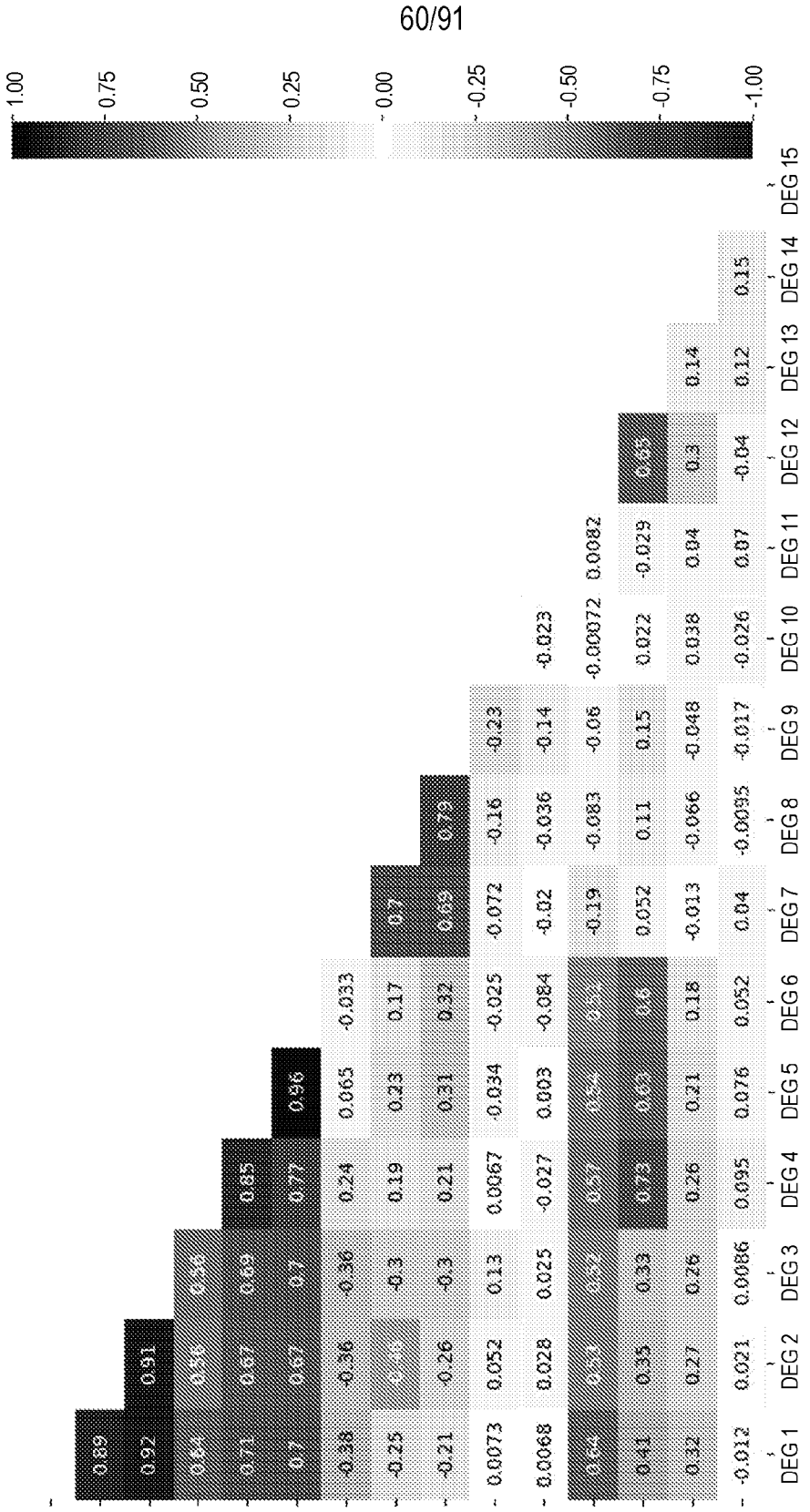

1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
3ng/mL IL32b, 6 hrs
30ng/mL IL32b, 6 hrs
300ng/mL IL32b, 6 hrs
3ng/mL IL32b, 24 hrs
30ng/mL IL32b, 24 hrs
300ng/mL IL32b, 24 hrs
5ng/mL TNF, 6 hrs
5ng/mL TNF, 24 hrs
60ng/mL IL6, 6 hrs
60ng/mL IL6, 24 hrs
DEG
DEG 1
DEG 2
DEG 3
DEG 4
DEG 5
DEG 6
DEG 7
DEG 8
DEG 9
DEG 10
DEG 11
DEG 12
DEG 13
DEG 14
DEG 15

FIG. 31

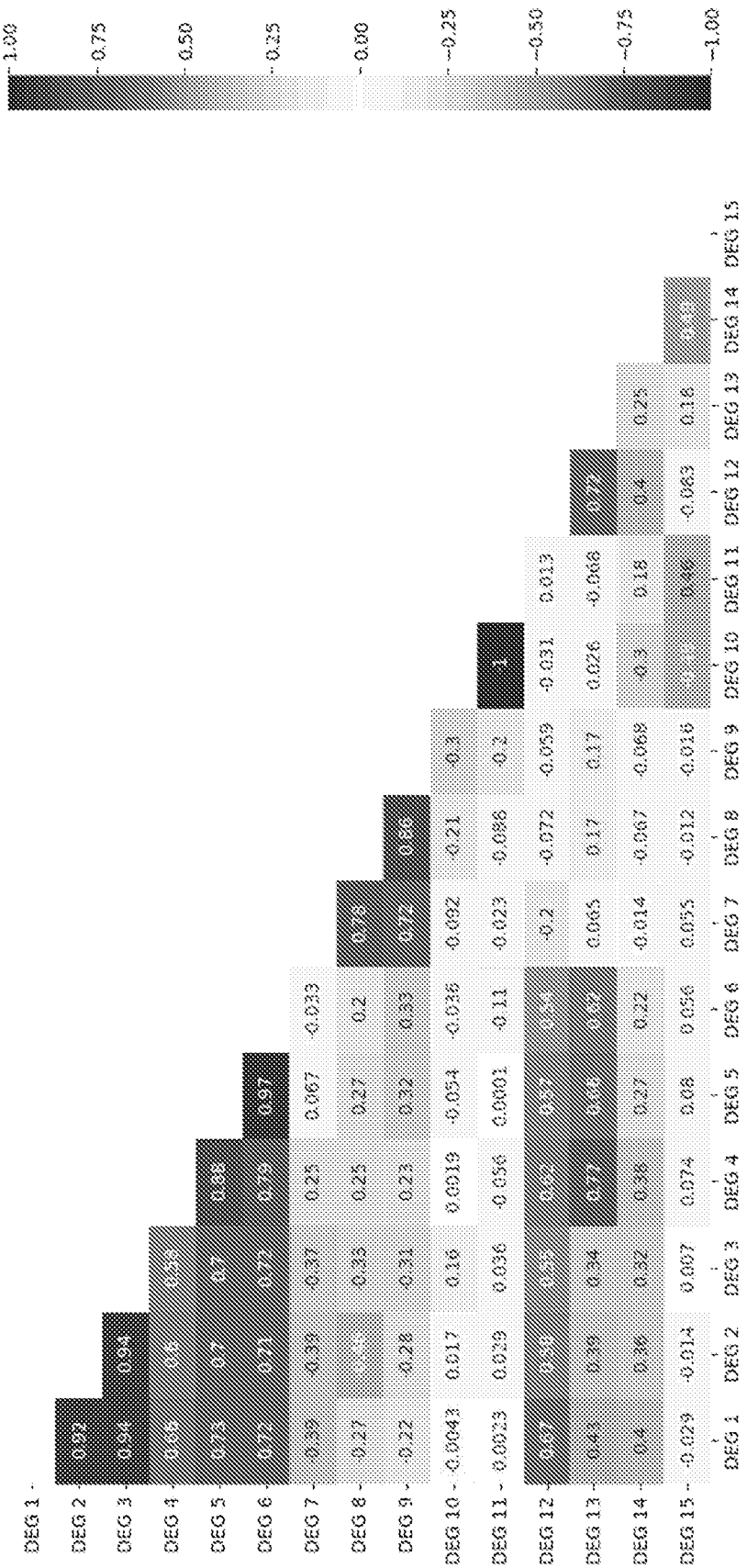

1.00
0.75
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
DEG 1
DEG 2
DEG 3
DEG 4
DEG 5
DEG 6
DEG 7
DEG 8
DEG 9
DEG 10
DEG 11
DEG 12
DEG 13
DEG 14
DEG 15

FIG. 32

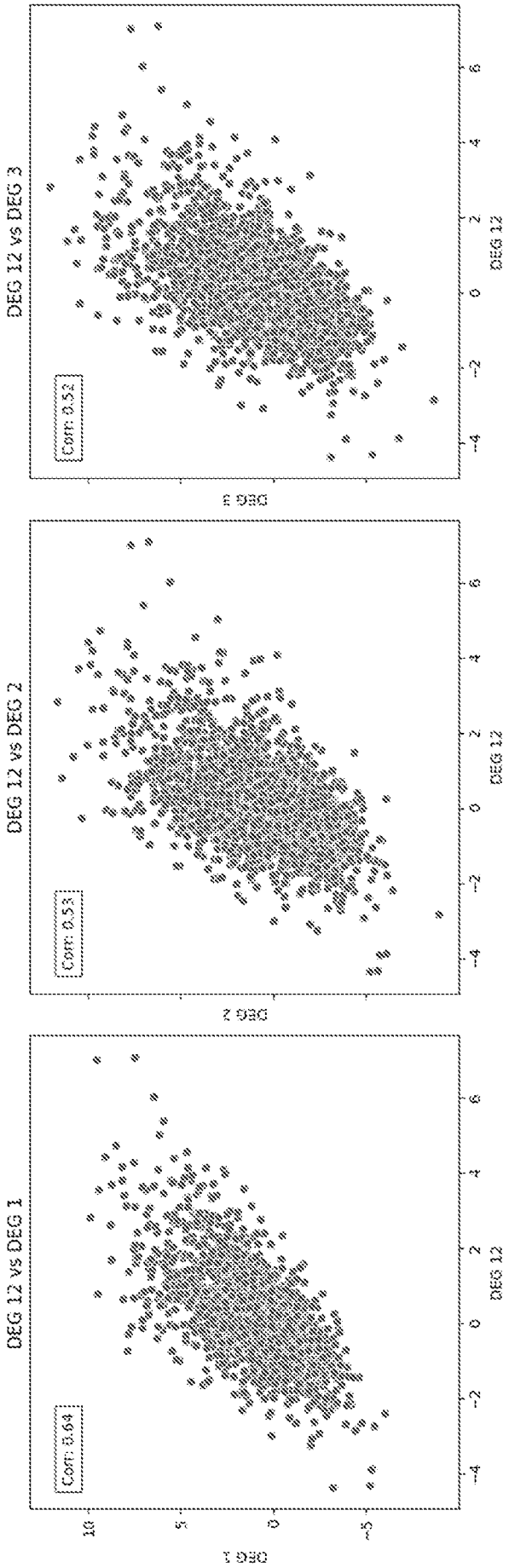


FIG. 33C

FIG. 33B

FIG. 33A

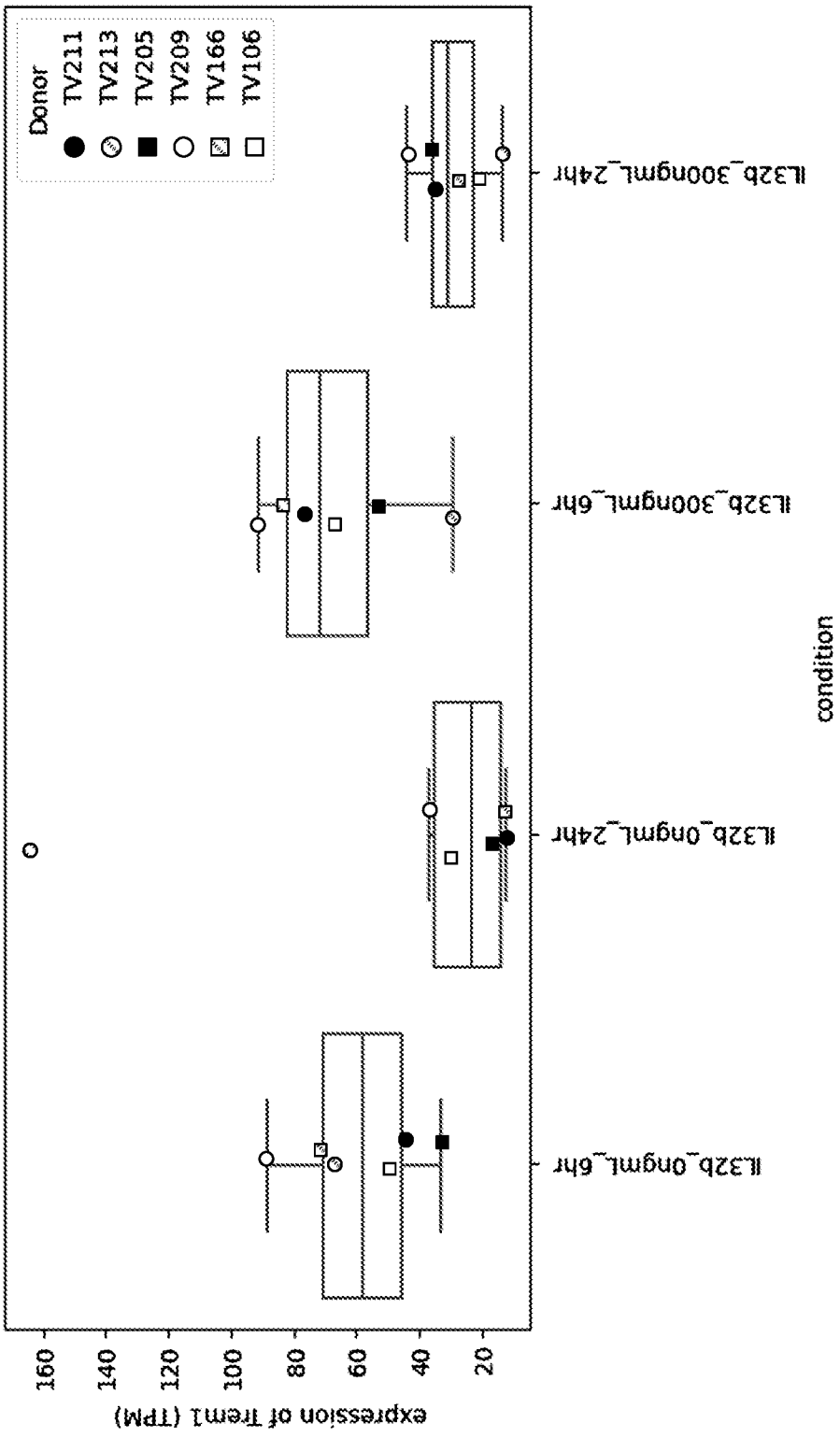

Donor
TV211
TV213
TV205
TV209
TV166
TV106
expression of Trem1 (TPM)
160
140
120
100
80
60
40
20
IL32b_0ngmL_6hr
IL32b_0ngmL_24hr
IL32b_300ngmL_6hr
IL32b_300ngmL_24hr
condition

FIG. 34A

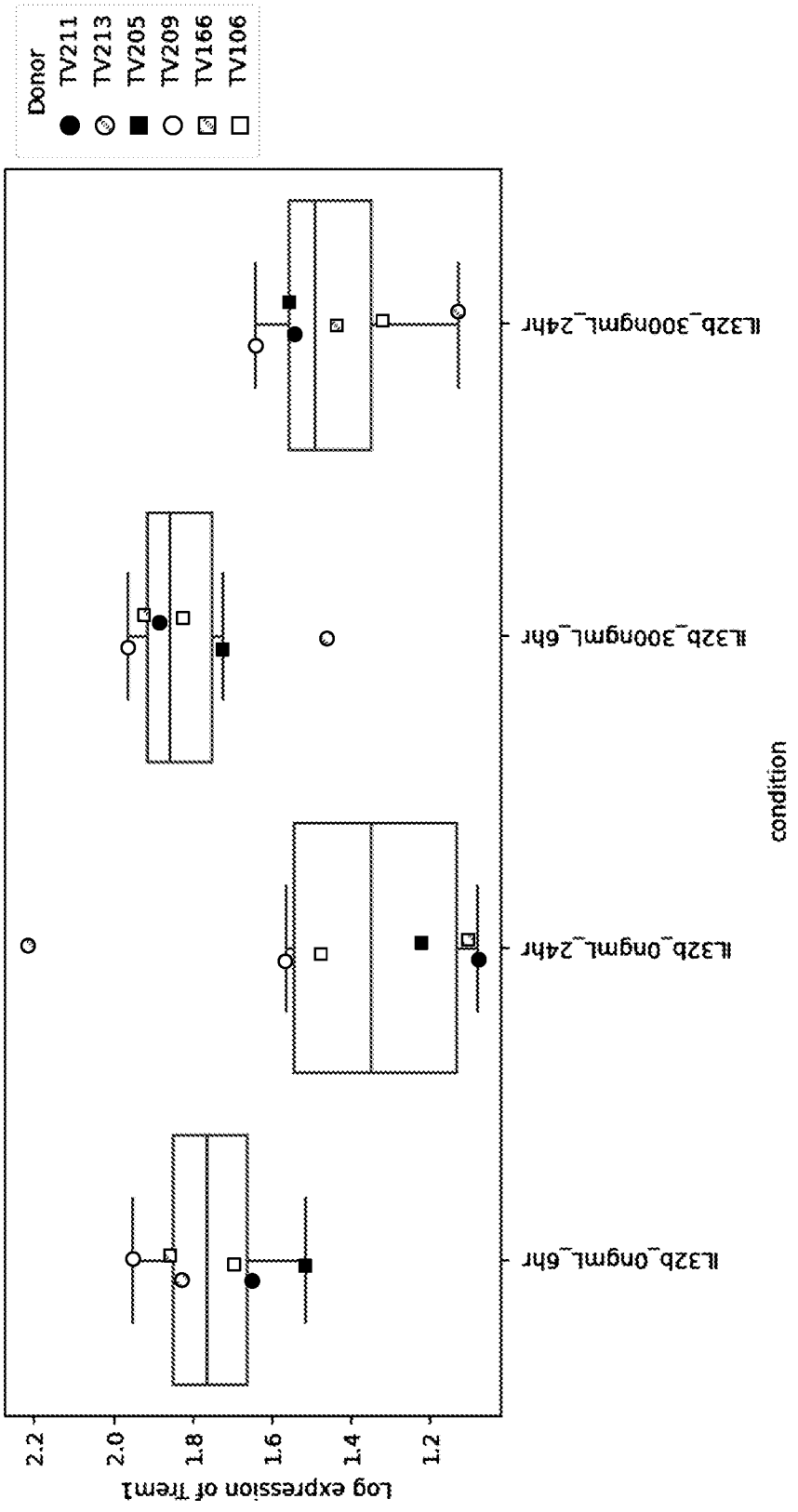

Donor
TV211
TV213
TV205
TV209
TV166
TV106
log expression of Trem1
2.2
2.0
1.8
1.6
1.4
1.2
IL32b_0ngmL_6hr
IL32b_0ngmL_24hr
IL32b_300ngmL_6hr
IL32b_300ngmL_24hr
condition

FIG. 34B

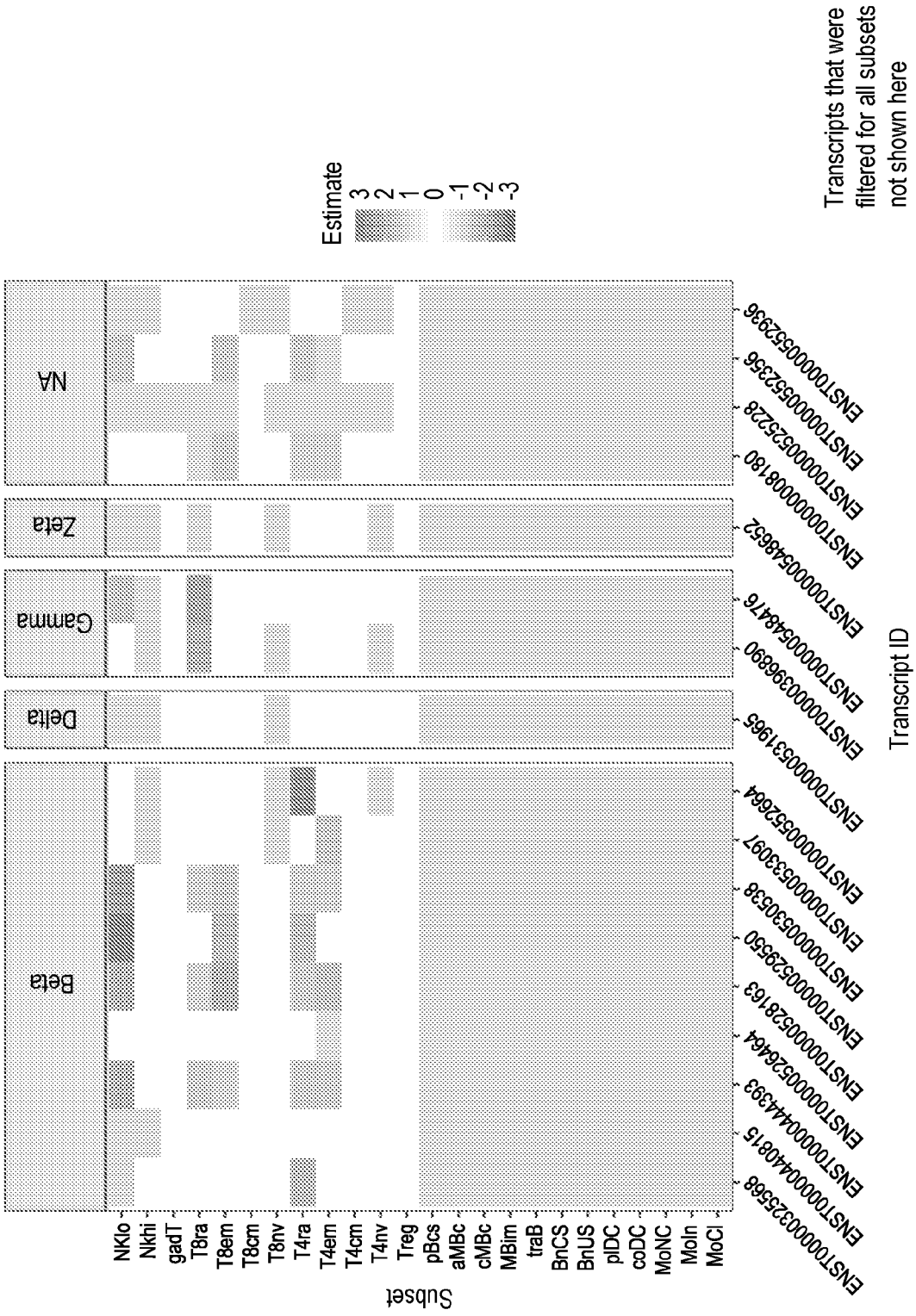

Transcripts that were filtered for all subsets not shown here
Estimate
3
2
1
0
-1
-2
-3
Beta
Delta
Gamma
Zeta
NA
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl
ENST00000325568
ENST00000440815
ENST00000444393
ENST00000526464
ENST00000528163
ENST00000529550
ENST00000530538
ENST00000533097
ENST00000526564
ENST00000531965
ENST00000396890
ENST00000548476
ENST00000548652
ENST00000008180
ENST00000525228
ENST00000523556
ENST00000529356
Transcript ID

FIG. 35

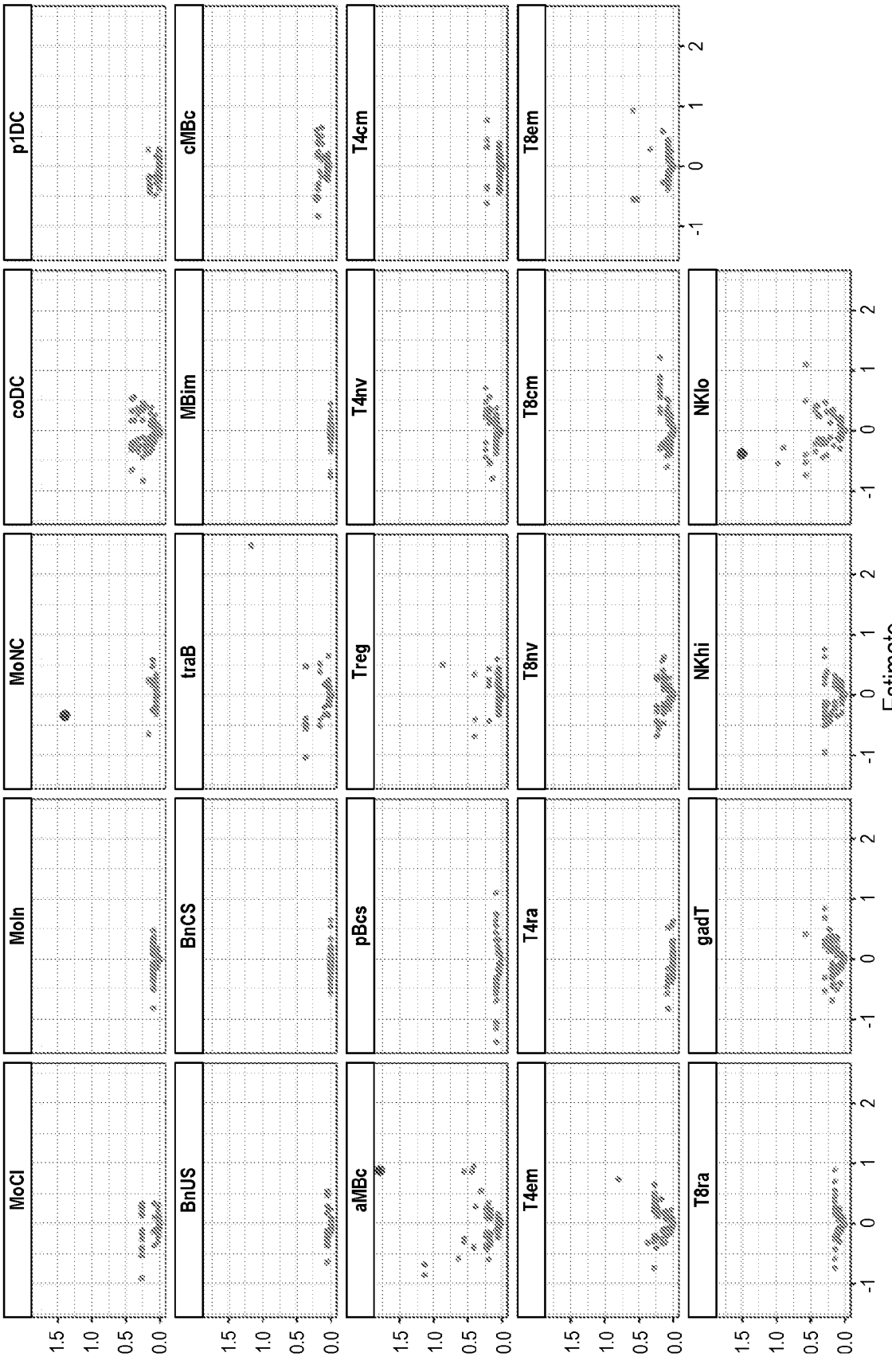

MoCl
MoIn
MoNC
coDC
p1DC
BnUS
BnCS
traB
MBim
cMBc
aMBc
pBcs
Treg
T4nv
T4cm
T4em
T4ra
T8nv
T8cm
T8em
T8ra
gadT
NKhi
NKlo
-log(fdr)
Estimate

FIG. 36

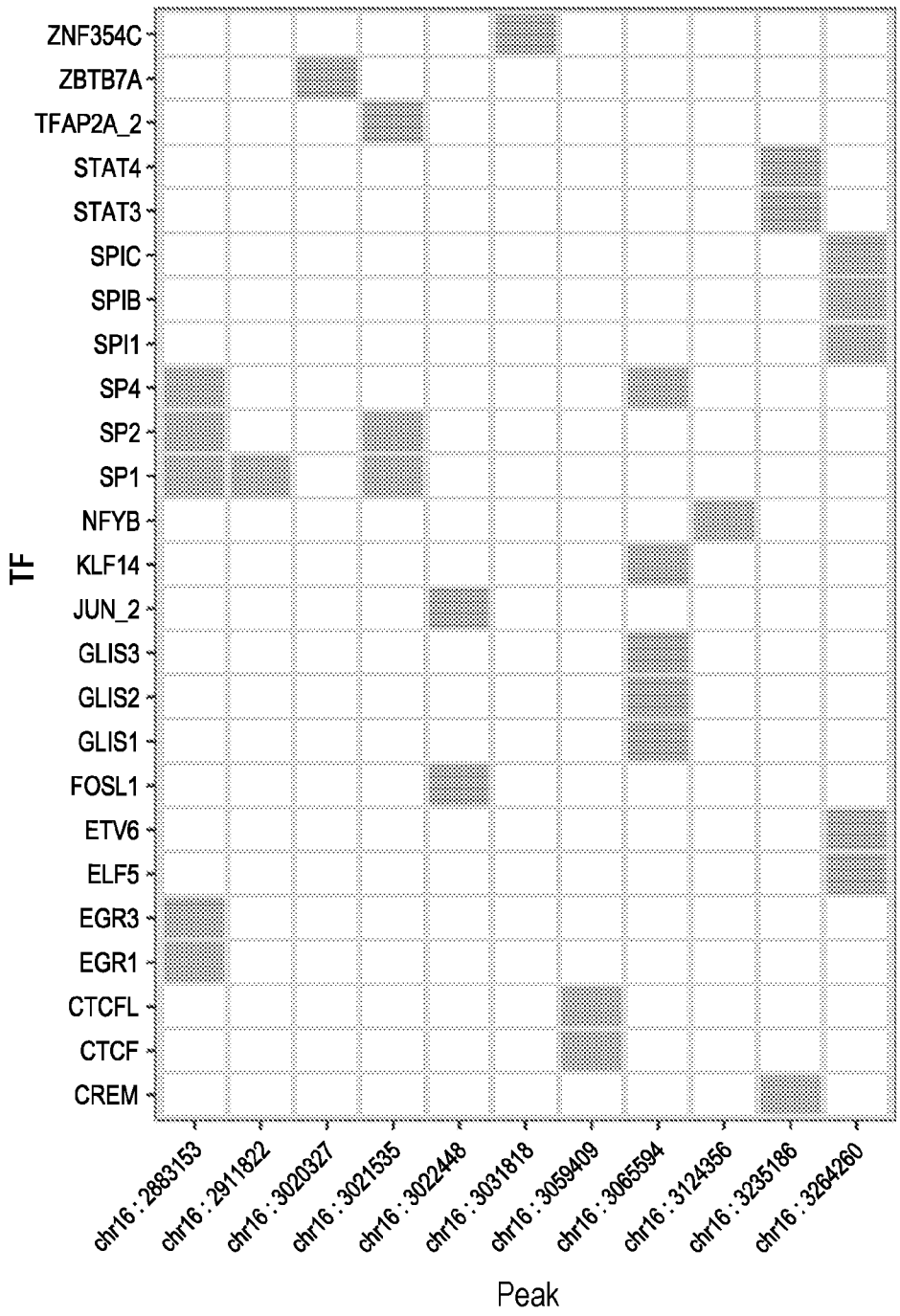

ZNF354C
ZBTB7A
TFAP2A_2
STAT4
STAT3
SPIC
SPIB
SPI1
SP4
SP2
SP1
NFYB
KLF14
JUN_2
GLIS3
GLIS2
GLIS1
FOSL1
ETV6
ELF5
EGR3
EGR1
CTCFL
CTCF
CREM
TF
chr16 : 2883153
chr16 : 2911822
chr16 : 3020327
chr16 : 3021535
chr16 : 3022448
chr16 : 3031818
chr16 : 3059409
chr16 : 3065594
chr16 : 3124356
chr16 : 3235186
chr16 : 3264260
Peak

FIG. 37

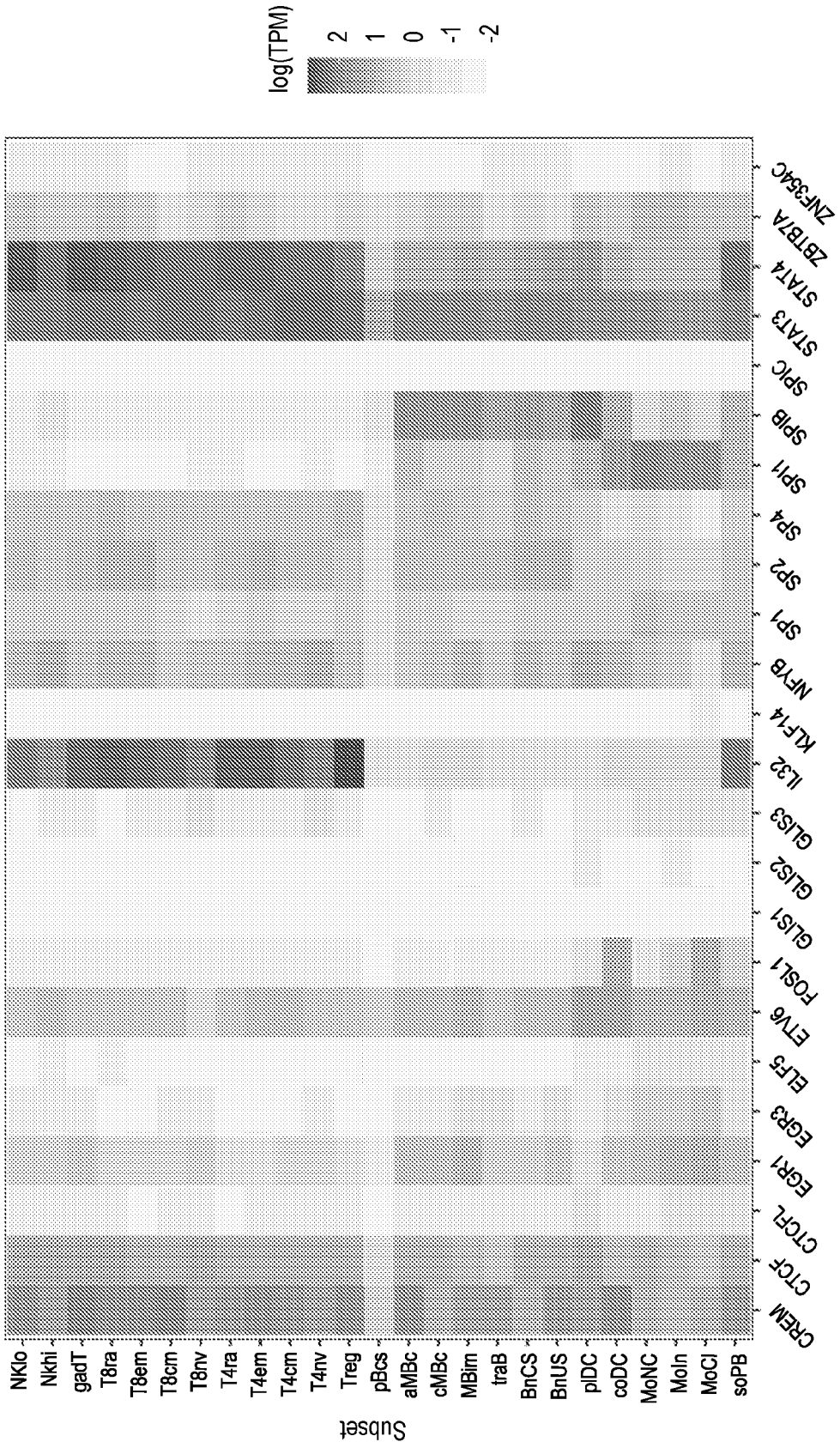

log(TPM)
2
1
0
-1
-2
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl
soPB
Gene
CREM
CTCF
CTCFL
EGR1
EGR3
ELF5
ETV6
FOSL1
GLIS1
GLIS2
GLIS3
IL32
KLF14
NFYB
SP1
SP2
SP4
SPI1
SPIB
SPIC
STAT3
STAT4
ZBTB7A
ZNF35AC

FIG. 38

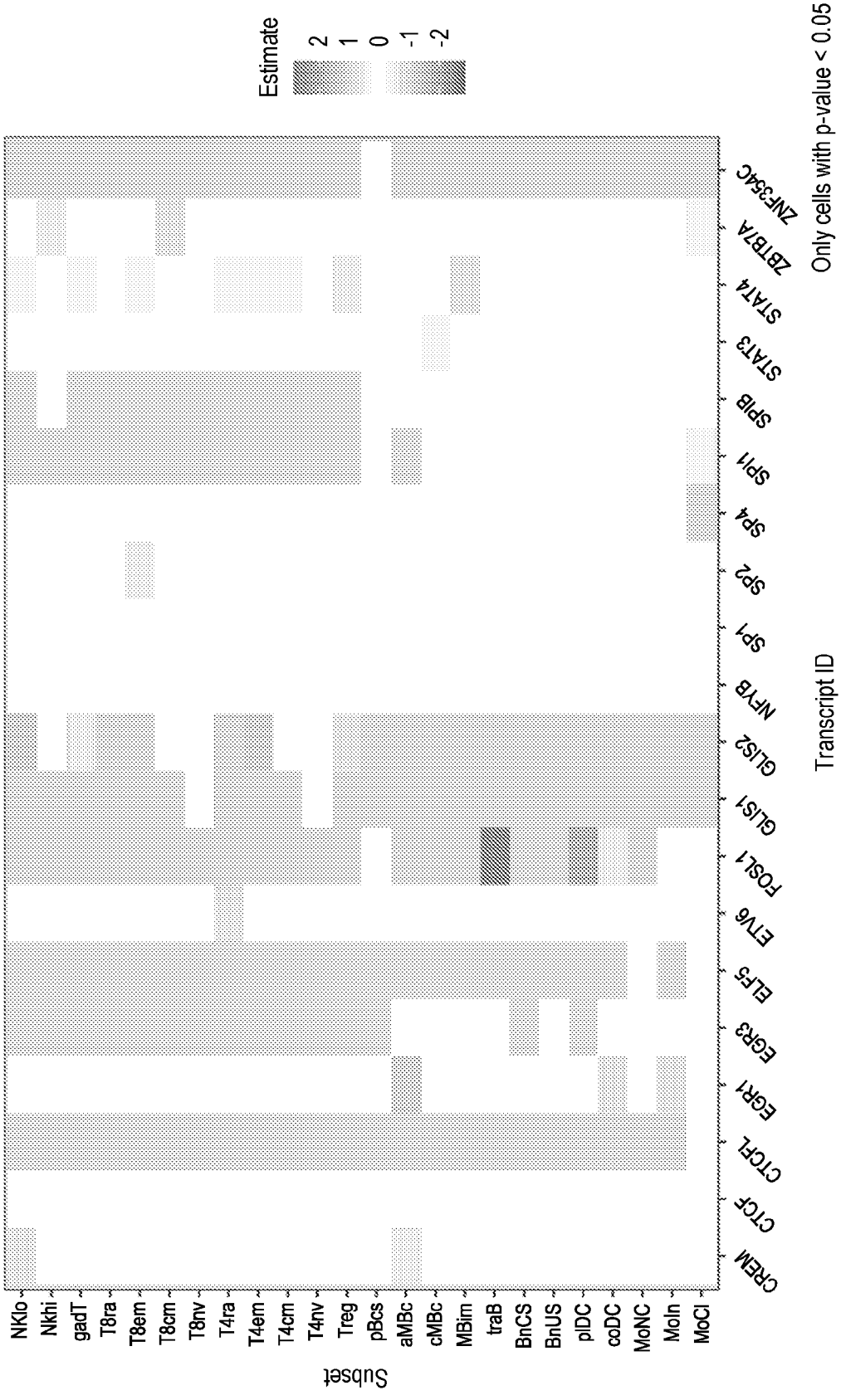

Estimate
2
1
0
-1
-2
Only cells with p-value < 0.05
(NOT FDR) are shown.
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
pIDC
coDC
MoNC
MoIn
MoCl
Transcript ID
CREM
CTCF
CTCFL
EGR1
EGR3
ELF5
ETV6
FOSL1
GLIS1
GLIS2
NFYB
SP1
SP2
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF354C

FIG. 39A

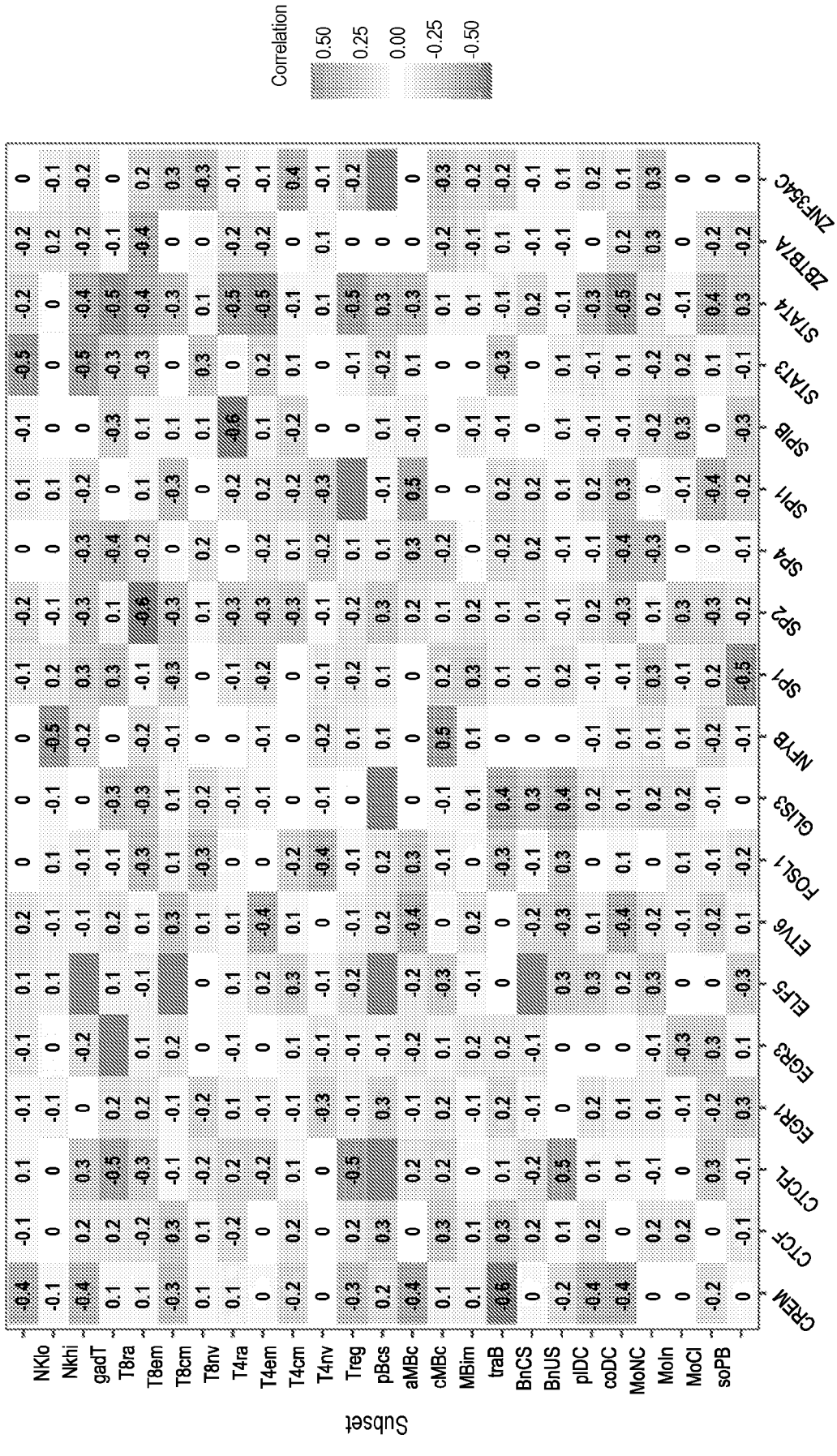

Correlation
0.50
0.25
0.00
-0.25
-0.50
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl
soPB
CREM
CTCF
CTCFL
EGR1
EGR3
ELF5
ETV6
FOSL1
GLIS3
NFYB
SPI1
SP2
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF354C
Gene

FIG. 39B

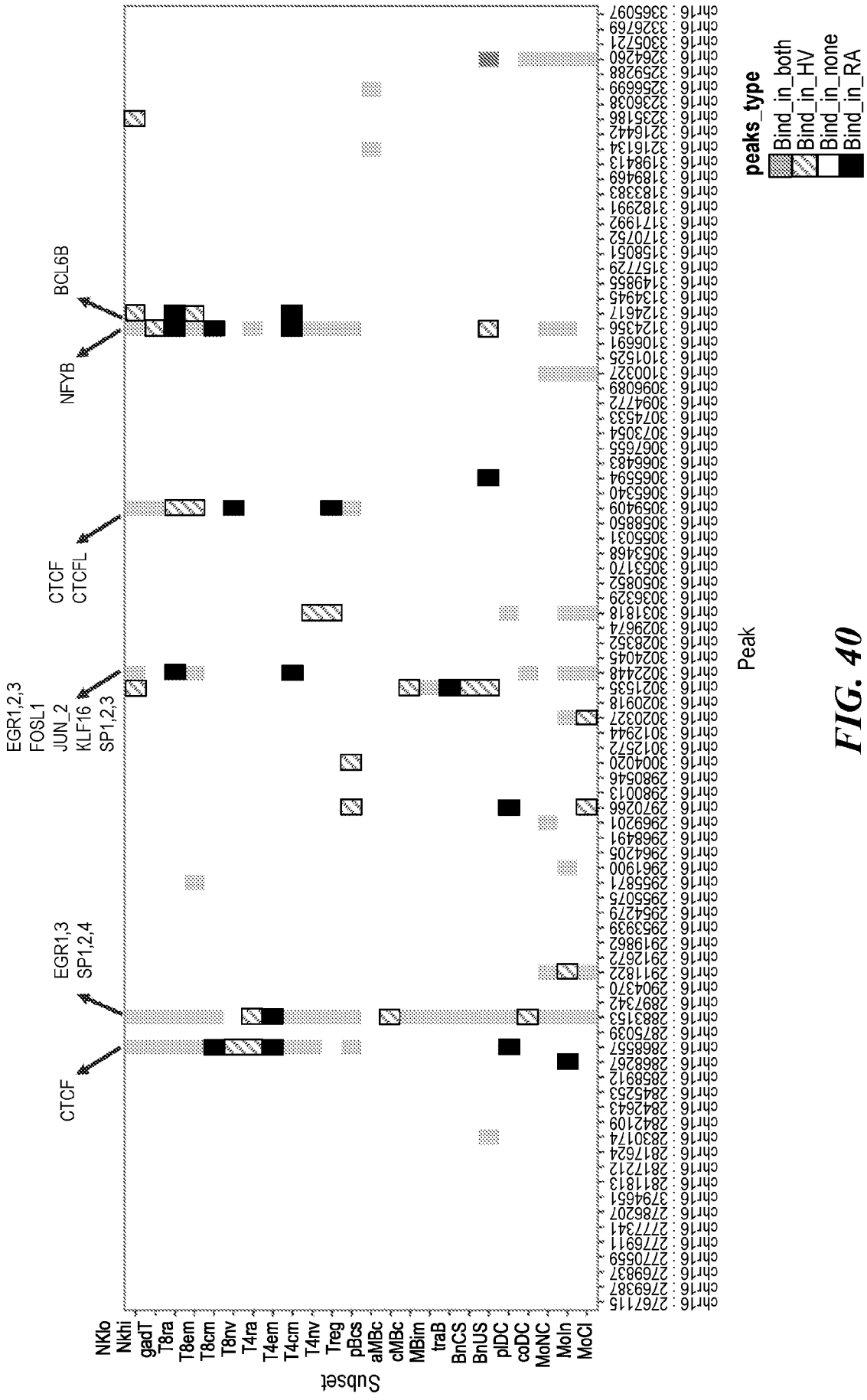

peaks_type
Bind_in_both
Bind_in_HV
Bind_in_none
Bind_in_RA
BCL6B
NFYB
CTCF
CTCFL
EGR1,2,3
FOSL1
JUN_2
KLF16
SP1,2,3
EGR1,3
SP1,2,4
CTCF
Peak
Subset
NKlo
NKhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl

FIG. 40

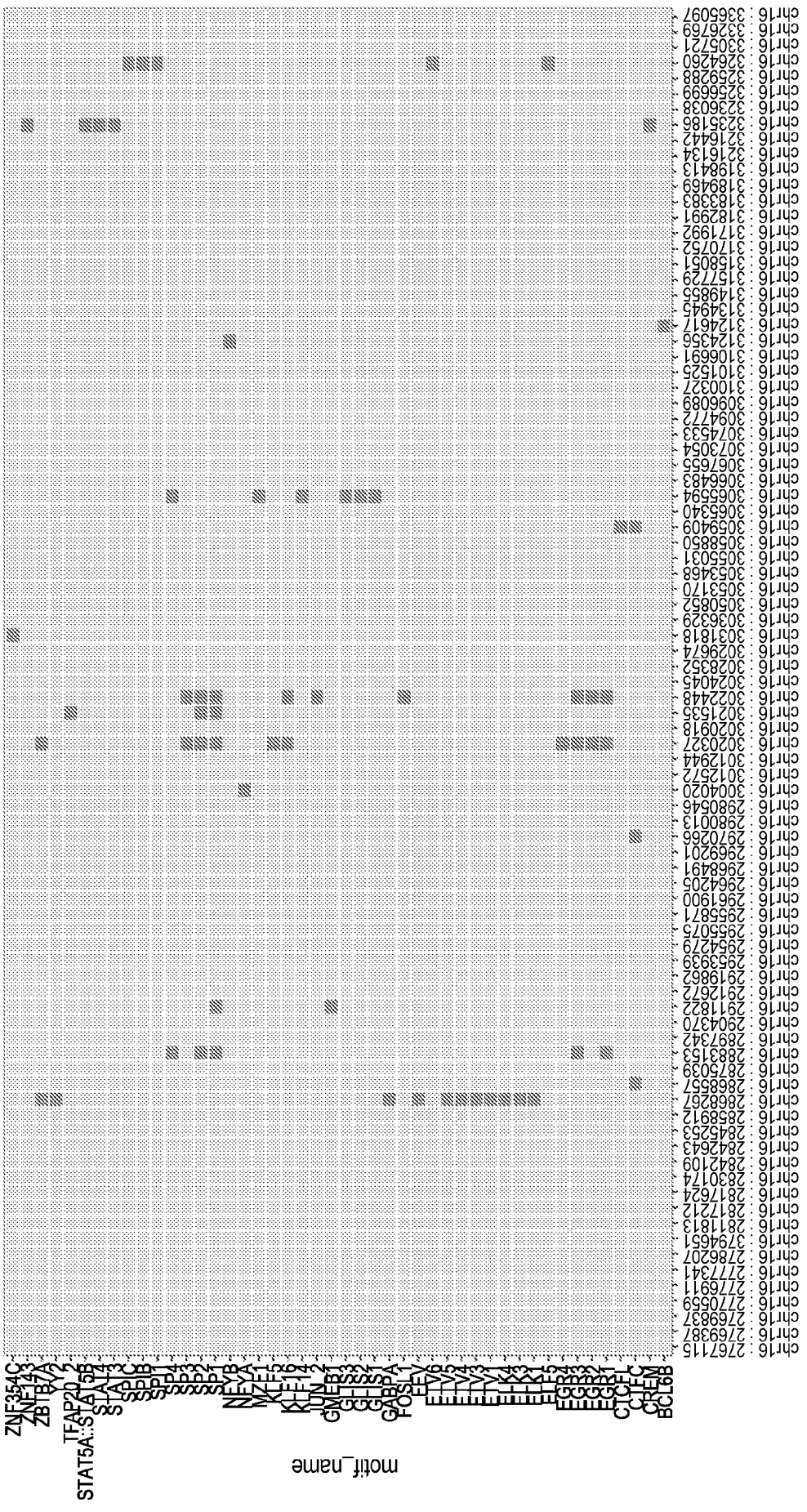

motif_name
seq_name
ZNF354C
ZNF143
ZBTB7A
YY2
TFAP2D
STAT5A::STAT5B
STAT4
STAT3
SPIB
SPI1
SP4
SP3
SP2
SP1
NFYA
MZF1
KLF5
KLF16
KLF14
JUND
GMEB1
FLI1
ELK3
GABPA
FOSL1
ELF5
ELF3
ELF2
ELF1
ELK4
ELK3
ELK1
ELF5
EGR4
EGR3
EGR2
EGR1
CTCFL
CTCF
CREM
BCL6B
chr16:27671153
chr16:27693873
chr16:27705593
chr16:27769113
chr16:27773413
chr16:27862073
chr16:27949513
chr16:28111813
chr16:28172123
chr16:28176243
chr16:28301743
chr16:28421093
chr16:28426433
chr16:28452533
chr16:28589123
chr16:28682673
chr16:28685573
chr16:28750393
chr16:28831533
chr16:28973423
chr16:29043703
chr16:29118223
chr16:29126723
chr16:29198623
chr16:29539393
chr16:29542793
chr16:29550753
chr16:29585713
chr16:29619003
chr16:29642053
chr16:29684913
chr16:29692013
chr16:29702663
chr16:29800133
chr16:29805463
chr16:30040203
chr16:30125723
chr16:30129443
chr16:30203273
chr16:30209183
chr16:30215353
chr16:30224483
chr16:30240453
chr16:30283523
chr16:30296743
chr16:30318183
chr16:30363293
chr16:30508523
chr16:30531703
chr16:30546683
chr16:30550313
chr16:30588503
chr16:30594093
chr16:30653403
chr16:30655943
chr16:30664833
chr16:30676553
chr16:30730543
chr16:30745333
chr16:30947723
chr16:30960893
chr16:31003273
chr16:31015253
chr16:31066913
chr16:31243563
chr16:31246173
chr16:31349453
chr16:31498553
chr16:31577293
chr16:31580513
chr16:31707523
chr16:31719923
chr16:31829913
chr16:31838353
chr16:31894693
chr16:31984133
chr16:32161343
chr16:32164423
chr16:32357183
chr16:32360383
chr16:32566993
chr16:32592883
chr16:32642603
chr16:33057213
chr16:33267693
chr16:33650973

FIG. 41

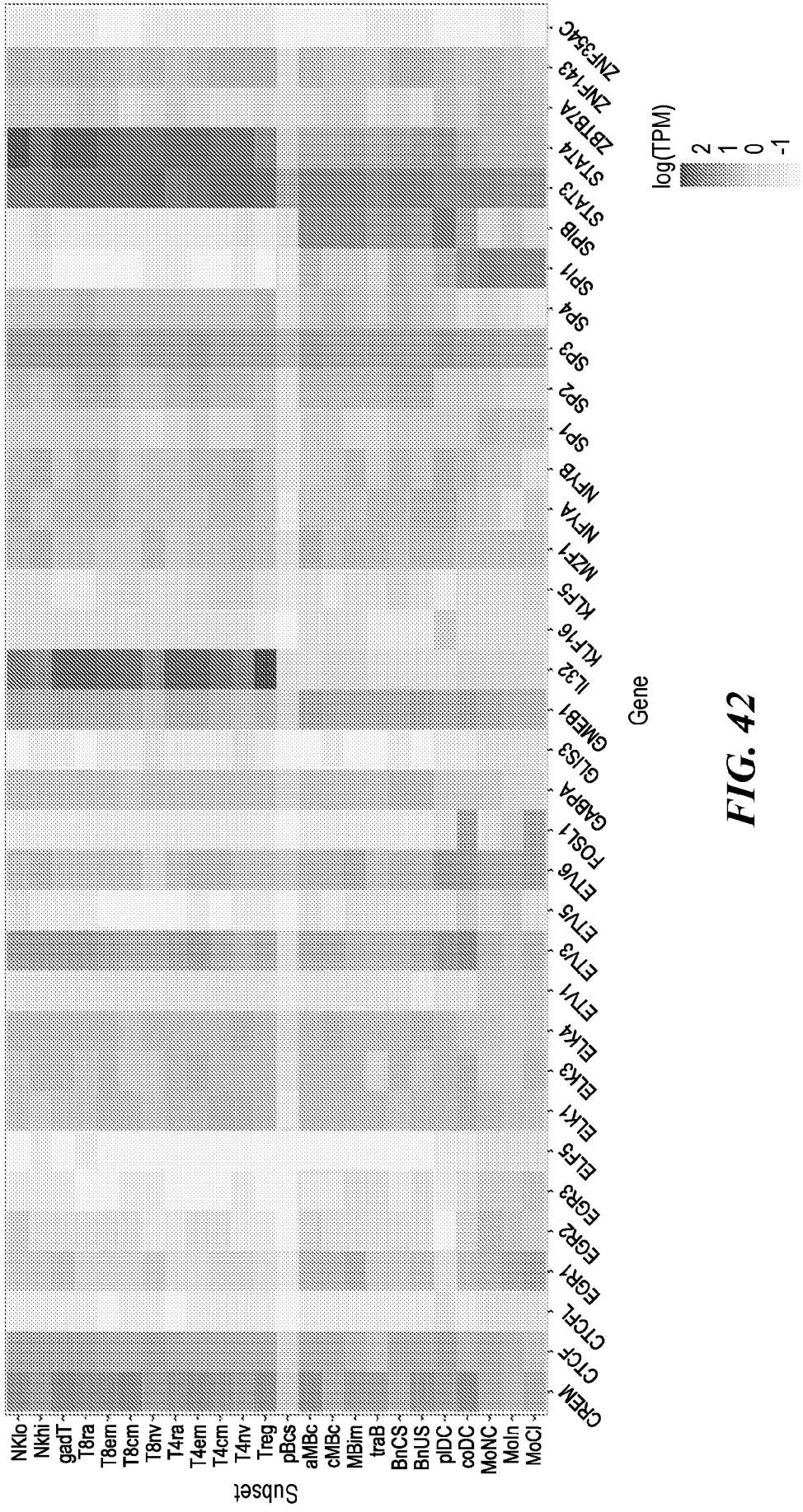

Subset
NKlo
NKhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
pIDC
coDC
MoNC
MoIn
MoCl
Gene
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
IL32
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF143
ZNF354C
log(TPM)
2
1
0
-1

FIG. 42


Estimate
2
0
-2
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
plDC
coDC
MoNC
MoIn
MoCl
Transcript ID
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
IL32
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
YY2
ZBTB7A
ZNF143
ZNF354C

FIG. 43

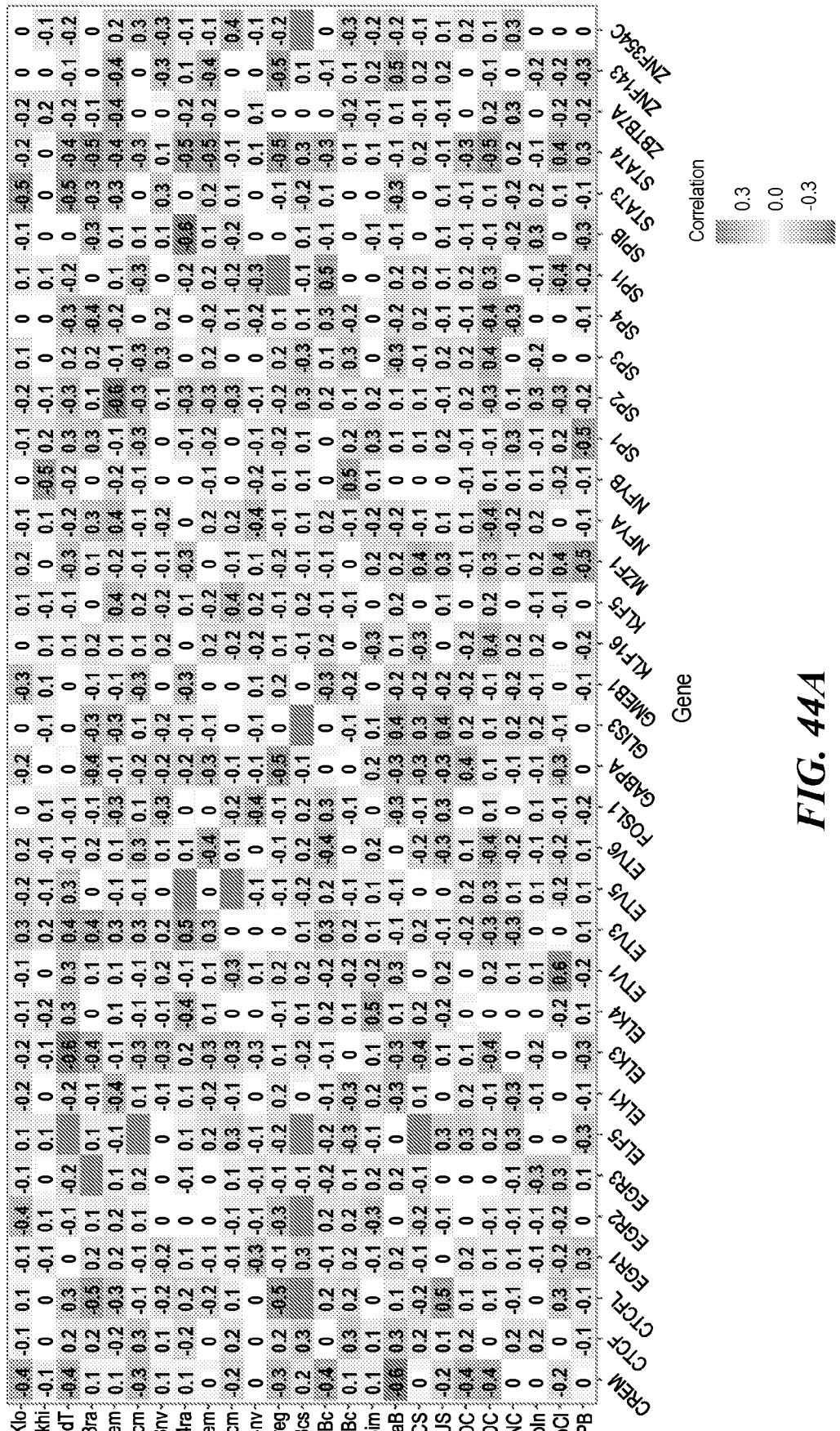

Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
cMBc
MBim
traB
BnCS
BnUS
plDC
coDC
MoNC
MoIn
MoCl
soPB
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF143
ZNF354C
Gene
Correlation
0.3
0.0
-0.3

FIG. 44A

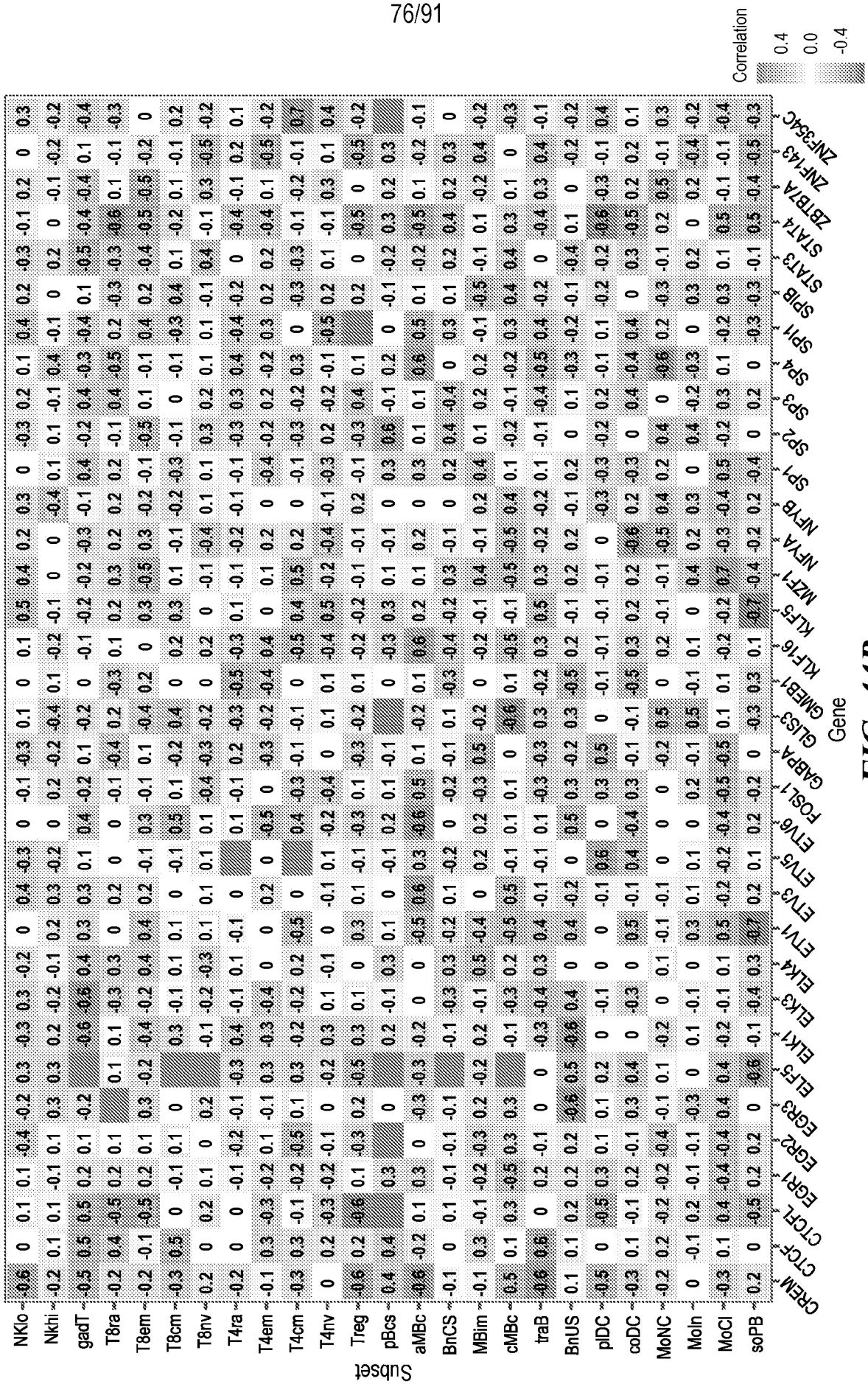

Correlation
0.4
0.0
-0.4
Gene
Subset
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
plDC
coDC
MoNC
MoIn
MoCl
soPB
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF143
ZNF354C

FIG. 44B

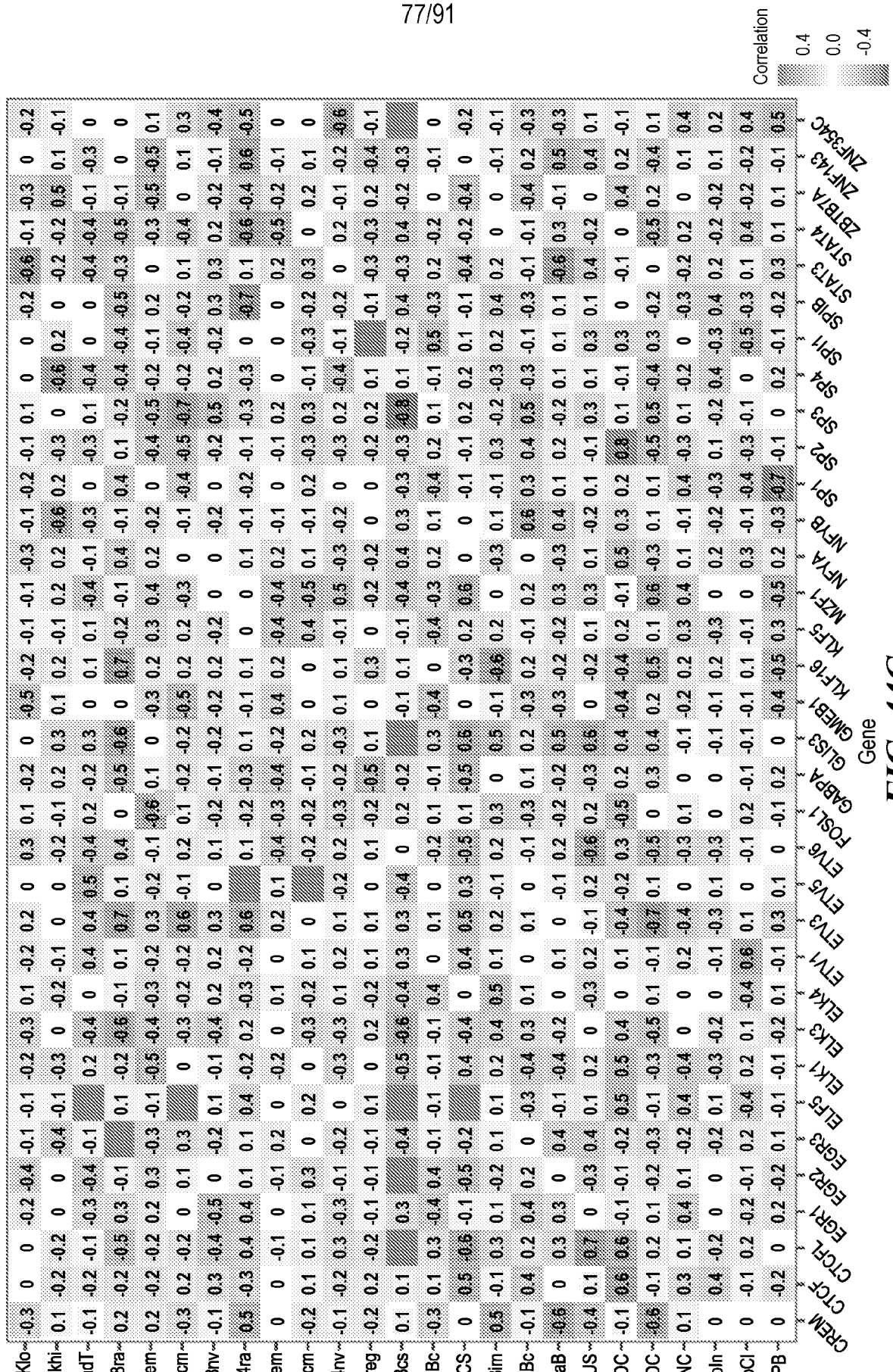

Correlation
0.4
0.0
-0.4
Subset
Gene
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
plDC
coDC
MoNC
MoIn
MoCl
soPB
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF143
ZNF354C

FIG. 44C

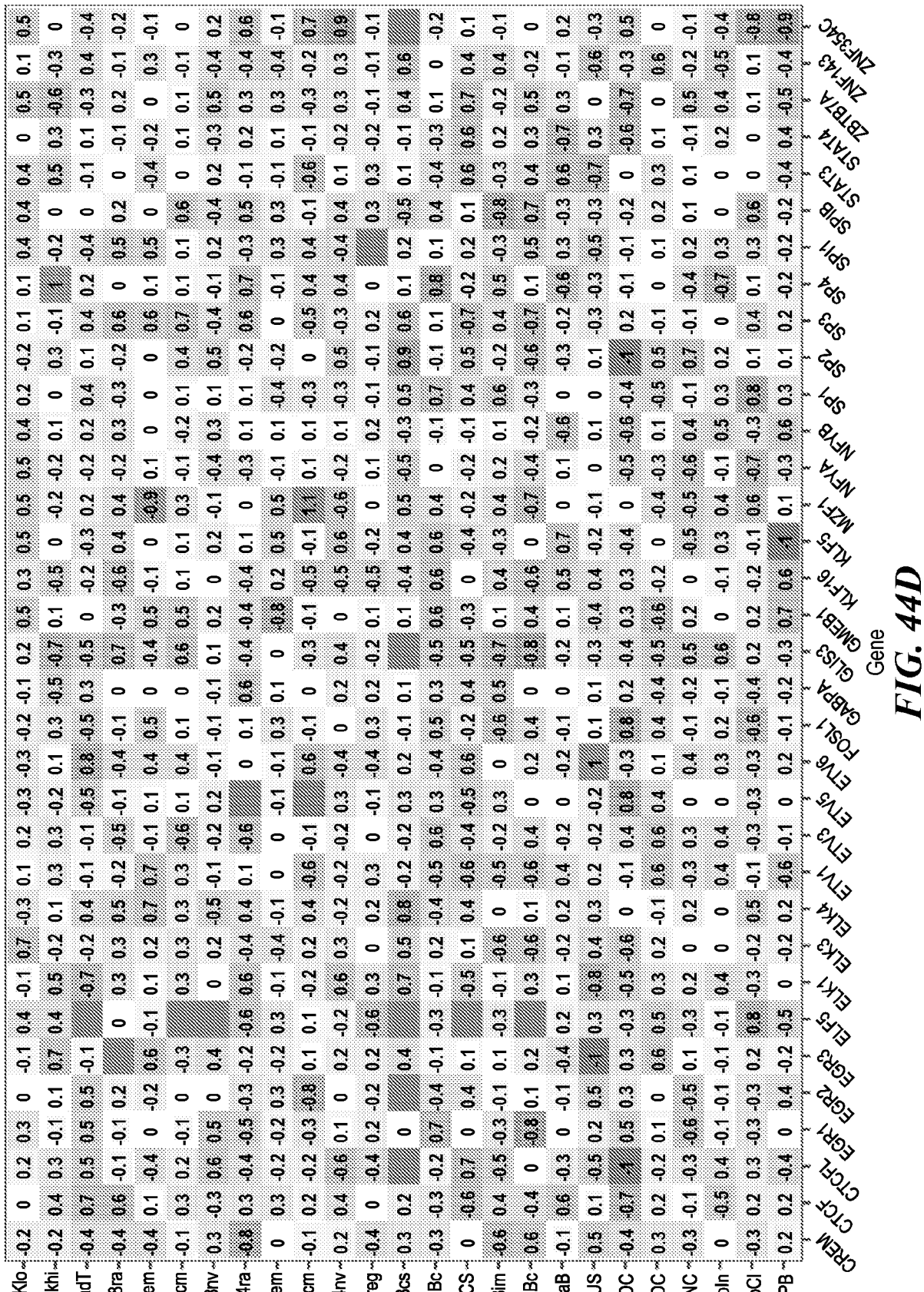

Correlation
1.0
0.5
0.0
-0.5
-1.0
Subset
Gene
NKlo
Nkhi
gadT
T8ra
T8em
T8cm
T8nv
T4ra
T4em
T4cm
T4nv
Treg
pBcs
aMBc
BnCS
MBim
cMBc
traB
BnUS
pIDC
coDC
MoNC
MoIn
MoCl
soPB
CREM
CTCF
CTCFL
EGR1
EGR2
EGR3
ELF5
ELK1
ELK3
ELK4
ETV1
ETV3
ETV5
ETV6
FOSL1
GABPA
GLIS3
GMEB1
KLF16
KLF5
MZF1
NFYA
NFYB
SP1
SP2
SP3
SP4
SPI1
SPIB
STAT3
STAT4
ZBTB7A
ZNF143
ZNF354C

FIG. 44D

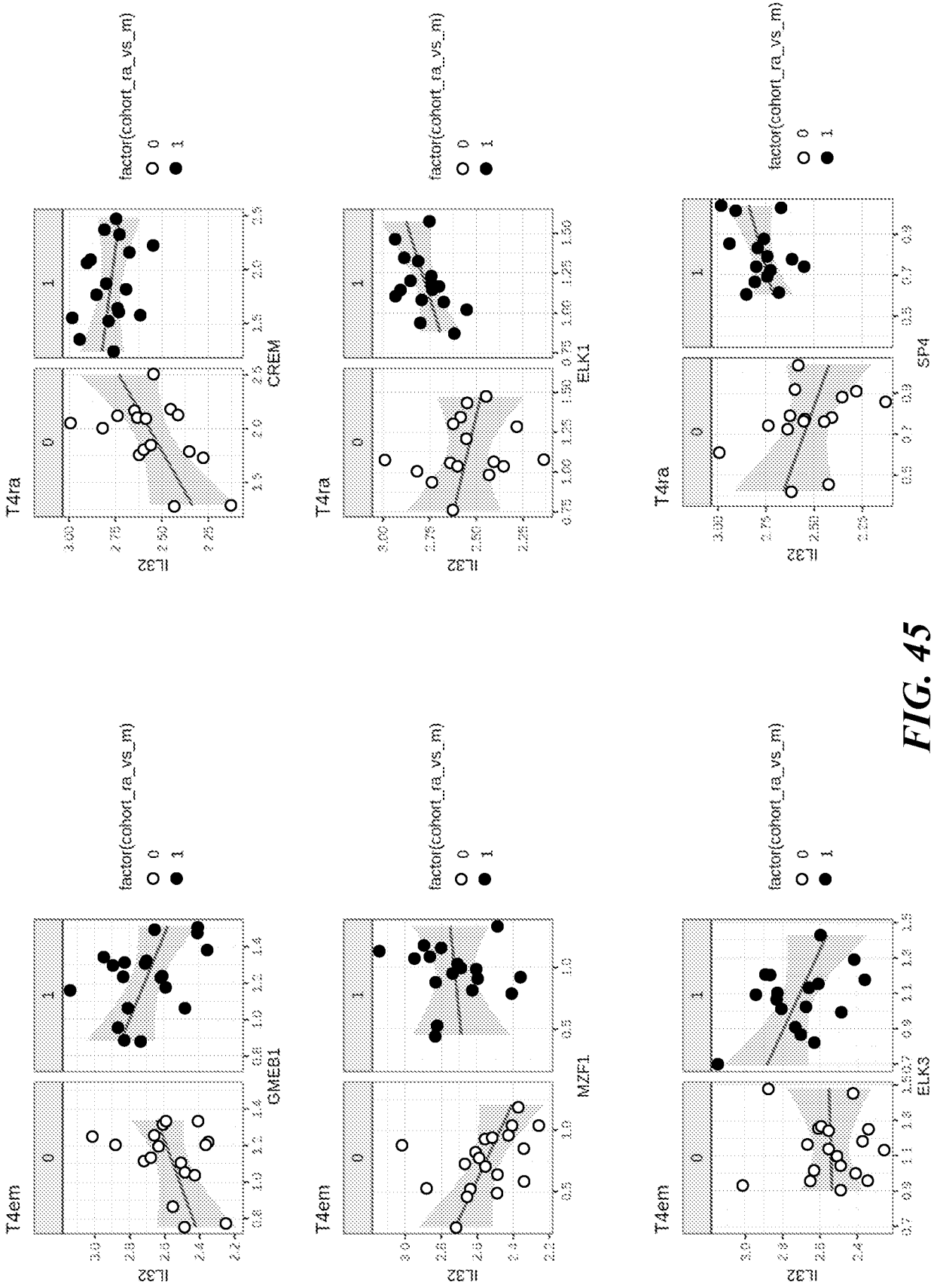

T4ra
T4em
IL32
CREM
ELK1
SP4
GME81
MZF1
ELK3
factor(cohort_ra_vs_m)
0
1

FIG. 45

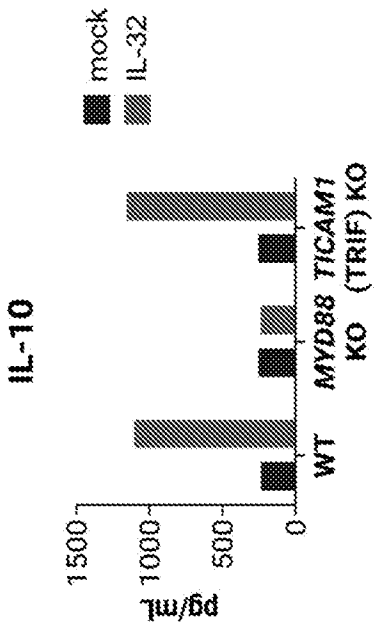


FIG. 46A

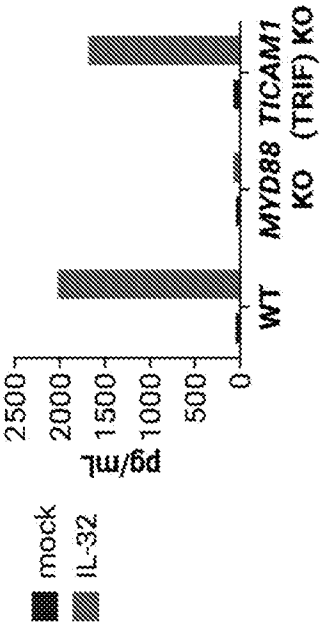


FIG. 46B

FIG. 46C

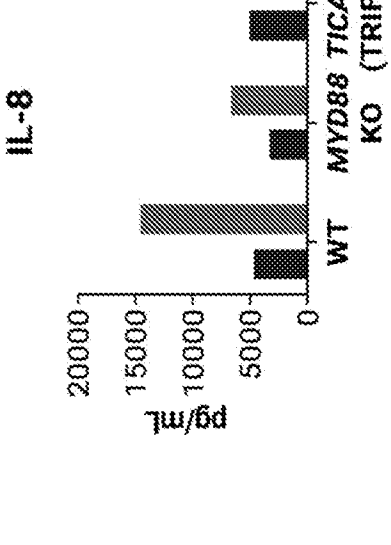


FIG. 46D

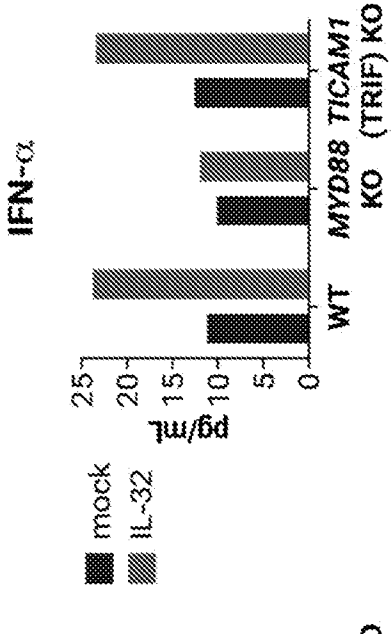


FIG. 46E

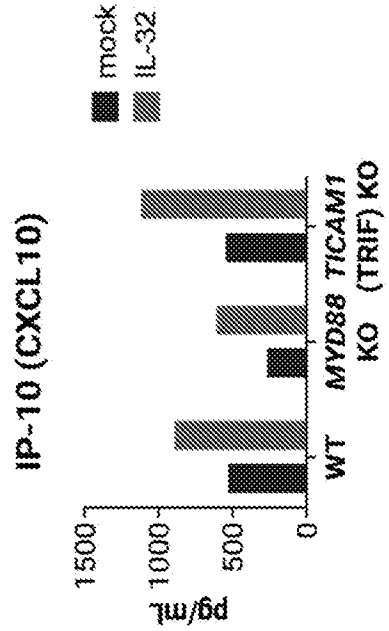


FIG. 46F

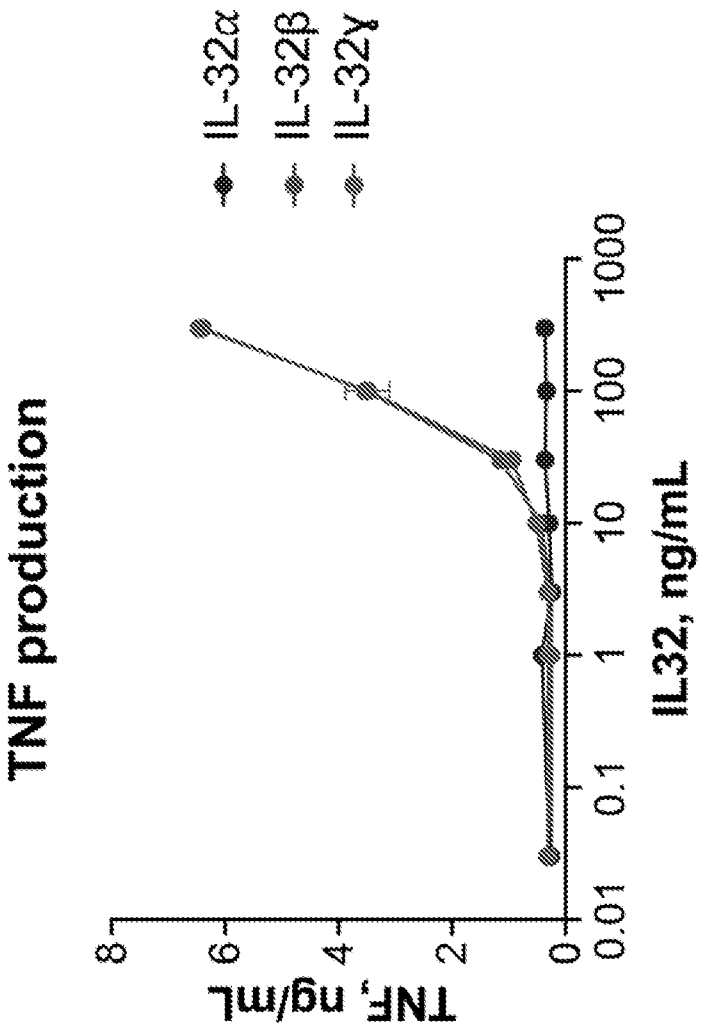

TNF production
IL-32α
IL-32β
IL-32γ
TNF, ng/mL
0
2
4
6
8
0.01
0.1
1
10
100
1000
IL32, ng/mL

FIG. 47

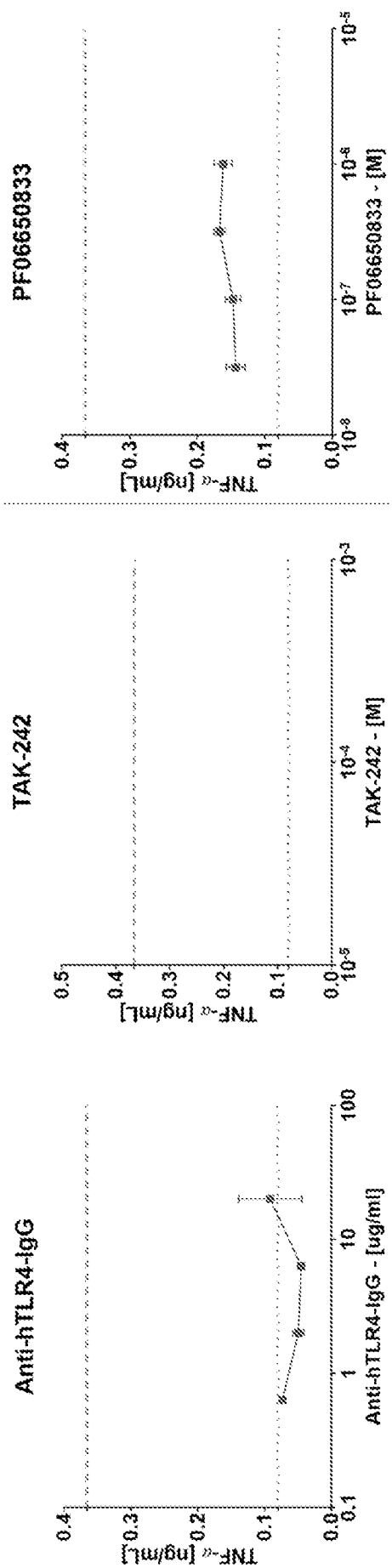


FIG. 48A

FIG. 48B

FIG. 48C

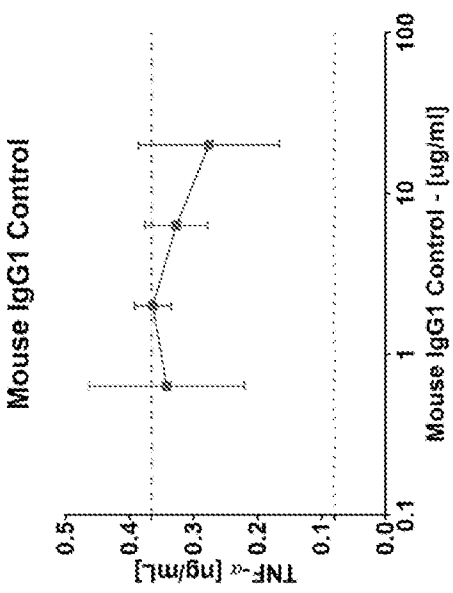


FIG. 48E

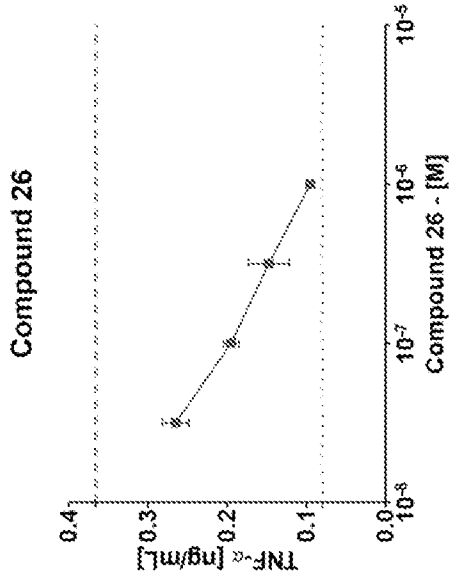


FIG. 48D

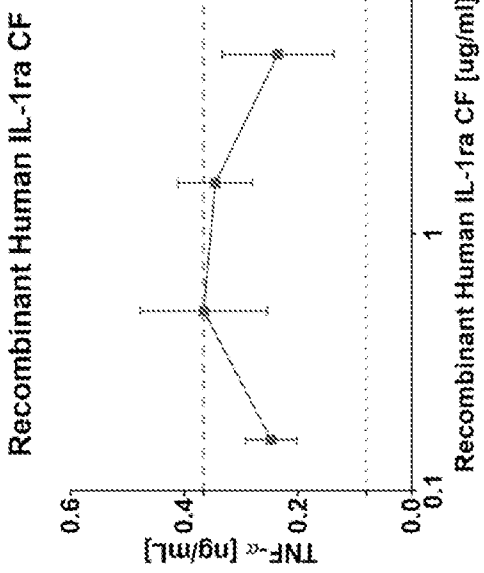


FIG. 49A

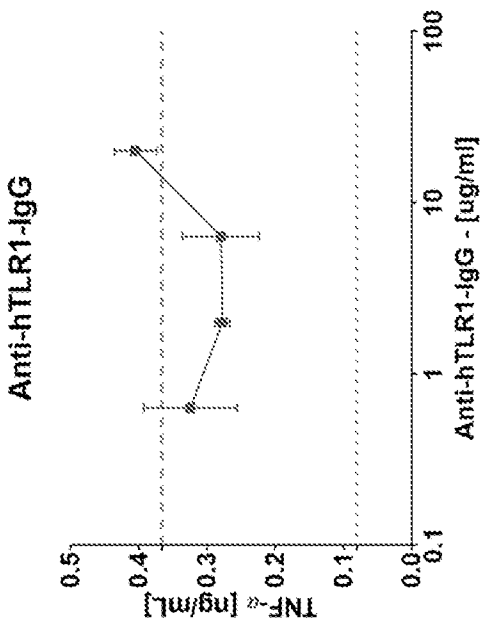


FIG. 49B

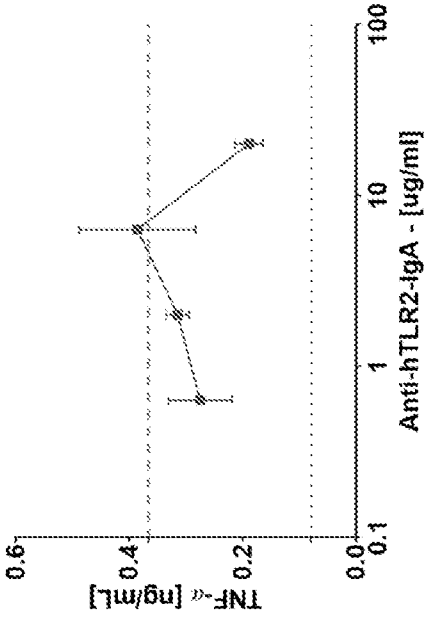


FIG. 49C

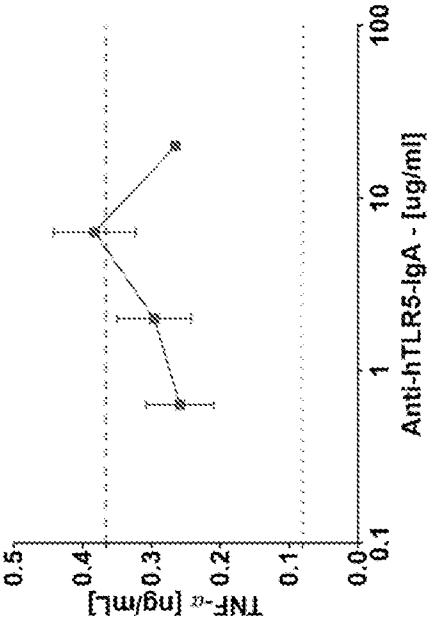


FIG. 49D

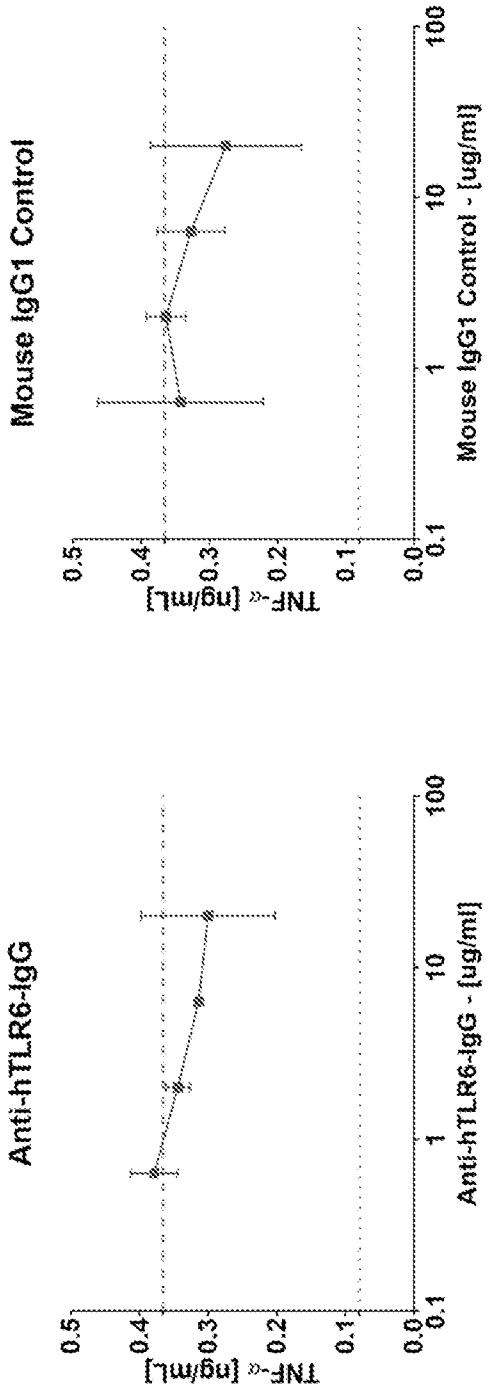


FIG. 49E

FIG. 49F

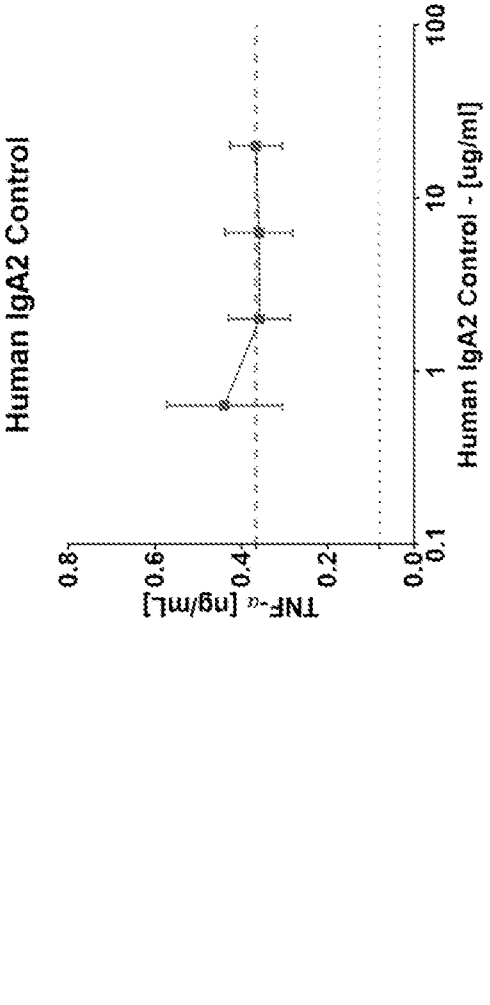


FIG. 49G

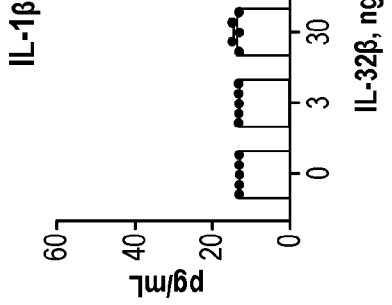


FIG. 50A

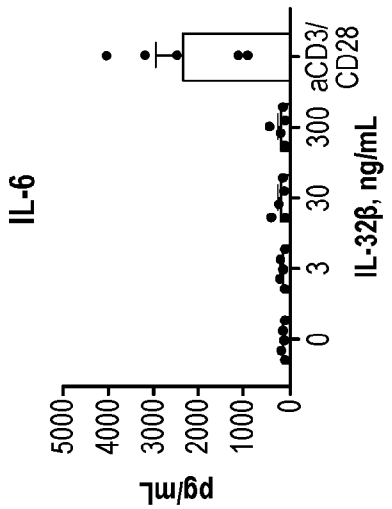


FIG. 50B

FIG. 50C

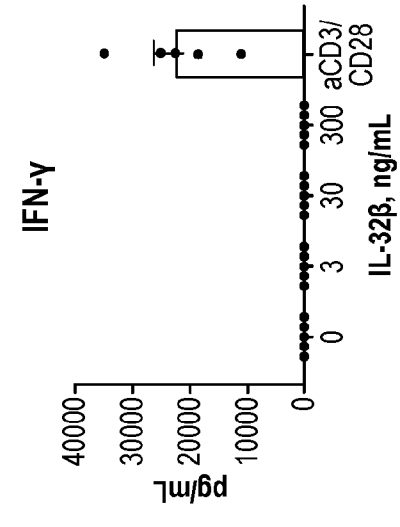


FIG. 50D

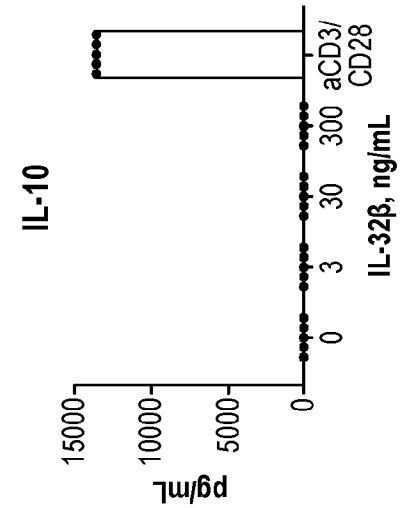


FIG. 50E

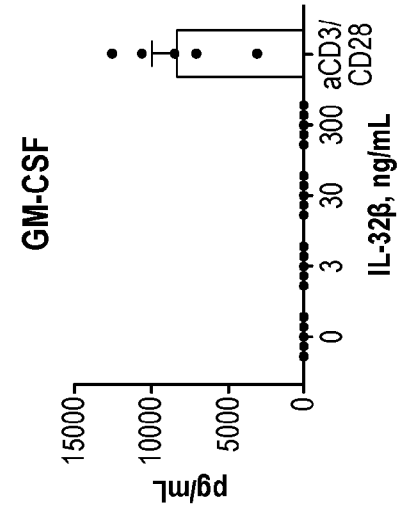


FIG. 50F

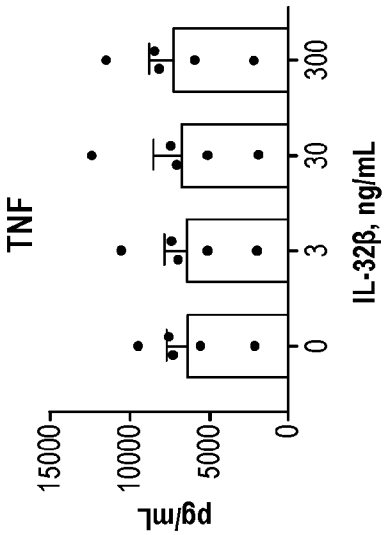


FIG. 51A

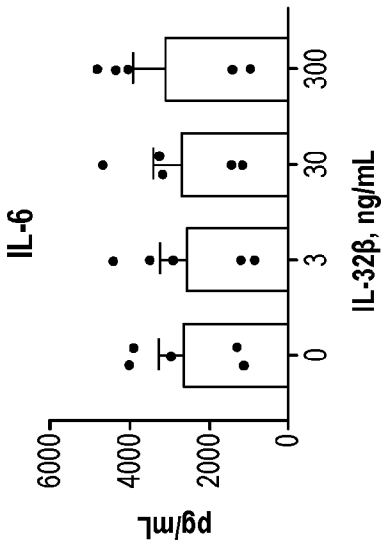


FIG. 51B

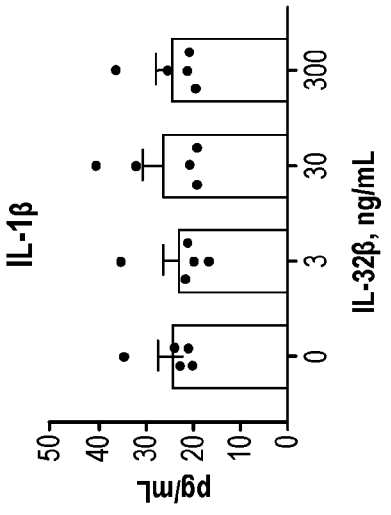


FIG. 51C

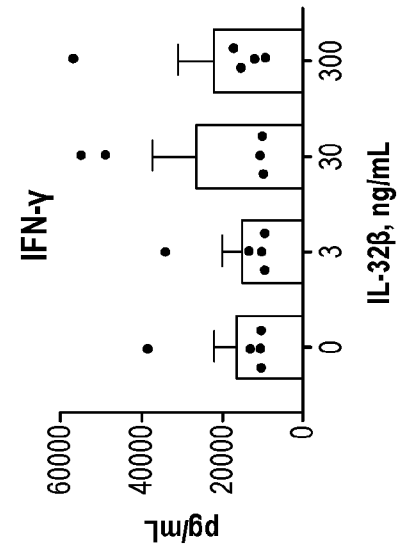


FIG. 51D

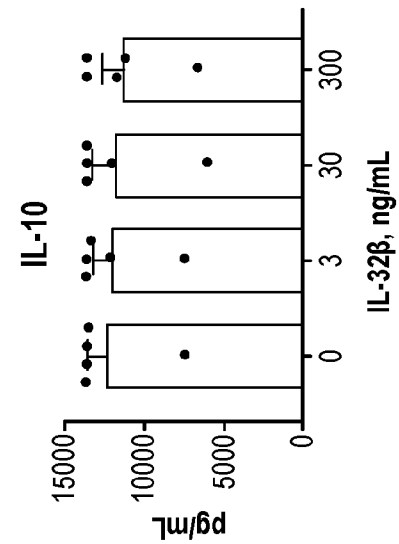


FIG. 51E

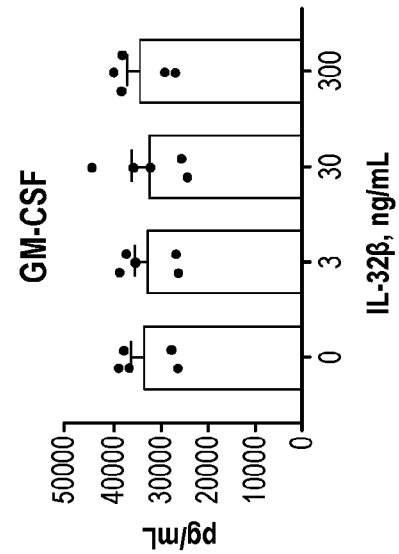


FIG. 51F

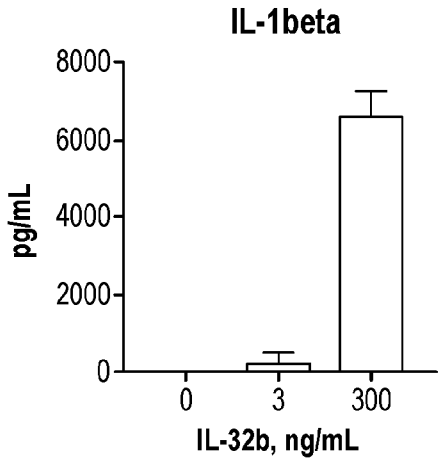


FIG. 52A

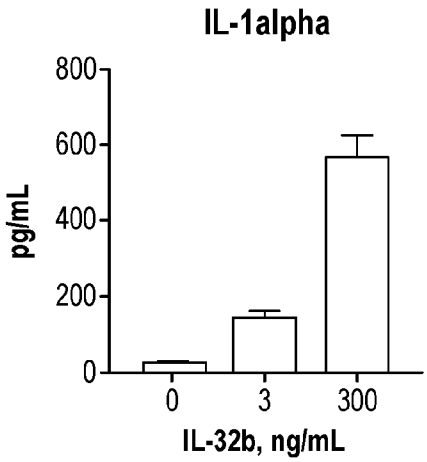


FIG. 52B

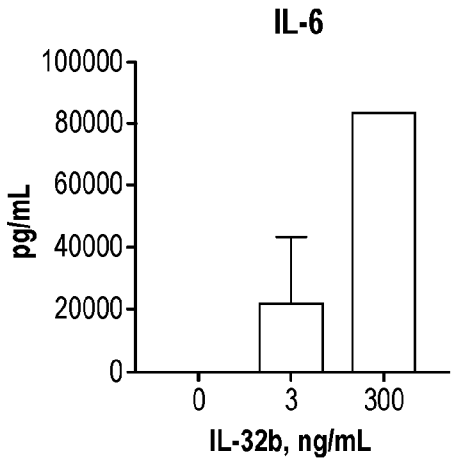


FIG. 52C

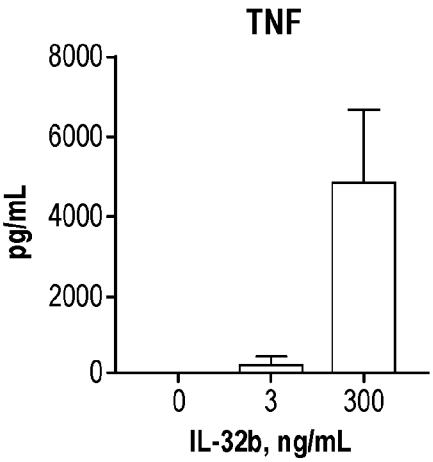


FIG. 52D

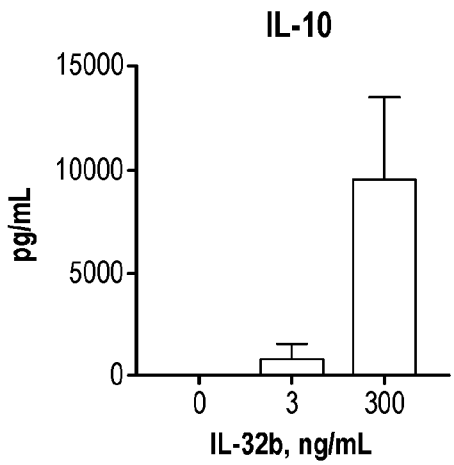


FIG. 52E

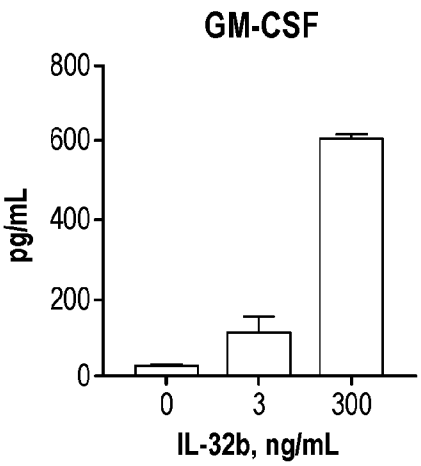


FIG. 52F

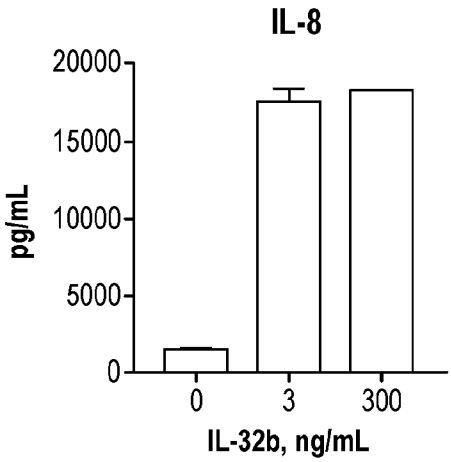


FIG. 52G

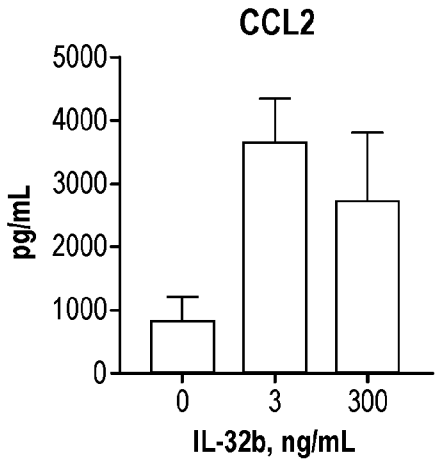


FIG. 52H

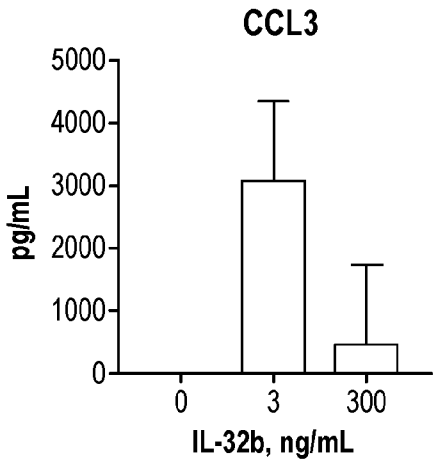


FIG. 52I

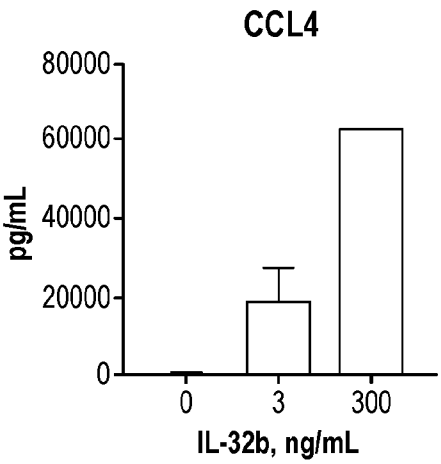


FIG. 52J

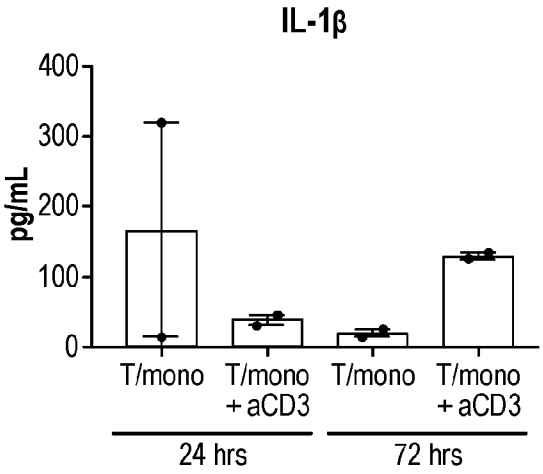


FIG. 53A

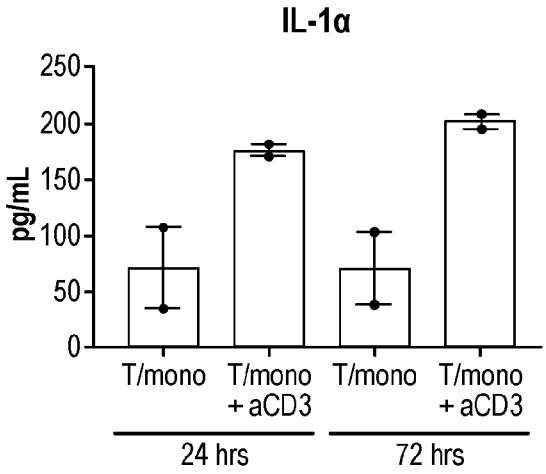


FIG. 53B

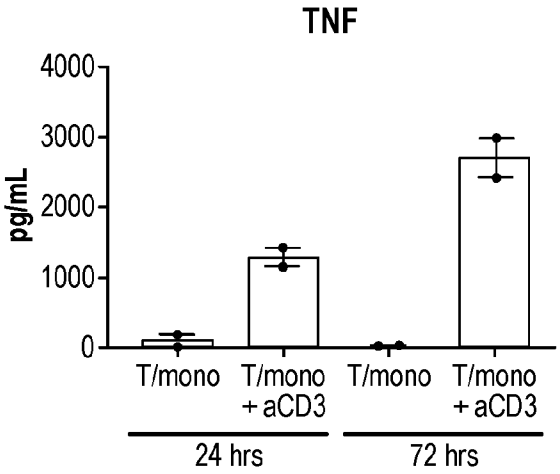


FIG. 53C

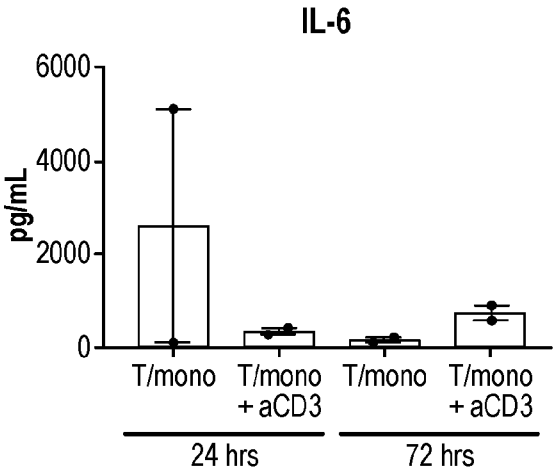


FIG. 53D

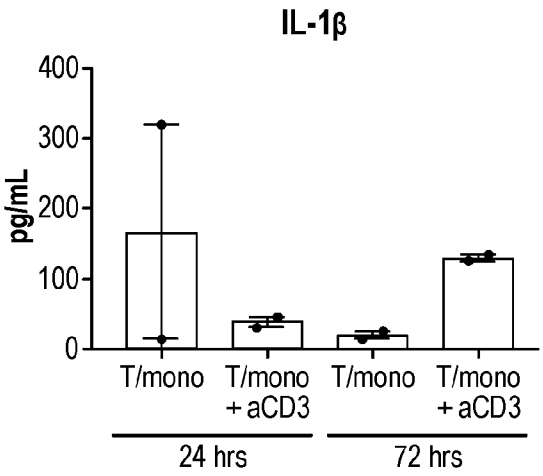


FIG. 53E

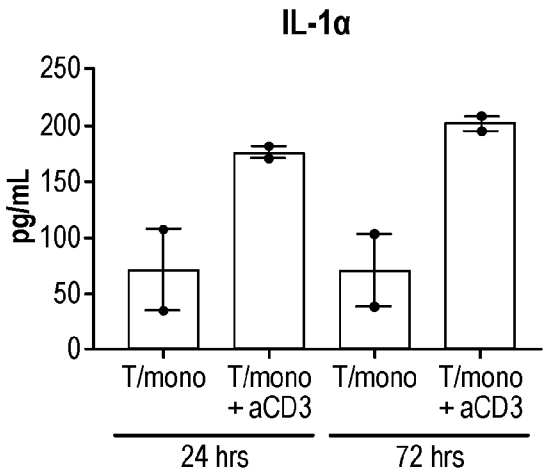


FIG. 53F

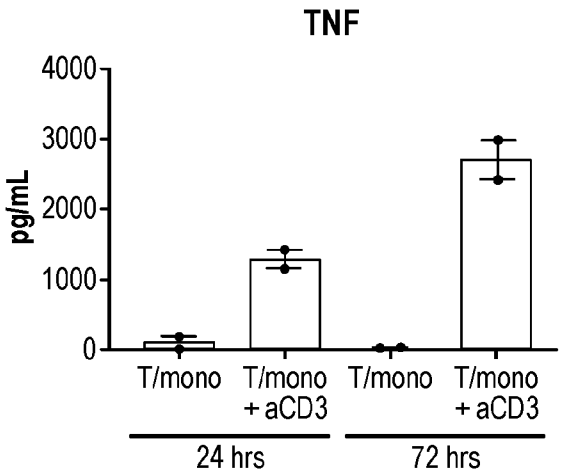


FIG. 53G

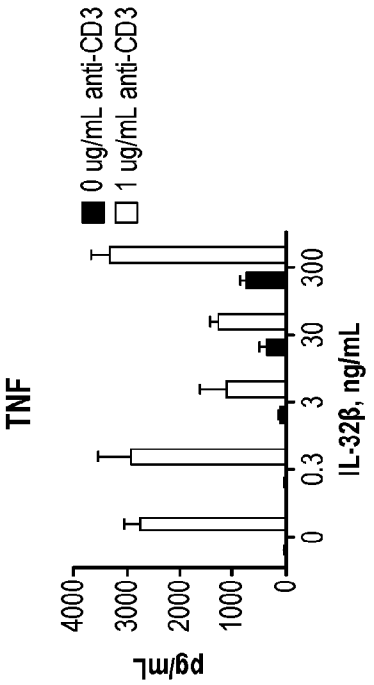


FIG. 54B

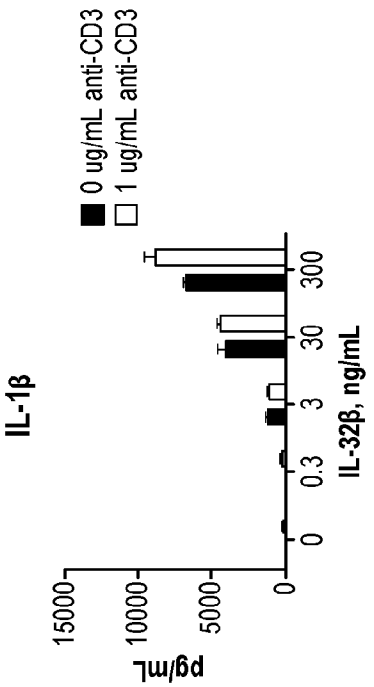


FIG. 54A

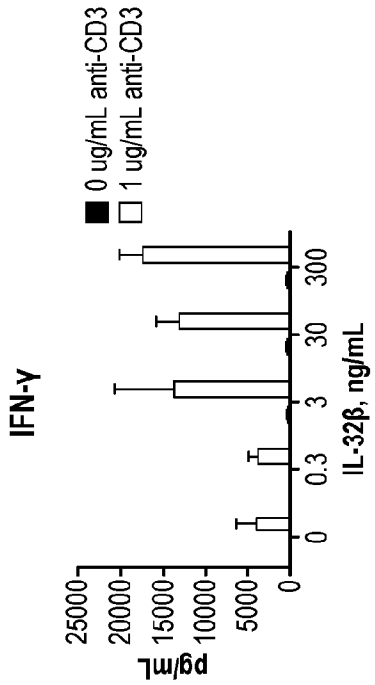


FIG. 54D

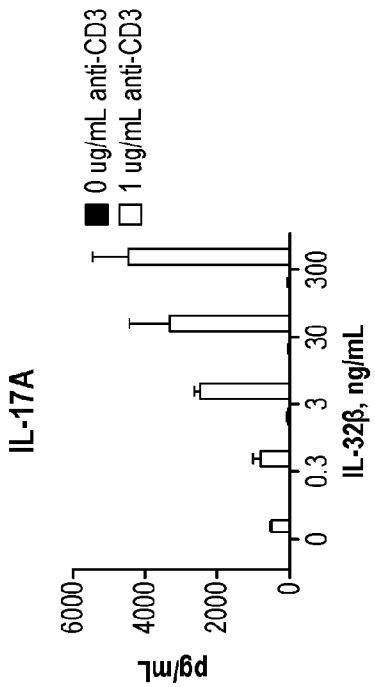


FIG. 54C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/061009

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/6883
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REVIRON DENIS ET AL: "Influence of shared epitope-negative HLA-DRB1 alleles on genetic susceptibility to rheumatoid arthritis", ARTHRITIS & RHEUMATISM, vol. 44, no. 3, 1 January 2001 (2001-01-01), pages 535-540, XP093259056, US ISSN: 0004-3591, DOI: 10.1002/1529-0131(200103)44:3<535::AID-ANR 101>3.0.CO;2-Z the whole document ----- -/--	1-4, 9-15, 17-19, 33,34, 48,50-82

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2025	28/05/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gabriels, Jan

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DU MONTCEL SOPHIE ET AL: "New classification of HLA-DRB1 alleles supports the shared epitope hypothesis of rheumatoid arthritis susceptibility", ARTHRITIS & RHEUMATISM, vol. 52, no. 4, 1 April 2005 (2005-04-01), pages 1063-1068, XP093259058, US ISSN: 0004-3591, DOI: 10.1002/art.20989 the whole document	1-4, 9-15, 17-19, 33,34, 48,50-82
X	KIRSTEN HOLGER ET AL: "Association of MICA with rheumatoid arthritis independent of known HLA-DRB1 risk alleles in a family-based and a case control study", ARTHRITIS RESEARCH AND THERAPY, BIOMED CENTRAL, LONDON, GB, vol. 11, no. 3, 1 May 2009 (2009-05-01), page R60, XP021053425, ISSN: 1478-6354, DOI: 10.1186/AR2683 the whole document	1-4, 9-15, 17-19, 33,34, 48,50-82
X	US 2019/017116 A1 (LIU LIANG [MO] ET AL) 17 January 2019 (2019-01-17) example 2; table 3	1-4, 9-15, 17-19, 33,34, 48,50-82
A	WO 2015/001010 A1 (IMMUNOQURE AG [DE]) 8 January 2015 (2015-01-08) page 32 - page 35	1
A	WO 2005/047478 A2 (UNIV COLORADO A BODY [US]; KIM SOO-HYUN [US] ET AL.) 26 May 2005 (2005-05-26) page 1 - page 3; claim 1	1
X	INOUE MARIKO ET AL: "Carriers of HLA-DRB1*04:05 have a better clinical response to abatacept in rheumatoid arthritis", SCIENTIFIC REPORTS, vol. 13, no. 1, 14 September 2023 (2023-09-14), XP093259175, US ISSN: 2045-2322, DOI: 10.1038/s41598-023-42324-6 Retrieved from the Internet: URL:https://www.nature.com/articles/s41598-023-42324-6> the whole document	1-15, 17-21, 33-36, 48,50-82

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/061009

C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 881 081 A1 (INNOGENETICS NV [BE]) 23 January 2008 (2008-01-23) claims 1,34 -----	1-4, 9-15, 17-19, 33,34, 48,50-82

1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/061009

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/061009

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
17-21, 33-36(completely); 1-15, 48, 50-82(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 17-21, 33-36(completely); 1-15, 48, 50-82(partially)

A method of diagnosing or prognosing rheumatoid arthritis (RA) in a subject comprising the steps of (a) receiving a sequence of at least one HLA-DRB1 loci by a memory component comprising a computer-executable program; (b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a); (c) comparing the sequence of (a) to the sequence of (b); (d) receiving a result from comparing the sequence of (a) and the sequence of (b); (e) diagnosing the subject as having RA or making a prognosis of RA if the sequence of (a) is different from the sequence of (b); and (f) developing a treatment plan for the subject based on the diagnosis/prognosis in (e).

---

2. claims: 16, 22-24, 37-39(completely); 1-15, 48, 50-82(partially)

A method of diagnosing or prognosing rheumatoid arthritis (RA) in a subject comprising the steps of (a) receiving a sequence comprising at least PTPN22 by a memory component comprising a computer-executable program; (b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a); (c) comparing the sequence of (a) to the sequence of (b); (d) receiving a result from comparing the sequence of (a) and the sequence of (b); (e) diagnosing the subject as having RA or making a prognosis of RA if the sequence of (a) is different from the sequence of (b); and (f) developing a treatment plan for the subject based on the diagnosis/prognosis in (e).

---

3. claims: 25-32, 40-47, 49(completely); 1-15, 48, 50-82(partially)

A method of diagnosing or prognosing rheumatoid arthritis (RA) in a subject comprising the steps of (a) receiving a sequence comprising at least IL-32 by a memory component comprising a computer-executable program; (b) receiving a sequence in a control sample for the same at least one loci in (a) by the memory component in (a); (c) comparing the sequence of (a) to the sequence of (b); (d) receiving a result from comparing the sequence of (a) and the sequence of (b); (e) diagnosing the subject as having RA or making a prognosis of RA if the sequence of (a) is different from the sequence of (b); and (f) developing a treatment plan for the subject based on the diagnosis/prognosis in (e).

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4. claims: 83-98

A method of treating or preventing RA in a subject comprising administering to the subject one or more

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

therapeutics that inhibit an activator of (a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or (b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6 or use of one or more therapeutics that inhibit an activator of (a) gene expression of one or more genes selected from the group consisting of TNF, IL1, and IL6, or (b) activity of one or more proteins selected from the group consisting of TNF, IL-1, and IL-6, for treating or preventing RA in a subject in need thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/061009

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2019017116 A1	17-01-2019	NONE	
WO 2015001010 A1	08-01-2015	AU 2014286128 A1	28-01-2016
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