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(54) Title: MULTI-CYCLIC IRAK1 AND IRAK4 INHIBITING COMPOUNDS AND USES THEREOF

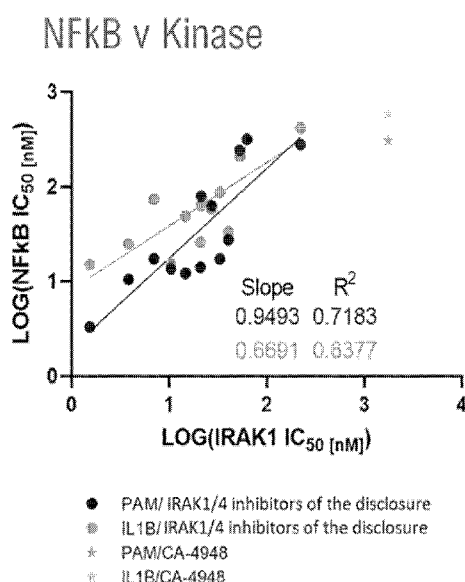


FIG. 1

(57) Abstract: The present disclosure provides a method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a subject comprising administering to the subject a compound that inhibits IRAK1 and IRAK4. The present disclosure further provides a method of determining a compound that is effective at treating an inflammatory disease/disorder, AML, or MDS.



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TITLE

Multi-Cyclic IRAK1 and IRAK4 Inhibiting Compounds and Uses Thereof

GOVERNMENT RIGHTS

5 This invention was made in the performance of a Cooperative Research and Development Agreement with the National Institutes of Health, an Agency of the Department of Health and Human Services. The Government of the United States has certain rights in this invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

10 The present application claims priority to U.S. Provisional Application No. 63/394,118, filed August 1, 2022, U.S. Provisional Application No. 63/377,812, filed September 30, 2022, and U.S. Provisional Application No. 63/487,079, filed February 27, 2023, each of which is incorporated by reference herein in its entirety.

BACKGROUND

15 IRAKs are a family of related kinases that operate at the nexus of multiple innate immune and inflammatory pathways implicated in myeloid malignancies. There is increasing interest in the role of the IRAK kinases as targets in the treatment of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) (reviewed in J Bennett and DT Starczynowski, Curr Opin Hematol 2022). IRAK1 and IRAK4 lie downstream of multiple receptors that stimulate the
20 canonical NF- κ B signaling pathway upstream of TRAF6 *via* the myddosome complex. While TRAF6 is necessary to preserve the tonic NF- κ B signaling that is required for hematopoietic stem cell (HSC) homeostasis (J Fang et. al. Cell Reports 2018), overactivity of the NF- κ B signaling pathway has been implicated in both MDS and AML (reviewed in MCJ Bosman et. al.,
25 Crit Rev Oncol/Hematol 2016; JJ Trowbridge and DT Starczynowski, J Exp Med 2021). The requirement for both IRAK1 and IRAK4 in this pathway has been explored using both genetic and pharmacologic technologies. The use of genetic loss-of-function approaches revealed that deletion and/or inhibition of IRAK4 results in a compensatory increase in IRAK1 protein and activation (data unpublished), suggesting that high potency antagonism of both kinases will be
30 required for optimal inhibition of NF- κ B-mediated transcriptional responses in disease-propagating MDS and AML cells. IRAK4 inhibitors have advanced into clinical trials for MDS

and AML validating IRAK4 as a therapeutic target. Early data from these trials has been encouraging; however, the overall responses remain modest.

MDS and AML exist along a continuous disease spectrum starting with early-stage MDS, which may progress to high-risk (HR) MDS and/or AML. AML is a heterogeneous malignancy characterized by suppression of normal hematopoiesis and overproduction of immature myeloid blast cells associated with a differentiation block. Most patients with HR-MDS and AML are not cured with available therapies, underscoring the urgent need for new therapeutic alternatives that will improve the clinical outcomes of these patients. Despite significant effort, the five-year relative survival of AML patients remains at only 25%. MDS and AML originate in hematopoietic stem and progenitor cells (HSPC, referred to as leukemic stem/progenitor cells [LSPC]) that acquire genetic and/or epigenetic abnormalities. A pool of LSPCs persist throughout the course of disease to replenish the bulk leukemic blast cells and contribute to treatment-related relapse when not eradicated. Recent therapies, such as Venetoclax with Azacytidine and Menin inhibitors, that target the LSPCs have shown improved clinical outcomes for patients with HR-MDS and AML. LSPCs also share cellular states and transcriptional programs with normal HSPCs, such as ones that maintain multi-potent self-renewal properties and prevent untimely differentiation. Like normal HSPCs, LSPCs have acquired an undifferentiated state that permits long-term expansion of progeny cells, properties which have been evaluated using surrogate in vitro progenitor assays (i.e., colony assays in methylcellulose) and in vivo hematopoietic transplantation models.

Uncovering targetable signaling dependencies unique to LSPCs is critical to improve therapeutic responses in patients. It was recently reported that patient-derived LSPCs from HR-MDS and across various AML subtypes exhibit a high frequency of dysregulated immune and inflammatory pathways. Dysregulation of immune-related genes is observed in >50% of MDS and AML, and chronic innate immune pathway activation increases the risk of developing myeloid malignancies. Moreover, a significant number of genetic and molecular alterations in MDS and AML directly impinge on effectors of the Toll-like receptor (TLR) and Interleukin 1 receptor (IL-1R) pathways, both of which converge on a signaling complex operated by the interleukin-1 receptor associated kinases (IRAK): IRAK1, IRAK2, and IRAK4. In the context of normal immune cell biology, activation of TLRs or IL-1R leads to recruitment of the adaptor protein MyD88, which then nucleates an oligomeric signaling complex (Myddosome) that

includes MyD88 and IRAK4. IRAK4 subsequently recruits and phosphorylates IRAK1 or IRAK2, which then induces multiple downstream effectors, including NF- κ B and MAPKs. Chronic activation of this MyD88-IRAK canonical signaling axis is presumed to underly malignant hematopoiesis in MDS/AML, a theory that is partially supported by the discovery of activating mutations in MyD88 that cause spontaneous assembly of the Myddosome complex in lymphomas. Consequently, IRAK4 inhibitors and proteolysis targeting chimeric (PROTAC) small molecule degraders are undergoing evaluation in pre-clinical studies and early phase clinical trials for hematologic malignancies and inflammatory conditions. The IRAK4 kinase inhibitor PF-06650833 (Zimlovisertib) is being evaluated for chronic inflammatory disorders, while CA-4948 (Emavusertib) is being evaluated in hematologic malignancies, including lymphoma, HR- and low-risk (LR)-MDS, and refractory/relapsed AML. The IRAK4 PROTACs, KT-474 and KT-413, are being evaluated in immuno-inflammatory disease and MyD88-mutant lymphomas, respectively. Safety data from these trials have revealed minimal on-target toxicity nor adverse effects, suggesting that targeting IRAK4 will have an acceptable safety profile and tolerability. Initial results from the early phase trials in HR-MDS and AML with CA-4948 showed complete or partial response rates of ~40% and additional patients having reductions in leukemic blast counts. Interestingly, 40% of AML patients with spliceosome mutations reached a complete response (CR) or CR with partial hematologic recovery (CRh), while 57% of HR-MDS patients achieved a CR. These clinical observations support the recent findings that mutations in the splicing factors U2AF1 and SF3B1 directly induce hypermorphic IRAK4 isoforms and active innate immune signaling in MDS and AML. The data emerging from the ongoing clinical studies suggest that IRAK4 is a relevant target in hematologic malignancies. However, the magnitude of clinical responses appears to depend on genetic background and suggests inadequacy of IRAK4 inhibitors as monotherapy. Thus, a better understanding of IRAK4 signaling is necessary to refine therapeutic strategies targeting dysregulated innate immune and inflammatory signaling in hematologic malignancies.

The present disclosure addresses this unmet need.

SUMMARY OF THE DISCLOSURE

In one aspect, the present disclosure provides a method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a

subject in need thereof, the method comprising administering to the subject a compound that inhibits IRAK1 and IRAK4. In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis. In one embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML. In one embodiment, the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2. In one embodiment, the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2. In one embodiment, the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, FLT3 expression, NF- κ B signaling, TLR signaling, IL-1 signaling, or a combination thereof. In one embodiment, the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, or a combination thereof. In one embodiment, the subject in need thereof has elevated FLT3 expression. In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 10 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 40. In one embodiment, the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes compared to a healthy control subject and/or decreased expression of one or more IRAK1/4-associated genes compared to a healthy control subject. In one embodiment, the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject. In one embodiment, the subject in need thereof has decreased expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3,

SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject. In one embodiment, the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject in need thereof. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof after the administration is stopped. In one embodiment, the compound continues to treat the

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calculating an IRAK4:IRAK1 potency ratio from the IRAK1 IC₅₀ and the IRAK4 IC₅₀ of

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less than about 10 nM. In one embodiment, the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS when administered to a subject in need thereof. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in a subject in need thereof after administration of the compound to the subject is stopped. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (IIf-5007)-(IIk-5007), (IIm-5007)-(IIt-5007), (IIIq-5007)-(IIIs-5007), (IV-5007), (VI-5003), (VII-5008), (IIf-5008)-(IIk-5008), (IIm-5008), (IIn-5008), (IIP-5008)-(IIu-5008), (IIIq-5008)-(IIIs-5008), (I-5009), (IIf-5009)-(IIj-5009), (I-5010), (Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

In yet another aspect, the present disclosure provides a method of determining effectiveness of a compound in treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining that the compound is an IRAK1/4 inhibitor which modifies the expression of one of more IRAK1/4-associated genes found to be differentially expressed in a subject with an inflammatory disease/disorder, AML, or MDS compared to a healthy control subject. In one embodiment, the method further comprises administering the compound to the subject, treating the inflammatory disease/disorder, AML, or MDS. In one embodiment, the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one or more IRAK1/4-associated

genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis. In one embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML. In one embodiment, the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2. In one embodiment, the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2. In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 10 nM. In one embodiment, the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS when administered to a subject in need thereof. In one embodiment, the sustained treatment is greater than the treatment provided from a compound

disease/disorder, AML, or MDS in the subject in need thereof for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010), (I_a-5010)-(I_d-5010), (II-5010), (II_a-5010), (II_b-5010), (III-5010), (III_a-5010), (III_b-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

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FIG. 2 depicts that the NFkB potency of Compounds 1-13, Compound 15, and comparative compounds correlates with their IRAK4 potency.

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FIG. 5 depicts the kinase profile of comparative compounds with their PAM and IL1 β IC₅₀.

FIG. 7 depicts the kinase profile of Compound 2, Compound 7, and Compound 8 with their PAM and IL1 β IC₅₀.

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stimulation with PAM3CSK4 in THP1-Blue NF- κ B SEAP reporter cells. FIG. 8B: Colony formation counts of THP-1 cells treated with 1 or 10 μ M PF-06650833 or vehicle control. FIG. 8C: Growth curves of THP-1 and MDS-L cells treated with 5 or 10 μ M CA-4948 or DMSO.

FIGS. 9A-9N depict that IRAK4 inhibition causes activation of IRAK1. FIG. 9A:

5 Colony formation in a panel of MDS/AML cell lines and patient-derived samples treated with the indicated concentrations of CA-4948 (two independent experiments). FIG. 9B: Immunoblots for IRAK4 in WT and IRAK4^{KO} AML cell lines and patient-derived samples. FIG. 9C: Colony formation of WT and IRAK4^{KO} AML cell lines and patient-derived samples. FIG. 9D: Experimental overview. RNA sequencing was performed on WT and IRAK4^{KO} THP1 cells, and
10 THP1 cells treated for 24 hours with the indicated inhibitors. Genes upregulated upon IRAK4 deficiency or chemical inhibition were used to annotate compensatory pathways. FIG. 9E: Venn diagrams of overlapping upregulated genes upon IRAK4 deficiency or IRAK4 chemical inhibition. FIG. 9F: Heatmap of differentially expressed genes upon treatment with IRAK4 inhibitors (fold-change > 1.5; $P < 0.05$). FIG. 9G: Heatmap of differentially expressed genes
15 upon treatment with IRAK4-degrader 1 (fold-change > 1.5; $P < 0.05$) or upon IRAK4 deletion (fold-change > 2.0; $P < 0.05$). FIG. 9H: Pathway enrichment of KEGG datasets using overlapping genes increased upon treatment with IRAK4 inhibitors. FIG. 9I: Pathway enrichment of KEGG datasets using overlapping genes increased upon treatment with IRAK4-degrader 1 or following deletion of IRAK4. FIG. 9J: Overview of canonical Myd88-dependent
20 signaling: Upon TLR ligation, MyD88 nucleates a complex with IRAK4, which signals through IRAK1 and/or IRAK2 and then TRAF6 to activate the NF- κ B and MAPK pathways. FIG. 9K: Immunoblots for IRAK1, IRAK2, TRAF6, and MyD88 in WT and IRAK4KO AML cell lines and patient-derived samples. FIG. 9L: Immunoblots for phospho-IRAK1, total IRAK1, and IRAK4 in WT and IRAK4^{KO} cell lines. FIG. 9M: Immunoblots for phospho-IRAK1, total
25 IRAK1, and IRAK4 in MDSL and THP1 cells treated for 24 hours with IRAK4-degrader 1. FIG. 9N: Immunoblots for phospho-IRAK1, total IRAK1, IRAK2, and IRAK4 in MDSL and AML(1714) treated for 24 hours with CA-4948 (10 μ M). Significance was determined with a Student's *t* test (*, $P < 0.05$; **, $P < 0.01$). Error bars represent the standard deviation.

FIGS. 10A-10F depict an evaluation of IRAK1/4-deficient AML cells. FIG. 10A:

30 Immunoblots for IRAK1 and IRAK4 in WT and IRAK1^{KO} THP1 and MDSL clones. FIG. 10B: Growth curves of WT and IRAK1^{KO} MDSL (10 μ M) and THP1 (20 μ M) treated with PF-

06650833 or DMSO (two independent experiments). FIG. 10C: Growth curve of WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells. FIG. 10D: Immunoblots for phospho-p38 MAPK, phospho-ERK1/2, phospho-IKKa/b, and phospho-JNK in WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells treated with IL-1b (10 ng/ml) as compared to DMSO. FIG. 10E: Immunoblots for phospho-p38, phospho-ERK1/2, phospho-IKKa/b, and phospho-JNK in WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells treated with PAM3CSK4 (1 ug/ml) as compared to DMSO. FIG. 10F: Immunoblots for phospho-p38 MAPK, phospho-ERK1/2, phospho-IKKa/b, and phospho-JNK in WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} MDSL cells treated with IL-1b (10 ng/ml) as compared to DMSO.

FIGS. 11A-11K depict that the inhibition of IRAK1 confers an exaggerated leukemic defect to IRAK4-deficient AML. FIG. 11A: Growth curves of WT and IRAK1^{KO} MDSL and THP1 cells treated with CA-4948 (10 μ M) or vehicle (two independent experiments). FIG. 11B: Colony formation of WT and IRAK1^{KO} MDSL and THP1 cells treated with CA-4948 (30 μ M) or vehicle (three independent experiments). FIG. 11C: Colony formation of WT and IRAK1^{KO} MDSL and THP1 cells treated with IRAK4-degrader 1 (MDSL, 5 μ M; THP1, 10 μ M) or vehicle. FIG. 11D: Immunoblots for IRAK1 and IRAK4 in WT and IRAK4^{KO} cell lines transduced with non-targeting control shRNA (shControl) or shIRAK1. FIG. 11E: Colony formation of WT and IRAK4^{KO} AML cell lines transduced with non-targeting control shRNA (shControl) or shIRAK1. FIG. 11F: Representative colony images of WT and IRAK4^{KO} AML(1294) cells transduced with non-target control shRNA (shControl) or shIRAK1. FIG. 11G: Immunoblots for IRAK1 and IRAK4 in WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells. FIG. 11H: Kaplan Meier survival analysis of NSGS mice (n = 7 mice/group) engrafted with WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells (Data represent one of two independent experiments with identical trends). FIG. 11I: Immunoblots for IRAK1 and IRAK4 in WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells. FIG. 11J: Bone marrow engraftment of WT (n = 4), IRAK4^{KO} (n = 5), IRAK1^{KO} (n = 5), and IRAK1/4^{dKO} (n = 5) THP1 cells in xenografted NSGS mice at time of death. Leukemic engraftment was determined as percentage of huCD45⁺huCD33⁺ cells. FIG. 11K: Representative images of livers collected from NSGS mice xenografted with WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells. Arrows indicate examples of THP1 cells infiltration. Significance was determined with a Student's t test (*, P < 0.05; **, P < 0.01). Error bars represent the standard deviation.

FIGS. 12A-12C depict that MyD88 is dispensable for LSPCs. FIG. 12A: Immunoblots for MyD88 and activation of downstream pathways (phospho-p38, phospho-JNK, phospho-IKK, phospho-ERK) in WT and MYD88^{KO} THP1 cells upon 30 minutes treatment with IL-1b (10 ng/ul) or the TLR1/2 ligand PAM3CSK4 (1 ug/ml) as compared to DMSO. FIG. 12B:

Immunoblots for IRAK4 and MyD88 in WT and MYD88^{KO} THP1 and MDSL cells transduced with non-targeting shRNA (shControl) or shIRAK4. FIG. 12C: Colony formation of WT and MYD88^{KO} THP1 and MDSL cells transduced with non-targeting shRNA (shControl) or shIRAK4. Significance was determined with a Student's t test (*, $P < 0.05$). Error bars represent the standard deviation.

FIGS. 13A-13C depict an evaluation of TRAF6-deficient AML cells. FIG. 13A: Immunoblots for TRAF6 in WT and TRAF6^{KO} THP1 cells. FIG. 13B: Colony formation of WT and TRAF6^{KO} THP1 cells. FIG. 13C: Representative colony images of WT and TRAF6^{KO} THP1 cells.

FIGS. 14A-14G depict that non-canonical IRAK1/4 signaling is essential for maintaining LSPCs in MDS/AML. FIG. 14A: Principal component analysis of gene expression profiles of WT, IRAK4^{KO}, IRAK1^{KO} and IRAK1/4^{dKO} THP1 cells. FIG. 14B: Volcano plots of differentially expressed genes in IRAK4^{KO}, IRAK1^{KO} and IRAK1/4^{dKO} THP1 cells relative to WT THP1 cells (>2-fold change; $P < 0.05$). FIG. 14C: Heatmap of differentially expressed genes in IRAK4^{KO}, IRAK1^{KO} and IRAK1/4^{dKO} THP1 relative to WT. Bars on the right denote differentially expressed genes attributed to deficiency of IRAK4 (red), IRAK1 (orange), or are unique to IRAK1/4^{dKO} (blue). FIG. 14D: Venn diagrams of overlapping upregulated or downregulated genes upon in IRAK4^{KO}, IRAK1^{KO} and IRAK1/4^{dKO} relative to WT THP1. FIG. 14E: Pathway enrichment of KEGG datasets of upregulated and downregulated genes in IRAK4^{KO}, IRAK1^{KO} and IRAK1/4^{dKO} THP1 cells. FIG. 14F: Gene set enrichment analysis (GSEA) of genes dysregulated in IRAK1/4^{dKO} versus WT THP1 cells. Absolute normalized enrichment score (NES) and corresponding P value is shown for each pathway. FIG. 14G: Representative Wright-Giemsa stains of WT and IRAK4^{KO} THP1, MDSL, TF1, and AML(1294) expressing non-targeting shRNA (shControl) and shIRAK1, respectively.

FIGS. 15A-15D depict an evaluation of MyD88-deficient AML cells. FIG. 15A: Volcano plots based on bulk RNA-sequencing showing differentially expressed genes in MYD88^{KO} relative to WT THP1 cells (>2-fold, $P < 0.05$). FIG. 15B: Heatmap of differentially

expressed genes in MYD88^{KO} relative to WT THP1 cells. FIG. 15C: Pathway enrichment using KEGG of upregulated and downregulated genes in MYD88^{KO} relative to WT THP1 cells. Bar plots depict pathways ranked by -Log(P value) of enrichment score. FIG. 15D: Representative Wright-Giemsa stains of WT and MYD88^{KO} THP1 and MDSL cells.

5 FIGS. 16A-16H depict that the IRAK1 and IRAK4 interactomes reveal non-canonical signaling in AML. FIG. 16A: Experimental overview of IRAK1 and IRAK4 proximity labeling in THP1 cells: Doxycycline-inducible IRAK4- and IRAK1-APEX2 fusion constructs were transduced into IRAK4^{KO} and IRAK1^{KO} THP1 cells, respectively. Functional rescue of canonical signaling was confirmed in NF- κ B assays. Biotin phenol was added to induce
10 proximity labeling with biotin. Biotinylated proteins were isolated and identified by mass-spectrometry. FIG. 16B: Venn diagram of unique and overlapping proteins in the IRAK4 and IRAK1 proximal proteins. FIG. 16C: Pathway enrichment using IRAK4-specific proximal proteins. Bars represent the number of IRAK4 interacting proteins that appear in the designated pathway. Dots represent -Log(q value) of the pathway enrichment. FIG. 16D: Pathway
15 enrichment using IRAK1-specific proximal proteins. Bars represent the number of IRAK1 interacting proteins that appear in the designated pathway. Dots represent -Log(q value) of the pathway enrichment. FIG. 16E: Pathway enrichment using proximal proteins common to IRAK1 and IRAK4. Bars represent the number of interacting proteins that appear in the designated pathway. Dots represent -Log(q value) of the pathway enrichment. FIG. 16F:
20 Interaction networks of proteins identified as IRAK4 interactors. FIG. 16G: Interaction networks of proteins identified as IRAK1 interactors. FIG. 16H: Interaction map highlighting IRAK4 interactors in the PRC2 complex and IRAK1 interactors in JAK/STAT/interferon signaling. Circle sizes indicate the adjusted P value for the identified interaction with IRAK1 or IRAK4.

 FIGS. 17A-17D depict IRAK1 and IRAK4 APEX2 proximity labeling in AML cells.
25 FIG. 17A: Immunoblots for V5, IRAK1, and phospho-IKKa/b in untreated versus doxycycline-treated WT THP1 transduced with empty vector and IRAK1^{KO} THP1 transduced with empty vector or inducible IRAK1-APEX2 fusion construct. For the phospho-IKK and vinculin immunoblots, cells were treated with IL-1b (10 ng/ml). FIG. 17B: Immunoblots for V5, IRAK1, and phospho-IKKa/b in untreated versus doxycycline-treated WT THP1 transduced with empty
30 vector and IRAK4^{KO} THP1 cells transduced with empty vector or the inducible IRAK4-APEX2 fusion construct. For the phospho-IKK and vinculin immunoblots, cells were additionally

treated with IL-1b (10 ng/ml). FIG. 17C: Imperial stain of biotinylated proteins pulled down with blocked-streptavidin in untreated and doxycycline-treated IRAK1^{KO} THP1 transduced with the IRAK1-APEX2 fusion construct following incubation with biotin phenol and APEX2 activation with hydrogen peroxide. FIG. 17D: Imperial stain of biotinylated proteins pulled down with blocked-streptavidin in untreated versus doxycycline-treated IRAK4^{KO} THP1 cells transduced with the IRAK4-APEX2 fusion construct following incubation with biotin phenol and APEX2 activation with hydrogen peroxide.

FIGS. 18A-18K depict that IRAK1/4 maintains undifferentiated leukemic cell states through chromatin and transcription factor networks. FIG. 18A: Heatmap of chromatin accessibility (ATAC-seq) peaks within a 3 kb distance of transcription start sites (TSS) of genes in WT, IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells. FIG. 18B: Total number of accessibility peaks lost and acquired in IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 relative to WT cells. FIG. 18C: Venn diagrams of overlap genes that are associated with both differential expression (RNA sequencing) and concordant changes in chromatin accessibility (ATAC-seq) in IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells. FIGS. 18D and 18E: Heatmaps of transcription factor enrichment among genes associated with downregulation and loss of chromatin peaks (FIG. 18D) or upregulation and acquisition of open chromatin peaks (FIG. 18E) in IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells relative to WT cells. Enrichment of transcription factor signatures was determined with the CHIP Enrichment Analysis (ChEA) 2022 library. Color intensity reflects the Log(P value) of the enrichment score. FIG. 18F: Heatmap of differential gene expression in AML patients (relative to healthy controls) using gene expression data curated from the Beat AML dataset. The heatmap represents a subset of genes that are downregulated and associated with loss of chromatin accessibility in IRAK1/4^{dKO} THP1 (“IRAK1/4 gene signature”). Unsupervised hierarchical clustering analysis resolved distinct cohorts of IRAK1/4-high signature (Group 1) and IRAK1/4-low/intermediate signature (Groups 2 and 3) AML patients. FIG. 18G: Enrichment of AML-associated mutations in IRAK1/4-high signature (Group 1) and IRAK1/4-low/intermediate signature (Groups 2 and 3) AML patients (from FIG. 18F) based on hypergeometric testing. FIG. 18H: Schematic of the CRISPR activation screen. WT and IRAK1/4^{dKO} THP1 cells were transduced with the pooled sgRNA library targeting more than 18,000 coding isoforms. After 2 weeks, deep sequencing was performed to identify candidate genes. FIG. 18I: Average MAGeCK score for candidate genes

from WT and IRAK1/4^{dKO} THP1 replicate samples. Blue circles represent genes selectively enriched in IRAK1/4^{dKO} THP1 cells. FIG. 18J: Most significant transcription factors (ENCODE/ChEA analysis) selectively enriched in IRAK1/4^{dKO} THP1 cells among the top 338 candidate genes. FIG. 18K: Most significant pathways (KEGG analysis) selectively enriched in
 5 IRAK1/4^{dKO} THP1 cells among the top 338 candidate genes.

FIGS. 19A-19D depict an evaluation of the IRAK1/4 signature in MDS and AML. FIG. 19A: Heatmap showing relative expression of genes in the IRAK1/4 signaling signature in CD34⁺ cells from IRAK1/4-high signature (Group 1) and IRAK1/4-low/intermediate signature (Group 2) MDS patients (GSE58831). The bottom panels indicate overall survival, International
 10 Prognostic Scoring System score, and MDS subtype for each individual patient in the analysis. FIG. 19B: The heatmap showing relative expression of genes in the IRAK1/4 signaling signature in pediatric AML patients using the TARGET dataset. FIG. 19C: Percent of AML patients (from the BEAT AML dataset) diagnosed with MOS were stratified on the IRAK1/4 signature. The number in the histogram represents the number of patients with prior MOS within each group.
 15 FIG. 19D: The heatmap represents a subset of genes that are downregulated and associated with loss of chromatin accessibility in IRAK1/4^{dKO} THP1 ("IRAK1/4 gene signature"). Unsupervised hierarchical clustering analysis resolved distinct cohorts of IRAK1/4-high signature (Group 1) and IRAK1/4-low/intermediate signature (Groups 2 and 3) AML patients from the TCGA dataset.

FIGS. 20A-20P depict that a dual IRAK1/4 inhibitor is more effective at suppressing MDS/AML as compared to a selective IRAK4 inhibitor. FIG. 20A: Chemical structures of Compound 14 (IRAK4-inh) and Compound 15 (IRAK1/4 dual-inh) with IC₅₀ and K_d values for IRAK1 and IRAK4. FIG. 20B: IC₅₀ curves for Compound 14 and Compound 15 in an assay measuring NF-κB activity upon TLR2 stimulation with PAM3CSK4 in THP1-Blue NF-κB
 25 SEAP reporter cells. FIG. 20C: Immunoblots for phospho-IRAK1 and total IRAK1 in THP1 and MDSL cells treated with DMSO, Compound 14 (500 nM), or Compound 15 (500 nM) for 24 hours. FIG. 20D: Heatmap of differentially expressed genes downregulated by both Compound 14 and Compound 15 ("IRAK4-dependent"), genes downregulated by Compound 15 ("IRAK1-dependent"), and genes representing the "IRAK1/4 AML signature" (from FIG. 18F). FIG. 20E:
 30 Colony formation of MDSL (250 nM), THP1 (1 μM), OCIAML3 (1 μM), AML(1714) (1 μM), AML(1294) (1 μM), AML(08) (250 nM), and MDS(3328) (250 nM) cells treated with DMSO,

Compound 14, or Compound 15. FIG. 20F: Annexin V staining of MDSL, THP1, OCIAML3, AML(1714), and AML(1294) cells treated with DMSO, Compound 14 (500 nM), or Compound 15 (500 nM) for 48 hours. FIG. 20G: Representative Wright-Giemsa stains of MDSL, THP1, OCIAML3, AML(1714), and AML(1294) cells treated with DMSO, Compound 14 (500 nM), or Compound 15 (500 nM) for 12 days. FIG. 20H: Graphical illustration of IRAK1/4 signaling in LSPCs. Significance was determined with a Student's t test (*, $P < 0.05$; **, $P < 0.01$). Error bars represent the standard error of the mean or standard deviation. FIG. 20I: Experimental overview: AML(1714) cells derived from patients were treated in vitro vehicle (DMSO), Compound 14 (500 nM), or Compound 15 (500 nM) for 21 days. Following treatment, live cells were evaluated for colony formation and in xenografted mice. FIG. 20J: Bone marrow engraftment of AML(1714) cells in xenografted NSGS mice at day 36. Leukemic engraftment was determined as percentage of $huCD45^+huCD33^+$ cells. FIG. 20K: Kaplan Meier survival analysis of NSGS mice ($n = 10$ mice/group) engrafted with AML(1714) cells pre-treated with the indicated inhibitors. FIG. 20L: Experimental overview: AML(64519), AML(0169), and MDS(76960) cells derived from patients were engrafted into NSGS mice. Two weeks post-engraftment, mice were randomized and treated orally (PO) daily with vehicle (PBS), Compound 14 (30 mg/kg), or Compound 15 (100 mg/kg). The concentrations were selected to equilibrate the free drug concentrations (Table 16 in the Appendix). FIGS. 20M-20O: Peripheral blood engraftment of AML(64519) (FIG. 20M), AML(0169) (FIG. 20N), and MDS(76960) (FIG. 20O) cells in xenografted NSGS mice at day 40, 29, and 48 post-treatment, respectively. Leukemic engraftment was determined as percentage of $huCD45^+huCD33^+$ cells. FIG. 20P: Kaplan Meier survival analysis of NSGS mice ($n = 8$ mice/group) engrafted with AML(0169) cells and treated with the indicated inhibitors. Significance was determined with a Student's t test (*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$). Error bars represent the standard error of the mean or standard deviation.

FIGS. 21A-21E depict an evaluation of the dual IRAK1/4 inhibitor in AML. FIG. 21A: Pathway enrichment using KEGG analysis of downregulated genes upon treatment with both Compound 14 and Compound 15 (IRAK4-dependent genes) as compared to vehicle control. Bar plots depict pathways ranked by $-\log(P \text{ value})$ of enrichment score. Enriched pathways were pulled from the KEGG 2021 dataset using Enrichr. FIG. 21B: Pathway enrichment using KEGG analysis of down-regulated genes upon treatment with Compound 15 (IRAK1-dependent genes)

as compared to Compound 14 and vehicle control. Bar plots depict pathways ranked by $-\text{Log(P value)}$ of enrichment score. FIG. 21C: Myeloid and erythroid colony formation of healthy donor CD34⁺ cells treated with DMSO, Compound 14, or Compound 15. FIG. 21D:

Immunophenotyping for CD38 expression on the indicated cells after treatment with DMSO,

Compound 14, or Compound 15 for 12 days. FIG. 21E: Colony formation of AML(1714) cells treated in vitro with DMSO, Compound 14, or Compound 15 for 3 weeks. Following in vitro treatment, 250 live cells were plated in methylcellulose to assess colony formation after 10 days.

FIGS. 22A-22B depict the evaluation of IRAK1/4-deficient AML cells. FIG. 22A:

Colony formation following a secondary replating of isogenic THP1 cells isolated from the

primary colony plating (see FIG. 11H). FIG. 22B: Kaplan Meier survival analysis of NSGS mice ($n = 4$ mice/group) engrafted with WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells.

FIG. 23 depicts liver engraftment of WT ($n = 4$), IRAK4^{KO} ($n = 5$), IRAK1^{KO} ($n = 5$), and IRAK1/4^{dKO} ($n = 5$) THP1 cells in xenografted NSGS mice at time of death. Leukemic engraftment was determined as percentage of huCD45⁺huCD33⁺ cells normalized to number of days.

FIG. 24 depicts immunophenotyping of the indicated cells for CD34 expression.

FIGS. 25A-25D demonstrate that IRAK1 and IRAK4 interactomes reveal non-canonical signaling in AML. FIG. 25A: Immunoblots for IRAK1 and IRAK4 in the nuclear (Nuc) and cytoplasmic (Cyto) fractions isolated from the indicated cells. FIG. 25B: Immunoprecipitation

of IRAK4 (or IgG control) followed by immunoblotting of IRAK4 and EZH2 from THP1 cells. FIG. 25C: Immunoblots for phospho-STAT5 and STAT5 in WT, IRAK4^{KO}, and IRAK1^{KO} THP1 cells. FIG. 25D: Colony formation of MyD88^{KO}, IRAK1^{KO} and IRAK4^{dKO} THP1 cells treated

with DMSO or BBI608 (STAT3 inhibitor) (500 nM). Error bars represent the standard error of the mean.

FIG. 26 depicts that targeting IRAK4 results in compensation by IRAK1.

FIG. 27 depicts data demonstrating that IRAK1/4 drives NF- κ B signaling.

FIG. 28 depicts that a compound of the present disclosure (Compound 8) provides enhanced survival in xenograft mice compared to emavusertib (CA-4948) and gilteritinib.

FIGS. 29A-29B depict the creation of an IRAK1/4 signature (FIG. 29A) and the analysis of the IRAK1/4 signature in patients (FIG. 29B).

DETAILED DESCRIPTION

The following related applications are incorporated by reference herein in their entirety, and for all purposes: International Publication No. WO 2018081738, TREATMENT OF DISEASES ASSOCIATED WITH ACTIVATED IRAK, filed October 30, 2017; U.S.

- 5 Publication No. 2021/0292843, TREATMENT OF DISEASES ASSOCIATED WITH ACTIVATED IRAK, filed April 4, 2019; International Publication No. WO 2014190163, Combination Therapy for MDS, filed May 22, 2014; U.S. Patent No. 9,168,257, Combination Therapy for MDS, issued October 27, 2015; U.S. Patent No. 9,504,706, Combination Therapy for MDS, issued November 29, 2016; U.S. Patent No. 9,855,273, Combination Therapy for MDS, issued January 2, 2018; International Publication No. WO 2018038988, Compounds, 10 Compositions, Methods for Treating Diseases, and Methods for Preparing Compounds, filed August 16, 2017; U.S. Patent No. 11,254,667, Substituted imidazo[1,2-a]pyridines as IRAK 1/4 and FLT3 inhibitors, issued February 2, 2022; U.S. Publication No. 2022/0213094, Substituted Imidazo[l,2-a]-pyridines as IRAK 1/4 and FLT3 Inhibitors, filed January 4, 2022; U.S. 15 Publication No. 2020/0199123, Substituted imidazo[1,2-a]pyridines as IRAK 1/4 and FLT3 inhibitors, filed February 28, 2020; U.S. Publication No. 2022/0235042, Substituted Imidazo[l,2-a]-pyridines as IRAK 1/4 and FLT3 Inhibitors, filed January 28, 2022; International Publication No. WO 2020252487, Rational therapeutic targeting of oncogenic immune signaling states in myeloid malignancies via the ubiquitin conjugating enzyme UBE2N, filed June 15, 2020; 20 International Publication No. WO 2022026935, Multi-Cyclic IRAK and FLT3 Inhibiting Compounds and Uses Thereof, filed July 31, 2021; International Publication No. WO 2022140647, Multi-Cyclic IRAK and FLT3 Inhibiting Compounds and Uses Thereof, filed December 23, 2021; International Publication No. WO 2023009833, Multi-Cyclic IRAK and FLT3 Inhibiting Compounds and Uses Thereof, filed July 29, 2022; International Patent 25 Application No. PCT/US2023/068520, Multi-Cyclic IRAK and FLT3 Inhibiting Compounds and Uses Thereof, filed June 15, 2023, and International Patent Application No. PCT/US2023/068897, Multi-Cyclic IRAK and FLT3 Inhibiting Compounds and Uses Thereof, filed June 22, 2023.

While embodiments encompassing the general disclosed concepts may take diverse 30 forms, various embodiments will be described herein, with the understanding that the present

disclosure is to be considered merely exemplary, and the general disclosed concepts are not intended to be limited to the disclosed embodiments.

Some embodiments of the disclosure include disclosed compounds. Other embodiments include compositions (e.g., pharmaceutical compositions) comprising the disclosed compound.

5 Still other embodiments of the disclosure include compositions for treating, for example, certain diseases using the disclosed compounds. Some embodiments include methods of using the disclosed compound (e.g., in compositions or in pharmaceutical compositions) for administering and treating. Further embodiments include methods for making the disclosed compound. Yet further embodiments include methods for determining whether a particular patient is likely to be
10 responsive to such treatment with the disclosed compounds and compositions.

Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according
15 to the standard rules of chemical valency known in the chemical arts.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

As used herein, in relation to compounds of Formulae (VI-5003), (I-5007), (VII-5008), (I-5009),
20 (I-5010), (II-5010), or (III-5010), etc., the term “attached” signifies a stable covalent bond, certain preferred points of attachment being apparent to those of ordinary skill in the art.

As used herein (unless otherwise specified), the term “alkyl” means a monovalent, straight or branched hydrocarbon chain, which can be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1 - C_{10}
25 means one to ten carbons). For example, the terms “ C_1 - C_7 alkyl” or “ C_1 - C_4 alkyl” refer to straight- or branched-chain saturated hydrocarbon groups having from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7), or 1 to 4 (e.g., 1, 2, 3, or 4), carbon atoms, respectively. Examples of C_1 - C_7 alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, n-hexyl, and n-septyl. Examples of C_1 - C_4 alkyl groups include, but are not
30 limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, and t-butyl.

As used herein (unless otherwise specified), the term “alkenyl” means a monovalent, straight or branched hydrocarbon chain that includes one or more (e.g., 1, 2, 3, or 4) double bonds. Double bonds can occur in any stable point along the chain and the carbon-carbon double bonds can have either the *cis* or *trans* configuration. For example, this definition shall include but is not limited to ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, 1,5-octadienyl, 1,4,7-nonatrienyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, ethylcyclohexenyl, butenylcyclopentyl, 1-pentenyl-3-cyclohexenyl, and the like. Similarly, “heteroalkenyl” refers to heteroalkyl having one or more double bonds. Further examples of alkenyl groups include, but are not limited to, vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, and 5-hexenyl.

As used herein (unless otherwise specified), the term “alkynyl” means a monovalent, straight or branched hydrocarbon chain that includes one or more (e.g., 1, 2, 3, or 4) triple bonds and that also may optionally include one or more (e.g. 1, 2, 3, or 4) double bonds in the chain. Examples of alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, and 5-hexynyl.

As used herein (unless otherwise specified), the term “alkoxy” means any of the above alkyl, alkenyl, or alkynyl groups which is attached to the remainder of the molecule by an oxygen atom (alkyl-O-). Examples of alkoxy groups include, but are not limited to, methoxy (sometimes shown as MeO-), ethoxy, isopropoxy, propoxy, and butyloxy.

The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, alkenyl, or alkynyl group, as exemplified, but not limited by, -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the compounds disclosed herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

As used herein (unless otherwise specified), the term “cycloalkyl” means a monovalent, monocyclic or bicyclic, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 membered hydrocarbon group. The rings can be saturated or partially unsaturated. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and

bicycloalkyls (e.g., bicyclooctanes such as [2.2.2]bicyclooctane or [3.3.0]bicyclooctane, bicyclononanes such as [4.3.0]bicyclononane, and bicyclodecanes such as [4.4.0]bicyclodecane (decalin), or spiro compounds). For a monocyclic cycloalkyl, the ring is not aromatic. For a bicyclic cycloalkyl, if one ring is aromatic, then the other is not aromatic. For a bicyclic cycloalkyl, one or both rings can be substituted.

The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized, and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N, P, S, and Si can be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two heteroatoms can be consecutive, such as, for example, -CH₂-NH-OCH₃.

Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)₂R'- represents both -C(O)₂R'- and -R'C(O)₂-. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R'', -OR', -SR', and/or -SO₂R'. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R'' or the like, it will be understood that the terms heteroalkyl and -NR'R'' are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R'' or the like.

As used herein (unless otherwise specified), the term “halogen” or “halo” means monovalent Cl, F, Br, or I. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

As used herein (unless otherwise specified), the term “aryl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 member aromatic hydrocarbon group and also means polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tolyl, and xylyl. For an aryl that is bicyclic, one or both rings can be substituted.

As used herein (unless otherwise specified), the term “heteroaryl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 membered, hydrocarbon group, where 1, 2, 3, 4, 5, or 6 carbon atoms are replaced by a hetero atom independently selected from nitrogen, oxygen, or sulfur atom, and the monocyclic or bicyclic ring system is aromatic. Heteroaryl groups (or rings) can contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Examples of heteroaryl groups include, but are not limited to, thienyl (or thiophenyl), furyl, indolyl, pyrrolyl, pyridinyl, pyrazinyl, oxazolyl, thiazolyl, quinolinyl, pyrimidinyl, imidazolyl, triazolyl, tetrazolyl, 1H-pyrazol-4-yl, 1-Me-pyrazol-4-yl, pyridin-3-yl, pyridin-4-yl, 3,5-dimethylisoxazolyl, 1H-pyrrol-3-yl, 3,5-di-Me-pyrazolyl, and 1H-pyrazol-4-yl. For a bicyclic heteroaryl, if one ring is

aryl, then the other is heteroaryl. For a bicyclic heteroaryl, one or both rings can have one or more hetero atoms. For a bicyclic heteroaryl, one or both rings can be substituted.

An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Accordingly, the term "aryl" can represent an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g. 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C₁₋₁₆alkyl, arylC₁₋₁₆alkyl, C₀₋₁₆alkyloxyC₀₋₁₆alkyl, arylC₀₋₁₆alkyloxyC₀₋₁₆alkyl, C₀₋₁₆alkylthioC₀₋₁₆alkyl, arylC₀₋₁₆alkylthioC₀₋₁₆alkyl, C₀₋₁₆alkylaminoC₀₋₁₆alkyl, arylC₀₋₁₆alkylaminoC₀₋₁₆alkyl, di(arylC₁₋₁₆alkyl)aminoC₀₋₁₆alkyl, C₁₋₁₆alkylcarbonylC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarbonylC₀₋₁₆alkyl, C₁₋₁₆alkylcarboxyC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarboxyC₀₋₁₆alkyl, C₁₋₁₆alkylcarbonylaminoC₀₋₁₆alkyl, arylC₁₋₁₆alkylcarbonylaminoC₀₋₁₆alkyl, -C₀₋₁₆alkylCOOR₄, -C₀₋₁₆alkylCONR₅R₆ wherein R₄, R₅ and R₆ are independently selected from hydrogen, C₁-C₁₁alkyl, arylC₀-C₁₁alkyl, or R₅ and R₆ are taken together with the nitrogen to which they are attached forming a cyclic system containing 3 to 8 carbon atoms with or without one C₁₋₁₆alkyl, arylC₀-C₁₆alkyl, or C₀-C₁₆alkylaryl substituent. Aryl includes but is not limited to pyrazolyl and triazolyl.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl," "aralkyl" and the like are meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like), or a sulfur atom. Accordingly, the terms "arylalkyl" and the like (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexyl, pyridylcyclopentyl) represents an aryl group as defined above attached through an alkyl group as defined above having the indicated number of carbon atoms.

The terms "cycloalkyl" and "heterocycloalkyl", also referred to as "heterocyclyl", by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Examples of cycloalkyl include, but are not limited to,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. As used herein (unless otherwise specified), the term “heterocycloalkyl” or “heterocyclyl” means a monovalent, monocyclic or bicyclic, 5, 6, 7, 8, 9, 10, 11, or 12 membered, hydrocarbon, where 1, 2, 3, 4, 5, or 6 carbon atoms are replaced by a hetero atom independently selected from nitrogen atom, oxygen atom, or sulfur atom, and the monocyclic or bicyclic ring system is not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, tetrahydropyran, pyrrolidinyl (e.g., pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, or pyrrolidin-4-yl), piperazinyl (e.g., piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, or piperazin-4-yl), piperidinyl (e.g., piperadin-1-yl, piperadin-2-yl, piperadin-3-yl, or piperadin-4-yl), and morpholinyl (e.g., morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, or morpholin-4-yl). For a bicyclic heterocyclyl, if one ring is aromatic (e.g., monocyclic aryl or heteroaryl), then the other ring is not aromatic. For a bicyclic heterocyclyl, one or both rings can have one or more hetero atoms. For a bicyclic heterocyclyl, one or both rings can be substituted and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

As used herein (unless otherwise specified), the term “hetero atom” means an atom selected from nitrogen atom, oxygen atom, or sulfur atom.

As used herein (unless otherwise specified), the terms “hydroxy” or “hydroxyl” means a monovalent -OH group.

The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom. The term “alkylsulfonyl,” as used herein, means a moiety having the formula -S(O₂)-R', where R' is an alkyl group as defined above. R' can have a specified number of carbons (e.g., “C₁-C₄ alkylsulfonyl”).

The term "carbonyloxy" represents a carbonyl group attached through an oxygen bridge. In the above definitions, the terms "alkyl" and "alkenyl" can be used interchangeably in so far as a stable chemical entity is formed, as would be apparent to those skilled in the art.

The term "linker" refers to attachment groups interposed between substituents. In some embodiments, the linker includes amido (-CONH-Rⁿ or -NHCO-Rⁿ), thioamido (-CSNH-Rⁿ or -NHCS-Rⁿ), carboxyl (-CO₂-Rⁿ or -OCORⁿ), carbonyl (-CO-Rⁿ), urea (-NHCONH-Rⁿ), thiourea (-NHCSNH-Rⁿ), sulfonamido (-NHSO₂-Rⁿ or -SO₂NH-Rⁿ), ether (-O-Rⁿ), sulfonyl (-SO₂-Rⁿ), sulfoxyl (-SO-Rⁿ), carbamoyl (-NHCO₂-Rⁿ or -OCONH-Rⁿ), or amino (-NHRⁿ) linking moieties.

Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl," and "heteroaryl," and so forth) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided herein.

As used herein (unless otherwise specified), the term "substituted" (e.g., as in substituted alkyl) means that one or more hydrogen atoms of a chemical group (with one or more hydrogen atoms) can be replaced by one or more non-hydrogen substituents selected from the specified options. The replacement can occur at one or more positions. The term "optionally substituted" means that one or more hydrogen atoms of a chemical group (with one or more hydrogen atoms) can be, but is not required to be substituted.

A "substituent group," as used herein, means a non-hydrogen substituent group that may be, and preferably is, a group selected from the following moieties:

(A) -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -N(CH₃)₂, ethynyl (-CCH), propynyl, sulfo (-SO₃H), CONH₂, -CON(CH₃)₂, unsubstituted C₁-C₇ alkyl, unsubstituted C₁-C₇ heteroalkyl, unsubstituted C₁-C₇ perfluorinated alkyl, unsubstituted C₁-C₇ alkoxy, unsubstituted C₁-C₇ haloalkoxy, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) C₁-C₇ alkyl, C₁-C₇ heteroalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -N(CH₃)₂, ethynyl (-CCH), propynyl, sulfo (-SO₃H), CONH₂, -CON(CH₃)₂, unsubstituted C₁-C₇ alkyl, unsubstituted C₁-C₇ heteroalkyl, unsubstituted C₁-C₇

perfluorinated alkyl, unsubstituted C₁-C₇ alkoxy, unsubstituted C₁-C₇ haloalkoxy, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) C₁-C₇ alkyl, C₁-C₇ heteroalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one
5 substituent selected from:

(a) -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -N(CH₃)₂, ethynyl (-CCH), propynyl, sulfo (-SO₃H), CONH₂, -CON(CH₃)₂, unsubstituted C₁-C₇ alkyl, unsubstituted C₁-C₇ heteroalkyl, unsubstituted C₁-C₇ perfluorinated alkyl, unsubstituted C₁-C₇ alkoxy, unsubstituted C₁-C₇ haloalkoxy, unsubstituted
10 cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) C₁-C₇ alkyl, C₁-C₇ heteroalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from: -NH₂, -SH, -CN, -CF₃, -NO₂, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -N(CH₃)₂, ethynyl (-CCH), propynyl, sulfo (-SO₃H),
15 CONH₂, -CON(CH₃)₂, unsubstituted C₁-C₇ alkyl, unsubstituted C₁-C₇ heteroalkyl, unsubstituted C₁-C₇ perfluorinated alkyl, unsubstituted C₁-C₇ alkoxy, unsubstituted C₁-C₇ haloalkoxy, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

A “size-limited substituent” or “size-limited substituent group,” as used herein, means a
20 group, e.g., selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2-20-membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₄-C₈ cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or
25 unsubstituted 4-8-membered heterocycloalkyl.

A “lower substituent” or “lower substituent group,” as used herein, means a group, e.g., selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2-8-membered heteroalkyl, each
30 substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₅-C₇ cycloalkyl, and

each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5-7-membered heterocycloalkyl.

The term “about” used in the context of a numeric value indicates a range of +/- 10% of the numeric value, unless expressly indicated otherwise.

5 Some compounds of the disclosure can have one or more chiral centers and can exist in and be isolated in optically active and racemic forms, for any of the one or more chiral centers. Some compounds can exhibit polymorphism. The compounds of the present disclosure (e.g., Formula I) encompass any optically active, racemate, stereoisomer form, polymorphism, or mixtures thereof. If a chiral center does not provide an indication of its configuration (i.e., R or
10 S) in a chemical structure, it should be considered to represent R, S or a racemate.

As used herein, the term “sample” encompasses a sample obtained from a subject or patient. The sample can be of any biological tissue or fluid. Such samples include, but are not limited to, sputum, saliva, buccal sample, oral sample, blood, serum, mucus, plasma, urine, blood cells (e.g., white cells), circulating cells (e.g. stem cells or endothelial cells in the blood), tissue, core or fine
15 needle biopsy samples, cell-containing body fluids, free floating nucleic acids, urine, stool, peritoneal fluid, and pleural fluid, tear fluid, or cells therefrom. Samples can also include sections of tissues such as frozen or fixed sections taken for histological purposes or microdissected cells or extracellular parts thereof. A sample to be analyzed can be tissue material from a tissue biopsy obtained by aspiration or punch, excision or by any other surgical
20 method leading to biopsy or resected cellular material. Such a sample can comprise cells obtained from a subject or patient. In some embodiments, the sample is a body fluid that include, for example, blood fluids, serum, mucus, plasma, lymph, ascitic fluids, gynecological fluids, or urine but not limited to these fluids. In some embodiments, the sample can be a non-invasive sample, such as, for example, a saline swish, a buccal scrape, a buccal swab, and the
25 like.

As used herein, “blood” can include, for example, plasma, serum, whole blood, blood lysates, and the like.

As used herein, the term “assessing” includes any form of measurement, and includes determining if an element is present or not. The terms “determining,” “measuring,”
30 “evaluating,” “assessing,” “analyzing,” and “assaying” can be used interchangeably and can include quantitative and/or qualitative determinations.

As used herein, the term “monitoring” with reference to a type of cancer refers to a method or process of determining the severity or degree of the type of cancer or stratifying the type of cancer based on risk and/or probability of mortality. In some embodiments, monitoring relates to a method or process of determining the therapeutic efficacy of a treatment being administered to a patient.

As used herein, “outcome” can refer to an outcome studied. In some embodiments, “outcome” can refer to survival / mortality over a given time horizon. For example, “outcome” can refer to survival / mortality over 1 month, 3 months, 6 months, 1 year, 5 years, or 10 years or longer. In some embodiments, an increased risk for a poor outcome indicates that a therapy has had a poor efficacy, and a reduced risk for a poor outcome indicates that a therapy has had a good efficacy.

As used herein, the term “high risk clinical trial” refers to one in which the test agent has “more than minimal risk” (as defined by the terminology used by institutional review boards, or IRBs). In some embodiments, a high risk clinical trial is a drug trial.

As used herein, the term “low risk clinical trial” refers to one in which the test agent has “minimal risk” (as defined by the terminology used by IRBs). In some embodiments, a low risk clinical trial is one that is not a drug trial. In some embodiments, a low risk clinical trial is one that involves the use of a monitor or clinical practice process. In some embodiments, a low risk clinical trial is an observational clinical trial.

As used herein, the terms “modulated” or “modulation,” or “regulated” or “regulation” and “differentially regulated” can refer to both up regulation (*i.e.*, activation or stimulation, *e.g.*, by agonizing or potentiating) and down regulation (*i.e.*, inhibition or suppression, *e.g.*, by antagonizing, decreasing or inhibiting), unless otherwise specified or clear from the context of a specific usage.

As used herein, the term “subject” refers to any suitable (*e.g.*, treatable) member of the animal kingdom. In the methods, the subject is preferably a mammal. In the methods, the subject is preferably a human patient. In the methods, the subject may be a mammalian pediatric patient. In the methods, the pediatric patient is a mammalian (*e.g.*, preferably human) patient under 18 years of age, while an adult patient is 18 or older.

As used herein, the term “treating” (and its variations, such as “treatment” “treating,” “treat,” and the like) is, unless stated otherwise, to be considered in its broadest context and

refers to obtaining a desired pharmacologic and/or physiologic effect. In particular, for example, the term “treating” may not necessarily imply or require that an animal is treated until total recovery. Accordingly, “treating” includes amelioration of the symptoms, relief from the symptoms or effects associated with a condition, decrease in severity of a condition, or preventing, preventively ameliorating symptoms, or otherwise reducing the risk of developing a particular condition. In some aspects, “treating” may not require or include prevention. As used herein, reference to “treating” an animal includes but is not limited to prophylactic treatment and therapeutic treatment. The effect can be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or can be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment,” as used herein, covers any treatment of a disease in a subject, preferably in a mammal (e.g., in a human), and may include one or more of: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression or elimination of the disease and/or relieving one or more disease symptoms. In particular aspects of the methods, such as conditions or disorders characterized by dysregulated IRAK expression or dysregulated (e.g., hyperactive) IRAK-mediated signaling pathway(s), treatment may be or include reducing such expression or signaling. “Treatment” can also encompass delivery of an agent or administration of a therapy in order to provide for a pharmacologic effect, even in the absence of a disease or condition. Any of the compositions (e.g., pharmaceutical compositions) described herein can be used to treat a suitable subject.

“Therapeutically effective amount” means an amount effective to achieve a desired and/or beneficial effect. An effective amount can be administered in one or more administrations. In the methods, a therapeutically effective amount is an amount appropriate to treat an indication. By treating an indication is meant achieving any desirable effect, such as one or more of palliate, ameliorate, stabilize, reverse, slow, or delay disease progression, increase the quality of life, or to prolong life. Such achievement can be measured by any suitable method, such as measurement of tumor size or blood cell count, or any other suitable measurement.

As used herein, the term “marker” or “biomarker” refers to a biological molecule, such as, for example, a nucleic acid, peptide, protein, hormone, and the like, whose presence or concentration can be detected and correlated with a known condition, such as a disease state. It

can also be used to refer to a differentially expressed gene whose expression pattern can be utilized as part of a predictive, prognostic or diagnostic process in healthy conditions or a disease state, or which, alternatively, can be used in methods for identifying a useful treatment or prevention therapy.

As used herein, an mRNA “isoform” is an alternative transcript for a specific mRNA or gene. This term includes pre-mRNA, immature mRNA, mature mRNA, cleaved or otherwise truncated, shortened, or aberrant mRNA, modified mRNA (e.g. containing any residue modifications, capping variants, polyadenylation variants, etc.), and the like.

“Antibody” or “antibody peptide(s)” refer to an intact antibody, or a binding fragment thereof that competes with the intact antibody for specific binding; this definition also encompasses monoclonal and polyclonal antibodies. Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Binding fragments include Fab, Fab', F(ab')₂, Fv, and single-chain antibodies. An antibody other than a “bispecific” or “bifunctional” antibody is understood to have each of its binding sites identical. An antibody, for example, substantially inhibits adhesion of a receptor to a counterreceptor when an excess of antibody reduces the quantity of receptor bound to counterreceptor by at least about 20%, 40%, 60% or 80%, and more usually greater than about 85% (as measured in an in vitro competitive binding assay).

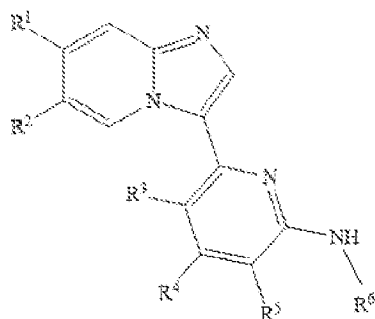
Embodiments of the disclosure set forth herein include disclosed compounds (e.g., compounds of Formulas (VI-5003), (I-5007), (VII-5008), (I-5009), (I-5010), (II-5010), or (III-5010)). Other embodiments include compositions (e.g., pharmaceutical compositions) comprising the disclosed compound. Still other embodiments of the disclosure include compositions (e.g., pharmaceutical compositions) for treating, for example, certain diseases using the disclosed compounds. Some embodiments include methods of using the disclosed compound (e.g., in compositions or in pharmaceutical compositions) for administering and treating (e.g., diseases such as cancer or blood disorders). Some embodiments include methods of determining whether a patient is suitable for, or likely to respond favorably to, a particular treatment. Further embodiments include methods for making the disclosed compounds. Additional embodiments of the disclosure are also discussed herein.

Compounds

In one aspect, the present disclosure provides a compound which inhibits IRAK1 and IRAK4. In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM, less than about 65 nM, less than about 55 nM, less than about 45 nM, less than about 35 nM, less than about 25 nM, less than about 15 nM, or less than about 5 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 70, less than about 60, less than about 50, less than about 40, less than about 30, or less than about 20. In one embodiment, the IRAK4:IRAK1 potency ratio is calculated from the IRAK1 and IRAK4 IC₅₀ measurements.

In one embodiment, the compound inhibits NF-κB-mediated signaling. In one embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits IRAK1, IRAK4, and FLT3.

In one aspect, the present disclosure provides a compound of Formula (I-5007)



Formula (I-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, salt of an isomer, prodrug, or derivative thereof, wherein:

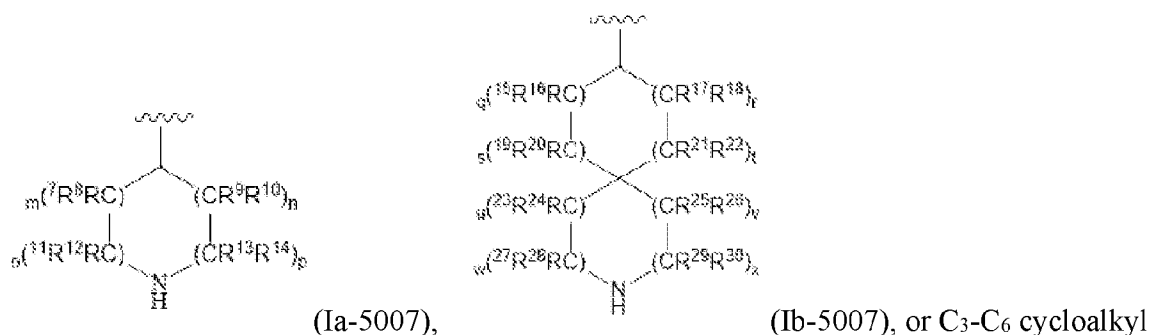
R¹ is selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, -C(=O)NR^{31a}R^{31b}, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H),

nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

5 R² is selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted
10 with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

15 R³, R⁴, and R⁵ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, -O-aryl, aryl, heteroaryl, or fused ring heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, -O-aryl, aryl, heteroaryl,
20 or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

25 R⁶ is selected from:



substituted with one or more -NR³³R³⁴;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₂-C₆ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen;

R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, which methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen;

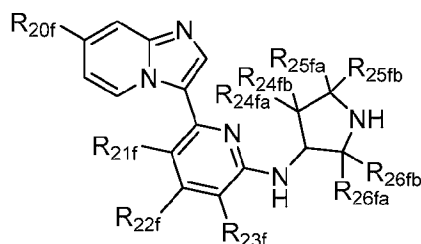
R^{31a} and R^{31b} are each independently selected from H, C₁-C₆ alkyl, -(CH₂)_a-(C₃-C₆ cycloalkyl), -(CH₂)_b-C₂-C₆ heterocyclyl, -(CH₂)_c-C₃-C₉ heteroaryl, and -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₂-C₆ heterocyclyl, and C₃-C₉ heteroaryl are each independently optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

R³³ and R³⁴ are each independently selected from H and C₁-C₆ alkyl;

a, b, and c are each independently selected from 0, 1, 2, 3, 4, 5, or 6; and

m, n, o, p, q, r, s, t, u, v, w, and x are each independently selected from 0, 1, 2, 3, 4, or 5, where $q+r+s+t$ is at least 1, and where $u+v+w+x$ is at least 1.

In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIf-5007):



Formula (IIf-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof, wherein:

R_{20f} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{27fa}R_{27fb}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

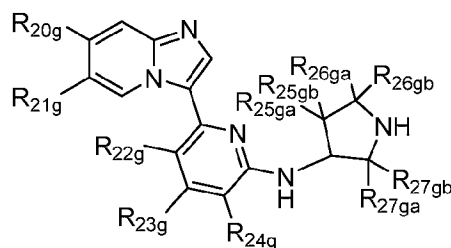
R_{21f}, R_{22f}, and R_{23f} are each independently selected from H and halogen;

R_{24fa}, R_{24fb}, R_{25fa}, R_{25fb}, R_{26fa}, and R_{26fb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

R_{27fa} and R_{27fb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen.

In an embodiment, one or more of R_{24fa}, R_{24fb}, R_{25fa}, R_{25fb}, R_{26fa}, and R_{26fb} is independently selected from halogen, -OH, optionally substituted C₁-C₆ alkyl, and optionally substituted C₁-C₆ alkoxy. In another embodiment, each of R_{24fa}, R_{24fb}, R_{25fa}, R_{25fb}, R_{26fa}, and R_{26fb} is H.

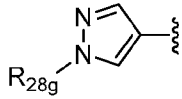
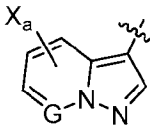
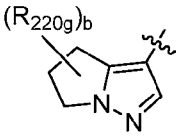
In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIg-5007):



Formula (IIg-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20g} is selected from H, C₁-C₆ alkoxy, imidazolyl, triazolyl, and -C(=O)NR_{29ga}R_{29gb}, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen atoms;

5 R_{21g} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, ,
, and , wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{22g}, R_{23g}, and R_{24g} are each independently selected from H and halogen;

10 R_{25ga}, R_{25gb}, R_{26ga}, R_{26gb}, R_{27ga}, and R_{27gb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms;

15 R_{28g} is selected from H, C₁-C₆ alkyl, and -(CH₂)_d-(C₃-C₆ cycloalkyl), wherein C₁-C₆ alkyl and -(CH₂)_d-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from -OH and halogen;

R_{29ga} and R_{29gb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen;

each R_{220g} is independently C₁-C₆ alkyl;

20 G is N or CH;

X is halogen;

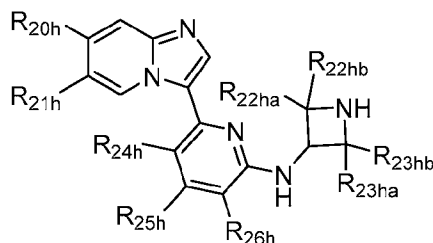
a is 0, 1, 2, or 3;

b is 0, 1, 2, 3, 4, 5, or 6; and

d is 0, 1, 2, or 3.

In an embodiment, one or more of R_{25ga} , R_{25gb} , R_{26ga} , R_{26gb} , R_{27ga} , and R_{27gb} is independently selected from halogen, -OH, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_1 - C_6 alkoxy. In another embodiment, each of R_{25ga} , R_{25gb} , R_{26ga} , R_{26gb} , R_{27ga} , and R_{27gb} is H.

5 In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIh-5007):



Formula (IIh-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20h} is selected from H, C_1 - C_6 alkoxy, imidazolyl, triazolyl, and $-C(=O)NR_{27ha}R_{27hb}$;

10 R_{21h} is selected from C_1 - C_6 alkyl and C_3 - C_6 cycloalkyl, wherein C_1 - C_6 alkyl and C_3 - C_6 cycloalkyl are each optionally substituted with one or more substituents selected from -OH and halogen;

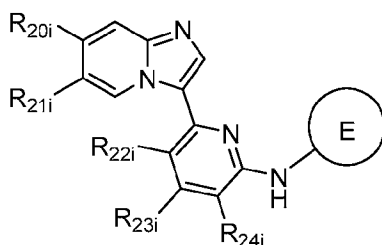
R_{22ha} , R_{22hb} , R_{23ha} , and R_{23hb} are each independently selected from H and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl is optionally substituted with one or more halogen atoms;

15 R_{24h} , R_{25h} , and R_{26h} are each independently selected from H and halogen; and

R_{27ha} and R_{27hb} are each independently selected from H, C_1 - C_6 alkyl, and C_3 - C_6 cycloalkyl, wherein C_1 - C_6 alkyl and C_3 - C_6 cycloalkyl are each optionally substituted with one or more halogen.

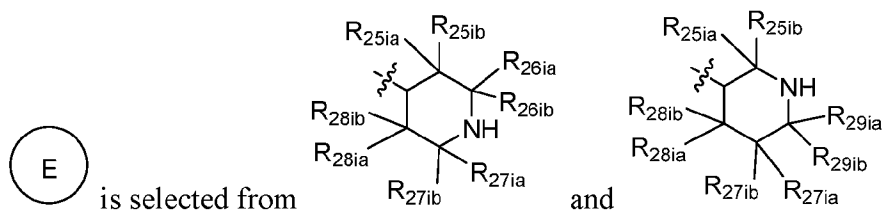
In an embodiment, one or more of R_{22ha} , R_{22hb} , R_{23ha} , and R_{23hb} is independently optionally substituted C_1 - C_6 alkyl. In another embodiment, each of R_{22ha} , R_{22hb} , R_{23ha} , and R_{23hb} is H.

In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIi-5007):



Formula (III-5007),

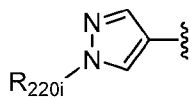
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



R_{20i} is selected from H, -O-(C₃-C₆ cycloalkyl), C₁-C₆ alkoxy, imidazolyl, triazolyl, and –

5 C(=O)NR_{221ia}R_{221ib}, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen atoms;

R_{21i} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and



10 by one or more substituents selected from OH and halogen;

R_{22i}, R_{23i}, and R_{24i} are each independently selected from H and halogen;

R_{25ia}, R_{25ib}, R_{26ia}, R_{26ib}, R_{27ia}, R_{27ib}, R_{28ia}, R_{28ib}, R_{29ia}, and R_{29ib} are each independently selected from H, halogen, -OH, or C₁-C₆ alkyl;

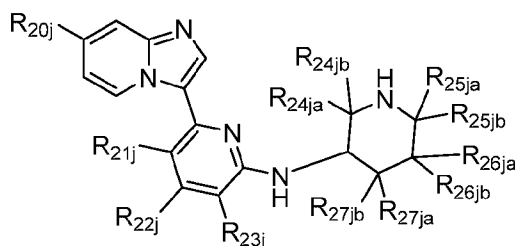
15 R_{220i} is selected from H, C₁-C₆ alkyl, and -(CH₂)_e-(C₃-C₆ cycloalkyl), wherein C₁-C₆ alkyl and -(CH₂)_e-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from OH and halogen;

R_{221ia} and R_{221ib} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen; and

20 e is 0, 1, 2, or 3.

In an embodiment, one or more of R_{25ia}, R_{25ib}, R_{26ia}, R_{26ib}, R_{27ia}, R_{27ib}, R_{28ia}, R_{28ib}, R_{29ia}, and R_{29ib} is independently selected from halogen, -OH, and C₁-C₆ alkyl. In another embodiment, each of R_{25ia}, R_{25ib}, R_{26ia}, R_{26ib}, R_{27ia}, R_{27ib}, R_{28ia}, R_{28ib}, R_{29ia}, and R_{29ib} is H.

In an embodiment, the compound of Formula (II-5007) is a compound of Formula (IIj-5007):



Formula (IIj-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

- 5 R_{20j} is selected from C_1 - C_6 alkoxy, $-O-(C_3-C_6$ cycloalkyl), imidazolyl, triazolyl, and $-C(=O)NR_{28ja}R_{28jb}$, wherein C_1 - C_6 alkoxy is optionally substituted with one or more halogen substituents;

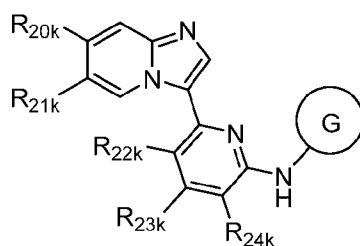
R_{21j} , R_{22j} , and R_{23j} are each independently selected from H and halogen;

- 10 R_{24ja} , R_{24jb} , R_{25ja} , R_{25jb} , R_{26ja} , R_{26jb} , R_{27ja} , and R_{27jb} are each independently selected from H, halogen, $-OH$, and C_1 - C_6 alkyl; and

R_{28ja} and R_{28jb} are each independently selected from H, C_1 - C_6 alkyl, and C_3 - C_6 cycloalkyl, wherein C_1 - C_6 alkyl and C_3 - C_6 cycloalkyl are each optionally substituted with one or more halogen.

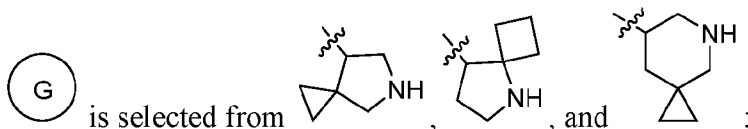
- 15 In an embodiment, one or more of R_{24ja} , R_{24jb} , R_{25ja} , R_{25jb} , R_{26ja} , R_{26jb} , R_{27ja} , and R_{27jb} is selected from halogen, $-OH$, and C_1 - C_6 alkyl. In another embodiment, each of R_{24ja} , R_{24jb} , R_{25ja} , R_{25jb} , R_{26ja} , R_{26jb} , R_{27ja} , and R_{27jb} is H.

In an embodiment, the compound of Formula (II-5007) is a compound of Formula (IIk-5007):

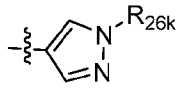


Formula (IIk-5007),

- 20 or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



R_{20k} is selected from H, C₁-C₆ alkoxy, imidazolyl, triazolyl, and $-C(=O)R_{25ka}R_{25kb}$, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen atoms;

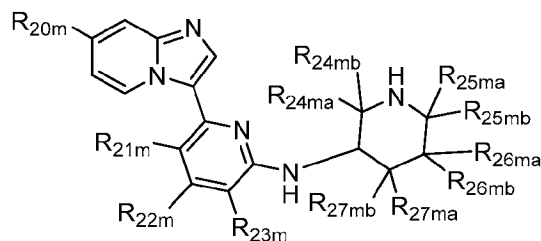
R_{21k} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and , wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{22k} , R_{23k} , and R_{24k} are each independently selected from H and halogen;

R_{25ka} and R_{25kb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen; and

R_{26k} is selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more substituents selected from halogen and -OH.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIm-5007):



Formula (IIm-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20m} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, $-O-(C_3-C_6 \text{ cycloalkyl})$, C₃-C₉ heteroaryl, and $-C(=O)NHR_{28m}$, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from halogen and -OH, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen, and wherein C₃-C₉ heteroaryl is optionally substituted with one or more C₁-C₆ alkyl;

R_{21m} , R_{22m} , and R_{23m} are each independently selected from H and halogen;

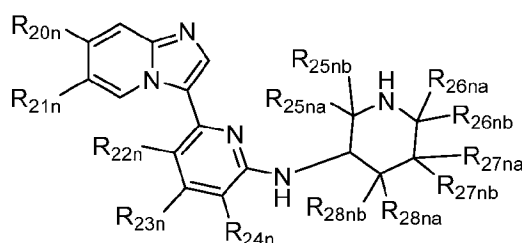
R_{24ma} , R_{24mb} , R_{25ma} , R_{25mb} , R_{26ma} , R_{26mb} , R_{27ma} , and R_{27mb} are each independently selected from H and halogen, wherein at least one of R_{24ma} , R_{24mb} , R_{25ma} , R_{25mb} , R_{26ma} , R_{26mb} , R_{27ma} , and R_{27mb} is halogen;

R_{28m} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₆ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more

substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (II-5007):



Formula (IIn-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20n} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and -C(=O)NHR_{220n};

R_{21n} is selected from C₁-C₆ alkyl and C₂-C₆ heterocyclyl, wherein the C₁-C₆ is optionally substituted with one or more substituents selected from -OH and halogen;

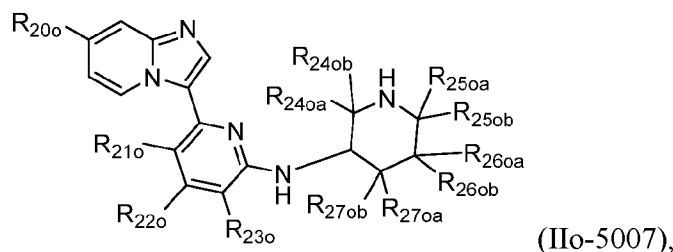
R_{22n}, R_{23n}, and R_{24n} are each independently selected from H and halogen;

R_{25na}, R_{25nb}, R_{26na}, R_{26nb}, R_{27na}, R_{27nb}, R_{28na}, and R_{28nb} are each independently selected from H and halogen, wherein at least one of R_{25na}, R_{25nb}, R_{26na}, R_{26nb}, R_{27na}, R_{27nb}, R_{28na}, and R_{28nb} is halogen;

R_{220n} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₆ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIo-5007):



or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20o} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, -O-(C₃-C₆ cycloalkyl), C₃-C₉ heteroaryl, and -C(=O)NHR_{28o}, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from halogen and -OH, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen, and wherein C₃-C₉ heteroaryl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

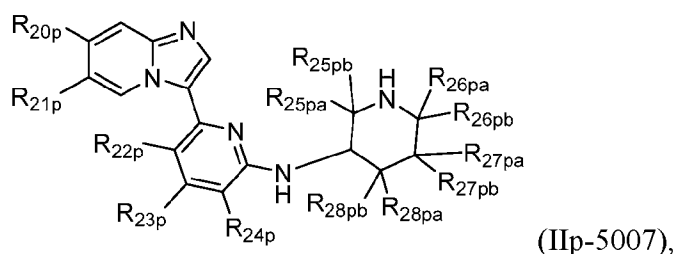
R_{21o}, R_{22o}, and R_{23o} are each independently selected from H and halogen;

R_{24oa}, R_{24ob}, R_{25oa}, R_{25ob}, R_{26oa}, R_{26ob}, R_{27oa}, and R_{27ob} are each H;

R_{28o} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₇ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIp-5007):



or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20p} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and -C(=O)NHR_{220p};

R_{21p} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₂-C₆ heterocyclyl, wherein the C₁-C₆ is optionally substituted with one or more substituents selected from -OH and halogen;

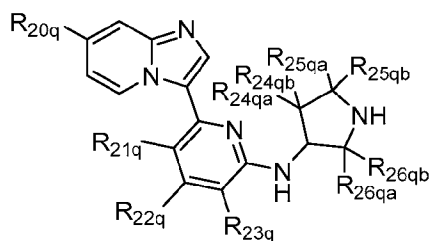
R_{22p}, R_{23p}, and R_{24p} are each independently selected from H and halogen;

R_{25pa}, R_{25pb}, R_{26pa}, R_{26pb}, R_{27pa}, R_{27pb}, R_{28pa}, and R_{28pb} are each H;

R_{220p} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₆ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIq-5007):



Formula (IIq-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20q} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, -O-(C₃-C₆ cycloalkyl), C₃-C₉ heteroaryl, and -C(=O)NHR_{28q}, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from halogen and -OH, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen, and wherein C₃-C₉ heteroaryl is optionally substituted with one or more C₁-C₆ alkyl;

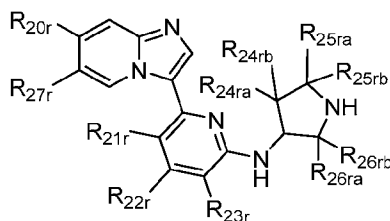
R_{21q}, R_{22q}, and R_{23q} are each independently selected from H and halogen;

R_{24qa}, R_{24qb}, R_{25qa}, R_{25qb}, R_{26qa}, and R_{26qb} are each independently selected from H and halogen, wherein at least one of R_{24qa}, R_{24qb}, R_{25qa}, R_{25qb}, R_{26qa}, and R_{26qb} is halogen;

R_{28q} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₇ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIr-5007):



Formula (IIr-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20r} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and -(C=O)NHR_{28r};

R_{21r}, R_{22r}, and R_{23r} are each independently selected from H and halogen;

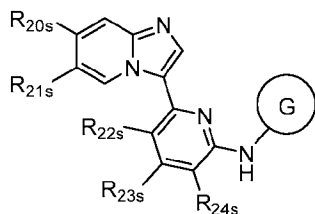
5 R_{24ra}, R_{24rb}, R_{25ra}, R_{25rb}, R_{26ra}, and R_{26rb} are each independently selected from H and halogen, wherein one or more of R_{24ra}, R_{24rb}, R_{25ra}, R_{25rb}, R_{26ra}, and R_{26rb} is halogen;

R_{27r} is selected from C₁-C₆ alkyl and C₂-C₆ heterocyclyl, wherein the C₁-C₆ is optionally substituted with one or more substituents selected from -OH and halogen;

10 R_{28r} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₇ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

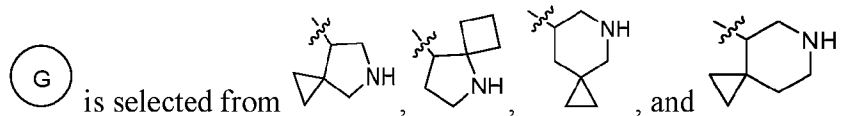
each n is independently 0, 1, 2, 3, 4, 5, or 6.

15 In one embodiment, the compound of Formula (I-5007) is a compound of Formula (IIs-5007):



Formula (IIs-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



20 R_{20s} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, -O-(C₃-C₆ cycloalkyl), C₃-C₉ heteroaryl, and -C(=O)NHR_{28s}, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from halogen and -OH, wherein C₁-C₆ alkoxy is optionally substituted with

one or more halogen, and wherein C₃-C₉ heteroaryl is optionally substituted with one or more C₁-C₆ alkyl;

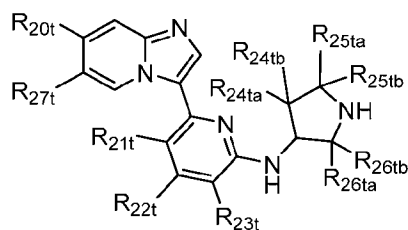
R_{21s} is selected from H, C₁-C₆ alkyl and C₂-C₆ heterocyclyl, wherein the C₁-C₆ is optionally substituted with one or more substituents selected from -OH and halogen;

5 R_{22s}, R_{23s}, and R_{24s} are each independently selected from H and halogen;

R_{28s} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₇ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more
10 substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

In one embodiment, the compound of Formula (I-5007) is a compound of Formula (II-5007):



Formula (II-5007),

15 or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20t} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and -(C=O)NHR_{28t};

R_{21t}, R_{22t}, and R_{23t} are each independently selected from H and halogen;

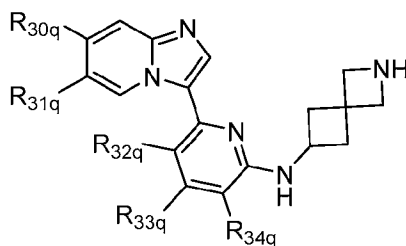
R_{24ta}, R_{24tb}, R_{25ta}, R_{25tb}, R_{26ta}, and R_{26tb} are each independently H;

R_{27t} is selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and C₂-C₆ heterocyclyl, wherein the
20 C₁-C₆ is optionally substituted with one or more substituents selected from -OH and halogen and the C₃-C₆ cycloalkyl is optionally substituted by one or more substituents selected from C₁-C₆ alkyl, OH, and halogen;

R_{28t} is selected from H, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(CH₂)_n-C₃-C₇ cycloalkyl, and -(CH₂)_n-C₂-C₆ heterocyclyl, wherein the C₁-C₆ alkyl is optionally substituted
25 with one or more substituents selected from -OH and halogen, and wherein the C₃-C₆ cycloalkyl and C₂-C₆ heterocyclyl are each independently optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

each n is independently 0, 1, 2, 3, 4, 5, or 6.

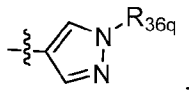
In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIIq-5007):



Formula (IIIq-5007),

5 or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{30q} is selected from H, C₁-C₆ alkoxy, imidazolyl, triazolyl, and -C(=O)NR_{35qa}R_{35qb};

R_{31q} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and ,

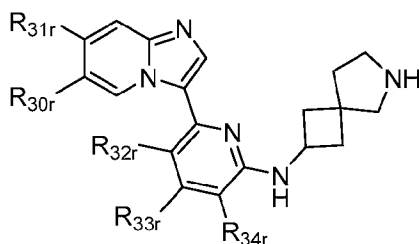
wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{32q}, R_{33q}, and R_{34q} are each independently selected from H and halogen;

R_{35qa} and R_{35qb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen; and

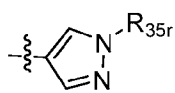
15 R_{36q} is selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally independently substituted with one or more substituents selected from halogen and -OH.

In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIIr-5007):



Formula (IIIr-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{30r} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and , wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

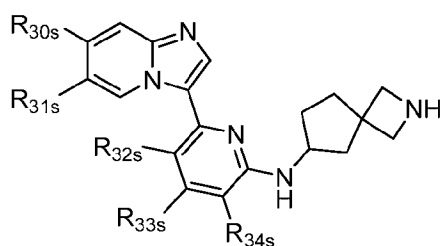
R_{31r} is selected from H, imidazolyl, triazolyl, and $-C(=O)NR_{36ra}R_{36rb}$;

R_{32r} , R_{33r} , and R_{34r} are each independently selected from H and halogen;

R_{35r} is selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more substituents selected from halogen and -OH; and

R_{36ra} and R_{36rb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen.

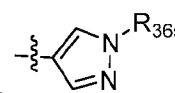
In an embodiment, the compound of Formula (I-5007) is a compound of Formula (IIIs-5007):



Formula (IIIs-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{30s} is selected from H, C₁-C₆ alkoxy, imidazolyl, triazolyl, and $-C(=O)NR_{35sa}R_{35sb}$;

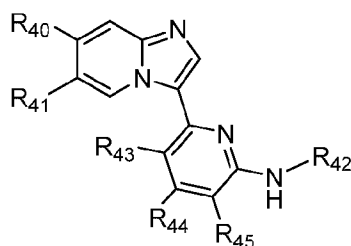
R_{31s} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and , wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{32s} , R_{33s} , and R_{34s} are each independently selected from H and halogen;

R_{35sa} and R_{35sb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen; and

R_{36s} is selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more substituents selected from halogen and -OH.

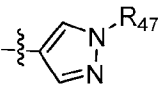
In an embodiment, R⁶ of Formula (I-5007) is C₃-C₆ cycloalkyl substituted with one or more -NR³³R³⁴, and the compound of Formula (I-5007) is a compound of Formula (IV-5007):



Formula (IV-5007),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R₄₀ is selected from H, C₁-C₆ alkoxy, imidazolyl, triazolyl, and -C(=O)NR_{46a}R_{46b}, wherein C₁-C₆ alkoxy is optionally substituted with one or more halogen atoms;

R₄₁ is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and , wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₄₂ is C₃-C₆ cycloalkyl substituted with one or more -NR_{48a}R_{48b};

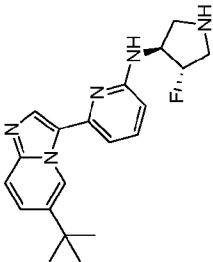
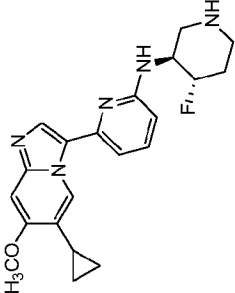
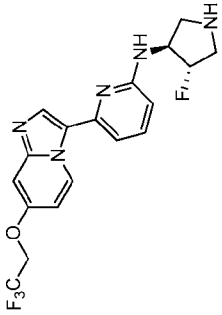
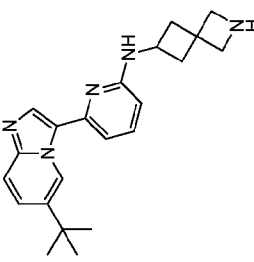
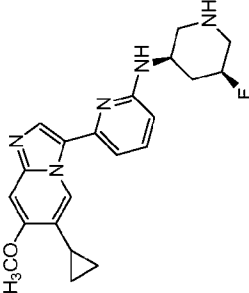
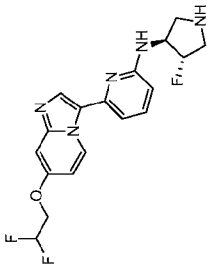
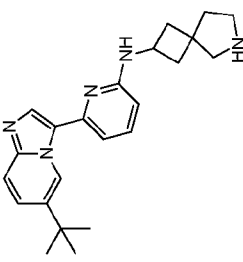
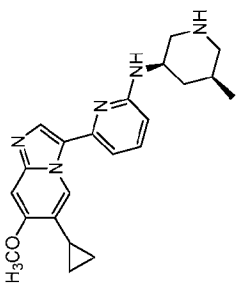
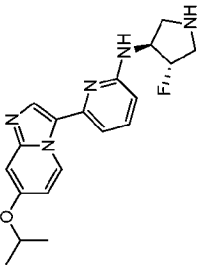
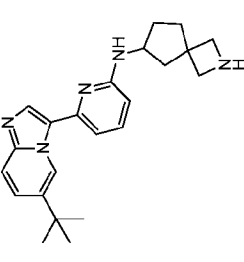
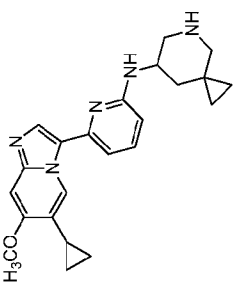
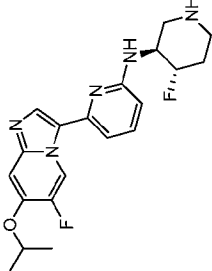
R₄₃, R₄₄, and R₄₅ are each independently selected from H and halogen;

R_{46a} and R_{46b} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more halogen;

R₄₇ is selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are each optionally substituted with one or more substituents selected from halogen and -OH; and

R_{48a} and R_{48b} are each independently selected from H and C₁-C₆ alkyl.

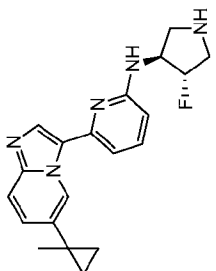
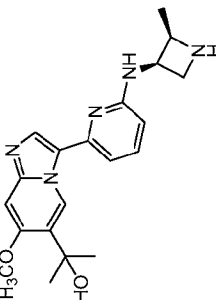
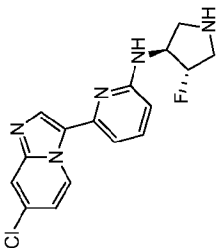
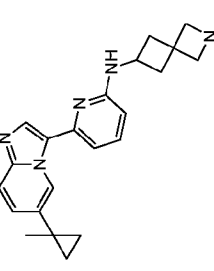
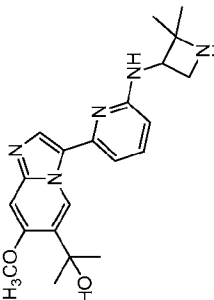
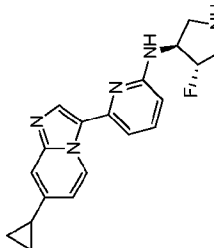
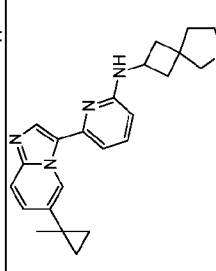
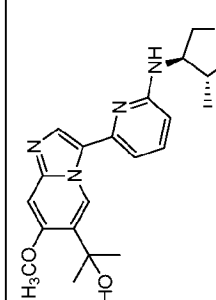
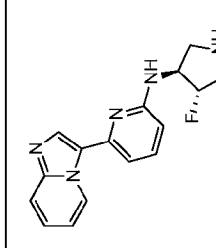
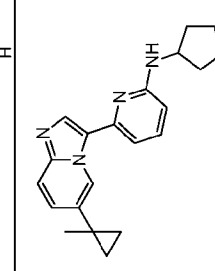
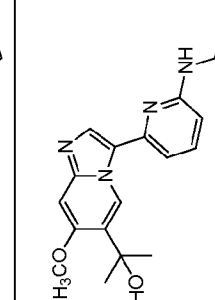
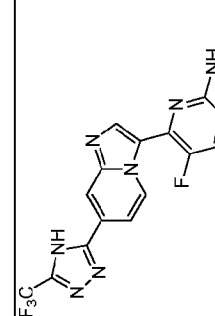
In one embodiment, the compound of Formula (I-5007) is selected from Compounds 1-7 to 295-7 or Compounds 1a-7 to 79a-7.

#	Structure	#-7	Structure	#	Structure
1-7		130-7		259-7	
2-7		131-7		260-7	
3-7		132-7		261-7	
4-7		133-7		262-7	

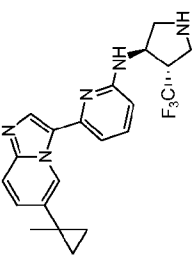
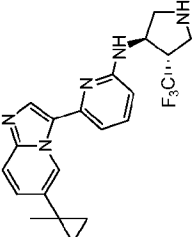
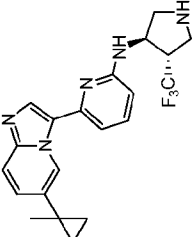
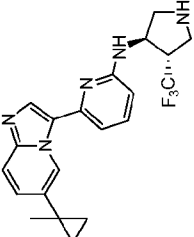
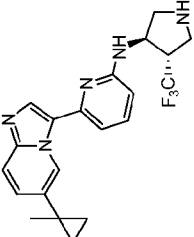
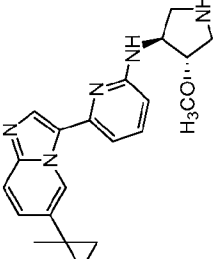
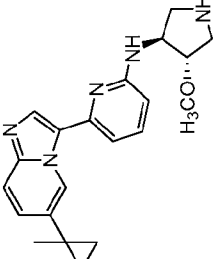
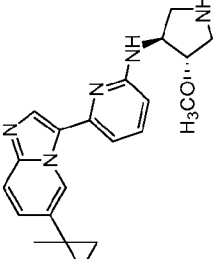
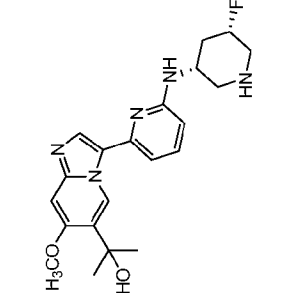
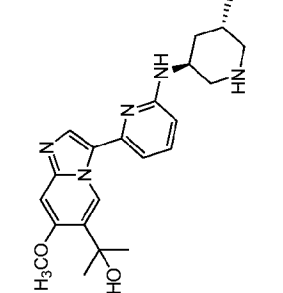
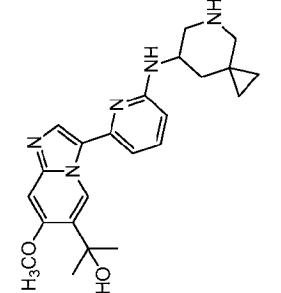
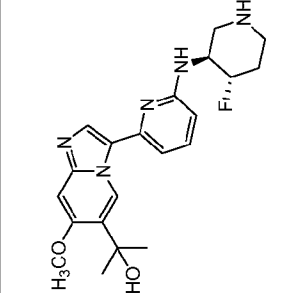
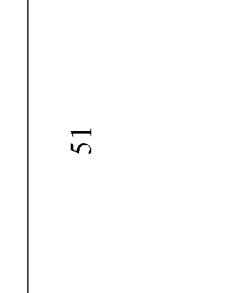
130364-5012-WO

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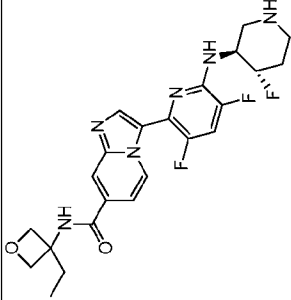
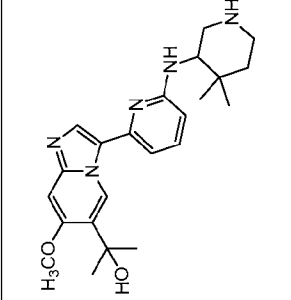
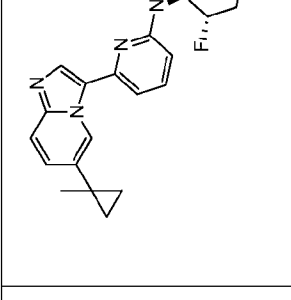
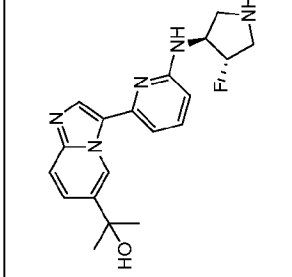
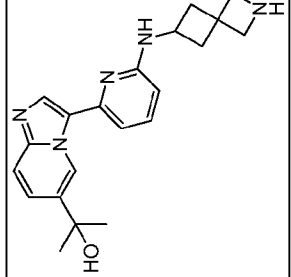
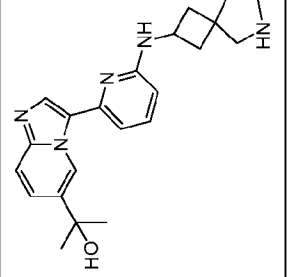
130364-5012-WO

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130364-5012-WO

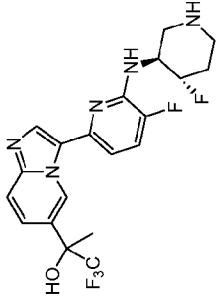
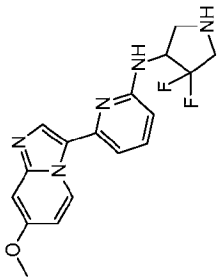
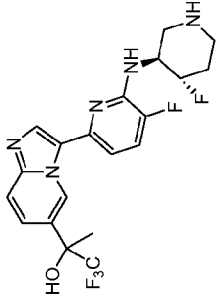
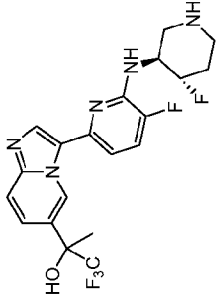
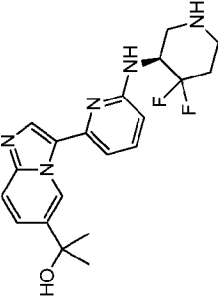
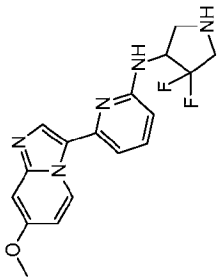
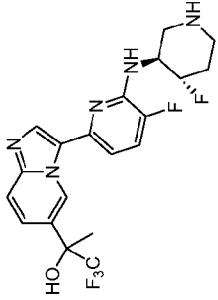
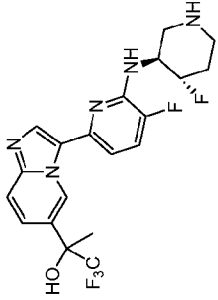
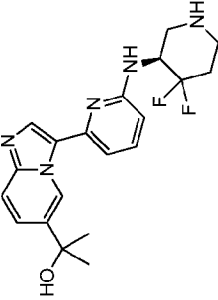
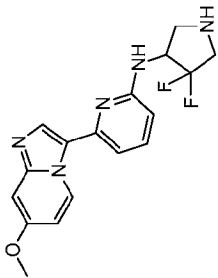
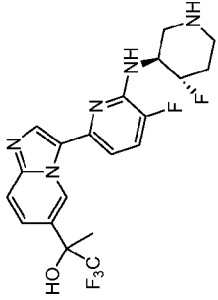
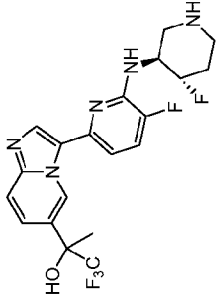
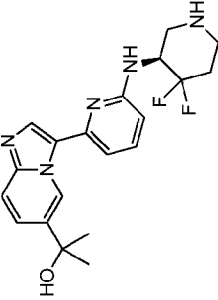
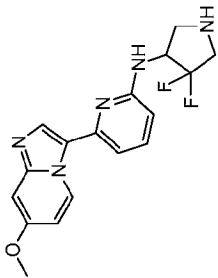
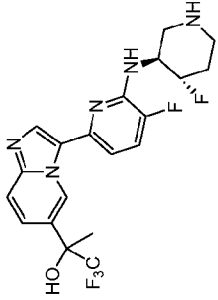
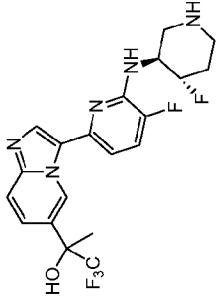
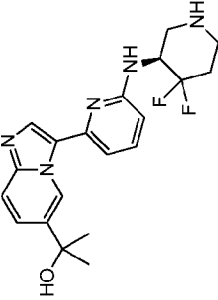
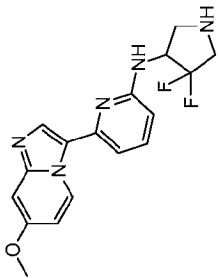
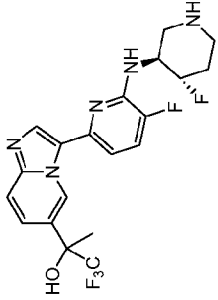
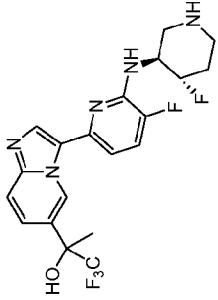
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130364-5012-WO

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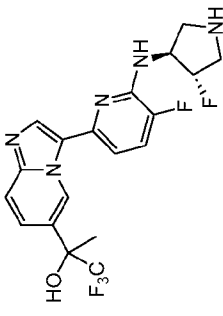
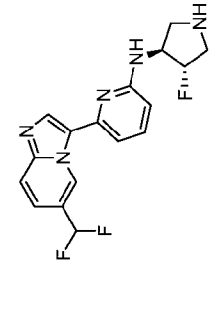
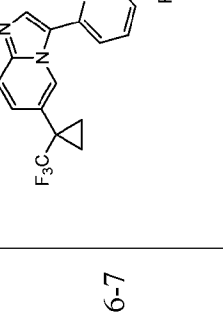
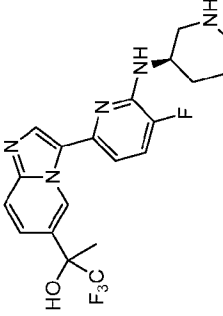
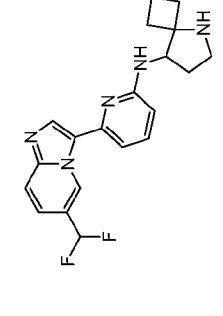
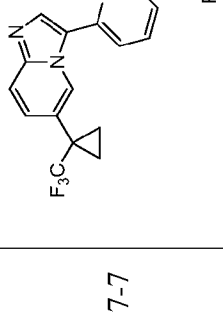
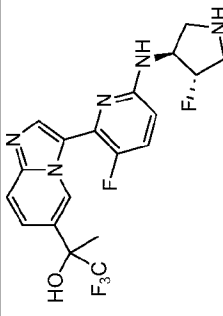
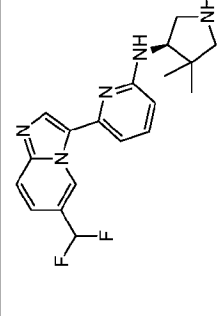
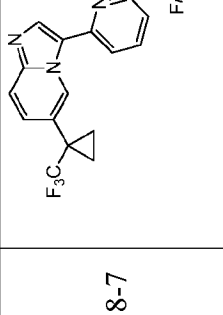
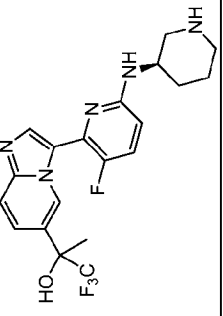
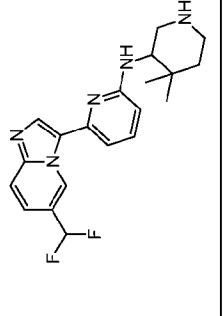
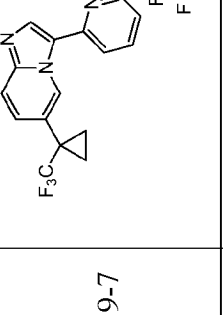
130364-5012-WO

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130364-5012-WO

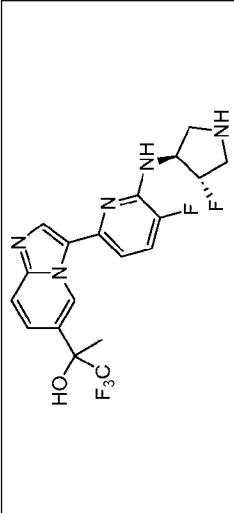
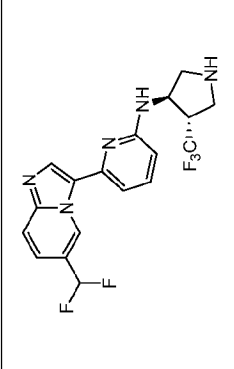
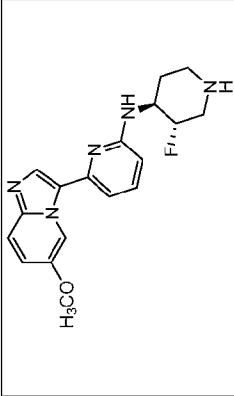
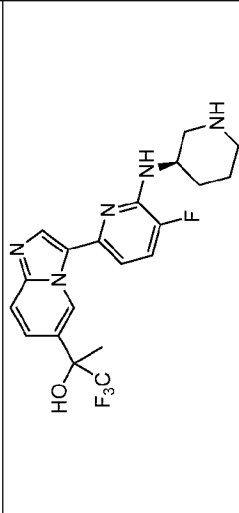
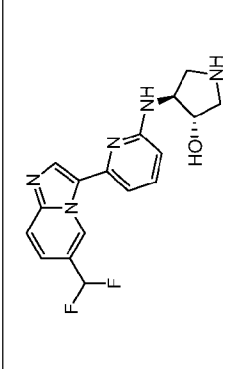
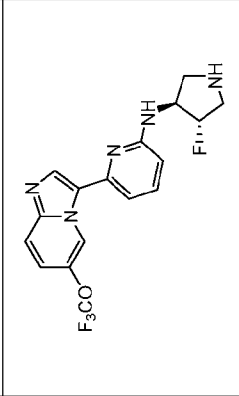
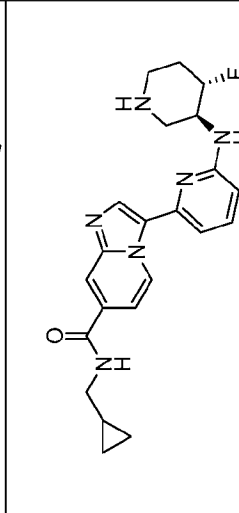
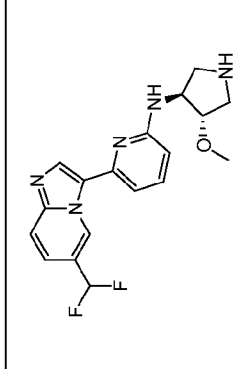
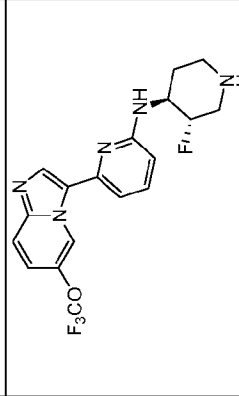
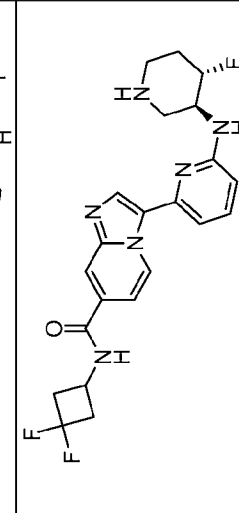
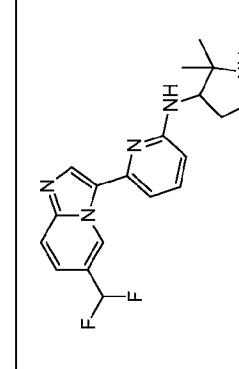
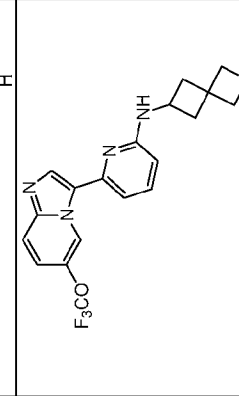
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130364-5012-WO

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	39-7		169-7		41-7	

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43-7		171-7		290-7	
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130364-5012-WO

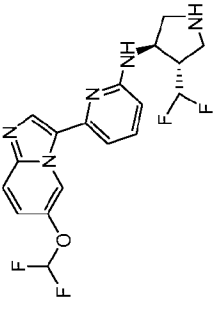
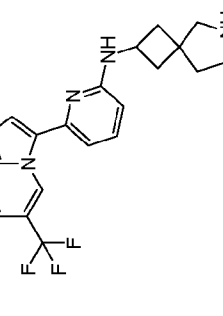
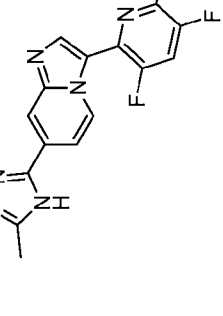
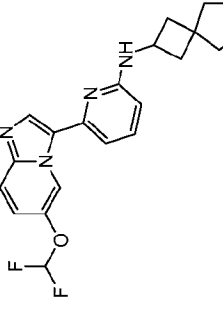
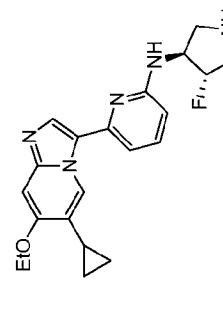
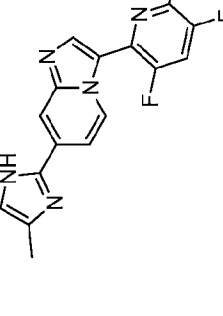
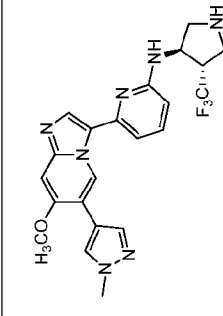
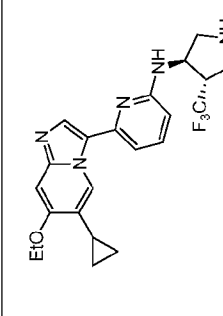
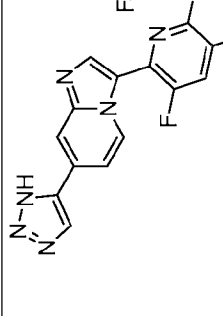
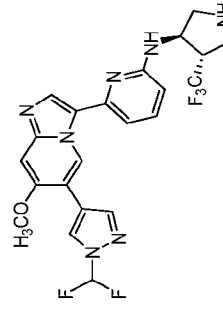
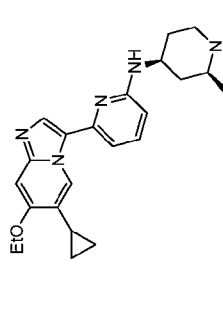
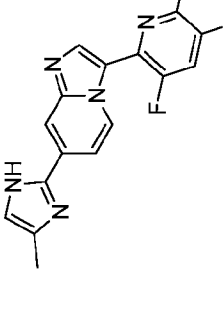
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130364-5012-WO

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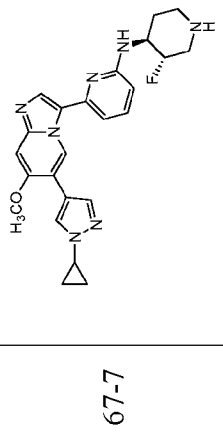
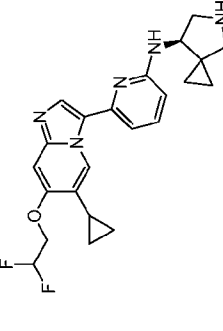
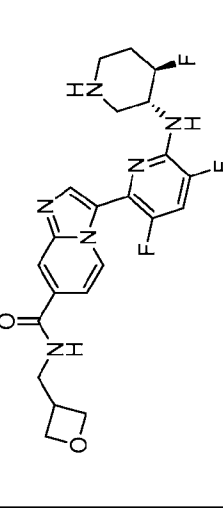
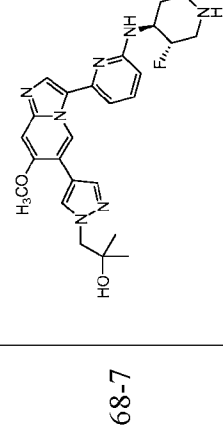
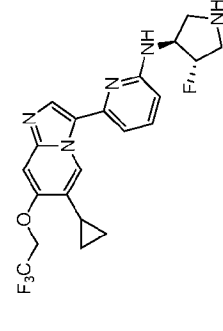
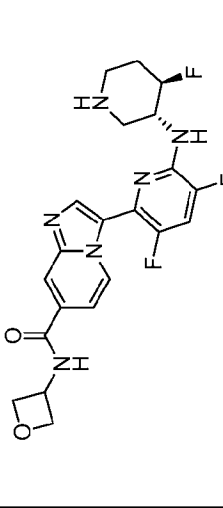
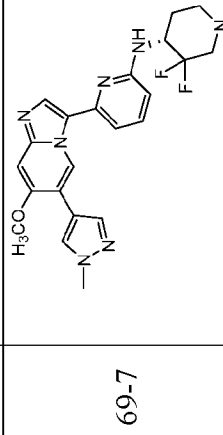
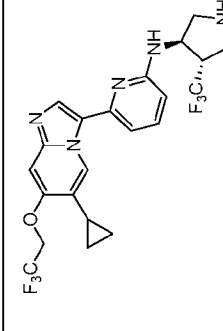
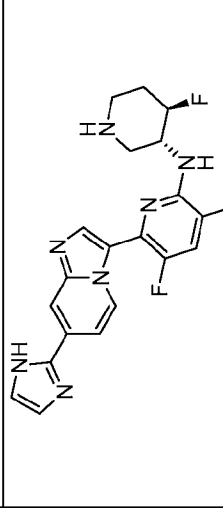
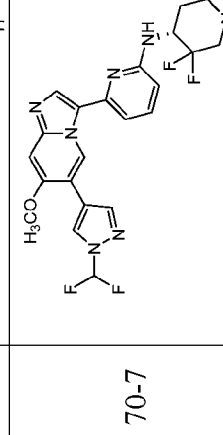
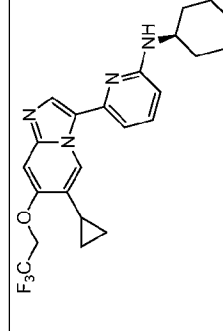
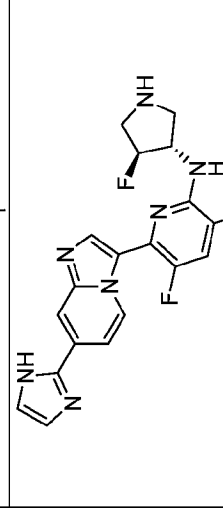
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130364-5012-WO

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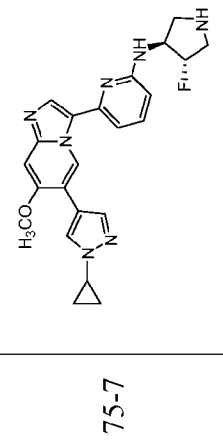
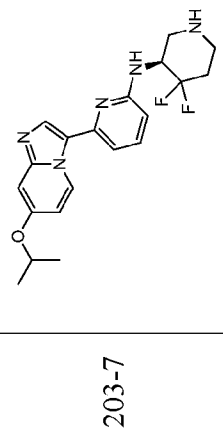
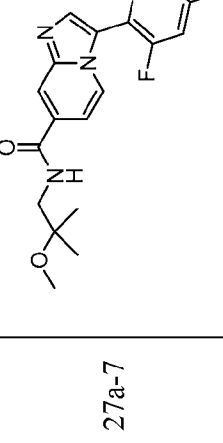
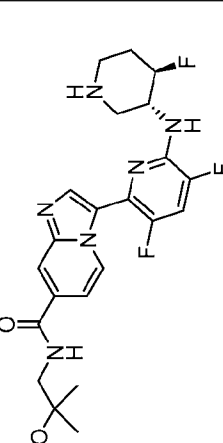
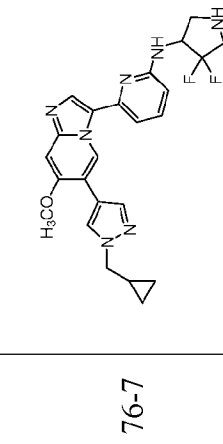
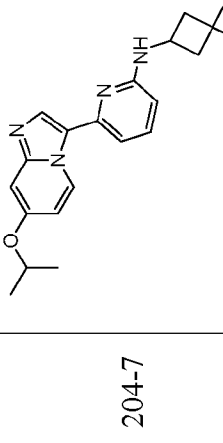
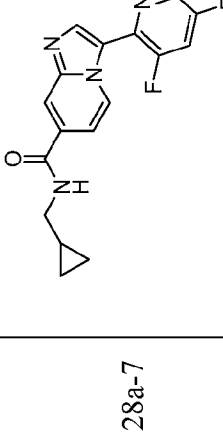
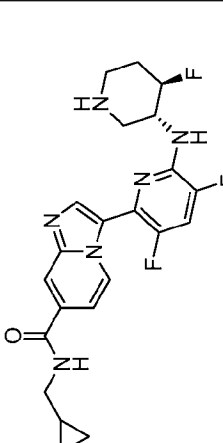
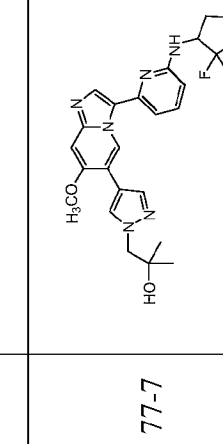
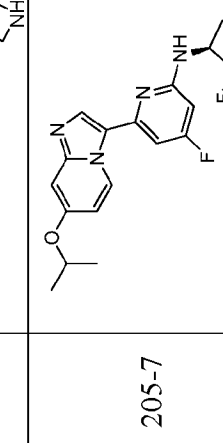
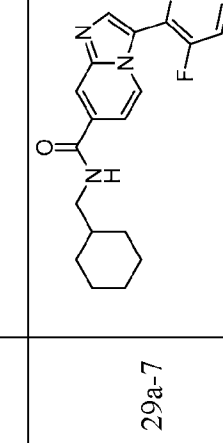
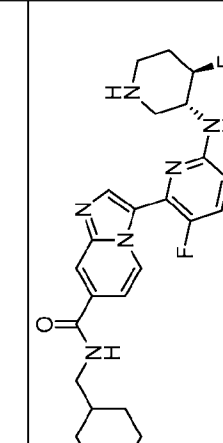
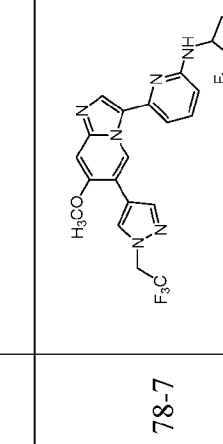
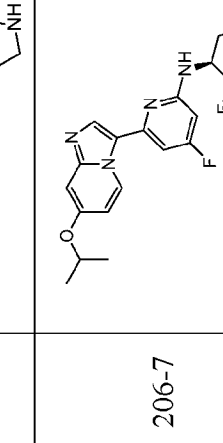
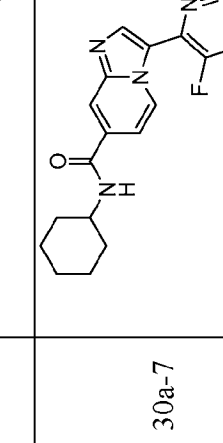
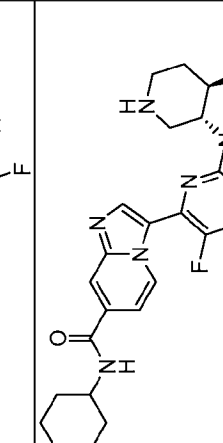
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130364-5012-WO

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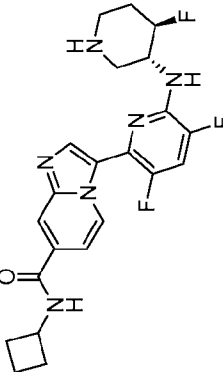
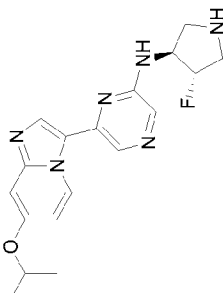
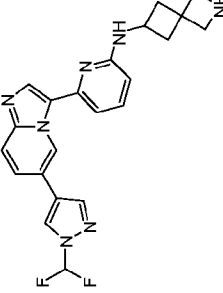
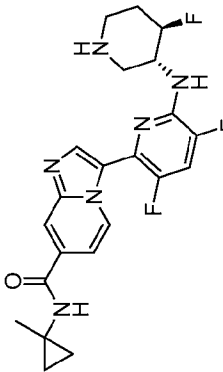
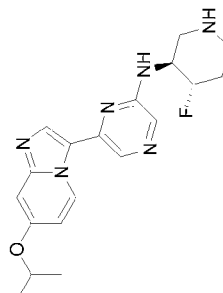
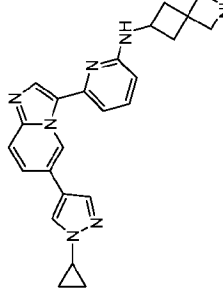
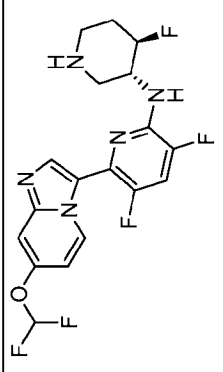
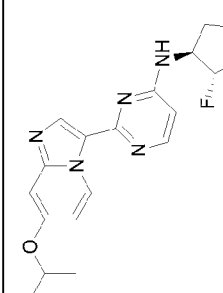
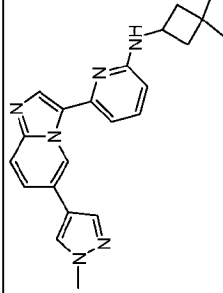
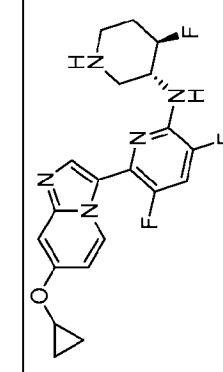
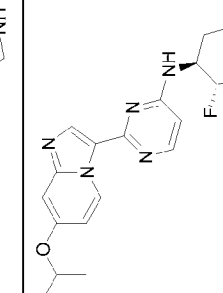
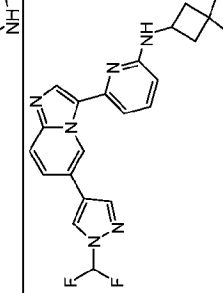
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130364-5012-WO

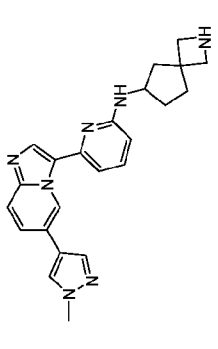
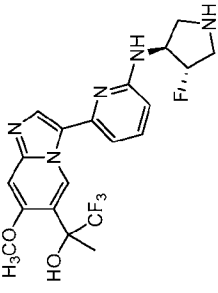
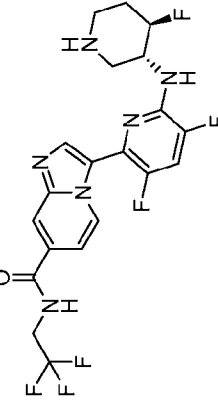
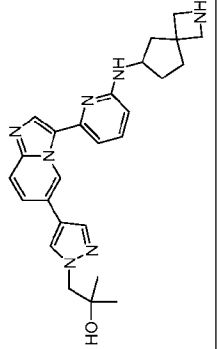
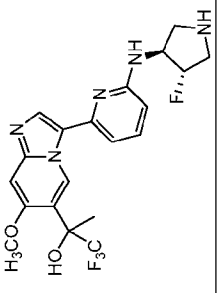
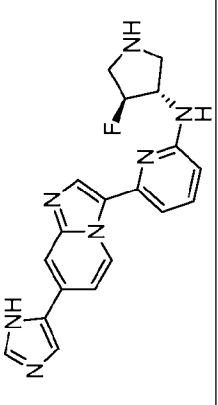
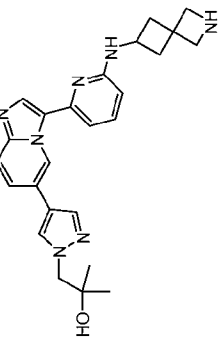
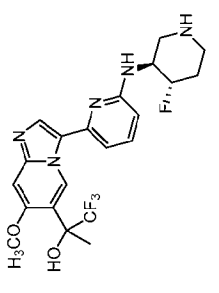
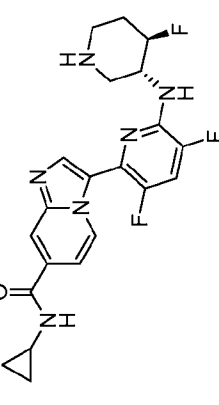
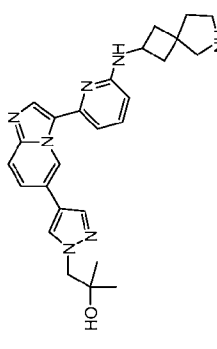
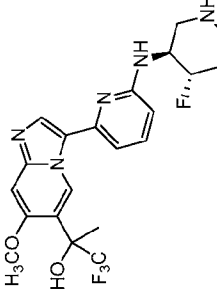
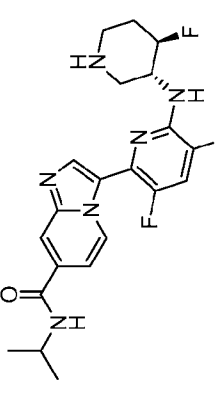
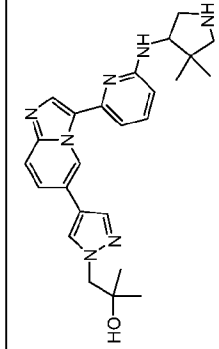
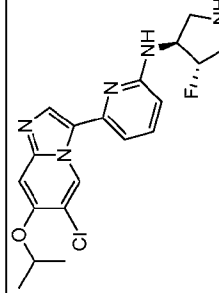
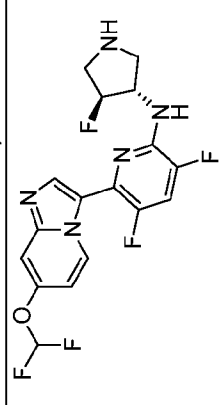
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	31a-7		32a-7		33a-7		34a-7
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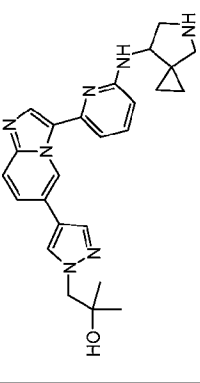
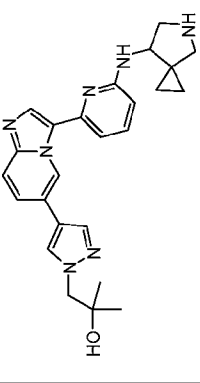
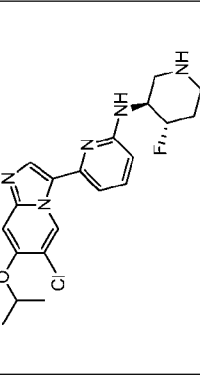
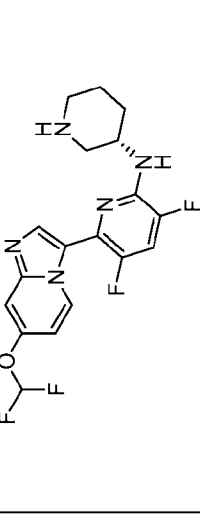
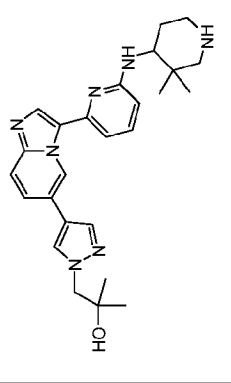
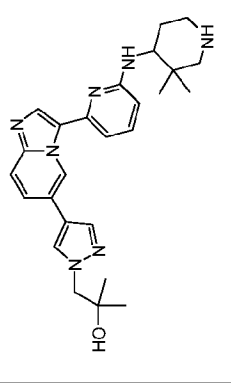
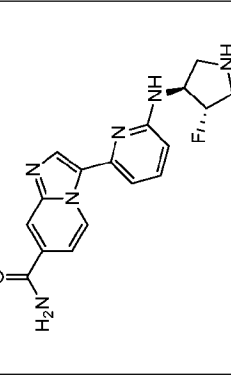
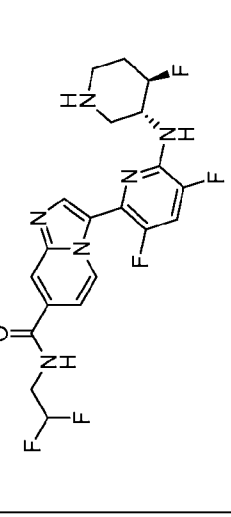
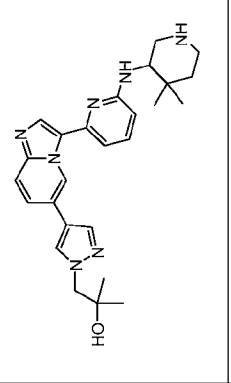
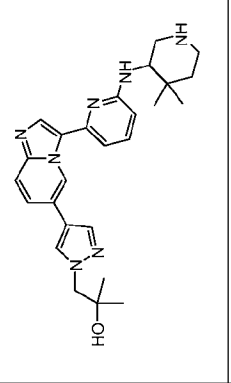
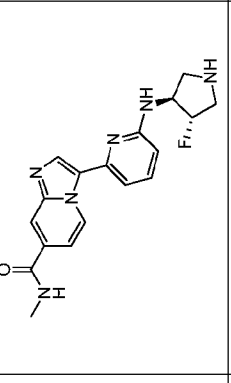
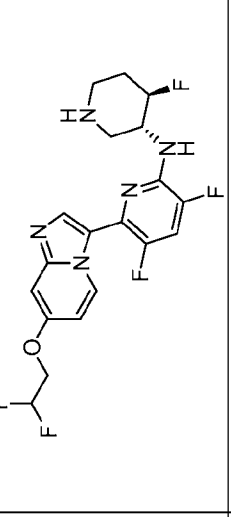
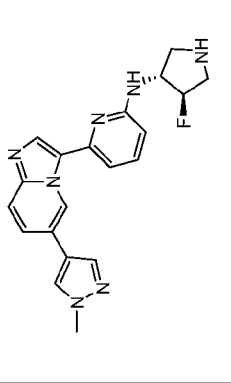
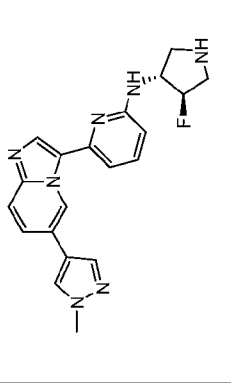
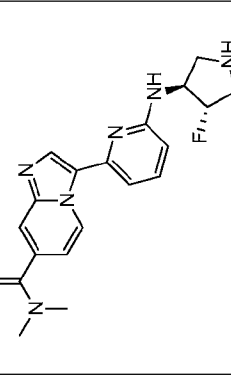
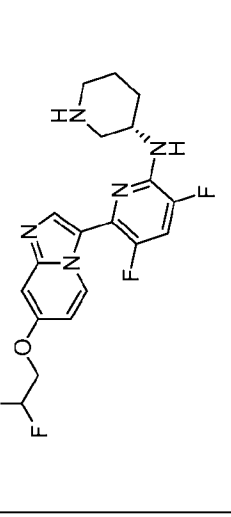
130364-5012-WO

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	86-7		214-7		38a-7	

130364-5012-WO

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88-7		216-7		40a-7	
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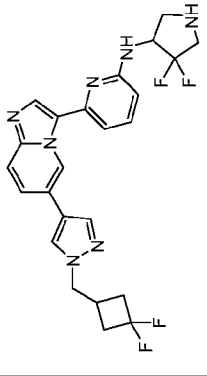
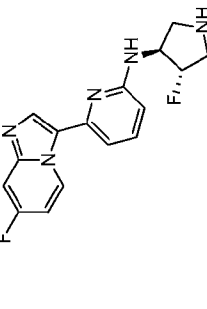
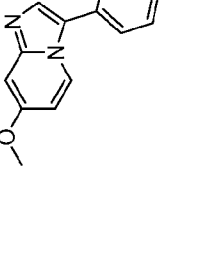
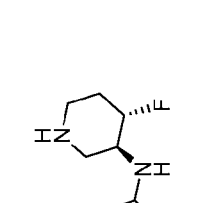
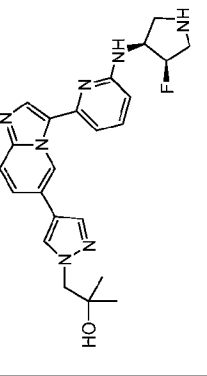
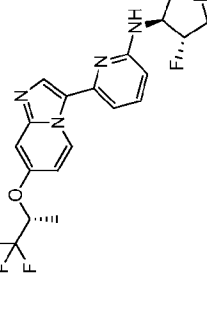
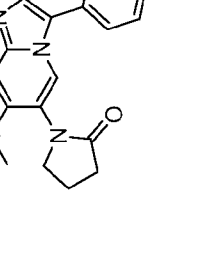
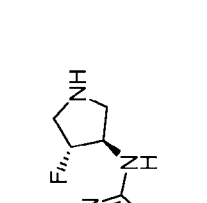
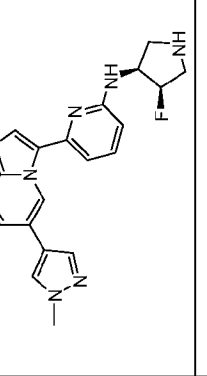
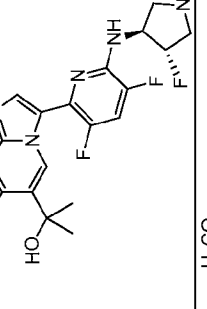
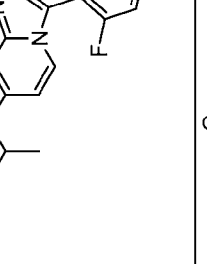
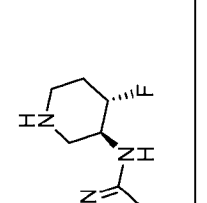
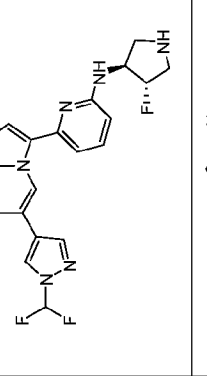
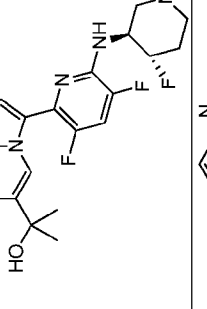
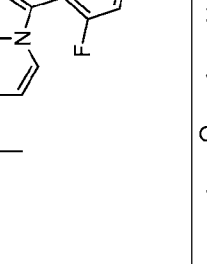
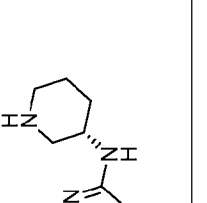
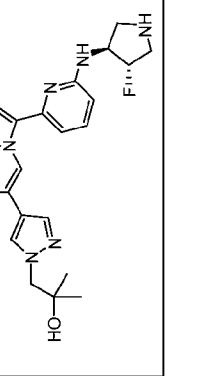
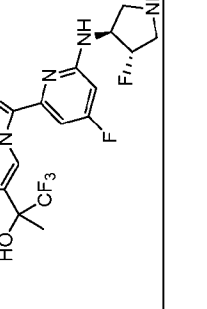
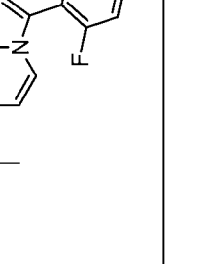
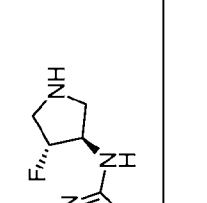
130364-5012-WO

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130364-5012-WO

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130364-5012-WO

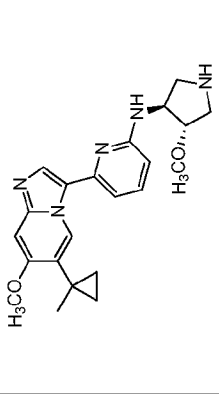
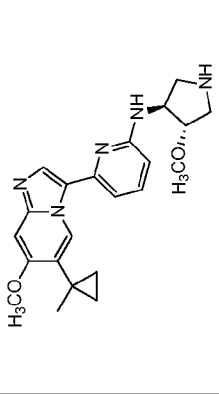
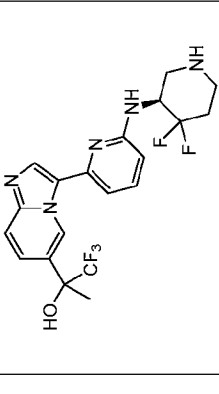
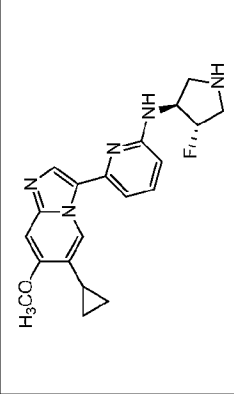
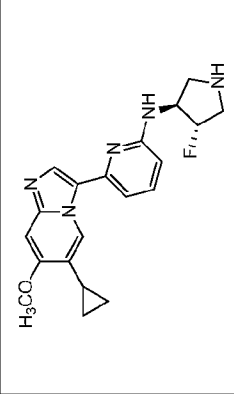
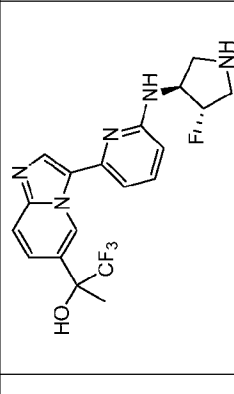
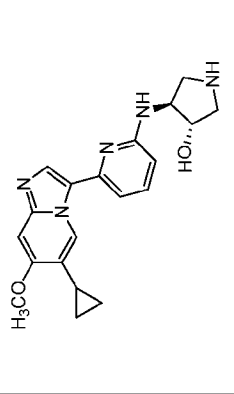
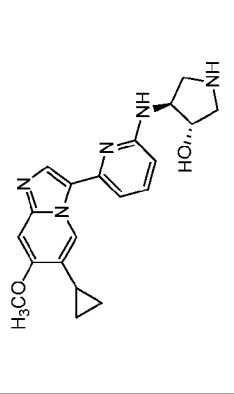
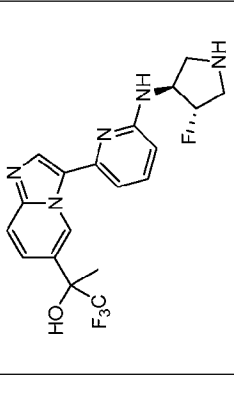
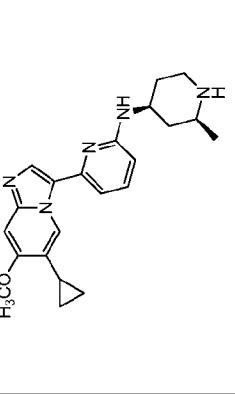
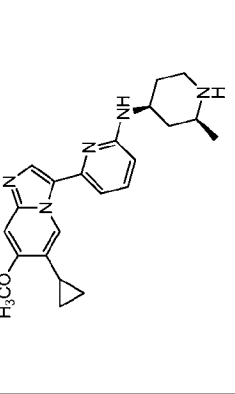
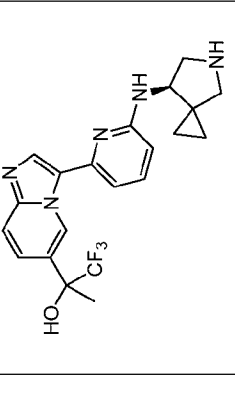
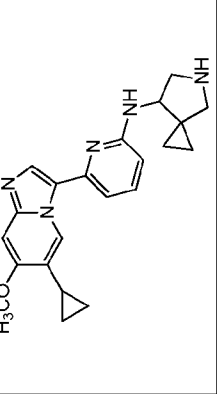
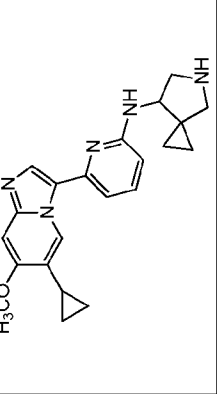
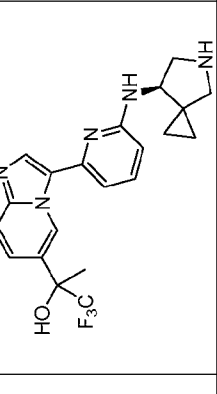
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	102-7		230-7		54a-7	
	103-7		231-7		55a-7	
	104-7		232-7		56a-7	
	105-7		233-7		57a-7	

130364-5012-WO

	106-7		234-7		235-7		236-7		237-7		238-7
	107-7		235-7		236-7		237-7		238-7		239-7
	108-7		236-7		237-7		238-7		239-7		240-7
	109-7		237-7		238-7		239-7		240-7		241-7
	110-7		238-7		239-7		240-7		241-7		242-7
	58a-7		59a-7		60a-7		61a-7		62a-7		63a-7

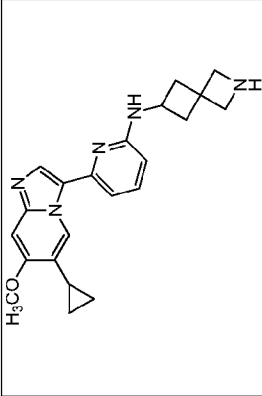
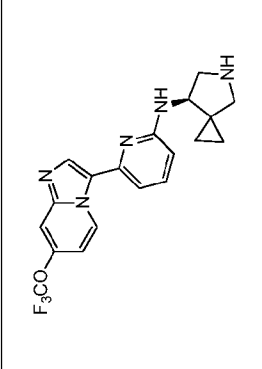
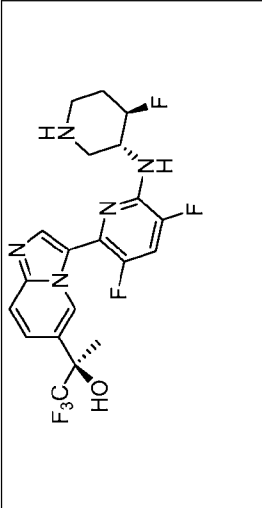
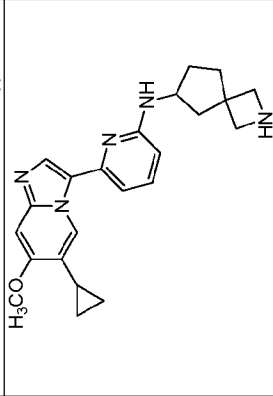
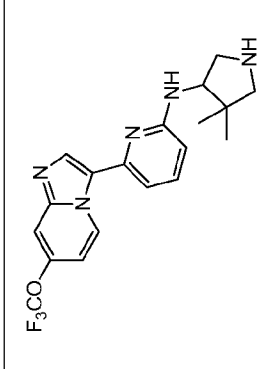
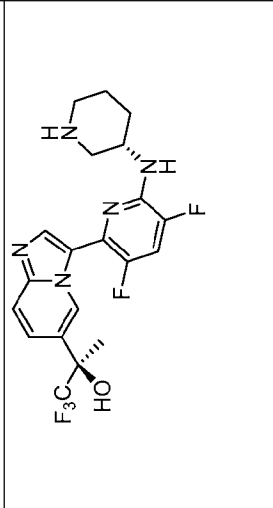
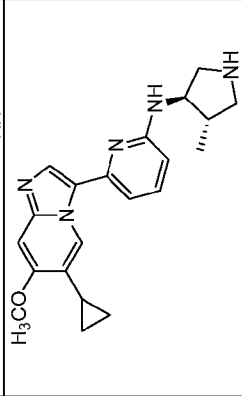
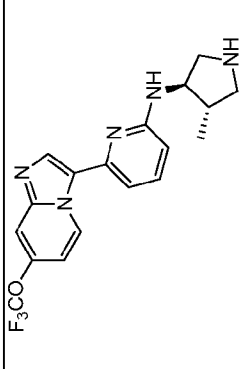
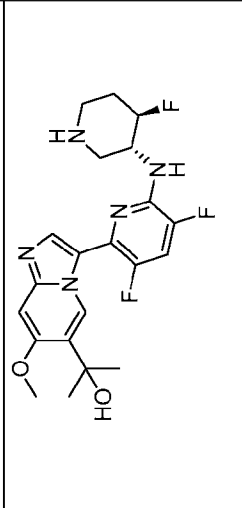
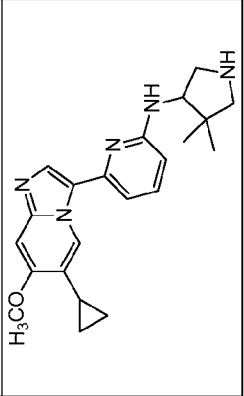
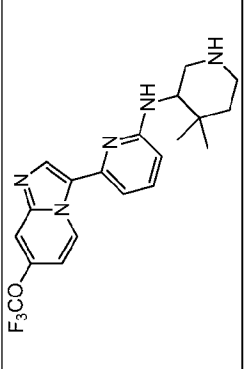
DB1/ 139322096.1

130364-5012-WO

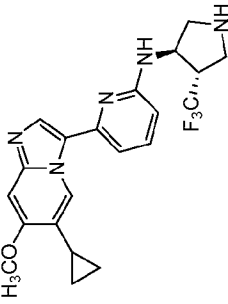
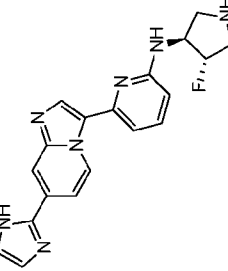
	116-7		244-7		68a-7
	117-7		245-7		69a-7
	118-7		246-7		70a-7
	119-7		247-7		71a-7
	120-7		248-7		72a-7

121-7		249-7		73a-7	
122-7		250-7		74a-7	
123-7		251-7		75a-7	
124-7		252-7		76a-7	

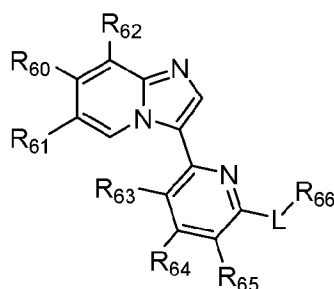
130364-5012-WO

	125-7	253-7		77a-7	
	126-7	254-7		78a-7	
	127-7	255-7		79a-7	
	128-7	256-7			

130364-5012-WO

129-7		257-7			
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In another embodiment, the compound is a compound of Formula (VI-5003):



Formula (VI-5003),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R₆₀ is selected from H, halogen, hydroxy, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, or C₁-C₆ alkoxy, wherein the C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, or C₁-C₆ alkoxy is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), ethynyl (-CCH), sulfo (-SO₃H), methyl, ethyl, or morpholinyl;

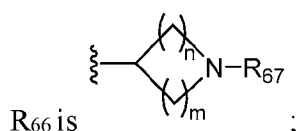
R₆₁ is selected from H, halogen, hydroxy, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₆ alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CON(CH₃)₂, C₁-C₃ alkyl, C₁-C₃ perfluorinated alkyl, or C₁-C₃ alkoxy;

R₆₂ is selected from H, halogen, hydroxy, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₁-C₂ alkoxy, wherein the C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₁-C₂ alkoxy is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), cyano (-CN), ethynyl (-CCH), sulfo (-SO₃H), methyl, or ethyl;

R₆₃ is selected from H, halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), sulfo (-SO₃H), C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₃ alkoxy, or -O-aryl, wherein the C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₁-C₃ alkoxy, or -O-aryl is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), ethynyl (-CCH), sulfo (-SO₃H), methyl, or ethyl;

R₆₄ is selected from H, halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), sulfo (-SO₃H), C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, or C₁-C₃ alkoxy, which C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, or C₁-C₃ alkoxy is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), ethynyl (-CCH), sulfo (-SO₃H), methyl, or ethyl;

R₆₅ is selected from H, halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), sulfo (-SO₃H), C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, or C₁-C₃ alkoxy, wherein the C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, or C₁-C₃ alkoxy is optionally substituted with one or more of halogen, hydroxy, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), ethynyl (-CCH), sulfo (-SO₃H), methyl, or ethyl;



R₆₇ is selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, methanoyl (-COH), ethanoyl (-COCH₃), benzoyl (-COC₆H₅), toluoyl, carboxy (-CO₂H), nitro (-NO₂), cyano (-CN), or -COCH₂CN;

L is selected from -NH-, -N(CH₃)-, -N(CH₂CH₃)-, -N(CH₂CH₂CH₃)-, -N[CH(CH₃)₂]-, or -O-;

n is 0, 1, 2, 3, 4, or 5; and

m is 0, 1, 2, 3, 4, or 5;

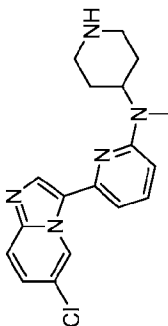
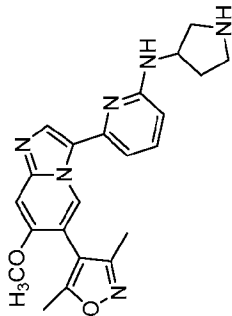
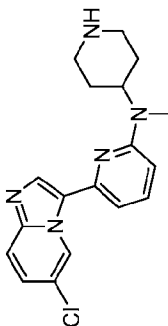
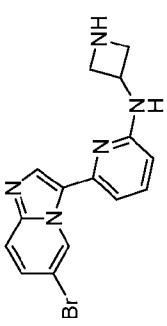
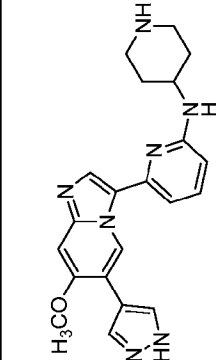
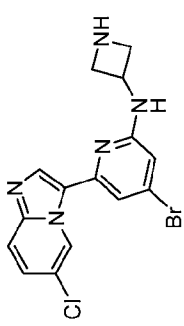
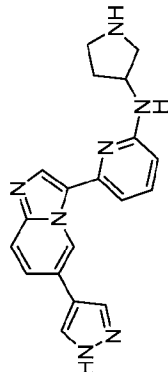
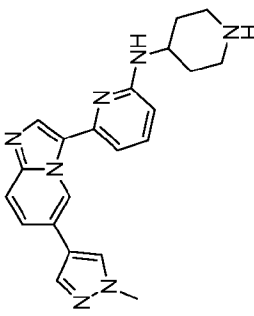
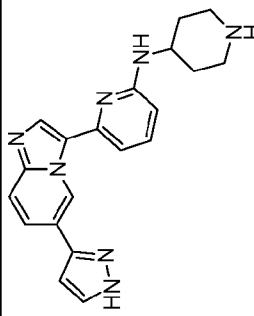
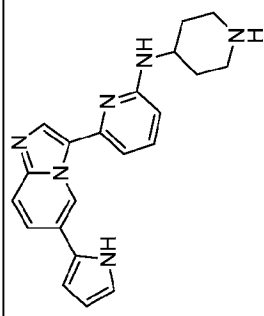
with the proviso that n+m is at least 1.

In one embodiment, the compound of Formula (VI-5003) is selected from Compound 1-3 to 68-3.

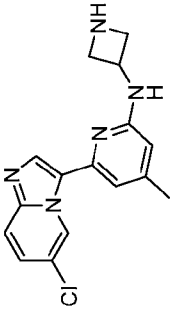
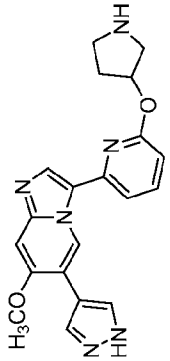
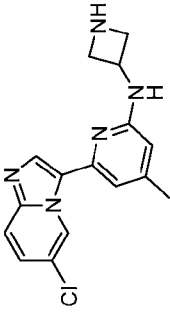
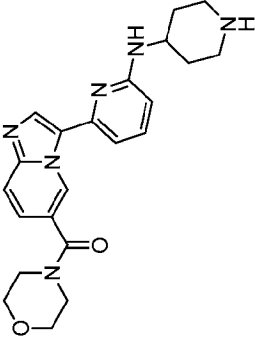
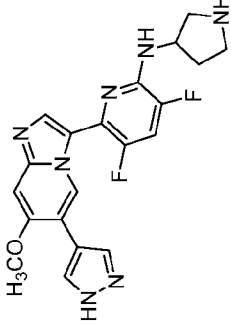
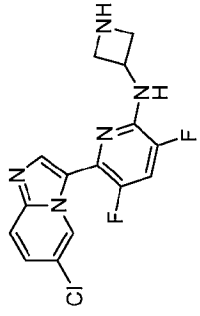
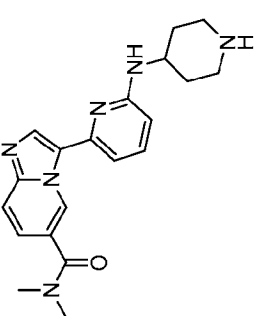
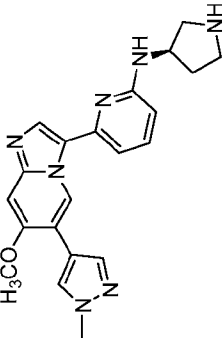
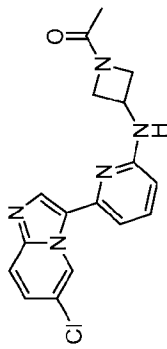
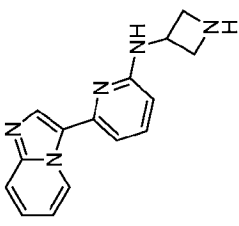
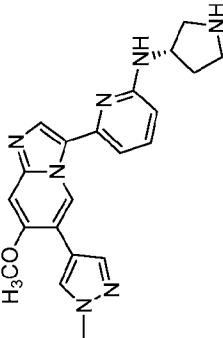
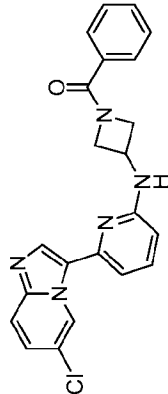
130364-5012-WO

#	Structure	#	Structure	#	Structure
1-3		24-3		47-3	
2-3		25-3		48-3	
3-3		26-3		49-3	
4-3		27-3		50-3	

130364-5012-WO

	5-3		28-3		51-3		52-3		30-3		53-3		54-3		6-3		7-3		8-3
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130364-5012-WO

	9-3		32-3		55-3
	10-3		33-3		56-3
	11-3		34-3		57-3
	12-3		35-3		58-3

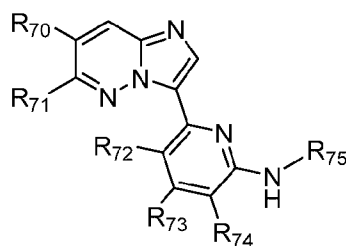
130364-5012-WO

13-3		36-3		59-3	
14-3		37-3		60-3	
15-3		38-3		61-3	
16-3		39-3		62-3	
17-3		40-3		63-3	

130364-5012-WO

18-3		41-3		64-3	
19-3		42-3		65-3	
20-3		43-3		66-3	
21-3		44-3		67-3	
22-3		45-3		68-3	
23-3		46-3			

In another embodiment, the compound is a compound of Formula (VII-5008):



Formula (VII-5008),

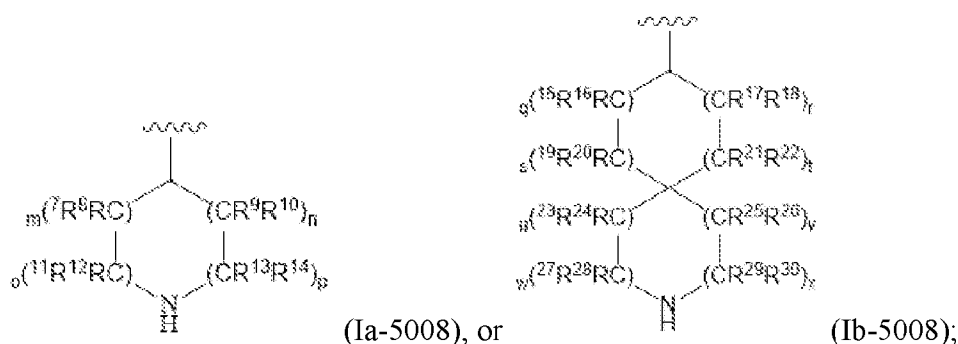
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R₇₀ is selected from H, halogen, hydroxy, oxo, -CN, amido, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ heteroalkyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein the amido, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -NHCH₃, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CONHCH₃, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ heteroalkyl, C₁-C₇ haloalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

R₇₁ is selected from H, halogen, hydroxy, oxo, -CN, amino, -O-aryl, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, heterocyclyl, spiro-fused cycloalkyl, aryl, heteroaryl, or fused ring heteroaryl, wherein the amino, -O-aryl, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ heteroalkyl, C₁-C₇ alkoxy, cycloalkyl, heterocyclyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -NHCH₃, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CONHCH₃, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ heteroalkyl, C₁-C₇ haloalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, cycloalkyl, heterocyclyl, spiro-fused cycloalkyl, aryl, fused ring aryl, heteroaryl, fused ring heteroaryl, or C₁-C₇ alkyl which is substituted with cycloalkyl;

R₇₂, R₇₃, and R₇₄ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, -O-aryl, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein the methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, -O-aryl, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -NHCH₃, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CONHCH₃, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ haloalkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;

R₇₅ is selected from



R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein the methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen;

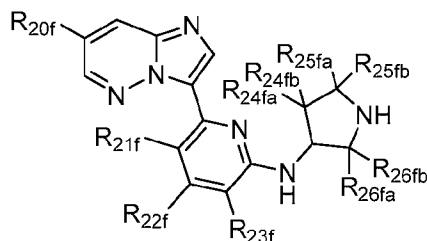
R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein the methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen; and

m, n, o, p, q, r, s, t, u, v, w, and x are each independently 0, 1, 2, 3, 4, or 5; with the provisos that:

q+r+s+t is at least 1, and

u+v+w+x is at least 1.

5 In an embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIf-5008):



Formula (IIf-5008),

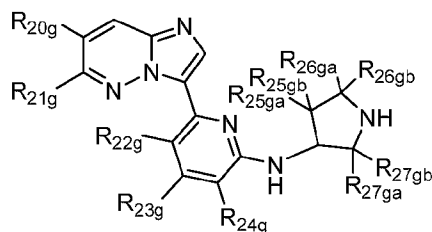
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

10 R20f is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and -O-(C₃-C₆ cycloalkyl), wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R21f, R22f, and R23f are each independently selected from H and halogen; and

15 R24fa, R24fb, R25fa, R25fb, R26fa, and R26fb are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIg-5008):



Formula (IIg-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R20g is selected from H and C₁-C₆ alkoxy;

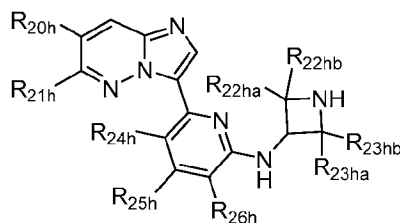
R_{21g} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₆-C₁₂ aryl), C₃-C₉ heterocyclyl, and -NR_{28ga}R_{28gb}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocyclyl, -OH, and halogen;

R_{22g}, R_{23g}, and R_{24g} are each independently selected from H and halogen;

R_{25ga}, R_{25gb}, R_{26ga}, R_{26gb}, R_{27ga}, and R_{27gb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

R_{28ga} and R_{28gb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIh-5008):



Formula (IIh-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

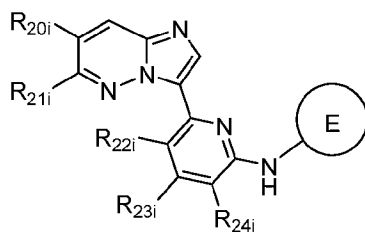
R_{20h} is selected from H and C₁-C₆ alkoxy;

R_{21h} is selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen and C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl, -OH, and halogen;

R_{22ha}, R_{22hb}, R_{23ha}, and R_{23hb} are each independently selected from H and C₁-C₆ alkyl, wherein C₁-C₆ alkyl is optionally substituted with one or more halogen atoms; and

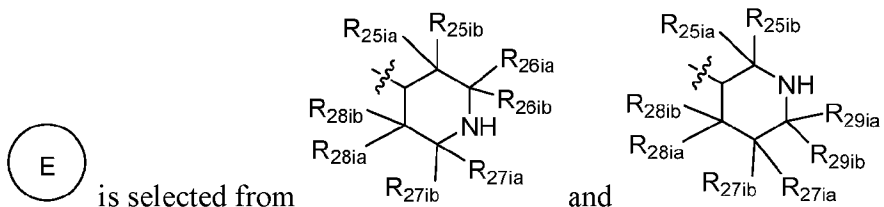
R_{24h}, R_{25h}, and R_{26h} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (III-5008):



Formula (IIi-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



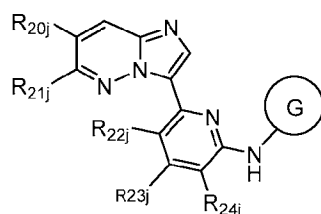
R_{20i} is selected from H, and C₁-C₆ alkoxy;

- 5 R_{21i} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocyclyl, -OH, -C=O, and halogen;

R_{22i}, R_{23i}, and R_{24i} are each independently selected from H and halogen; and

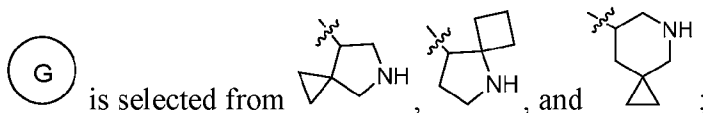
R_{25ia}, R_{25ib}, R_{26ia}, R_{26ib}, R_{27ia}, R_{27ib}, R_{28ia}, R_{28ib}, R_{29ia}, and R_{29ib} are each independently selected from H, halogen, -OH, or C₁-C₆ alkyl.

- 15 In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIj-5008):



Formula (IIj-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

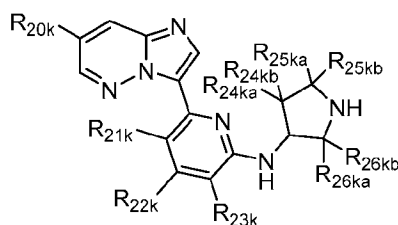


R_{20j} is selected from H, and C₁-C₆ alkoxy;

R_{21j} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

5 R_{22j}, R_{23j}, and R_{24j} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIk-5008):



Formula (IIk-5008),

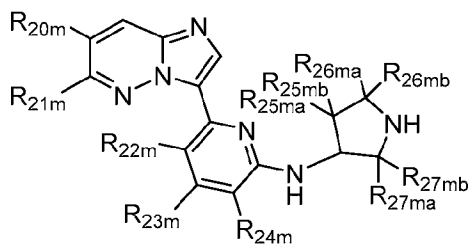
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

10 R_{20k} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and -O-(C₃-C₆ cycloalkyl), wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and wherein C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

15 R_{21k}, R_{22k}, and R_{23k} are each independently selected from H, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl is optionally substituted with one or more halogen; and

R_{24ka}, R_{24kb}, R_{25ka}, R_{25kb}, R_{26ka}, and R_{26kb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms.

20 In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIIm-5008):



Formula (IIIm-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20m} is selected from C₁-C₆ alkyl and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen;

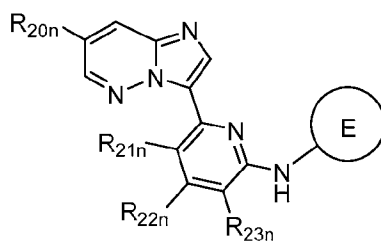
R_{21m} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₅-C₁₂ spiro-fused cycloalkyl, -O-(C₆-C₁₂ aryl), C₃-C₉ heterocyclyl, and -NR_{28ma}R_{28mb}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, wherein C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, wherein C₁-C₆ alkyl is optionally substituted with one or more -OH, and wherein C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocyclyl, -OH, and halogen;

R_{22m}, R_{23m}, and R_{24m} are each independently selected from H, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl is optionally substituted with one or more halogen;

R_{25ma}, R_{25mb}, R_{26ma}, R_{26mb}, R_{27ma}, and R_{27mb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

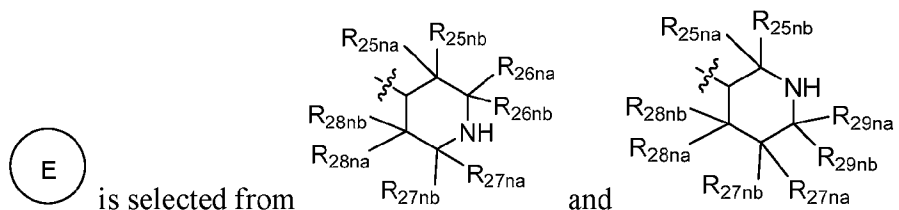
R_{28ma} and R_{28mb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIIn-5008):



Formula (IIIn-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



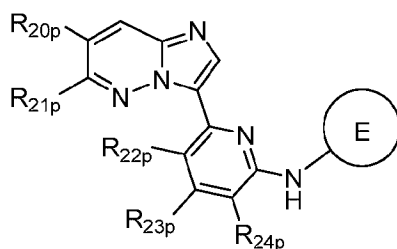
R_{20n} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and -O-(C₃-C₆ cycloalkyl), wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with

one or more substituents selected from -OH and halogen, and wherein C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{21n}, R_{22n}, and R_{23n} are each independently selected from H, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl is optionally substituted with one or more halogen; and

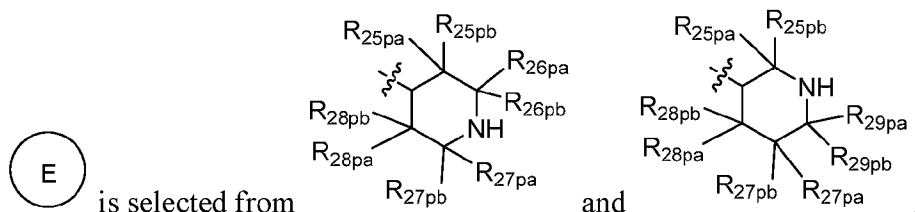
R_{25na}, R_{25nb}, R_{26na}, R_{26nb}, R_{27na}, R_{27nb}, R_{28na}, R_{28nb}, R_{29na}, and R_{29nb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, or C₁-C₆ alkoxy wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIp-5008):



Formula (IIp-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



R_{20p} is selected from C₁-C₆ alkyl and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen;

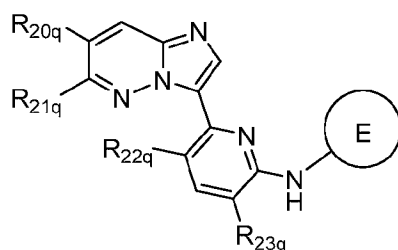
R_{21p} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₅-C₁₂ spiro-fused cycloalkyl, -O-(C₆-C₁₂ aryl), C₃-C₉ heterocyclyl, and -NR_{220pa}R_{220pb}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, wherein C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and wherein C₃-C₉ heterocycyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocyclyl, -OH, and halogen;

R_{22p}, R_{23p}, and R_{24p} are each independently selected from H, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl is optionally substituted with one or more halogen;

R_{25pa}, R_{25pb}, R_{26pa}, R_{26pb}, R_{27pa}, R_{27pb}, R_{28pa}, R_{28pb}, R_{29pa}, and R_{29pb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

R_{220pa} and R_{220pb} are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl.

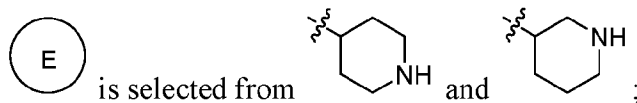
In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIq-5008):



Formula (IIq-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof;

wherein:

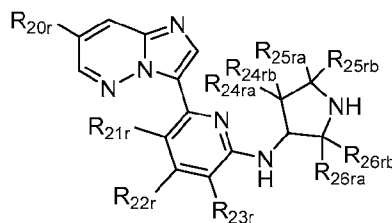


R_{20q} is C₁-C₆ alkoxy optionally substituted with one or more substituents selected from -OH and halogen;

R_{21q} is C₃-C₆ cycloalkyl optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

R_{22q} and R_{23q} are each independently halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIr-5008):



Formula (IIr-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

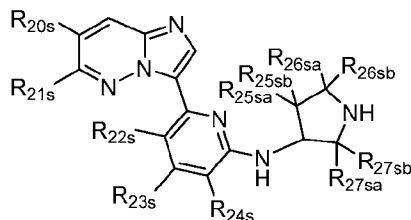
R_{20r} is C₁-C₆ alkoxy optionally substituted with one or more substituents selected from -OH and halogen;

R_{21r} and R_{23r} are each independently halogen;

R_{22r} is H; and

R_{24ra}, R_{24rb}, R_{25ra}, R_{25rb}, R_{26ra}, and R_{26rb} are each independently selected from H and halogen, wherein one or more of R_{24ra}, R_{24rb}, R_{25ra}, R_{25rb}, R_{26ra}, and R_{26rb} is halogen.

5 In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIs-5008):



Formula (IIs-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

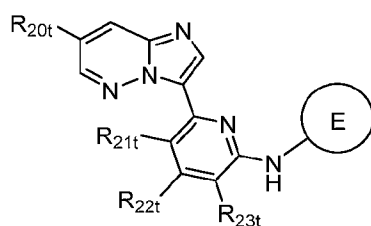
10 R_{20s} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, and -OH, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen;

R_{21s} is selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₅-C₁₂ spiro-fused cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{22s}, R_{23s}, and R_{24s} are each independently selected from H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, and -O-(C₆-C₁₂ aryl), wherein C₁-C₆ alkyl is optionally substituted with one or more halogen; and

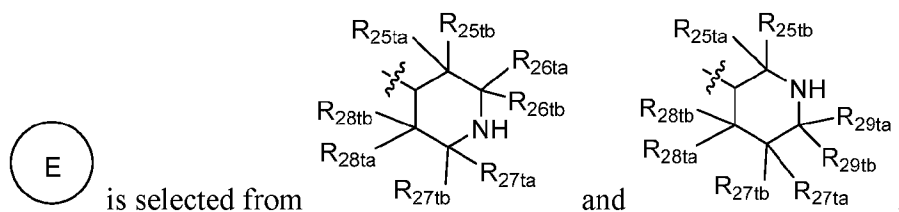
20 R_{25sa}, R_{25sb}, R_{26sa}, R_{26sb}, R_{27sa}, and R_{27sb} are each independently selected from H and halogen, wherein one or more of R_{25sa}, R_{25sb}, R_{26sa}, R_{26sb}, R_{27sa}, and R_{27sb} is halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIt-5008):



Formula (IIt-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



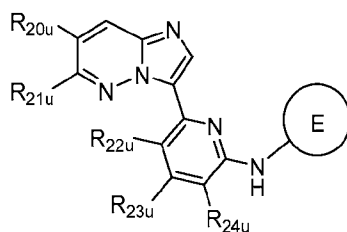
R_{20t} is C₁-C₆ alkoxy optionally substituted with one or more substituents selected from -OH and halogen;

R_{21t} and R_{23t} are each independently halogen;

5 R_{22t} is H; and

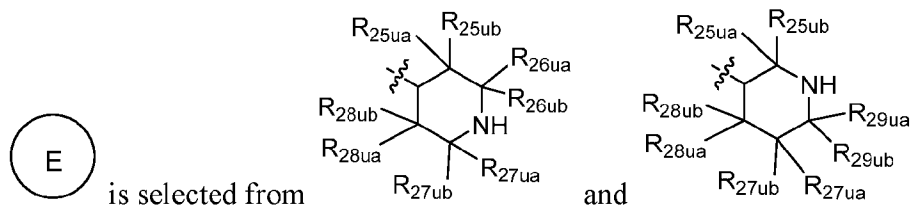
R_{25ta}, R_{25tb}, R_{26ta}, R_{26tb}, R_{27ta}, R_{27tb}, R_{28ta}, R_{28tb}, R_{29ta}, and R_{29tb} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIu-5008):



Formula (IIu-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



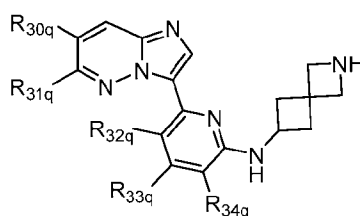
R_{20u} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, and -OH, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen;

R_{21u} is selected from C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₅-C₁₂ spiro-fused cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl is optionally substituted with one or more substituents selected from -OH and halogen and C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R_{22u}, R_{23u}, and R_{24u} are each independently selected from H, CN, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, and -O-(C₆-C₁₂ aryl), wherein C₁-C₆ alkyl is optionally substituted with one or more halogen; and

R_{25ua}, R_{25ub}, R_{26ua}, R_{26ub}, R_{27ua}, R_{27ub}, R_{28ua}, R_{28ub}, R_{29ua}, and R_{29ub} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIIq-5008):



Formula (IIIq-5008),

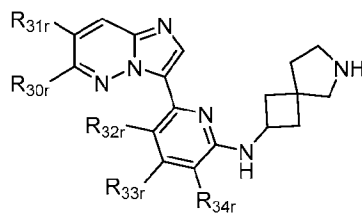
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{30q} is selected from H and C₁-C₆ alkoxy;

R_{31q} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocyclyl, C₆-C₁₂ aryl, -OH, -C=O, and halogen; and

R_{32q}, R_{33q}, and R_{34q} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIIr-5008):



Formula (IIIr-5008),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

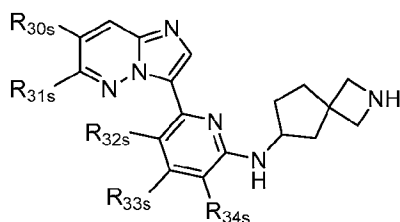
R_{30r} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more

substituents selected from -OH and halogen, C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and C₃-C₉ heterocycyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocycyl, C₆-C₁₂ aryl, -OH, -C=O, and halogen;

5 R_{31r} is selected from H and C₁-C₆ alkoxy; and

R_{32r}, R_{33r}, and R_{34r} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is a compound of Formula (IIIs-5008):



Formula (IIIs-5008),

10 or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{30s} is selected from H and C₁-C₆ alkoxy;

R_{31s} is selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and C₃-C₉ heterocycyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and C₃-C₉ heterocycyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl, C₃-C₆-cycloalkyl, C₃-C₉-heterocycyl, C₆-C₁₂ aryl, -OH, -C=O, and halogen; and

R_{32s}, R_{33s}, and R_{34s} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (VII-5008) is selected from Compounds

20 1-8 to 137-8 or Compounds 1a-8 to 84a-8.

#	Structure	#	Structure	#	Structure
1-8		76-8		14a-8	
2-8		77-8		15a-8	
3-8		78-8		16a-8	
4-8		79-8		17a-8	
5-8		80-8		18a-8	

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	6-8		81-8		19a-8		20a-8		21a-8		22a-8		23a-8
	7-8		82-8		83-8		84-8		85-8		9-8		10-8

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11-8		86-8		24a-8	
12-8		87-8		25a-8	
13-8		88-8		26a-8	
14-8		89-8		27a-8	

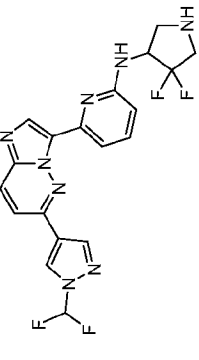
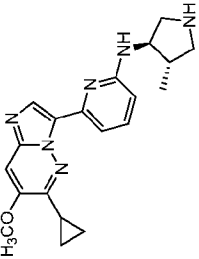
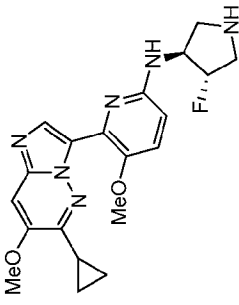
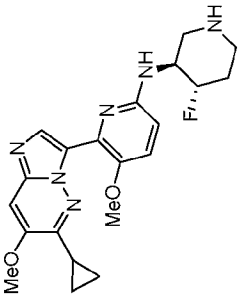
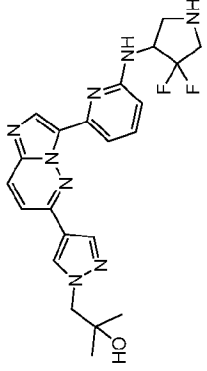
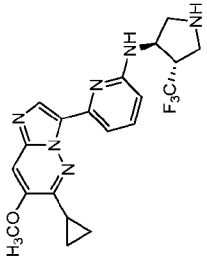
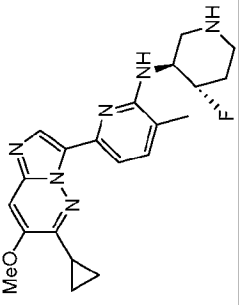
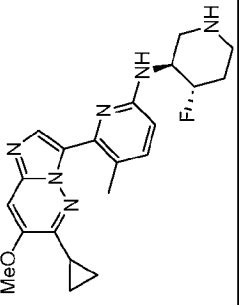
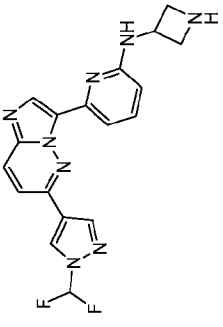
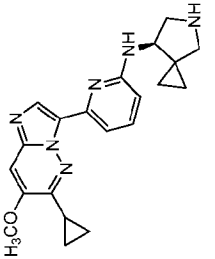
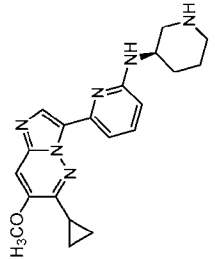
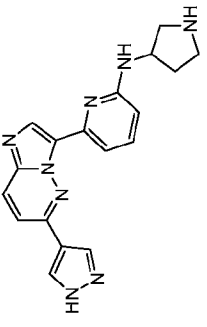
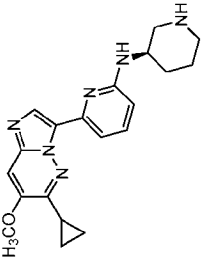
130364-5012-WO

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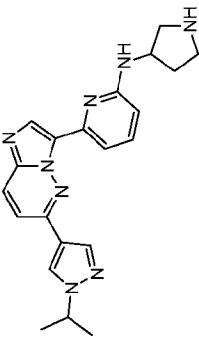
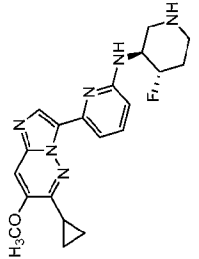
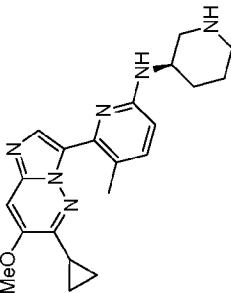
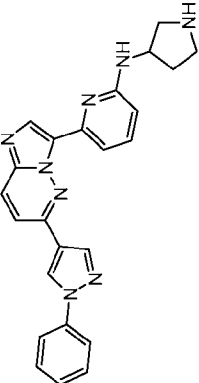
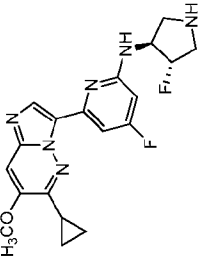
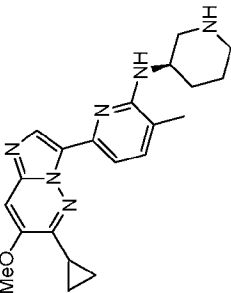
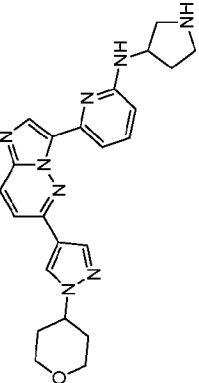
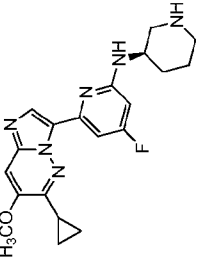
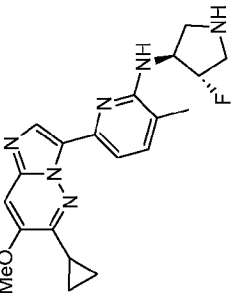
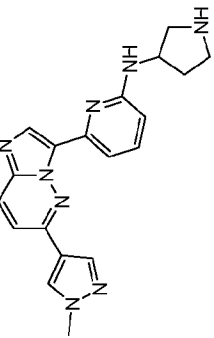
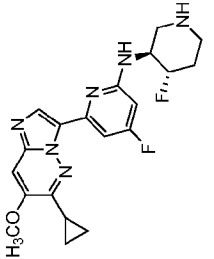
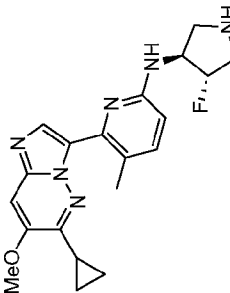
130364-5012-WO

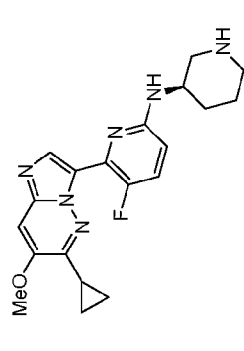
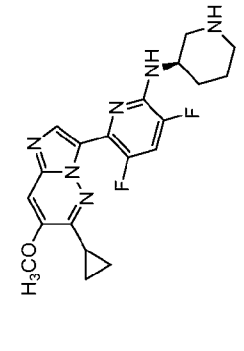
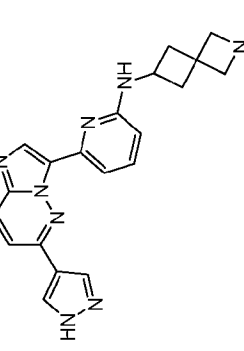
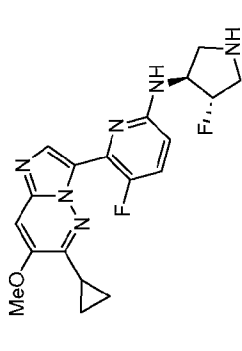
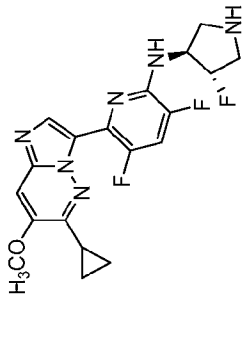
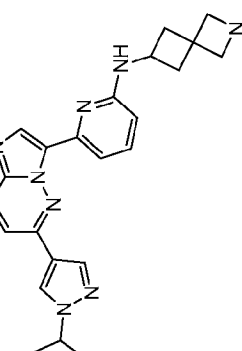
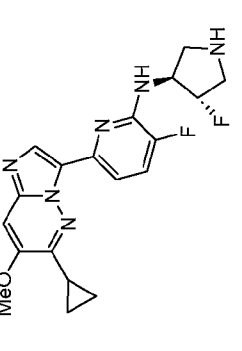
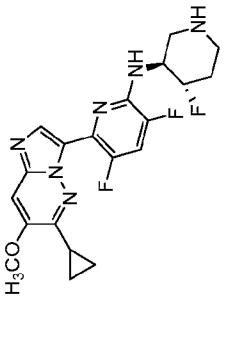
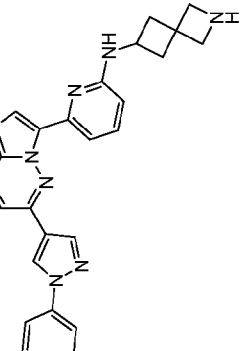
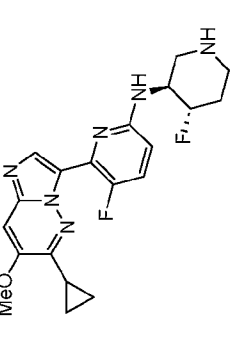
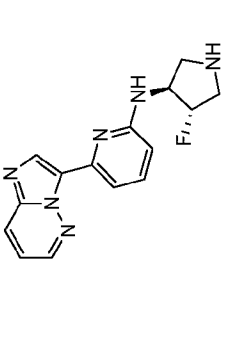
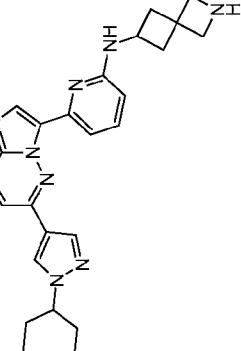
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130364-5012-WO

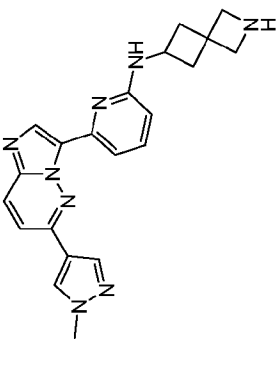
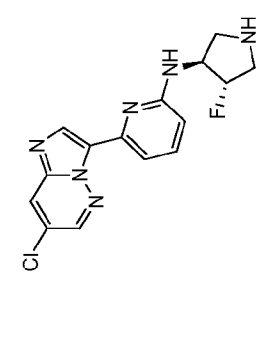
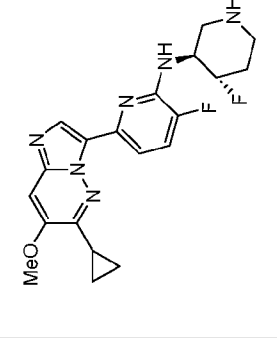
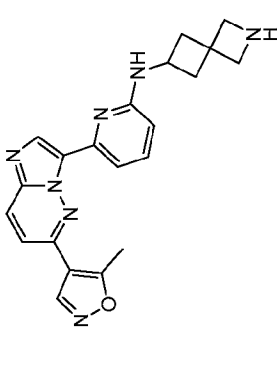
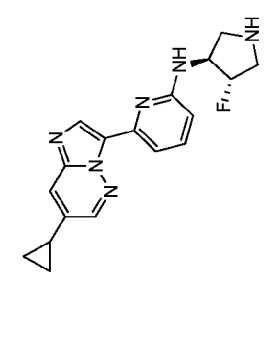
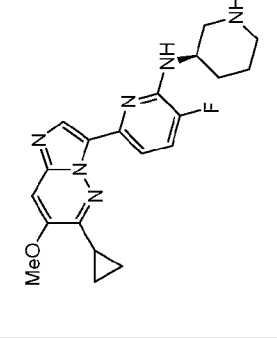
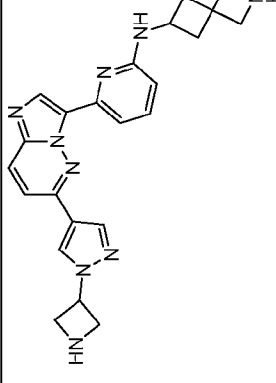
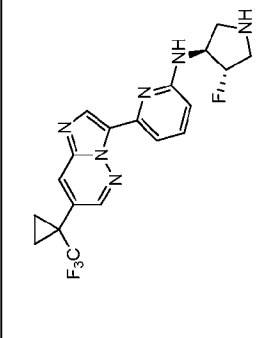
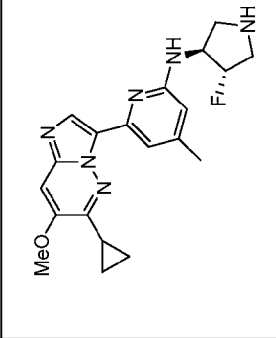
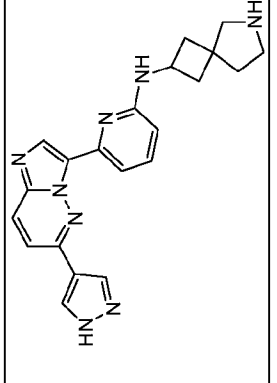
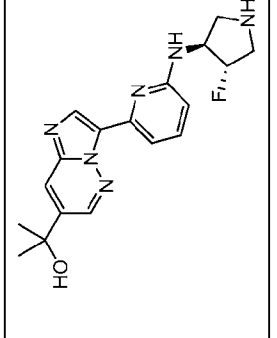
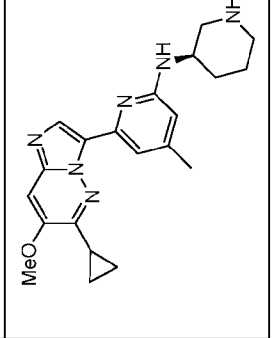
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130364-5012-WO

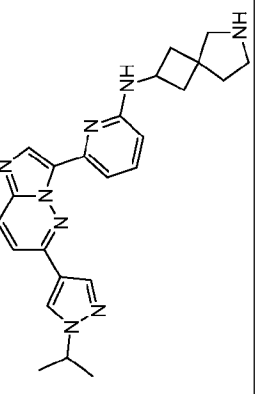
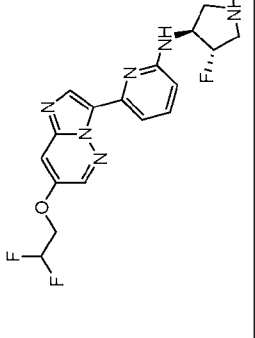
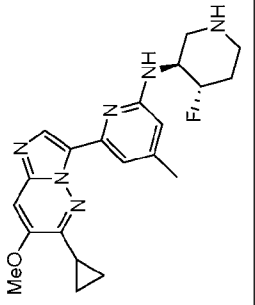
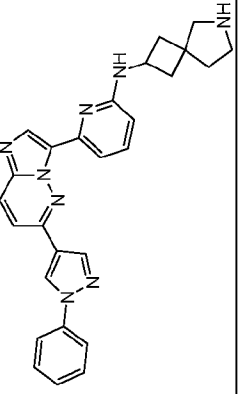
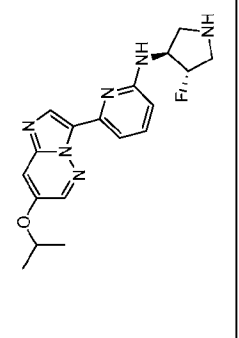
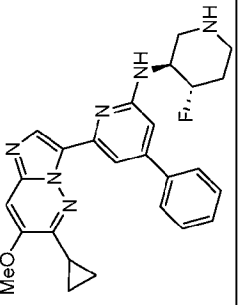
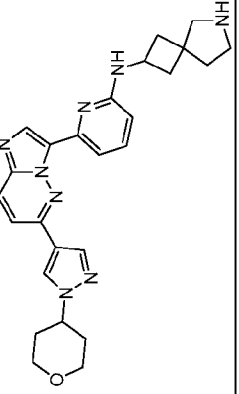
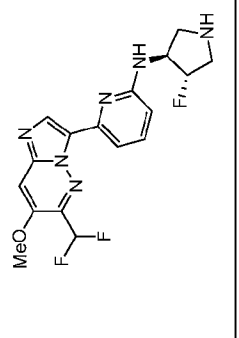
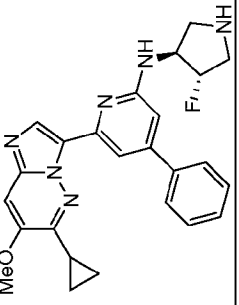
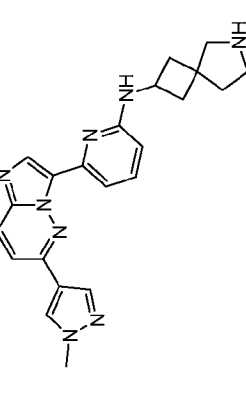
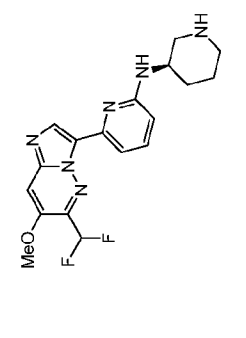
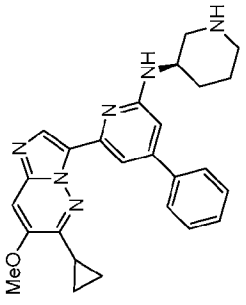
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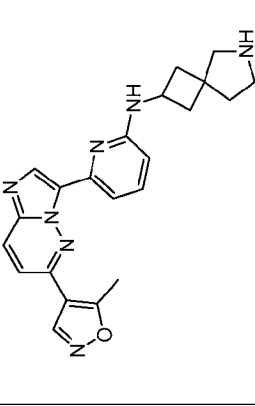
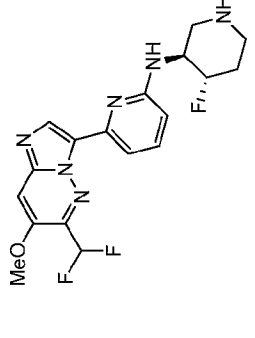
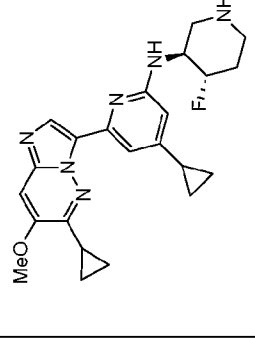
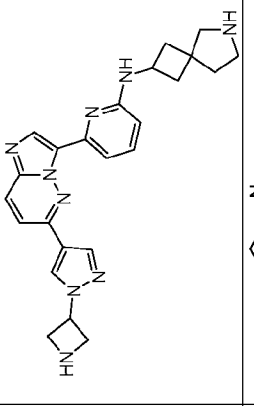
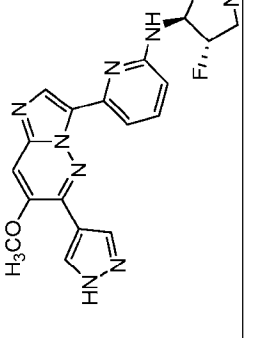
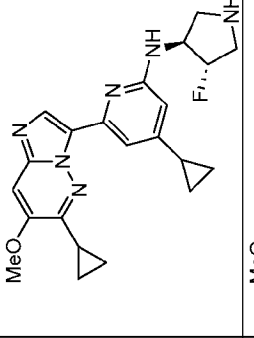
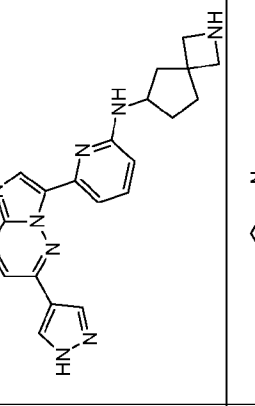
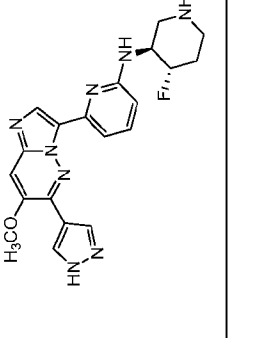
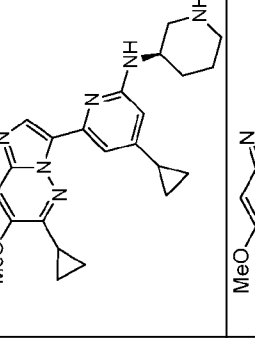
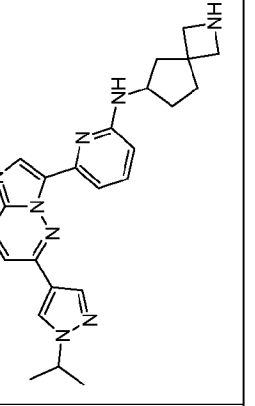
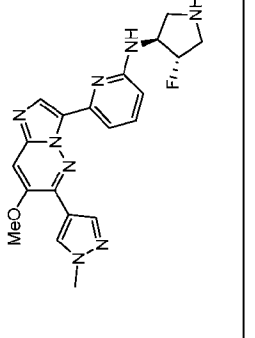
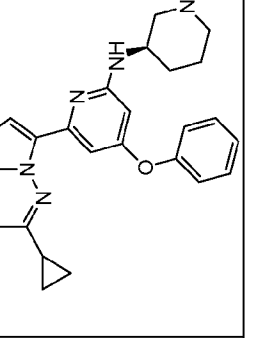
130364-5012-WO

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130364-5012-WO

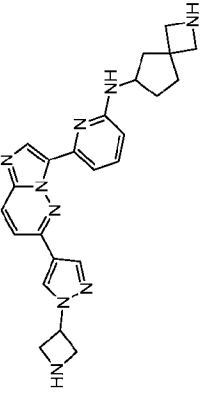
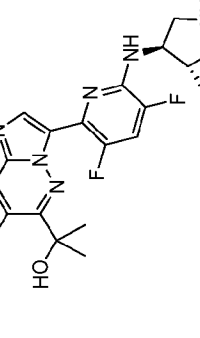
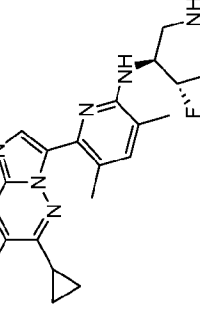
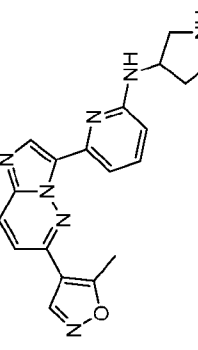
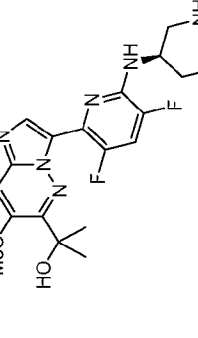
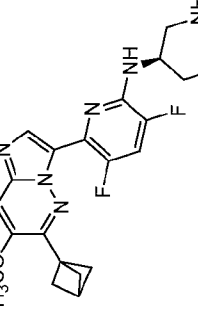
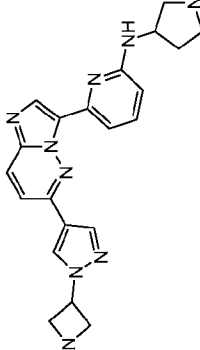
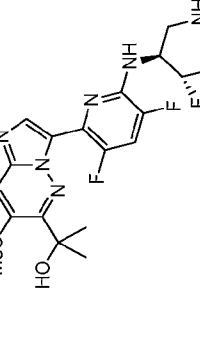
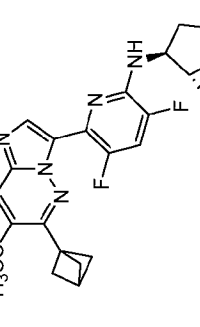
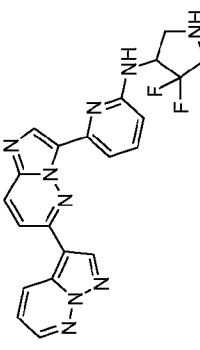
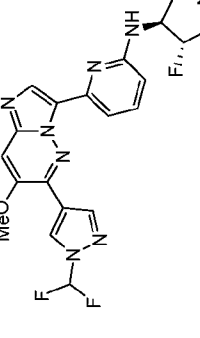
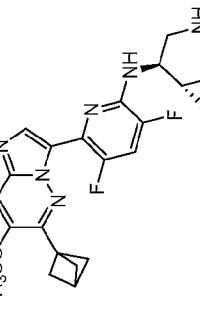
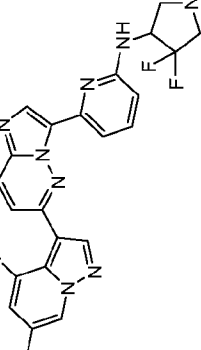
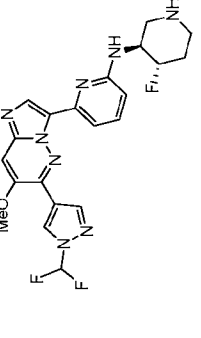
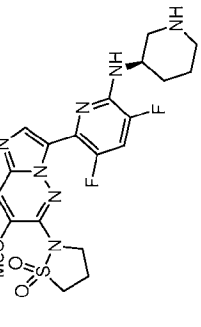
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130364-5012-WO

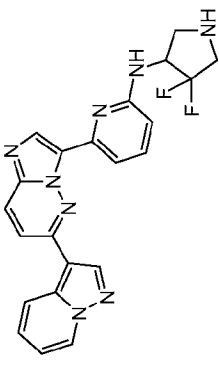
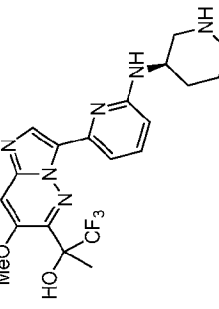
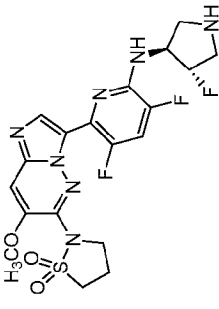
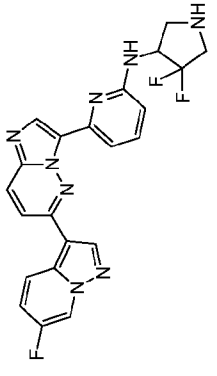
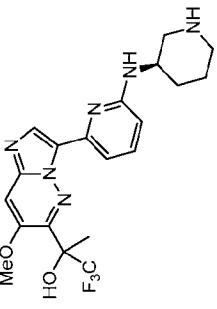
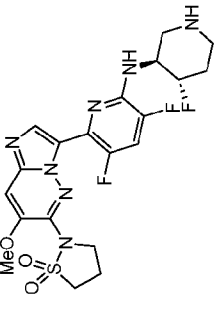
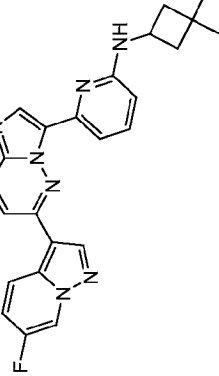
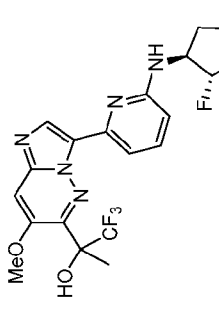
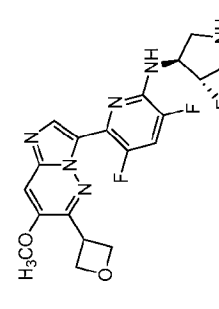
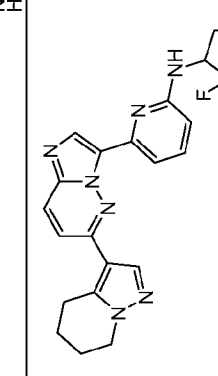
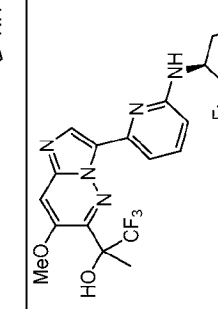
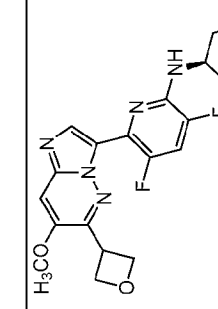
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	45-8		120-8		58a-8
	46-8		121-8		59a-8

47-8		122-8		60a-8	
48-8		123-8		61a-8	
49-8		124-8		62a-8	
50-8		125-8		63a-8	

130364-5012-WO

	51-8		126-8		64a-8
	52-8		127-8		65a-8
	53-8		128-8		66a-8
	54-8		129-8		67a-8
	55-8		130-8		68a-8

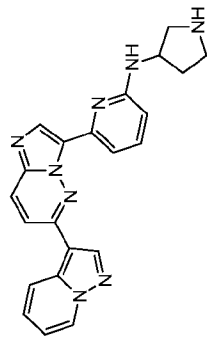
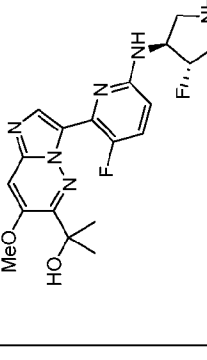
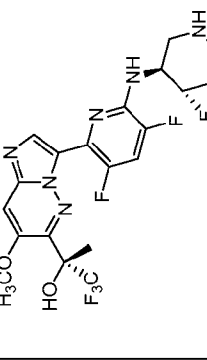
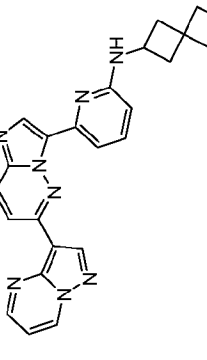
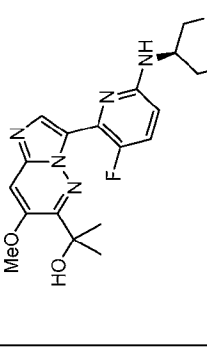
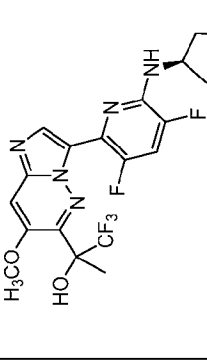
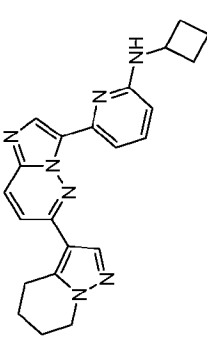
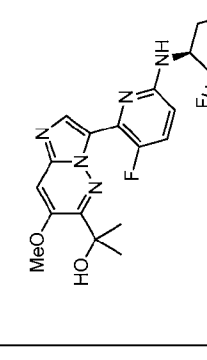
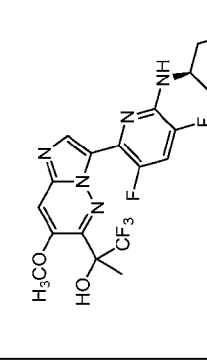
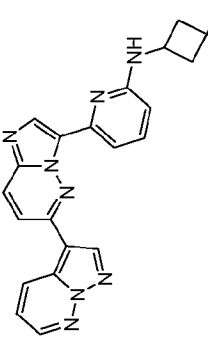
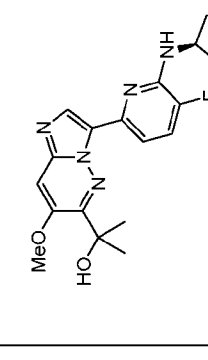
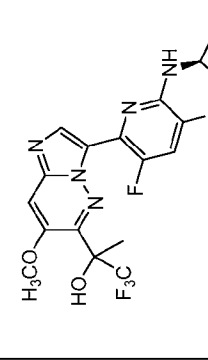
130364-5012-WO

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	58-8		133-8		71a-8
	59-8		134-8		72a-8

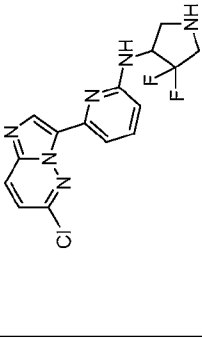
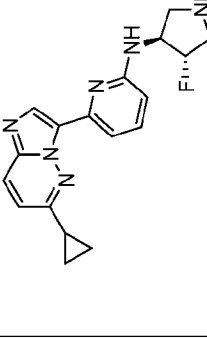
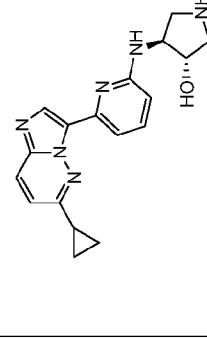
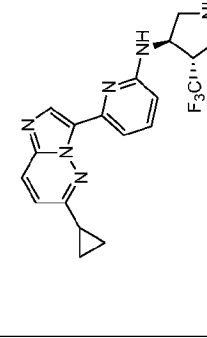
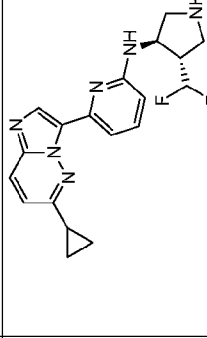
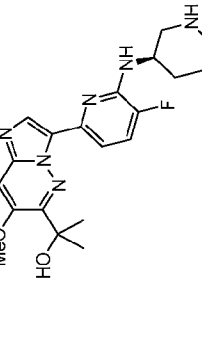
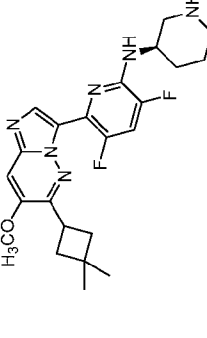
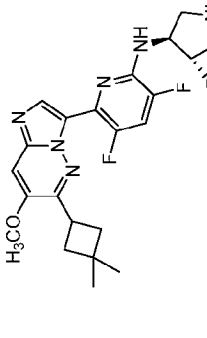
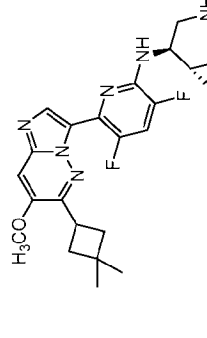
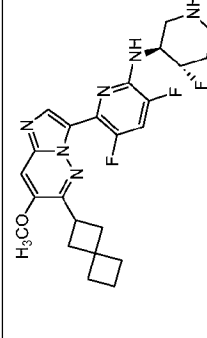
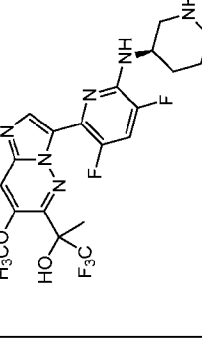
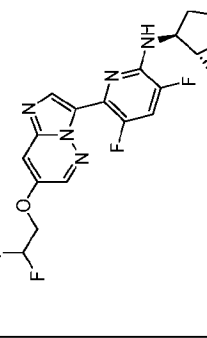
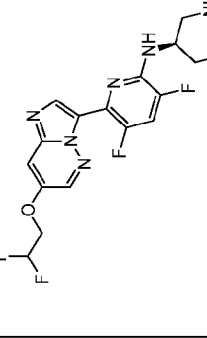
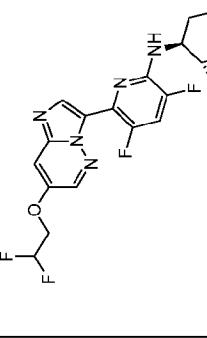
130364-5012-WO

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	135-8		136-8		137-8		1a-8
	60-8		61-8		62-8		63-8

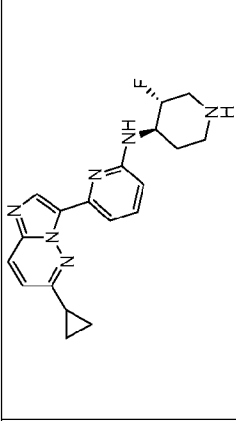
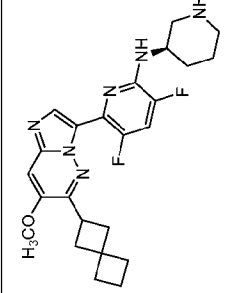
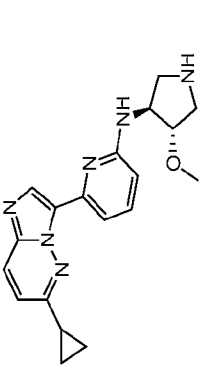
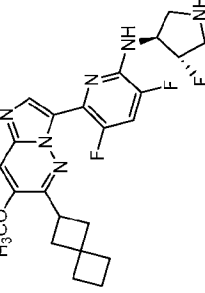
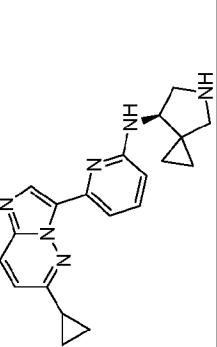
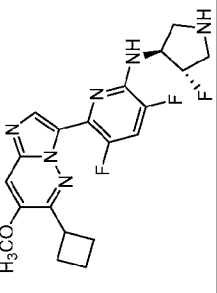
130364-5012-WO

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	66-8		4a-8		79a-8
	67-8		5a-8		80a-8

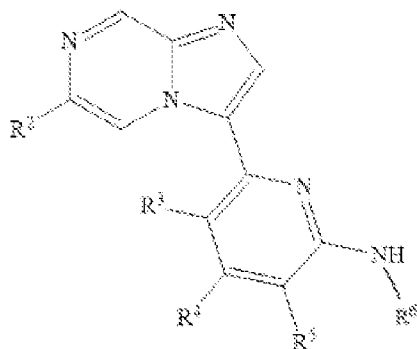
130364-5012-WO

				
68-8	69-8	70-8	71-8	72-8
				
6a-8	7a-8	8a-8	9a-8	10a-8
				
81a-8	82a-8	83a-8	84a-8	

130364-5012-WO

73-8		11a-8			
74-8		12a-8			
75-8		13a-8			

In one embodiment, the compound is a compound of Formula (I-5009):

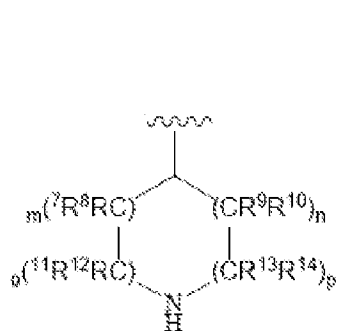


Formula (I-5009),

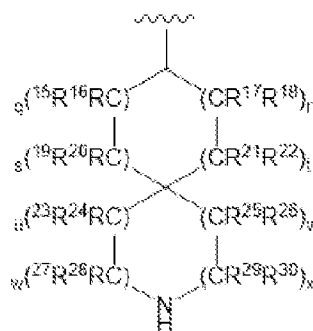
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

- R^2 , R^3 , R^4 , and R^5 are each independently selected from H, halogen, hydroxy, oxo (=O), -CN, amino, amido, -O-aryl, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ heteroalkyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein amino, amido, -O-aryl, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, methanoyl (-COH), carboxy (-CO₂H), nitro (-NO₂), -NH₂, -NHCH₃, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, sulfo (-SO₃H), heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -CO-morpholin-4-yl, -CONH₂, -CONHCH₃, -CON(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl, wherein two adjacent optional substituents can bond or fuse to form a ring;

R^6 is selected from



(Ia-5009), or



(Ib-5009);

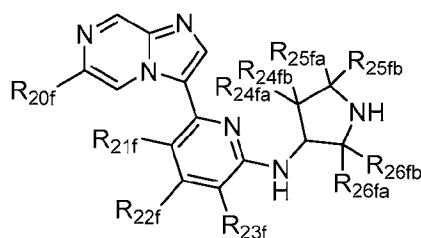
R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇

alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen and/or C₁-C₆ alkyl;

5 R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{29} , R^{29} , and R^{30} are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted
10 with one or more halogen and/or C₁-C₆ alkyl; and

m, n, o, p, q, r, s, t, u, v, w, and x are each independently selected from 0, 1, 2, 3, 4, or 5; where q+r+s+t is at least 1, and where u+v+w+x is at least 1.

In one embodiment, the compound of Formula (I-5009) is a compound of Formula (IIf-
15 5009):



Formula (IIf-5009),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

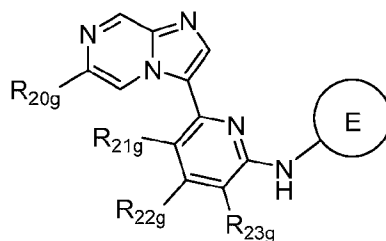
R_{20f} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(CH₂)_a-(C₃-C₆ cycloalkyl), and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each
20 optionally substituted with one or more substituents selected from -OH and halogen, wherein C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and wherein C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, and =O wherein two adjacent optional substituents can bond or fuse to form a ring;

25 R_{21f} , R_{22f} , and R_{23f} are each independently selected from H and halogen;

R_{24fa}, R_{24fb}, R_{25fa}, R_{25fb}, R_{26fa}, and R_{26fb} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

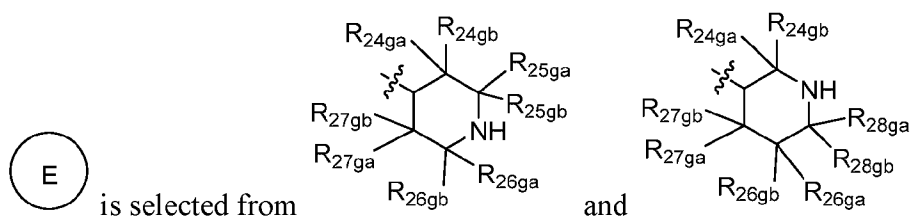
a is selected from 0, 1, 2, 3, 4, 5, and 6.

5 In one embodiment, the compound of Formula (I-5009) is a compound of Formula (IIg-5009):



Formula (IIg-5009),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



is selected from

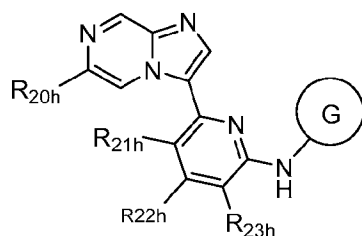
and

10 R_{20g} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, and C₃-C₉ heterocyclyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, wherein C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen, and wherein C₃-C₉ heterocyclyl is optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₃-C₆-cycloalkyl, -OH, and =O;

R_{21g}, R_{22g}, and R_{23g} are each independently selected from H and halogen; and

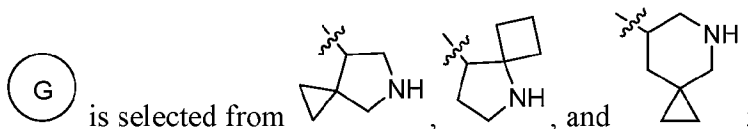
R_{24ga}, R_{24gb}, R_{25ga}, R_{25gb}, R_{26ga}, R_{26gb}, R_{27ga}, R_{27gb}, R_{28ga}, and R_{28gb} are each independently selected from H, halogen, -OH, and C₁-C₆ alkyl.

20 In one embodiment, the compound of Formula (I-5009) is a compound of Formula (IIh-5009):



Formula (IIh-5009),

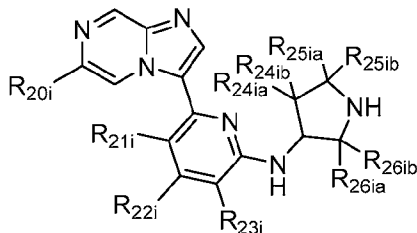
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



R_{20h} is selected from H, C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from halogen and -OH, and wherein C₃-C₆ cycloalkyl is optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen; and

R_{21h}, R_{22h}, and R_{23h} are each independently selected from H and halogen.

In one embodiment, the compound of Formula (I-5009) is a compound of Formula (III-5009):



Formula (IIIi-5009),

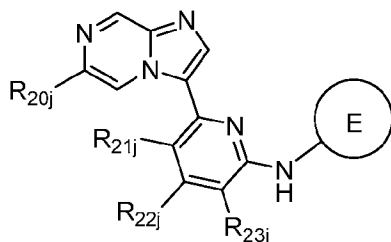
or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R_{20i} is selected from C₁-C₆ alkyl and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen;

R_{21i}, R_{22i}, and R_{23i} are each independently selected from H and halogen; and

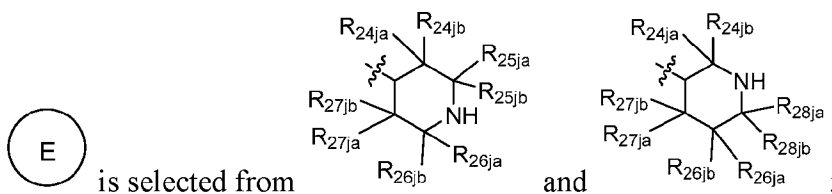
R_{24ia}, R_{24ib}, R_{25ia}, R_{25ib}, R_{26ia}, and R_{26ib} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms.

In one embodiment, the compound of Formula (I-5009) is a compound of Formula (IIj-5009):



Formula (IIj-5009),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:



R_{20j} is selected from C_1 - C_6 alkyl and C_1 - C_6 alkoxy, wherein C_1 - C_6 alkyl and C_1 - C_6 alkoxy

5 are each optionally substituted with one or more substituents selected from -OH and halogen;

R_{21j} , R_{22j} , and R_{23j} are each independently selected from H and halogen; and

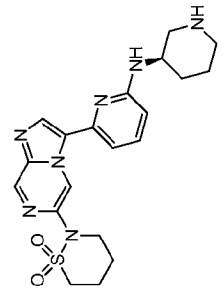
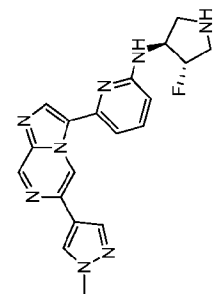
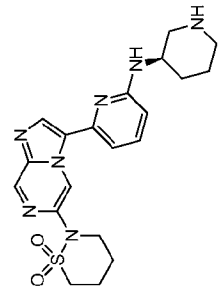
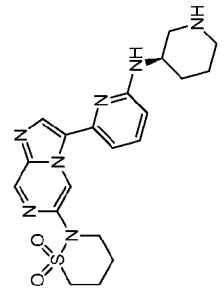
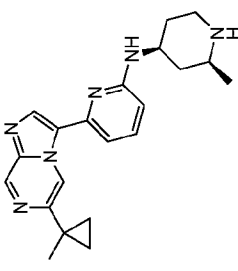
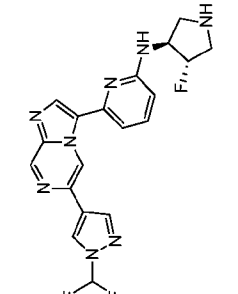
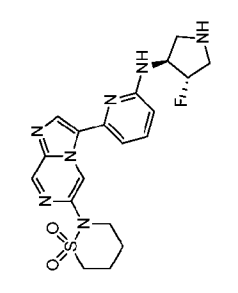
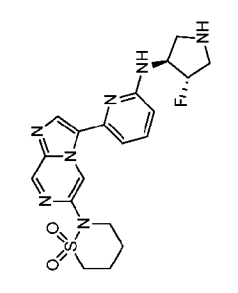
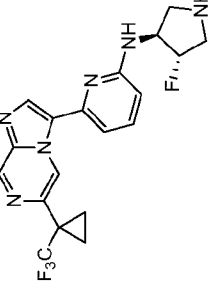
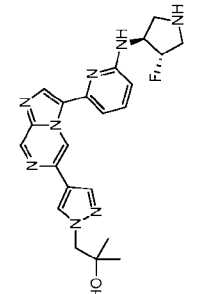
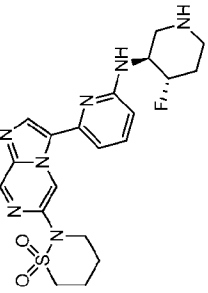
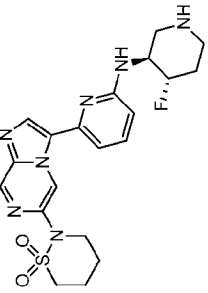
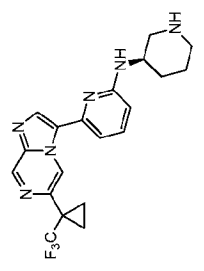
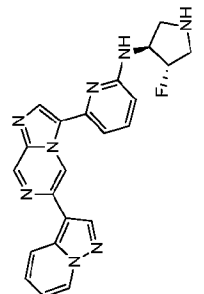
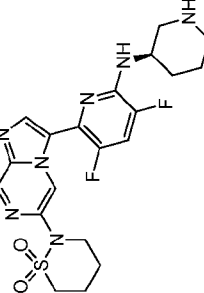
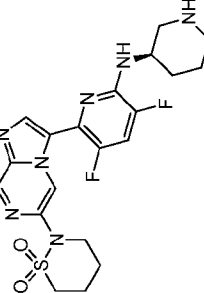
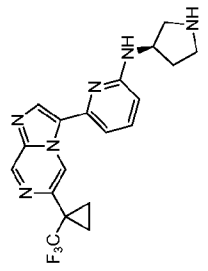
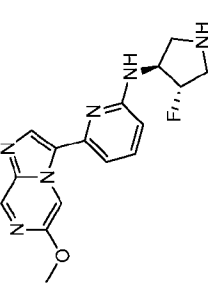
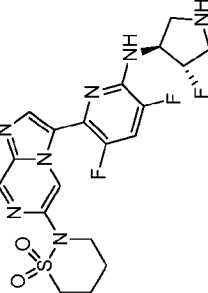
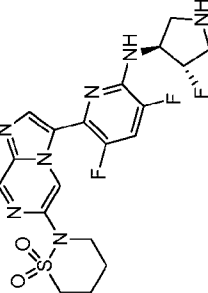
R_{24ja} , R_{24jb} , R_{25ja} , R_{25jb} , R_{26ja} , R_{26jb} , R_{27ja} , R_{27jb} , R_{28ja} , and R_{28jb} are each independently selected from H, halogen, -OH, and C_1 - C_6 alkyl.

10 In one embodiment, the compound of Formula (I-5009) is selected from Compounds 1-9 to 138-9.

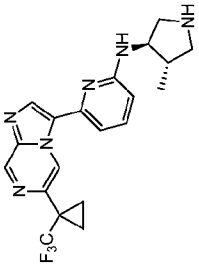
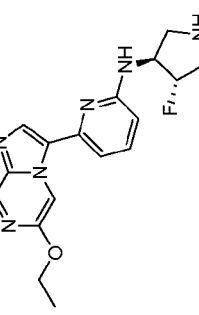
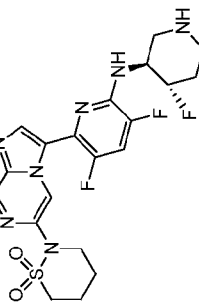
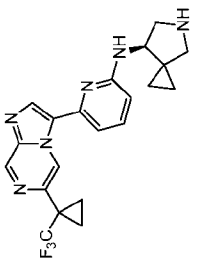
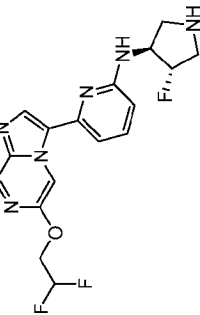
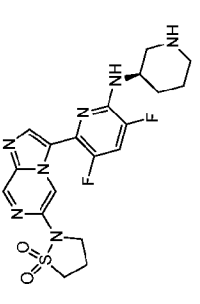
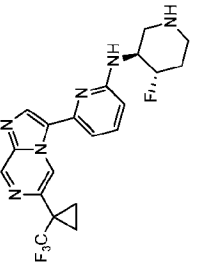
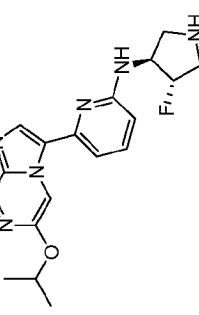
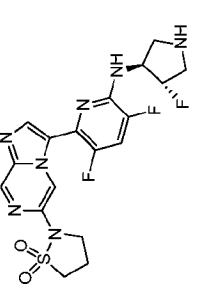
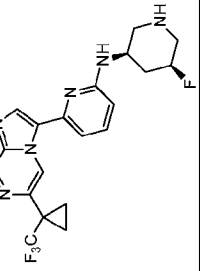
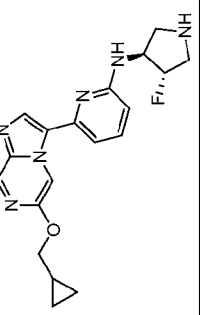
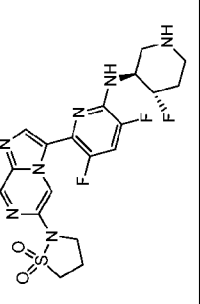
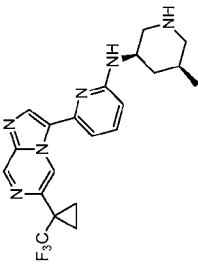
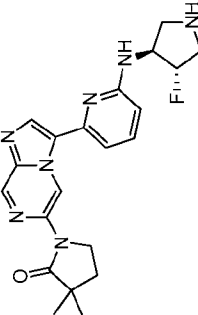
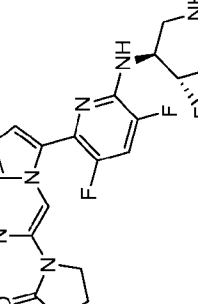
130364-5012-WO

#	Structure	#	Structure	#	Structure
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4-9		50-9		96-9	
5-9		51-9		97-9	

130364-5012-WO

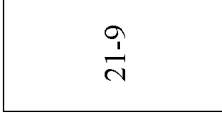
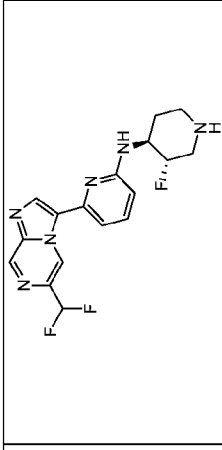
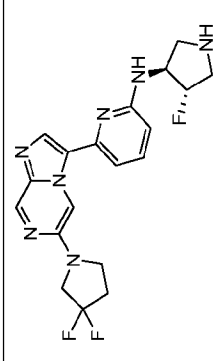
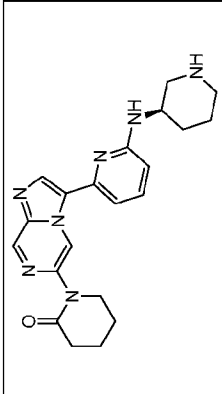
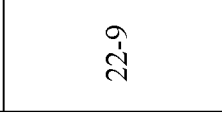
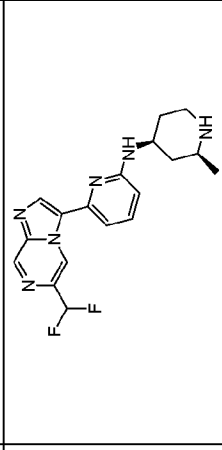
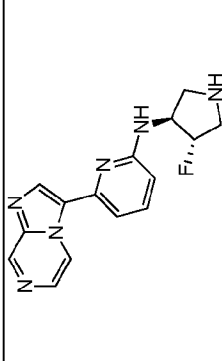
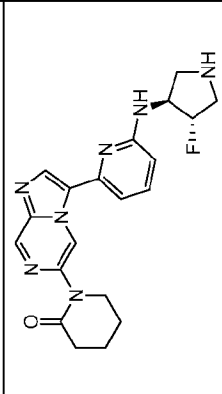
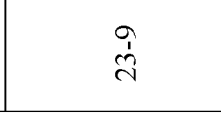
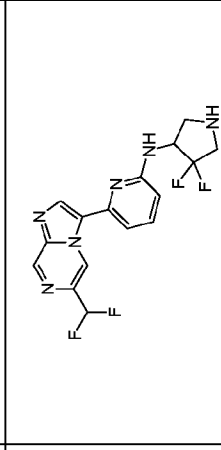
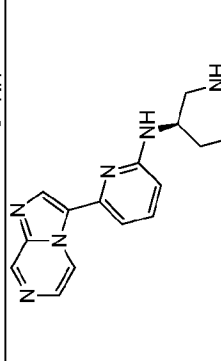
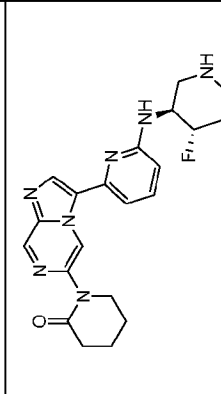
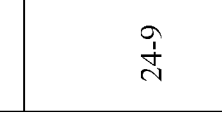
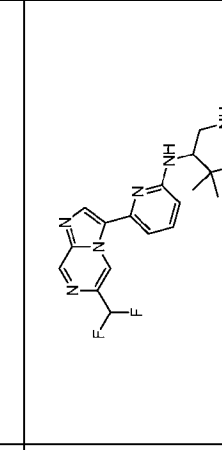
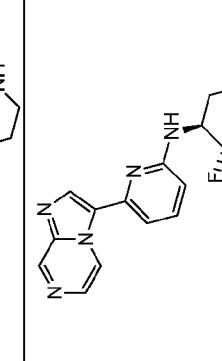
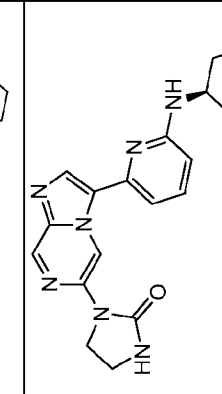
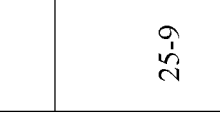
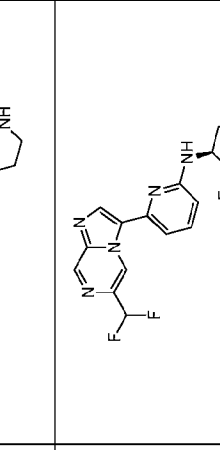
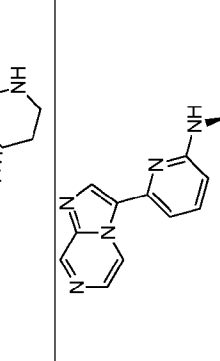
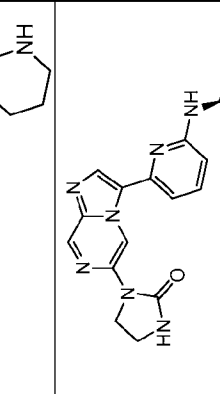
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	9-9		55-9		104-9		105-9
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130364-5012-WO

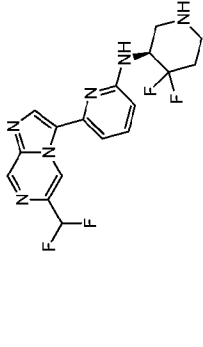
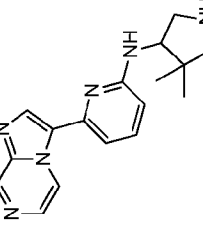
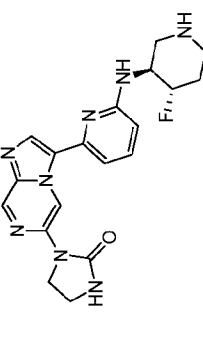
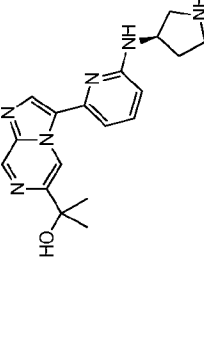
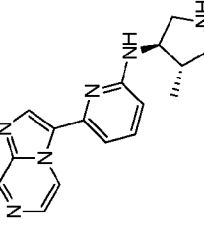
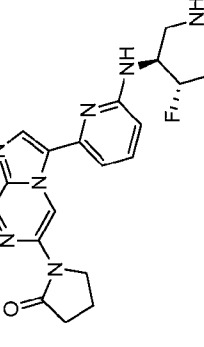
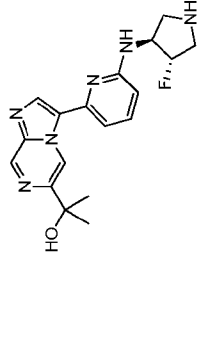
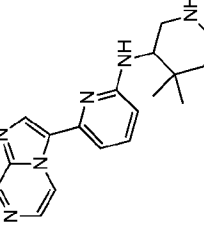
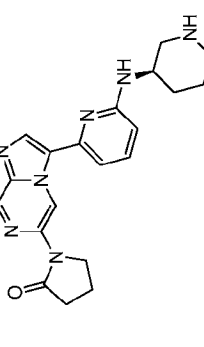
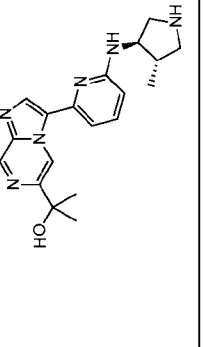
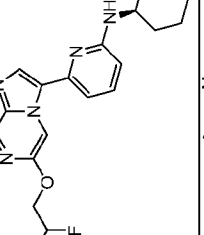
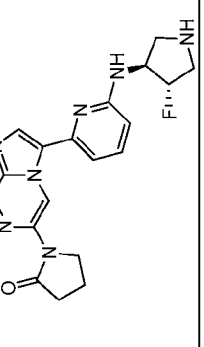
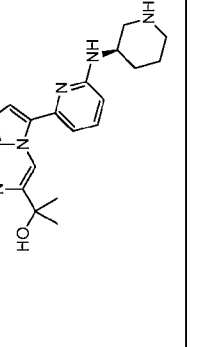
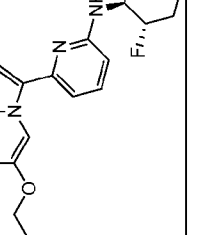
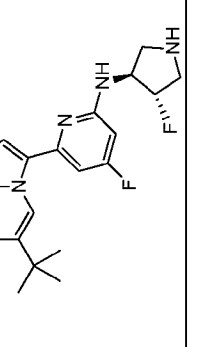
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16-9		62-9	108-9	
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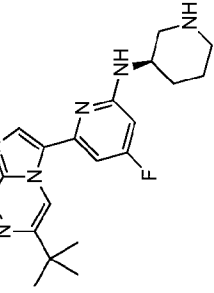
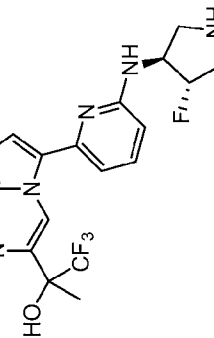
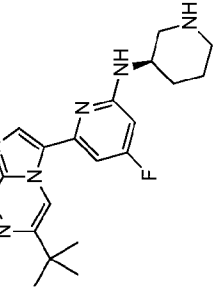
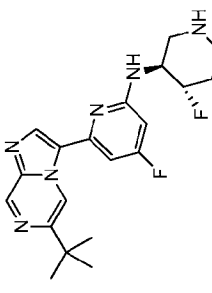
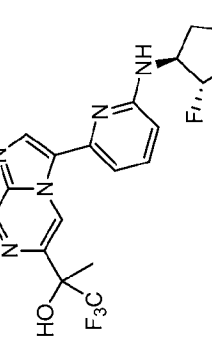
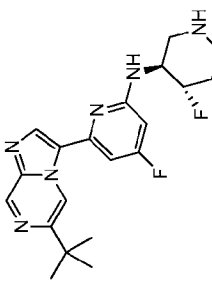
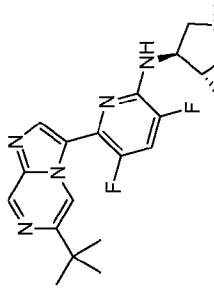
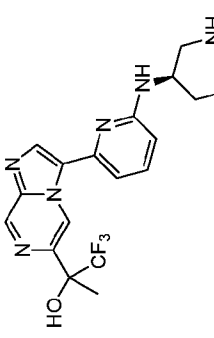
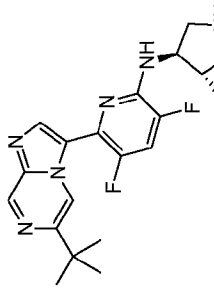
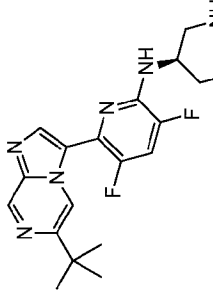
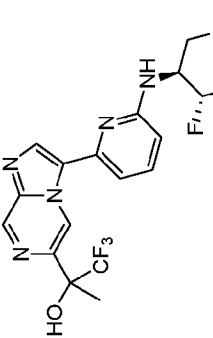
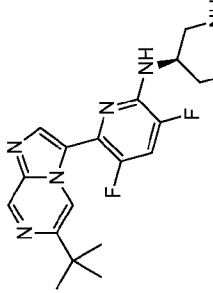
130364-5012-WO

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130364-5012-WO

	26-9		72-9		118-9
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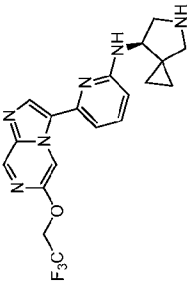
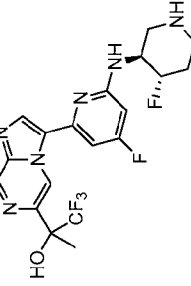
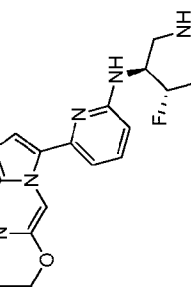
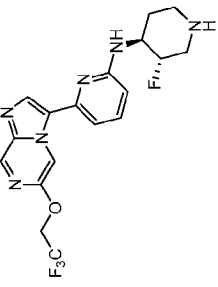
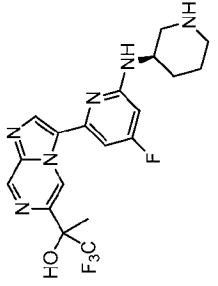
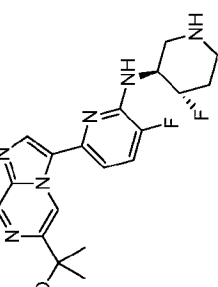
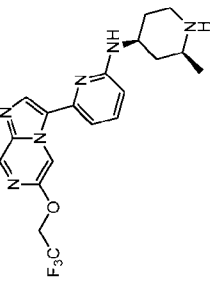
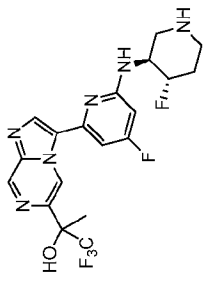
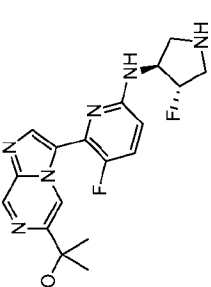
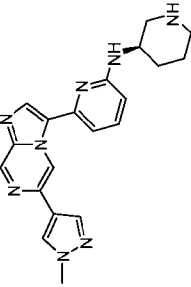
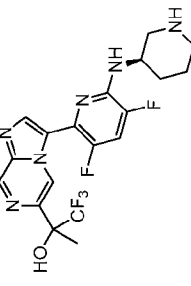
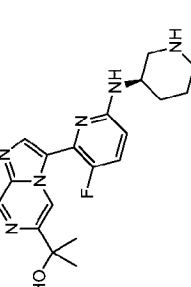
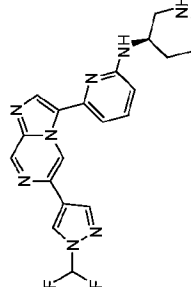
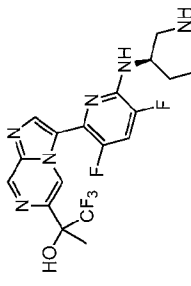
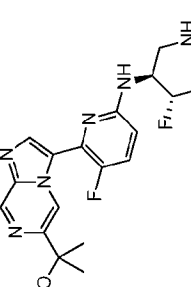
130364-5012-WO

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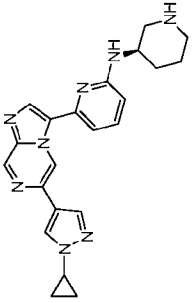
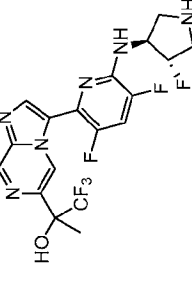
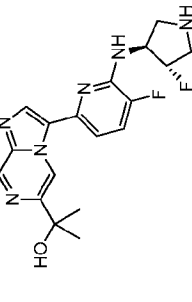
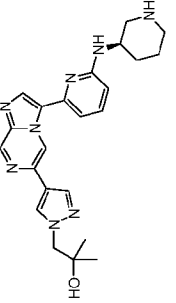
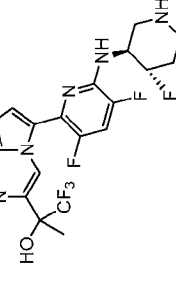
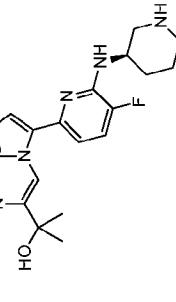
130364-5012-WO

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		128-9	
		129-9	
		130-9	
		131-9	

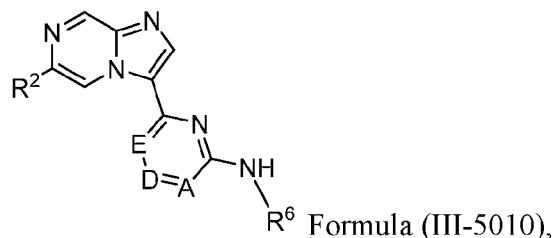
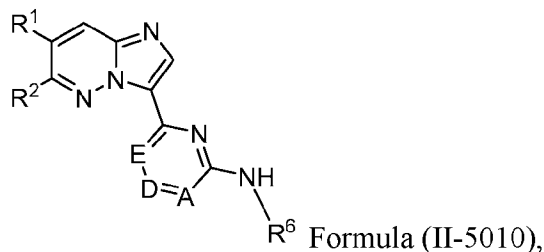
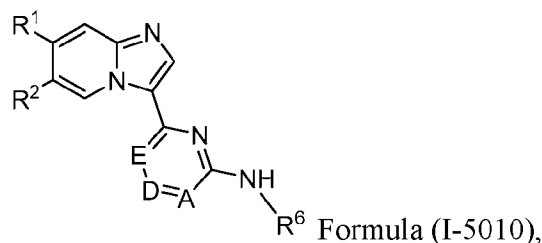
130364-5012-WO

	40-9		86-9		132-9
	41-9		87-9		133-9
	42-9		88-9		134-9
	43-9		89-9		135-9
	44-9		90-9		136-9

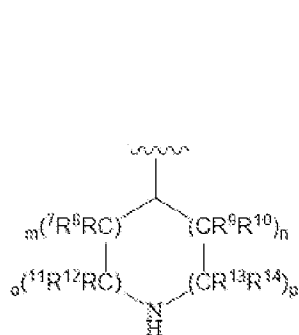
130364-5012-WO

45-9		91-9		137-9	
46-9		92-9		138-9	

In one embodiment, the compound is a compound of Formula (I-5010), (II-5010), or (III-5010):

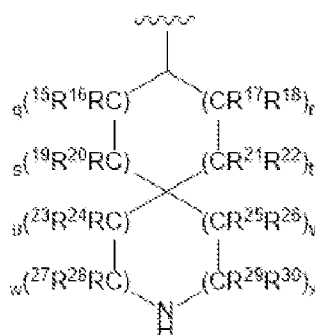


- 5 or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:
- A is selected from N and CR⁵;
 - D is selected from N and CR⁴;
 - E is selected from N and CR³;
 - at least one of A, D, and E is N;
- 10 R¹, R², R³, R⁴, and R⁵ are each independently selected from H, halogen, hydroxy, oxo, -CN, -C(=O)H, -C(=O)OH, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, -C(=O)NR³¹R³², cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, -O-aryl, aryl, heteroaryl, or fused ring heteroaryl, wherein -C(=O)H, -C(=O)OH, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, -O-aryl, aryl, heteroaryl, or fused
- 15 ring heteroaryl is optionally substituted with one or more of halogen, hydroxy, oxo, -C(=O)H, -C(=O)OH, nitro (-NO₂), -NH₂, -N(CH₃)₂, cyano (-CN), ethynyl (-CCH), propynyl, -SO₃H, heterocyclyl, aryl, heteroaryl, pyrrolyl, piperidyl, piperazinyl, morpholinyl, -C(=O)-morpholin-4-yl, -C(=O)NH₂, -C(=O)N(CH₃)₂, C₁-C₇ alkyl, C₁-C₇ perfluorinated alkyl, C₁-C₇ alkoxy, C₁-C₇ haloalkoxy, or C₁-C₇ alkyl which is substituted with cycloalkyl;



R⁶ is

(Ia-5010), or



(Ib-5010), or C₃-C₆

cycloalkyl substituted with one or more -NR³³R³⁴;

R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each independently selected from H, halogen, hydroxy, oxo, -CN, -C(=O)H, -C(=O)OH, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein -C(=O)H, -C(=O)OH, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen;

R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are each independently selected from H, halogen, hydroxy, oxo, -CN, methanoyl (-COH), carboxy (-CO₂H), C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl, wherein -C(=O)H, -C(=O)OH, C₁-C₇ alkyl, C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₁-C₇ alkoxy, cycloalkyl, spiro-fused cycloalkyl, heterocyclyl, aryl, heteroaryl, or fused ring heteroaryl is optionally substituted with one or more halogen;

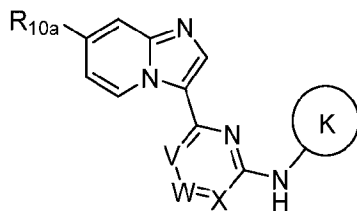
R³¹ and R³² are each independently selected from H, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl, wherein C₁-C₆ alkyl and C₃-C₆ cycloalkyl are optionally substituted with one or more halogen;

R³³ and R³⁴ are each independently selected from H and C₁-C₆ alkyl; and

m, n, o, p, q, r, s, t, u, v, w, and x are independently selected from 0, 1, 2, 3, 4, or 5,

where q+r+s+t is at least 1, and where u+v+w+x is at least 1.

In one embodiment, the compound of Formula (I-5010) is a compound of Formula (Ia-5010):



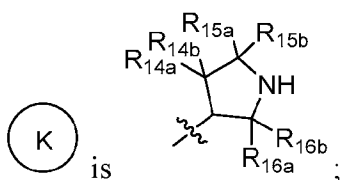
Formula (Ia-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

V is N or CR₁₁;

W is N or CR₁₂;

5 X is N or CR₁₃;



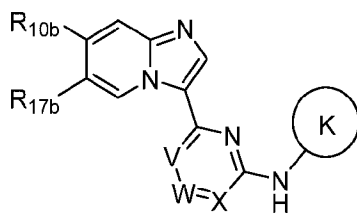
R_{10a} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₁₁, R₁₂, and R₁₃ are each independently selected from H and halogen;

R_{14a}, R_{14b}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18a}, and R_{18b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of V, W, or X is N.

In one embodiment, the compound of Formula (I-5010) is a compound of Formula (Ib-5010):



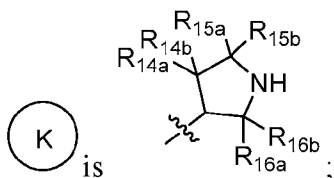
Formula (Ib-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

V is N or CR₁₁;

W is N or CR₁₂;

X is N or CR₁₃;



R_{10b} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

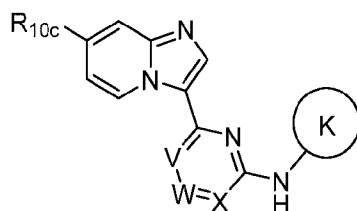
R_{17b} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), C₃-C₉ heterocyclyl, imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₁₁, R₁₂, and R₁₃ are each independently selected from H and halogen;

R_{14a}, R_{14b}, R_{15a}, R_{15b}, R_{16a}, R_{16b}, R_{18a}, and R_{18b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of V, W, or X is N.

In one embodiment, the compound of Formula (I-5010) is a compound of Formula (Ic-5010):



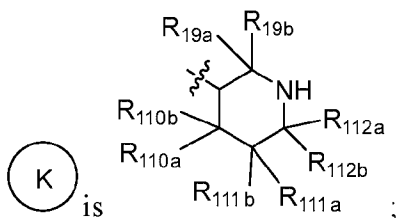
Formula (Ic-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

V is N or CR₁₁;

W is N or CR₁₂;

X is N or CR₁₃;

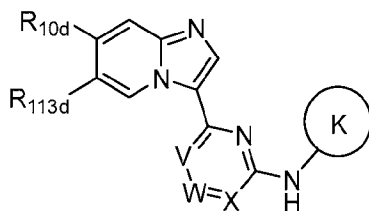


R_{10c} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₁₁, R₁₂, and R₁₃ are each independently selected from H and halogen;

R_{18a}, R_{18b}, R_{19a}, R_{19b}, R_{110a}, R_{110b}, R_{111a}, R_{111b}, R_{112a}, and R_{112b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and one of V, W, or X is N.

In one embodiment, the compound of Formula (I-5010) is a compound of Formula (Id-5010):



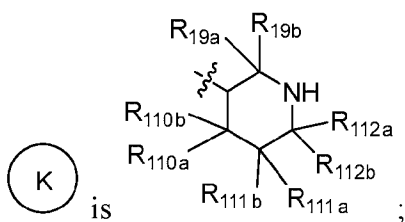
Formula (Id-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

V is N or CR₁₁;

W is N or CR₁₂;

X is N or CR₁₃;



R_{10d} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

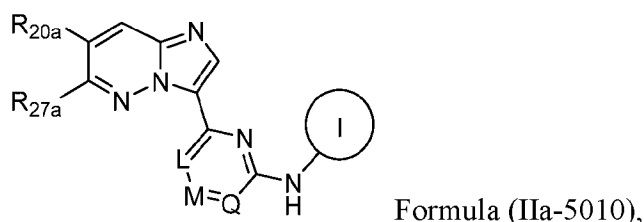
R_{113d} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{18a}R_{18b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₁₁, R₁₂, and R₁₃ are each independently selected from H and halogen;

R_{18a}, R_{18b}, R_{19a}, R_{19b}, R_{110a}, R_{110b}, R_{111a}, R_{111b}, R_{112a}, and R_{112b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of V, W, or X is N.

In one embodiment, the compound of Formula (II-5010) is a compound of Formula (IIa-5010):

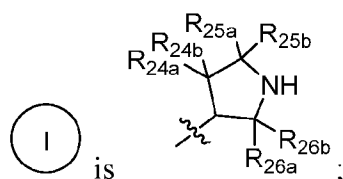


or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

L is N or CR₂₁;

M is N or CR₂₂;

Q is N or CR₂₃;



R_{20a} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{28a}R_{28b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy

are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

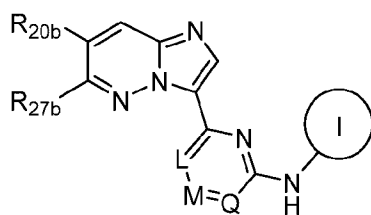
R_{27a} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{28a}R_{28b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₂₁, R₂₂, and R₂₃ are each independently selected from H and halogen;

R_{24a}, R_{24b}, R_{25a}, R_{25b}, R_{26a}, R_{26b}, R_{28a}, and R_{28b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of L, M, or Q is N.

In one embodiment, the compound of Formula (II-5010) is a compound of Formula (IIb-5010):



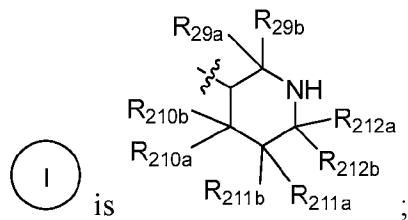
Formula (IIb-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

L is N or CR₂₁;

M is N or CR₂₂;

Q is N or CR₂₃;



R_{20b} is selected from H, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{28a}R_{28b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen,

and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

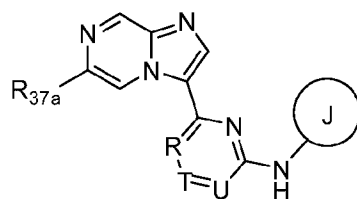
R_{27b} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, and -C(=O)NR_{28a}R_{28b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₂₁, R₂₂, and R₂₃ are each independently selected from H and halogen;

R_{29a}, R_{29b}, R_{210a}, R_{210b}, R_{211a}, R_{211b}, R_{212a}, and R_{212b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of L, M, or Q is N.

In one embodiment, the compound of Formula (III-5010) is a compound of Formula (IIIa-5010):



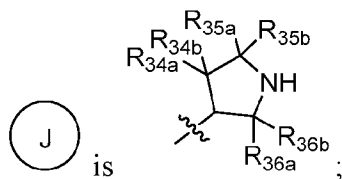
Formula (IIIa-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R is N or CR₃₁;

T is N or CR₃₂;

U is N or CR₃₃;



R_{37a} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, 2-pyrrolidinonyl, and -C(=O)NR_{38a}R_{38b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from -

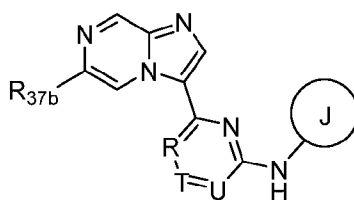
OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₃₁, R₃₂, and R₃₃ are each independently selected from H and halogen;

R_{34a}, R_{34b}, R_{35a}, R_{35b}, R_{36a}, R_{36b}, R_{38a}, and R_{38b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of R, T, or U is N.

In one embodiment, the compound of Formula (III-5010) is a compound of Formula (IIIb-5010):



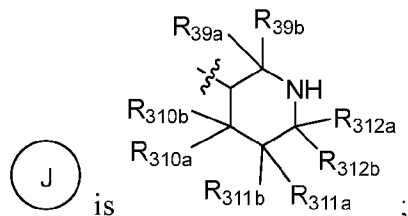
Formula (IIIb-5010),

or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer thereof; wherein:

R is N or CR₃₁;

T is N or CR₃₂;

U is N or CR₃₃;



R_{37b} is selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -O-(C₃-C₆ cycloalkyl), imidazolyl, triazolyl, 2-pyrrolidinonyl, and -C(=O)NR_{38a}R_{38b}, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more substituents selected from - OH and halogen, and C₃-C₆ cycloalkyl and -O-(C₃-C₆ cycloalkyl) are each optionally substituted with one or more substituents selected from C₁-C₆ alkyl and halogen;

R₃₁, R₃₂, and R₃₃ are each independently selected from H and halogen;

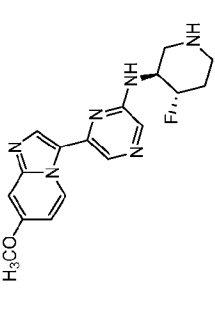
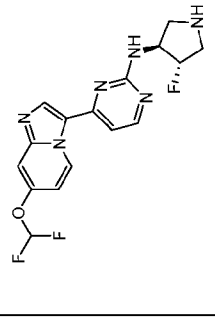
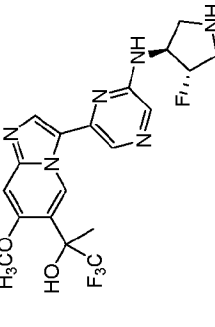
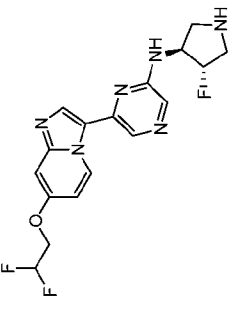
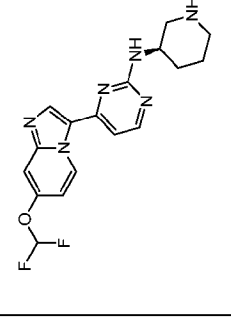
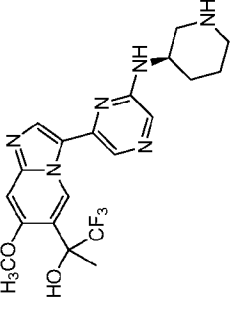
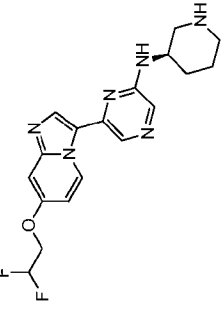
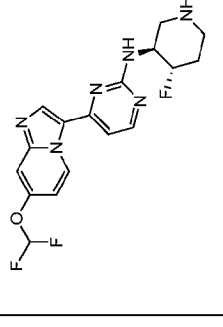
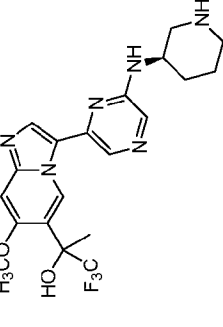
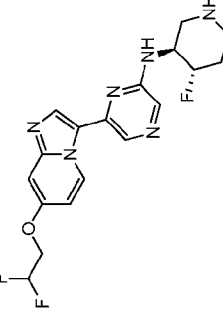
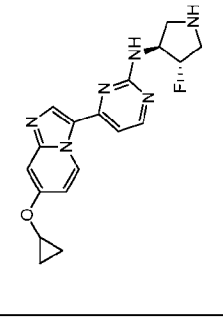
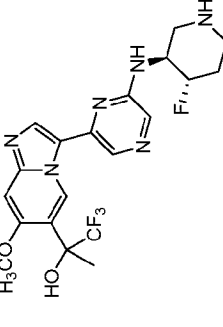
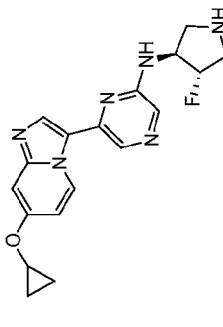
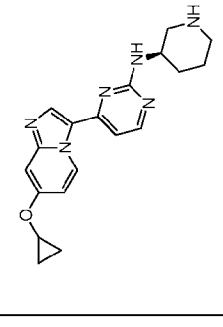
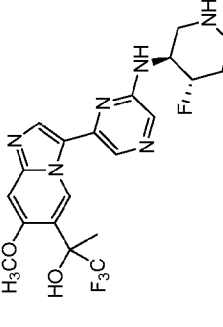
R_{38a}, R_{38b}, R_{39a}, R_{39b}, R_{310a}, R_{310b}, R_{311a}, R_{311b}, R_{312a}, and R_{312b} are each independently selected from H, halogen, -OH, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein C₁-C₆ alkyl and C₁-C₆ alkoxy are each optionally substituted with one or more halogen atoms; and

one of R, T, or U is N.

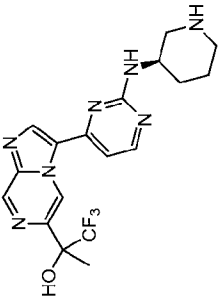
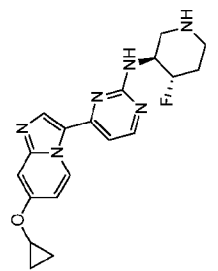
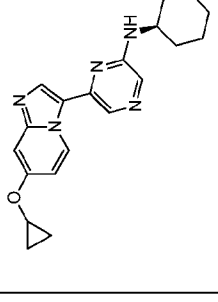
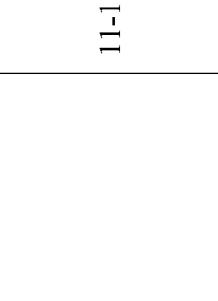
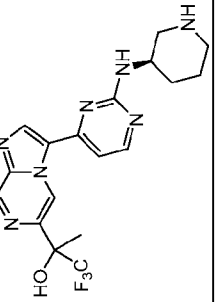
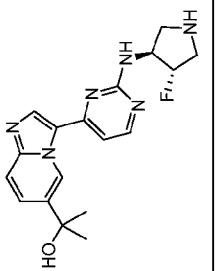
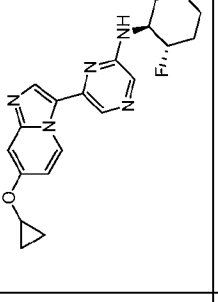
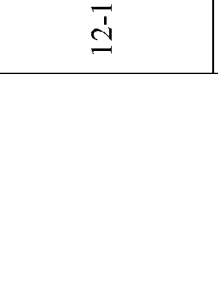
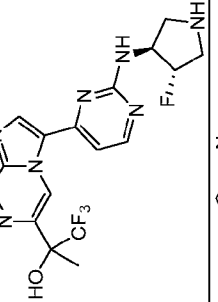
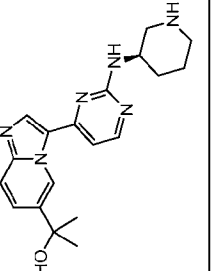
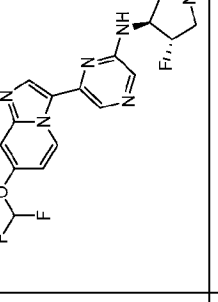
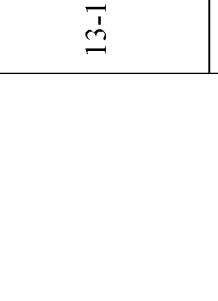
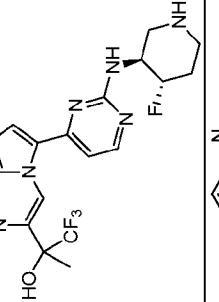
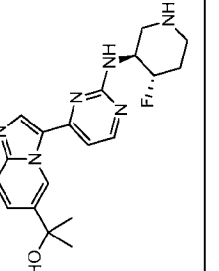
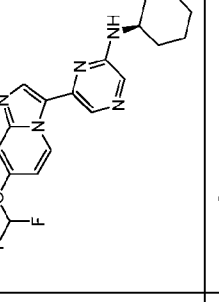
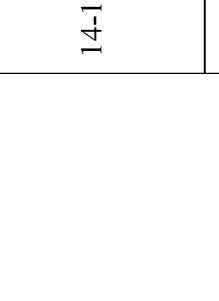
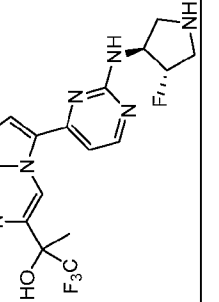
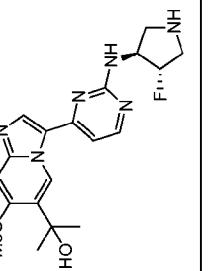
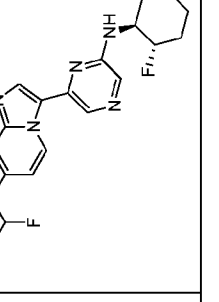
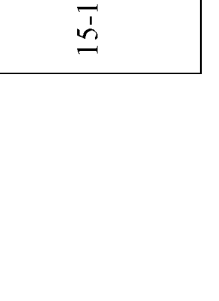
In one embodiment, the compound of Formula (I-5010), (II-5010), or (III-5010) is selected from Compounds 1-10 to 84-10.

#	Structure	#	Structure	#	Structure
1-10		29-10		57-10	
2-10		30-10		58-10	
3-10		31-10		59-10	
4-10		32-10		60-10	
5-10		33-10		61-10	

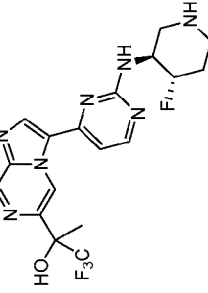
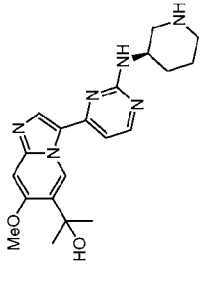
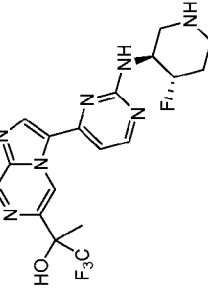
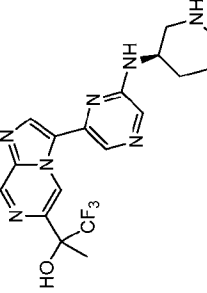
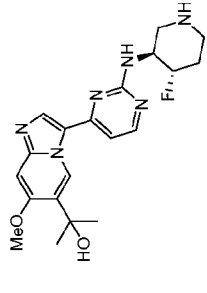
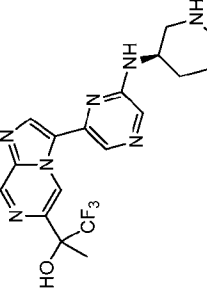
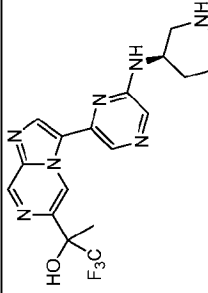
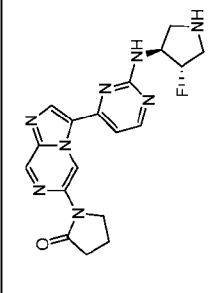
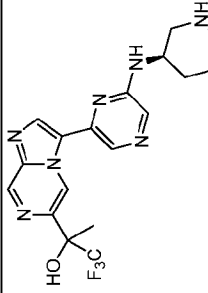
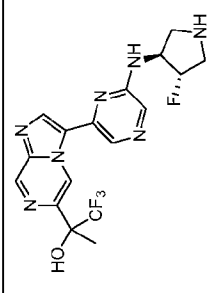
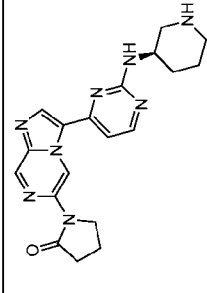
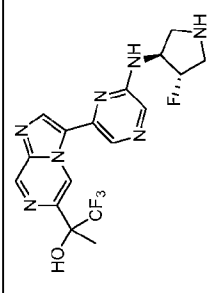
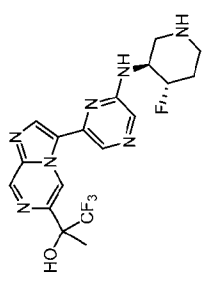
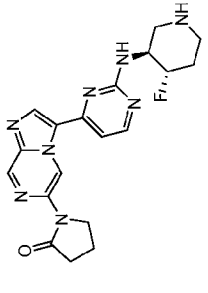
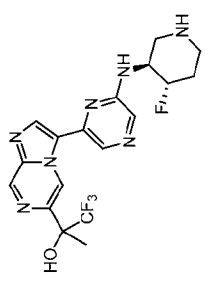
130364-5012-WO

	6-10		34-10		62-10
	7-10		35-10		63-10
	8-10		36-10		64-10
	9-10		37-10		65-10
	10-10		38-10		66-10

130364-5012-WO

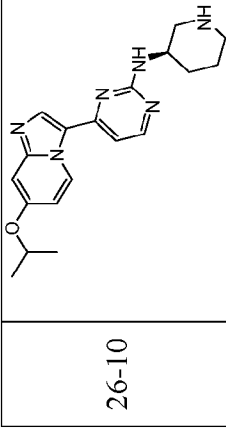
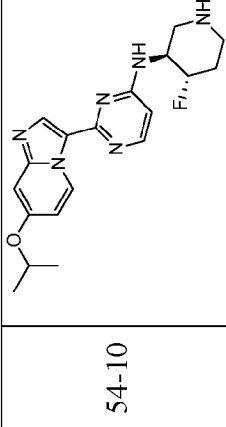
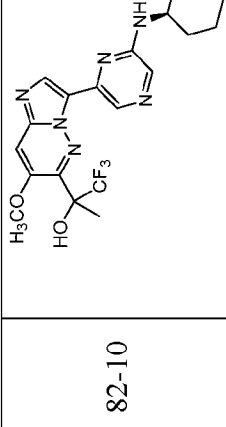
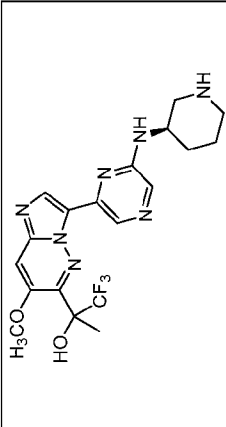
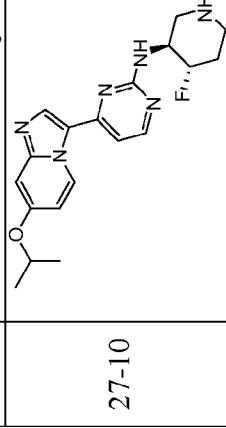
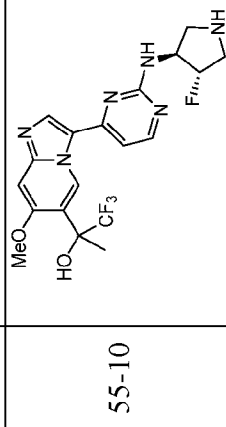
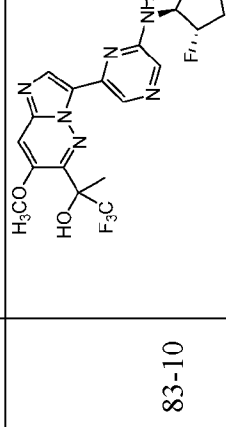
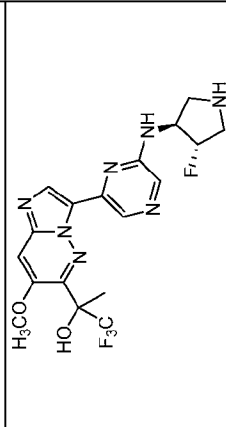
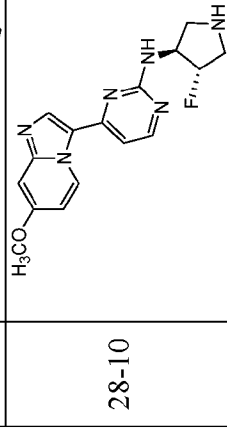
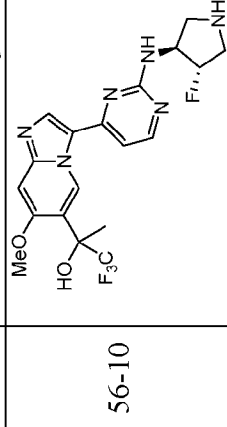
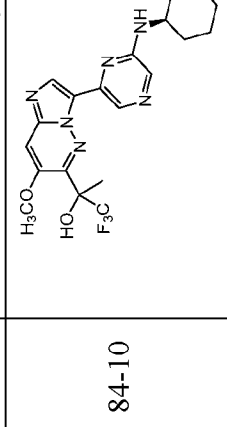
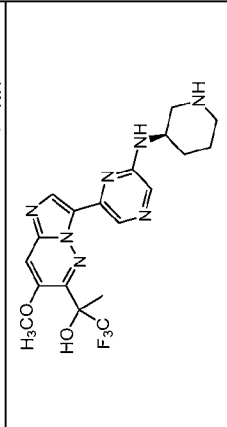
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	69-10		41-10		43-10	
	70-10		45-10		47-10	
	71-10		49-10		51-10	
	72-10		54-10		56-10	

130364-5012-WO

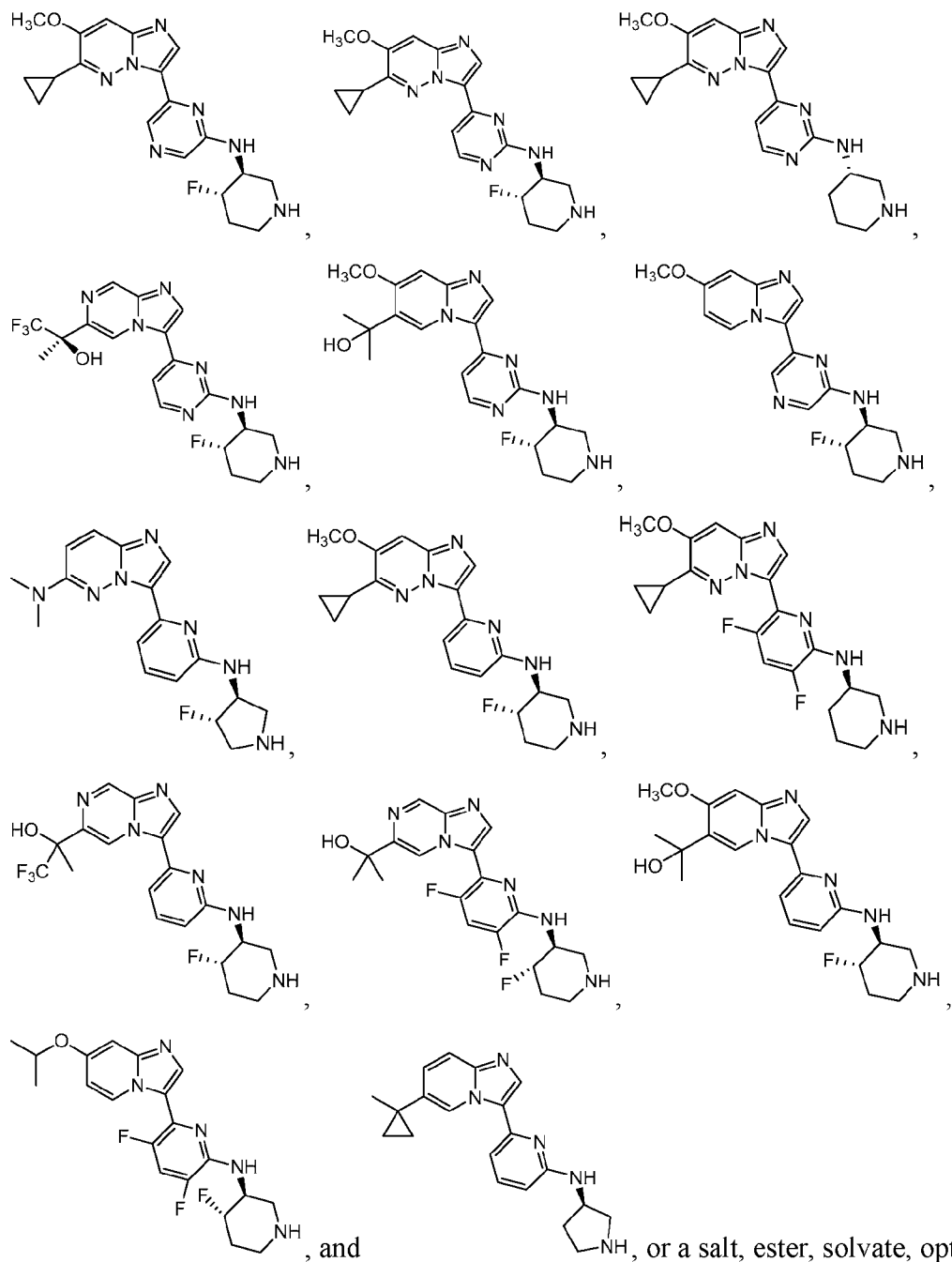
	16-10		44-10		72-10
	17-10		45-10		73-10
	18-10		46-10		74-10
	19-10		47-10		75-10
	20-10		48-10		76-10

21-10		49-10		77-10	
22-10		50-10		78-10	
23-10		51-10		79-10	
24-10		52-10		80-10	
25-10		53-10		81-10	

130364-5012-WO

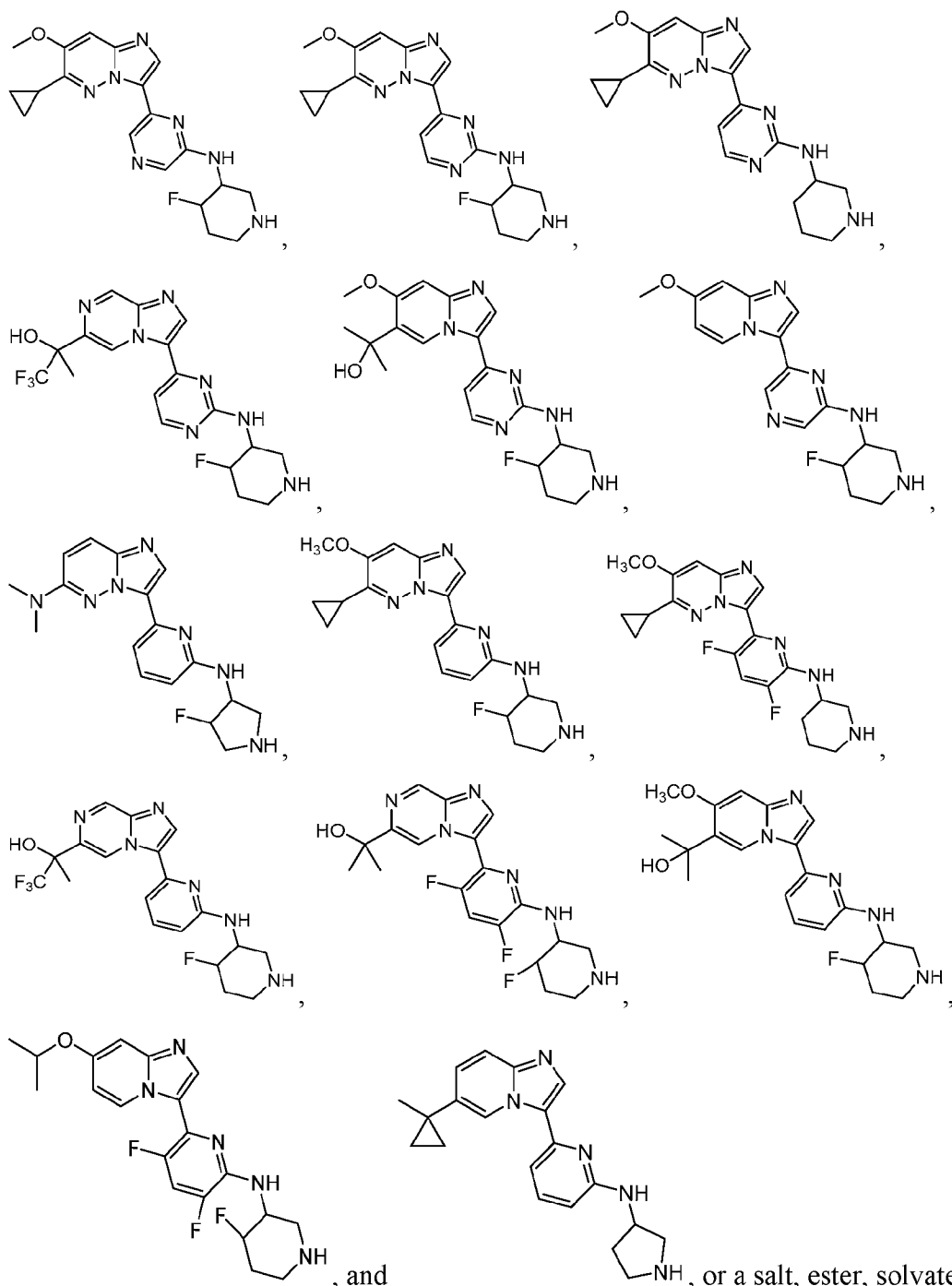
	26-10		54-10		82-10	
	27-10		55-10		83-10	
	28-10		56-10		84-10	

In one embodiment, the compound is selected from:



geometric isomer, or salt of an isomer of any one thereof.

In one embodiment, the compound is selected from:



, and
isomer, geometric isomer, or salt of an isomer of any one thereof.

Methods

In another aspect, the present disclosure provides a method of treating an inflammatory
disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a

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sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be differentially expressed in the subject compared to a healthy control subject. In one embodiment, compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound increases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG,

PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D,

5 SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one, two, three, four, five, six, seven,
 10 eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1,
 15 SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

In one embodiment, the compound inhibits NF-kB-mediated signaling. In one
 20 embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-kB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits IRAK1, IRAK4, and FLT3. In one embodiment, the compound inhibits FLT3. In one embodiment, the compound treats AML and/or MDS in the subject by suppressing
 25 leukemic stem/progenitor cell (LSPC) function and inducing differentiation. In one embodiment, the inhibition of IRAK1 and IRAK4 by the compound of the disclosure promotes the suppression of LSPC function and the induction of differentiation in the subject with AML and/or MDS.

In one embodiment, the compound provides sustained treatment of the inflammatory
 30 disease/disorder, AML, or MDS in the subject. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting

IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound treats MDS or AML. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010), (I_a-5010)-(I_d-5010), (II-5010), (II_a-5010), (II_b-5010), (III-5010), (III_a-5010), (III_b-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof. In one embodiment, the compound is selected from Compounds 1-7 to 295-7, 1_a-7 to 79_a-7, 1-3 to 68-3, 1-8 to 137-8, 1_a-8 to 84_a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

In another aspect, the present disclosure provides a method of determining a compound that is effective at treating an inflammatory disease/disorder, AML, or MDS, comprising:

determining from the IRAK1 IC₅₀ and IRAK4 IC₅₀ of the compound that the compound inhibits IRAK1 and IRAK4;

calculating from the IRAK1 and IRAK4 IC₅₀ of the compound that the compound has an IRAK4:IRAK1 potency ratio of less than about 40; and

administering the compound to a subject with an inflammatory disease/disorder, AML, or MDS, thus treating the inflammatory disease/disorder, AML, or MDS.

In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis. In one embodiment, the subject has AML or is suspected of having AML. In one embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance

In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM, less than about 65 nM, less than about 55 nM, less than about 45 nM, less than about 35 nM, less than about 25 nM, less than about 15 nM, or less than about 5 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 70, less than about 60, less than about 50, less than about 40, less than about 30, or less than about 20. In one embodiment, the compound inhibits NF-κB-mediated signaling. In one embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits FLT3. In one embodiment, the compound treats AML and/or MDS in the subject by suppressing leukemic stem/progenitor cell (LSPC) function and inducing differentiation. In one embodiment, the inhibition of IRAK1 and IRAK4 by the compound of the disclosure promotes the suppression of LSPC function and the induction of differentiation in the subject with AML and/or MDS.

5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof. In one embodiment, the compound is selected from Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

In yet another aspect, the present disclosure provides a method of determining a compound that is effective at treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining that the compound is an IRAK1/4 inhibitor which modifies the expression of one of more IRAK1/4-associated genes found to be differentially expressed in a subject with an inflammatory disease/disorder, AML, or MDS compared to a healthy control subject; and administering the compound to the subject, treating the inflammatory disease/disorder, AML, or MDS.

In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis. In one embodiment, the subject has AML or is suspected of having AML. In one embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML. In one embodiment, the subject has MDS or is suspected of having MDS.

In one embodiment, the compound decreases the expression of one or more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound increases the

expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one

5 embodiment, the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6,

10 PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45,

15 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX,

20 LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP,

25 DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound increases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen,

30 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2,

AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM, less than about 65 nM, less than about 55 nM, less than about 45 nM, less than about 35 nM, less than about 25 nM, less than about 15 nM, or less than about 5 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 70, less than about 60, less than about 50, less than about 40, less than about 30, or less than about 20. In one embodiment, the compound inhibits NF-κB-mediated signaling. In one embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits FLT3. In one embodiment, the compound treats AML and/or MDS in the subject by suppressing leukemic stem/progenitor cell (LSPC) function and inducing differentiation. In one embodiment, the inhibition of IRAK1 and IRAK4 by the compound of the disclosure promotes the suppression of LSPC function and the induction of differentiation in the subject with AML and/or MDS.

In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound

5 treats MDS or AML. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (II-5007)-(IIk-5007), (IIl-5007)-(IIo-5007), (IIp-5007)-(IIr-5007), (IIs-5007), (II-5003), (II-5008), (II-5008)-(IIk-5008), (IIl-5008), (IIm-5008), (IIn-5008), (IIO-5008), (IIp-5008)-(IIr-5008), (IIq-5008)-(IIr-5008), (II-5009), (II-5009)-(IIj-5009), (II-5010), (IIa-5010)-(IIb-5010), (II-5010), (IIa-5010), (IIb-5010), (II-5010), (IIa-5010), (IIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof. In one embodiment, the compound is selected from Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

10 In yet another aspect, the present disclosure provides a method of determining a subject with a disease/disorder that can be treated by the administration of a compound which inhibits IRAK1 and IRAK4, comprising:

determining that a subject with an inflammatory disease/disorder, AML, or MDS has elevated IRAK1 expression, IRAK4 expression, FLT3 expression, NF- κ B signaling, TLR
15 signaling, IL-1 signaling, or a combination thereof; and

administering to the subject a compound that inhibits IRAK1 and IRAK4, wherein the compound has an IRAK4:IRAK1 potency ratio of less than about 40, as calculated from the IRAK1 and IRAK4 IC₅₀ of the compound, thus treating the inflammatory disease/disorder, AML, or MDS.

20 In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis. In one embodiment, the subject has AML or is suspected of having AML. In one
25 embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML. In one embodiment, the subject has MDS or is suspected of having MDS.

30 In one embodiment, the subject has elevated IRAK1 expression, IRAK4 expression, or a combination thereof. In one embodiment, the subject has elevated FLT3 expression. In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM, less than about 65 nM,

less than about 55 nM, less than about 45 nM, less than about 35 nM, less than about 25 nM, less than about 15 nM, or less than about 5 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 70, less than about 60, less than about 50, less than about 40, less than about 30, or less than about 20. In one embodiment, the compound inhibits NF-κB-mediated signaling. In one embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits FLT3. In one embodiment, the compound inhibits IRAK1, IRAK4, and FLT3. In one embodiment, the compound treats AML and/or MDS in the subject by suppressing leukemic stem/progenitor cell (LSPC) function and inducing differentiation. In one embodiment, the inhibition of IRAK1 and IRAK4 by the compound of the disclosure promotes the suppression of LSPC function and the induction of differentiation in the subject with AML and/or MDS.

In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound treats MDS or AML. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (II-5007)-(IIk-5007), (IIl-5007)-(IIo-5007), (IIp-5007)-(IIs-5007), (IV-5007), (VI-5003), (VII-5008), (II-5008)-(IIk-5008), (IIl-5008), (IIo-5008), (IIp-5008)-(IIu-5008), (IIq-5008)-(IIs-5008), (I-5009), (II-5009)-(IIj-5009), (I-5010), (Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof. In one embodiment, the compound is selected from Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8,

1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

In yet another aspect, the present disclosure provides a method of determining a subject with a disease/disorder that can be treated by the administration of a compound which inhibits

5 IRAK1 and IRAK4, comprising:

determining that a subject with an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) has one of more IRAK1/4-associated genes that are differentially expressed compared to a healthy control subject; and

10 administering to the subject a compound that inhibits IRAK1 and IRAK4, thus treating the inflammatory disease/disorder, AML, or MDS.

In one embodiment, the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and
15 colitis. In one embodiment, the subject has AML or is suspected of having AML. In one embodiment, the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML. In one embodiment, the subject has MDS or is suspected of having MDS.

20 In one embodiment, the compound modifies the expression of one or more IRAK1/4-associated genes found to be differentially expressed in the subject compared to the healthy control subject. In one embodiment, the compound modifies the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37,
25 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 more IRAK1/4-associated genes found to be differentially expressed in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten,
30 eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49,

or 50 IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject. In one embodiment, the compound increases the expression of one or more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound increases the expression of one, two, three, four, 5 five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject. In one embodiment, the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, 10 SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, 15 PCED1B-AS1, and BAG3 in the subject. In one embodiment, the compound decreases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, 20 ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one 25 embodiment, the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, 30 PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject. In one

embodiment, the compound increases the expression of one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

In one embodiment, the compound has an IRAK1 IC₅₀ of less than about 75 nM, less than about 65 nM, less than about 55 nM, less than about 45 nM, less than about 35 nM, less than about 25 nM, less than about 15 nM, or less than about 5 nM. In one embodiment, the compound has an IRAK4 IC₅₀ of less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM. In one embodiment, the compound has IRAK4:IRAK1 potency ratio of less than about 70, less than about 60, less than about 50, less than about 40, less than about 30, or less than about 20. In one embodiment, the compound inhibits NF-κB-mediated signaling. In one embodiment, inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling. In one embodiment, the compound inhibits TLR signaling and IL-1 signaling. In one embodiment, the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling. In one embodiment, the compound inhibits FLT3. In one embodiment, the compound inhibits IRAK1, IRAK4, and FLT3. In one embodiment, the compound treats AML and/or MDS in the subject by suppressing leukemic stem/progenitor cell (LSPC) function and inducing differentiation. In one embodiment, the inhibition of IRAK1 and IRAK4 by the compound of the disclosure promotes the suppression of LSPC function and the induction of differentiation in the subject with AML and/or MDS.

In one embodiment, the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject. In one embodiment, the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1. In one embodiment, the compound

continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped. In one embodiment, the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped. In one embodiment, the compound treats MDS or AML. In one embodiment, the compound is a compound of any one of Formulas (I-5007), (II-5007)-(III-5007), (II-5007)-(III-5007), (III-5007)-(III-5007), (IV-5007), (VI-5003), (VII-5008), (II-5008)-(III-5008), (II-5008), (II-5008), (II-5008)-(III-5008), (III-5008)-(III-5008), (I-5009), (II-5009)-(III-5009), (I-5010), (Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof. In one embodiment, the compound is selected from Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clauses of the disclosure

The following clauses describe certain embodiments.

Clause 1. A method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a subject comprising administering to the subject a compound that inhibits IRAK1 and IRAK4.

Clause 2. The method of clause 1, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

Clause 3. The method of clause 1 or 2, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

Clause 4. The method of any one of clauses 1 to 3, wherein the compound has IRAK4:IRAK1 potency ratio of less than about 40.

Clause 5. The method of any one of clauses 1 to 4, wherein the compound inhibits NF-κB-mediated signaling.

Clause 6. The method of clause 5, wherein inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling.

Clause 7. The method of any one of clauses 1 to 6, wherein the compound inhibits TLR signaling and IL-1 signaling.

Clause 8. The method of clause 7, wherein the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling.

Clause 9. The method of any one of clauses 1 to 8, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 10. The method of clause 9, wherein the inhibition of IRAK1 and IRAK4 inhibits cancer cell colony formation and/or cancer progenitor cell function.

Clause 11. The method of any one of clauses 1 to 10, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

Clause 12. The method of clause 11, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 13. The method of any one of clauses 1 to 12, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped.

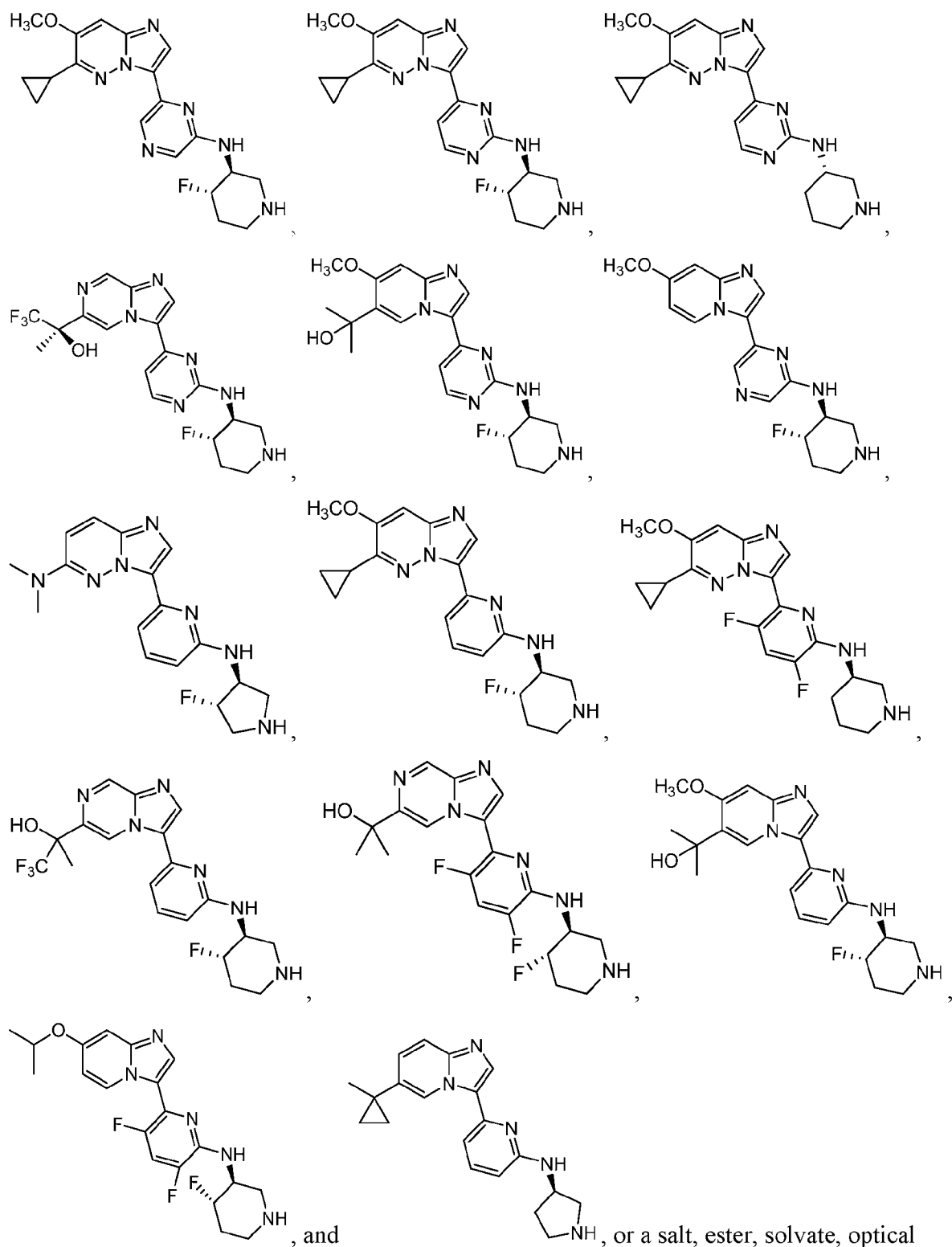
Clause 14. The method of clause 13, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 15. The method of any one of clauses 1 to 14, wherein the compound treats MDS or AML.

Clause 16a. The method of any one of clauses 1 to 15, wherein the compound is a compound of Formula (I-5007), (VI-5003), (VII-5008), (I-5009), (I-5010), (II-5010), (III-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 16b. The method of any one of clauses 1 to 16a, wherein the compound is selected from any one of Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 17. The method of any one of clauses 1 to 16, wherein the compound is selected from:



Clause 18. A method of determining a compound that is effective at treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining from the IRAK1 IC₅₀ and IRAK4 IC₅₀ of the compound that the compound
5 inhibits IRAK1 and IRAK4;

calculating from the IRAK1 and IRAK4 IC₅₀ of the compound that the compound has an IRAK4:IRAK1 potency ratio of less than about 40; and

administering the compound to a subject with an inflammatory disease/disorder, AML, or MDS, treating the inflammatory disease/disorder, AML, or MDS.

10 Clause 19. The method of clause 18, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

Clause 20. The method of clause 18 or 19, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

Clause 21. The method of any one of clauses 18 to 20, wherein the compound inhibits NF-κB-mediated signaling.
15

Clause 22. The method of clause 21, wherein inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling.

Clause 23. The method of any one of clauses 18 to 22, wherein the compound inhibits TLR signaling and IL-1 signaling.

20 Clause 24. The method of clause 23, wherein the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling.

Clause 25. The method of any one of clauses 18 to 24, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without
25 inhibiting IRAK1.

Clause 26. The method of clause 25, wherein the inhibition of IRAK1 and IRAK4 inhibits cancer cell colony formation and/or cancer progenitor cell function.

Clause 27. The method of any one of clauses 18 to 26, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

Clause 28. The method of clause 27, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

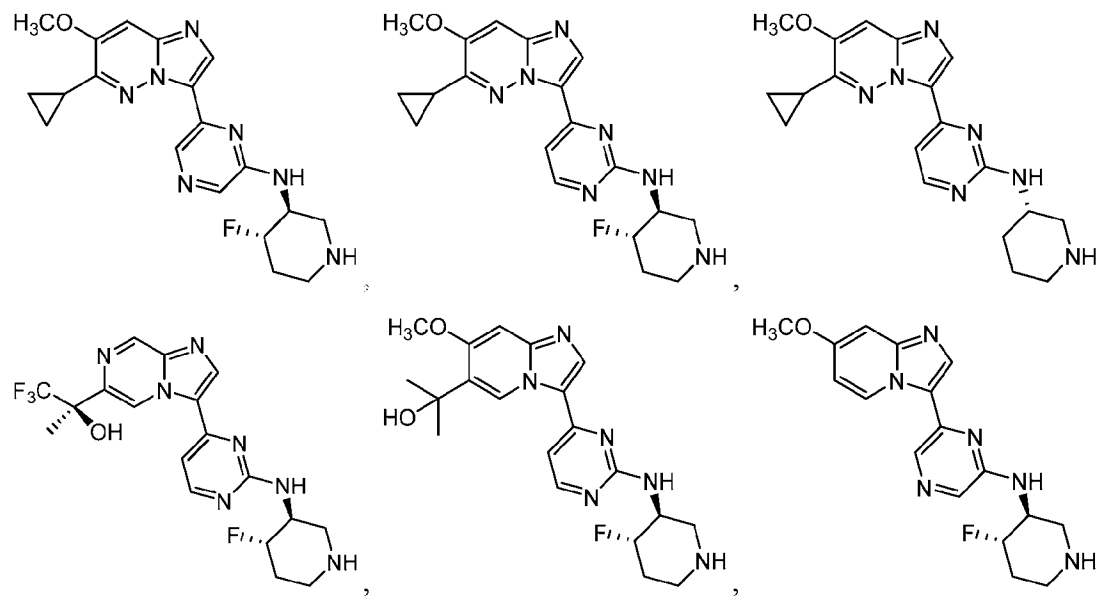
Clause 29. The method of any one of clauses 18 to 28, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped.

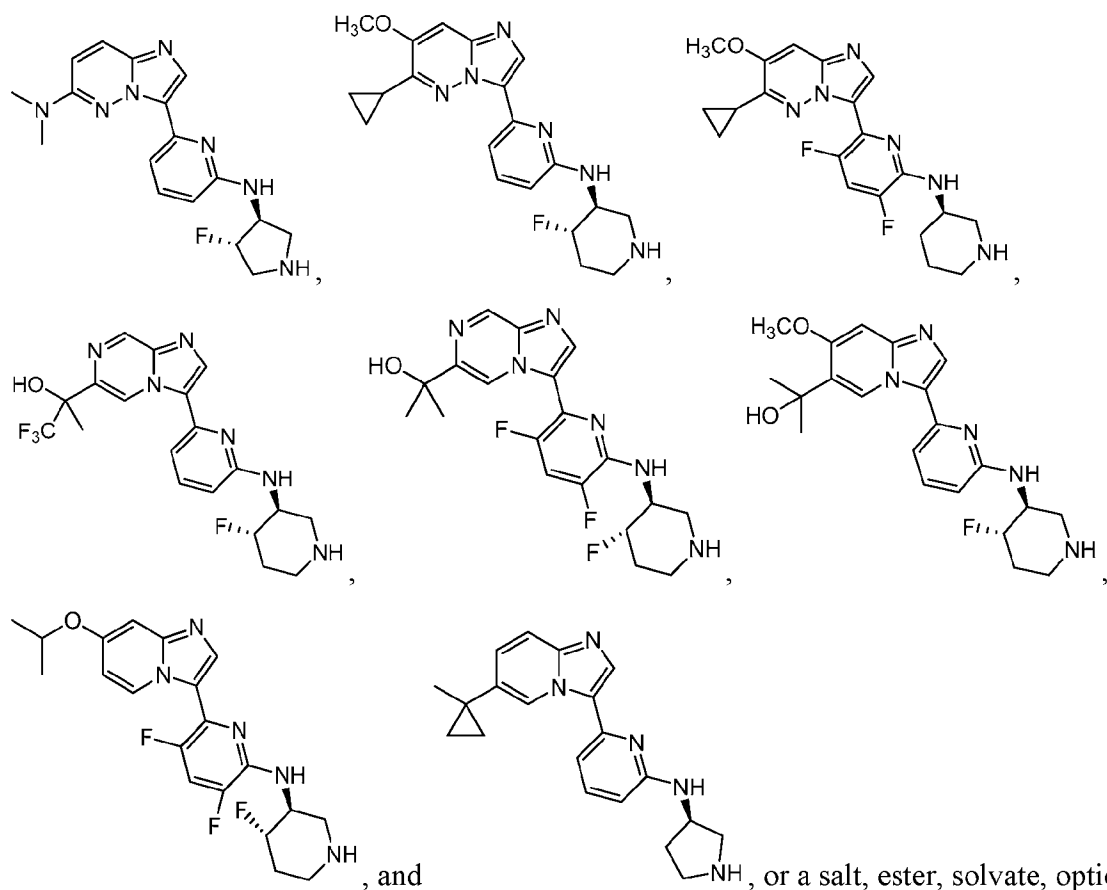
Clause 30. The method of clause 29, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 31. The method of any one of clauses 18 to 30, wherein the compound treats MDS or AML.

Clause 32. The method of any one of clauses 18 to 31, wherein the compound is a compound of Formula (I-5007), (VI-5003), (VII-5008), (I-5009), (I-5010), (II-5010), (III-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 33. The method of any one of clauses 18 to 32, wherein the compound is selected from:





isomer, geometric isomer, or salt of an isomer of any one thereof.

- 5 Clause 34. A method of determining a subject with a disease/disorder that can be treated by the administration of a compound which inhibits IRAK1 and IRAK4, comprising:

determining that a subject with an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) has elevated IRAK1 expression, IRAK4 expression, FLT3 expression, NF- κ B signaling, TLR signaling, IL-1 signaling, or a combination thereof; and

administering to the subject a compound that inhibits IRAK1 and IRAK4 wherein the compound has an IRAK4:IRAK1 potency ratio of less than about 40, as calculated from the IRAK1 and IRAK4 IC_{50} of the compound, thus treating the inflammatory disease/disorder, AML, or MDS.

- 15 Clause 35. The method of clause 34, wherein the subject has elevated IRAK1 expression, IRAK4 expression, or a combination thereof.

Clause 36. The method of clause 34 or 35, wherein the subject has elevated FLT3 expression.

Clause 37. The method of any one of clauses 34 to 36, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

Clause 38. The method of any one of clauses 34 to 37, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

5 Clause 39. The method of any one of clauses 34 to 38, wherein the compound inhibits NF-κB-mediated signaling.

Clause 40. The method of clause 39, wherein inhibition of IRAK1 and IRAK4 inhibits NF-κB-mediated signaling.

10 Clause 41. The method of any one of clauses 34 to 40, wherein the compound inhibits TLR signaling and IL-1 signaling.

Clause 42. The method of clause 41, wherein the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling.

15 Clause 43. The method of any one of clauses 34 to 42, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 44. The method of clause 43, wherein the inhibition of IRAK1 and IRAK4 inhibits cancer cell colony formation and/or cancer progenitor cell function.

20 Clause 45. The method of any one of clauses 34 to 44, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

Clause 46. The method of clause 45, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

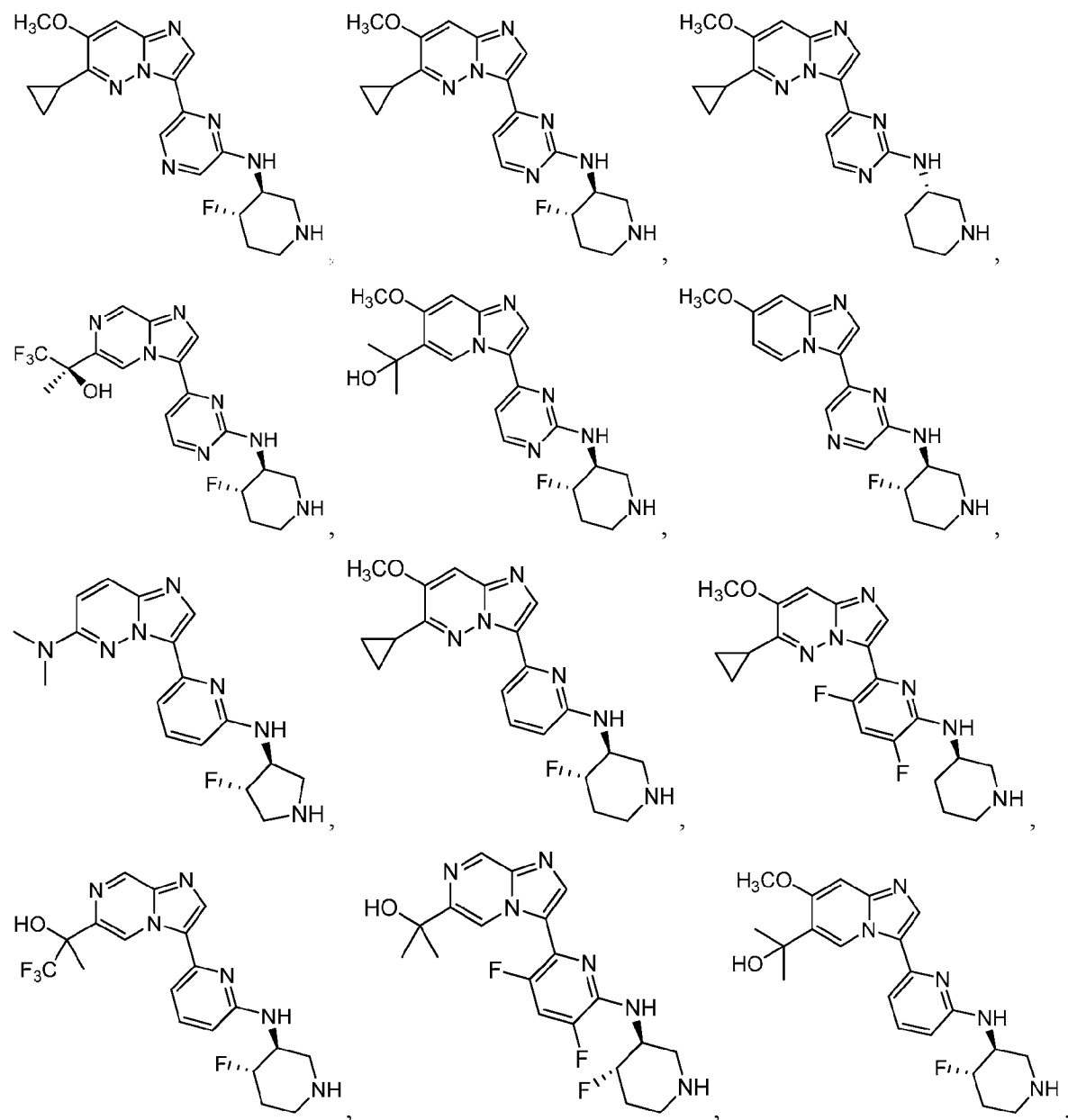
25 Clause 47. The method of any one of clauses 34 to 46, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped.

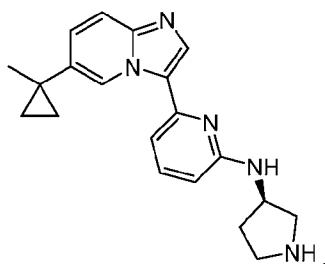
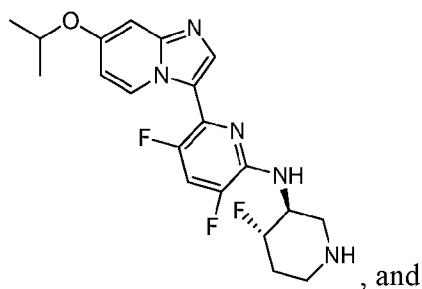
30 Clause 48. The method of clause 47, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 49. The method of any one of clauses 34 to 48, wherein the compound treats MDS or AML.

Clause 50. The method of any one of clauses 34 to 49, wherein the compound is a compound of Formula (I-5007), (VI-5003), (VII-5008), (I-5009), (I-5010), (II-5010), (III-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 51. The method of any one of clauses 34 to 50, wherein the compound is selected from:





, and

, or a salt, ester, solvate, optical

isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 101. A method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a subject in need thereof, the method

5 comprising administering to the subject a compound that inhibits IRAK1 and IRAK4.

Clause 102. The method of clause 101, wherein the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and

10 colitis.

Clause 103. The method of clause 101, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

15 Clause 104. The method of any one of clauses 101 to 103, wherein the compound has an IRAK1 IC_{50} of less than about 75 nM.

Clause 105. The method of any one of clauses 101 to 104, wherein the compound has an IRAK4 IC_{50} of less than about 10 nM.

20 Clause 106. The method of any one of clauses 101 to 105, wherein the compound has IRAK4:IRAK1 potency ratio of less than about 40.

Clause 107. The method of any one of clauses 101 to 106, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes compared to a healthy control subject and/or decreased expression of one or more IRAK1/4-associated genes compared to a healthy control subject.

25 Clause 108. The method of clause 107, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2,

TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.

Clause 109. The method of clause 107 or 108, wherein the subject in need thereof has decreased expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.

Clause 110. The method of any one of clauses 107 to 109, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

Clause 111. The method of clause 110, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 112. The method of clause 110 or 111, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7,

ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 113. The method of any one of clauses 101 to 112, wherein the compound inhibits NF-
5 kB-mediated signaling.

Clause 114. The method of clause 113, wherein inhibition of IRAK1 and IRAK4 inhibits NF-
kB-mediated signaling.

Clause 115. The method of any one of clauses 101 to 114, wherein the compound inhibits TLR
signaling and IL-1 signaling.

10 Clause 116. The method of clause 115, wherein the inhibition of IRAK1 and IRAK4 inhibits
TLR signaling and IL-1 signaling.

Clause 117. The method of any one of clauses 101 to 116, wherein the compound is more
effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when
compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4
15 without inhibiting IRAK1.

Clause 118. The method of clause 117, wherein the inhibition of IRAK1 and IRAK4 inhibits
cancer cell colony formation and/or cancer progenitor cell function.

Clause 119. The method of any one of clauses 101 to 118, wherein the compound provides
sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

20 Clause 120. The method of clause 119, wherein the sustained treatment is greater than the
treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or
inhibits IRAK4 without inhibiting IRAK1.

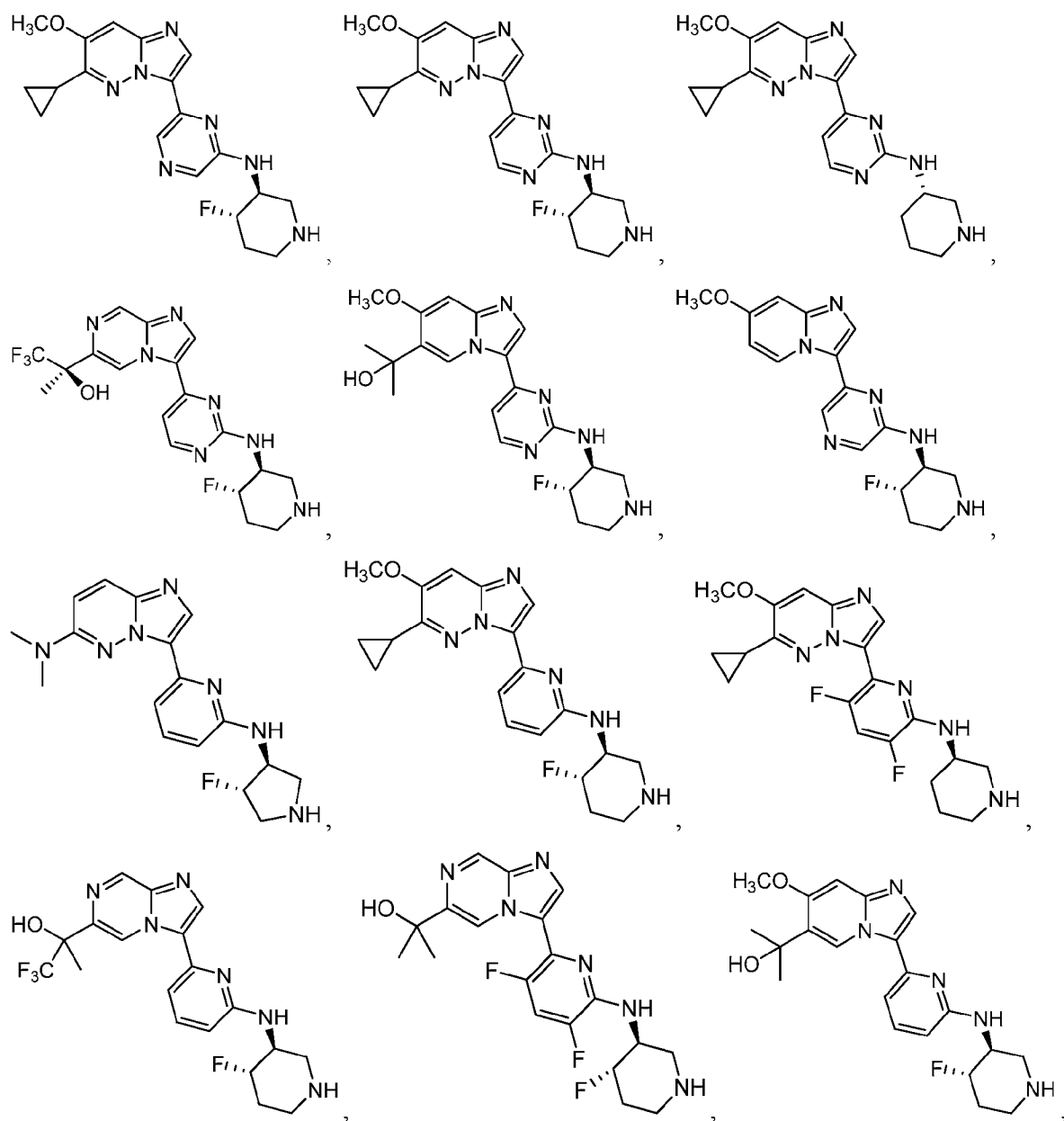
Clause 121. The method of any one of clauses 101 to 120, wherein the compound continues to
treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is
25 stopped.

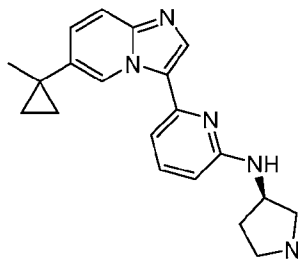
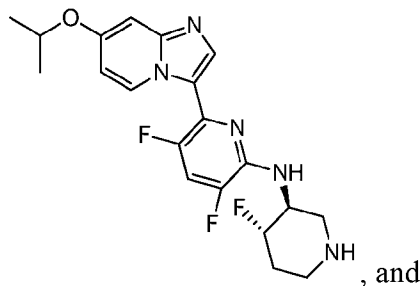
Clause 122. The method of clause 121, wherein the compound continues to treat the
inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about
3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three
weeks, or about a month after the administration is stopped.

30 Clause 123. The method of any one of clauses 101 to 122, wherein the compound treats MDS or
AML.

Clause 124. The method of any one of clauses 101 to 123, wherein the compound is a compound of any one of Formulas (I-5007), (II-5007)-(IIk-5007), (II-5007)-(II-5007), (III-5007)-(III-5007), (IV-5007), (VI-5003), (VII-5008), (II-5008)-(IIk-5008), (II-5008), (II-5008), (II-5008)-(IIu-5008), (III-5008)-(III-5008), (I-5009), (II-5009)-(IIj-5009), (I-5010), (Ia-5010)-
 5 (Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 125. The method of any one of clauses 101 to 124, wherein the compound is selected from:





, and
isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 126. A method of determining a compound that is effective at treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS),

5 comprising:

determining from the IRAK1 IC_{50} and IRAK4 IC_{50} of the compound that the compound inhibits IRAK1 and IRAK4;

calculating from the IRAK1 and IRAK4 IC_{50} of the compound that the compound has an IRAK4:IRAK1 potency ratio of less than about 40; and

10 administering the compound to a subject with an inflammatory disease/disorder, AML, or MDS, treating the inflammatory disease/disorder, AML, or MDS.

Clause 127. A method of determining a compound that is effective at treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

15 determining that the compound is an IRAK1/4 inhibitor which modifies the expression of one of more IRAK1/4-associated genes found to be differentially expressed in a subject with an inflammatory disease/disorder, AML, or MDS compared to a healthy control subject; and

administering the compound to the subject, treating the inflammatory disease/disorder, AML, or MDS.

20 Clause 128. The method of clause 127, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

Clause 129. The method of clause 127 or 128, wherein the compound decreases the expression
25 of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1,

ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the
5 subject.

Clause 130. The method of any one of clauses 127 to 129, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP,
10 JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 131. The method of any one of clauses 126 to 130, wherein the inflammatory
15 disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis.

Clause 132. The method of any one of clauses 126 to 131, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents,
20 AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

Clause 133. The method of any one of clauses 126 to 132, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

25 Clause 134. The method of any one of clauses 126 to 133, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

Clause 135. The method of any one of clauses 126 to 134, wherein the compound inhibits NF-kB-mediated signaling.

Clause 136. The method of clause 135, wherein inhibition of IRAK1 and IRAK4 inhibits NF-
30 kB-mediated signaling.

Clause 137. The method of any one of clauses 126 to 136, wherein the compound inhibits TLR signaling and IL-1 signaling.

Clause 138. The method of clause 137, wherein the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling.

5 Clause 139. The method of any one of clauses 126 to 138, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

10 Clause 140. The method of clause 139, wherein the inhibition of IRAK1 and IRAK4 inhibits cancer cell colony formation and/or cancer progenitor cell function.

Clause 141. The method of any one of clauses 126 to 140, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

15 Clause 142. The method of clause 141, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

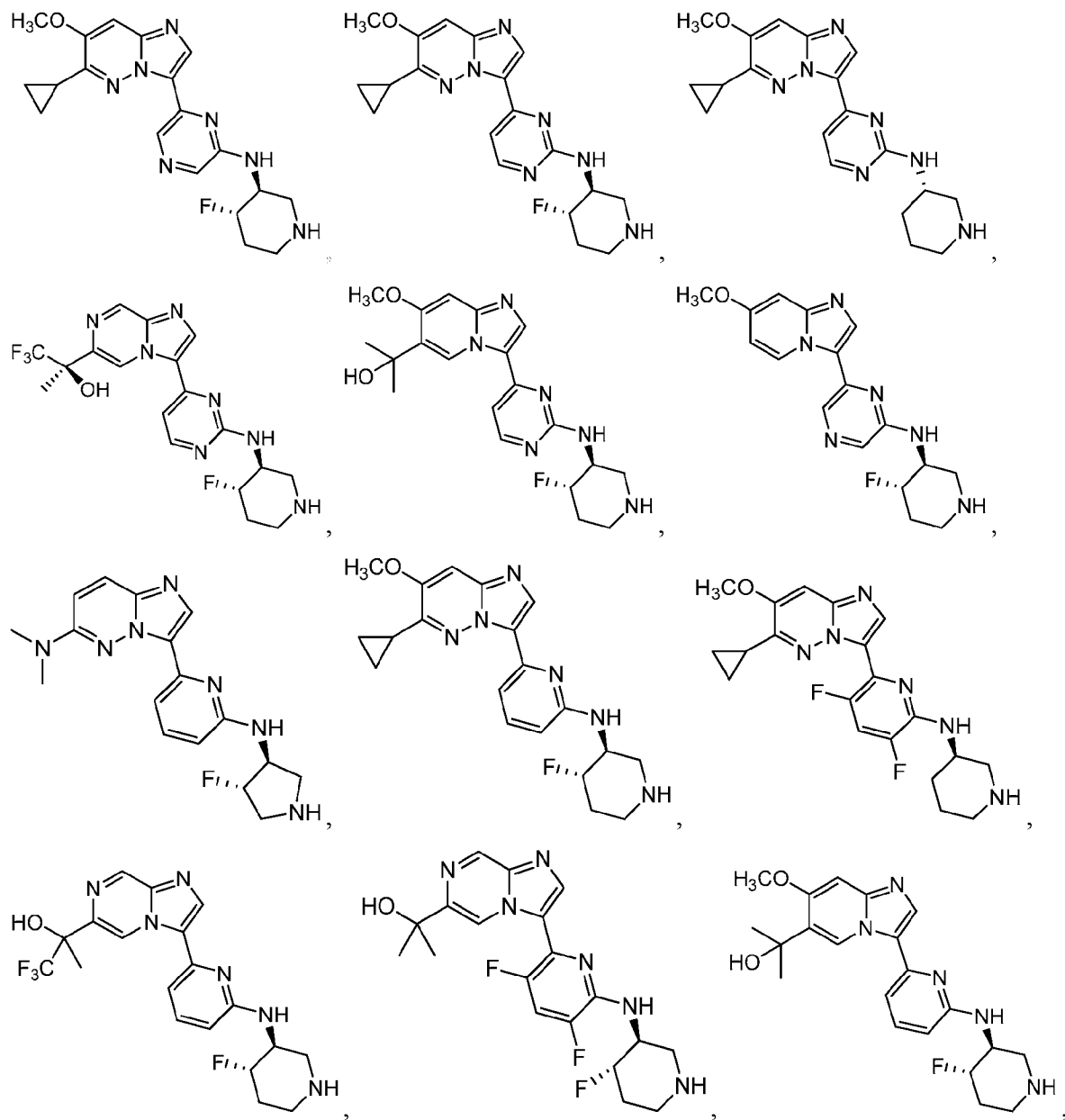
Clause 143. The method of any one of clauses 126 to 142, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped.

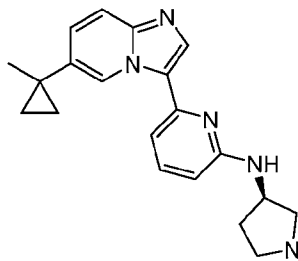
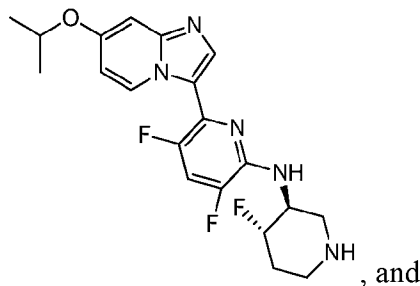
20 Clause 144. The method of clause 143, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 145. The method of any one of clauses 126 to 144, wherein the compound treats MDS or AML.

25 Clause 146. The method of any one of clauses 20 to 33, wherein the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010), (I_a-5010)-(I_d-5010), (II-5010), (II_a-5010), (II_b-5010), (III-5010), (III_a-5010), (III_b-5010), or a salt, ester,
30 solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 147. The method of any one of clauses 126 to 146, wherein the compound is selected from:





, and
isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 148. A method of determining a subject with a disease/disorder that can be treated by the administration of a compound which inhibits IRAK1 and IRAK4, comprising:

determining that a subject with an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) has elevated IRAK1 expression, IRAK4
5 expression, FLT3 expression, NF- κ B signaling, TLR signaling, IL-1 signaling, or a combination thereof; and

administering to the subject a compound that inhibits IRAK1 and IRAK4 wherein the compound has an IRAK4:IRAK1 potency ratio of less than about 40, as calculated from the IRAK1 and IRAK4 IC₅₀ of the compound, thus treating the inflammatory disease/disorder, AML,
10 or MDS.

Clause 149. The method of 148, wherein the subject has elevated IRAK1 expression, IRAK4 expression, or a combination thereof.

Clause 150. The method of clause 148 or 149, wherein the subject has elevated FLT3 expression.

15 Clause 151. A method of determining a subject with a disease/disorder that can be treated by the administration of a compound which inhibits IRAK1 and IRAK4, comprising:

determining that a subject with an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) has elevated expression of one or more IRAK1/4-associated genes compared to a healthy control subject and/or decreased expression of
20 one or more IRAK1/4-associated genes compared to a healthy control subject; and

administering to the subject a compound that inhibits IRAK1 and IRAK4, thus treating the inflammatory disease/disorder, AML, or MDS.

Clause 152. The method of clause 151, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy

control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

Clause 153. The method of clause 151 or 152, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2,

5 AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the
10 subject.

Clause 154. The method of any one of clauses 151 to 153, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP,
15 JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 155. The method of any one of clauses 148 to 154, wherein the inflammatory
20 disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis.

Clause 156. The method of any one of clauses 148 to 155, wherein the AML is relapsed AML,
25 refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

Clause 157. The method of any one of clauses 148 to 156, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

30 Clause 158. The method of any one of clauses 148 to 157, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

Clause 159. The method of any one of clauses 148 to 158, wherein the compound inhibits NF-kB-mediated signaling.

Clause 160. The method of clause 159, wherein inhibition of IRAK1 and IRAK4 inhibits NF-kB-mediated signaling.

5 Clause 161. The method of any one of clauses 148 to 160, wherein the compound inhibits TLR signaling and IL-1 signaling.

Clause 162. The method of clause 161, wherein the inhibition of IRAK1 and IRAK4 inhibits TLR signaling and IL-1 signaling.

10 Clause 163. The method of any one of clauses 148 to 162, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 164. The method of clause 163, wherein the inhibition of IRAK1 and IRAK4 inhibits cancer cell colony formation and/or cancer progenitor cell function.

15 Clause 165. The method of any one of clauses 148 to 164, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject.

Clause 166. The method of clause 165, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

20 Clause 167. The method of any one of clauses 148 to 166, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject after the administration is stopped.

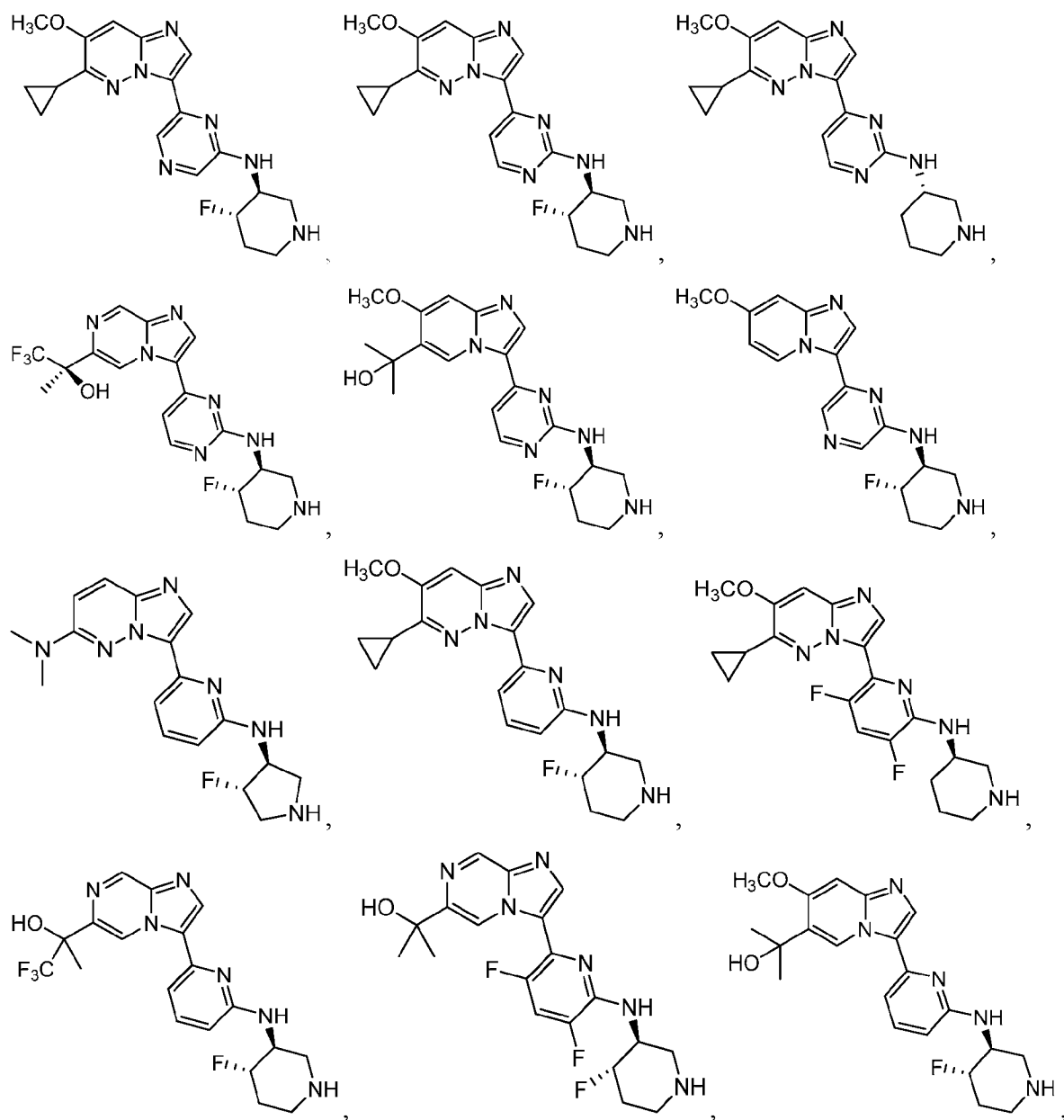
Clause 168. The method of clause 167, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject for about 1 day, about 2 days, about
25 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

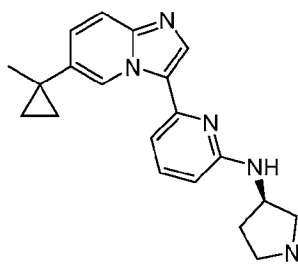
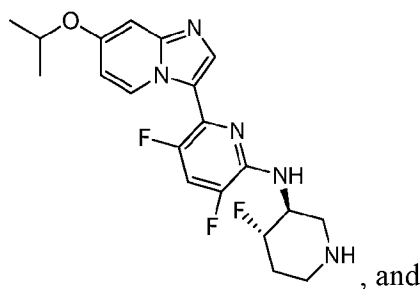
Clause 169. The method of any one of clauses 148 to 168, wherein the compound treats MDS or AML.

30 Clause 170. The method of any one of clauses 148 to 169, wherein the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-

5008)-(Ilu-5008), (IIIq-5008)-(IIIs-5008), (I-5009), (IIf-5009)-(IIj-5009), (I-5010), (Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 171. The method of any one of clauses 148 to 170, wherein the compound is selected from:





, and

, or a salt, ester, solvate, optical

isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 201. A method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a subject in need thereof, the method

5 comprising administering to the subject a compound that inhibits IRAK1 and IRAK4.

Clause 202. The method of clause 201, wherein the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and

10 colitis.

Clause 203. The method of clause 201, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

15 Clause 204. The method of clause 201, wherein the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2.

Clause 205. The method of clause 204, wherein the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2.

20 Clause 206. The method of any one of clauses 201 to 205, wherein the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, FLT3 expression, NF-κB signaling, TLR signaling, IL-1 signaling, or a combination thereof.

Clause 207. The method of clause 206, wherein the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, or a combination thereof.

25 Clause 208. The method of clause 206 or 207, wherein the subject in need thereof has elevated FLT3 expression.

Clause 209. The method of any one of clauses 201 to 208, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

Clause 210. The method of any one of clauses 201 to 209, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

5 Clause 211. The method of any one of clauses 201 to 210, wherein the compound has IRAK4:IRAK1 potency ratio of less than about 40.

Clause 212. The method of any one of clauses 201 to 211, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes compared to a healthy control subject and/or decreased expression of one or more IRAK1/4-associated genes compared to a
10 healthy control subject.

Clause 213. The method of clause 212, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP,
15 JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.

Clause 214. The method of clause 212 or 213, wherein the subject in need thereof has decreased
20 expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD,
25 ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.

Clause 215. The method of any one of clauses 212 to 214, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-
30 associated genes found to be decreased in the subject compared to the healthy control subject.

Clause 216. The method of clause 215, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 217. The method of clause 215 or 216, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 218. The method of any one of clauses 201 to 217, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 219. The method of any one of clauses 201 to 218, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject in need thereof.

Clause 220. The method of clause 219, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 221. The method of any one of clauses 201 to 220, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof after the administration is stopped.

Clause 222. The method of clause 221, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof for about 1 day,

about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 223a. The method of any one of clauses 201 to 222, wherein the compound is a compound of any one of Formulas (I-5007), (II-5007)-(IIk-5007), (IIl-5007)-(IIt-5007), (IIu-5007)-(IIv-5007), (IV-5007), (V-5007), (VI-5007), (VII-5007), (II-5008)-(IIk-5008), (IIl-5008), (IIm-5008), (IIn-5008), (IIp-5008)-(IIu-5008), (IIv-5008)-(IIw-5008), (I-5009), (II-5009)-(IIj-5009), (I-5010), (Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 223b. The method of any one of clauses 201 to 223a, wherein the compound is selected from any one of Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 224. A method of determining effectiveness of a compound in treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining the compound's IRAK1 IC₅₀ and IRAK4 IC₅₀;

calculating an IRAK4:IRAK1 potency ratio from the IRAK1 IC₅₀ and the IRAK4 IC₅₀ of the compound;

wherein a potency ratio of less than about 40 is indicative of effectiveness of the compound in treating the inflammatory disease/disorder, AML, or MDS.

Clause 225. The method of clause 224, further comprising administering the compound to a subject with an inflammatory disease/disorder, AML, or MDS, treating the inflammatory disease/disorder, AML, or MDS.

Clause 226. A method of determining effectiveness of a compound in treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining that the compound is an IRAK1/4 inhibitor which modifies the expression of one of more IRAK1/4-associated genes found to be differentially expressed in a subject with an inflammatory disease/disorder, AML, or MDS compared to a healthy control subject.

Clause 227. The method of clause 226, further comprising administering the compound to the subject, treating the inflammatory disease/disorder, AML, or MDS.

Clause 228. The method of clause 226 or 227, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

5 Clause 229. The method of any one of clauses 226 to 228, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP,
10 SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

Clause 230. The method of any one of clauses 226 to 229, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2,
15 TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1,
20 and BAG3 in the subject.

Clause 231. The method of any one of clauses 224 to 230, wherein the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes
25 mellitus, Crohn's disease, and colitis.

Clause 232. The method of any one of clauses 224 to 230, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

Clause 233. The method of any one of clauses 224 to 230, wherein the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2.

Clause 234. The method of clause 233, wherein the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2.

Clause 235. The method of any one of clauses 224 to 234, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

Clause 236. The method of any one of clauses 224 to 235, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

Clause 237. The method of any one of clauses 224 to 236, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 238. The method of any one of clauses 224 to 237, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS when administered to a subject in need thereof.

Clause 239. The method of clause 238, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

Clause 240. The method of any one of clauses 224 to 239, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in a subject in need thereof after administration of the compound to the subject is stopped.

Clause 241. The method of clause 240, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

Clause 242a. The method of any one of clauses 224 to 241, wherein the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010),

(Ia-5010)-(Id-5010), (II-5010), (IIa-5010), (IIb-5010), (III-5010), (IIIa-5010), (IIIb-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

Clause 242b. The method of any one of clauses 224 to 242a, wherein the compound is selected from any one of Compounds 1-7 to 295-7, 1a-7 to 79a-7, 1-3 to 68-3, 1-8 to 137-8, 1a-8 to 84a-8, 1-9 to 138-9, and 1-10 to 84-10, or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

EXAMPLES

Example 1: Inhibition of Both IRAK1 and IRAK4 is Required for Complete Suppression of NF- κ B Signaling Across Multiple Receptor-Mediated Pathways in MDS and AML

In this report, a pharmacological approach was used in which a series of IRAK inhibitors of varying relative potency at IRAK4:IRAK1 were examined for both inhibition of NF- κ B activation in AML cells and inhibition of leukemic progenitor cell function in vitro. It was found that potency and efficacy for antagonism at NF- κ B requires effective inhibition of both IRAK1 and IRAK4. It was also found that the relative potency of NF- κ B inhibition correlates with suppression of leukemic progenitor cell function in vitro, providing pharmacological validation that inhibition of both IRAK1 and IRAK4 are necessary for optimal inhibition of NF- κ B and effect on leukemia progenitor cell function.

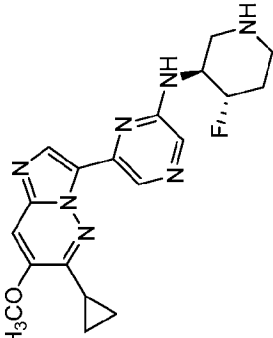
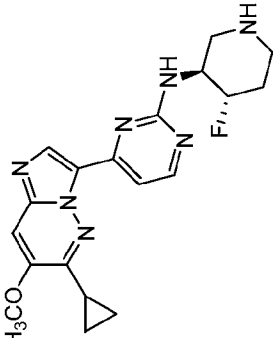
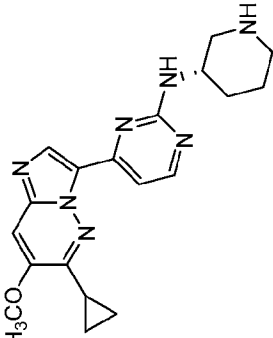
An NF- κ B reporter system expressed in human AML cells (THP1) was used to measure NF- κ B dependent activation in response to a variety of IRAK4, IRAK1, or IRAK1/4 antagonists. The cells are highly responsive to both TLR agonists as well as to IL-1 β , which allows for measurement of IRAK-mediated antagonism of multiple receptor-mediated pathways. Using the IRAK4-selective antagonists PF-06650833 and BAY 1834845 it was found that both compounds fully suppress signaling through TLR2 (IC₅₀ vs. Pam3CSK4 = 7.2 and 150 nM, respectively). The IRAK4 antagonists inhibit signaling through the IL-1R with similar relative potency (IC₅₀ vs. IL-1 β = 5.7 and 81 nM), but do not fully suppress signaling through this receptor (Span = 75% and 59%, respectively). Interestingly, the IRAK1 selective covalent inhibitor JH-X-119-01 does not inhibit signaling against either the TLR or the IL-1 receptor agonist. Together these data imply that neither IRAK4 nor IRAK1 inhibition alone is sufficient to fully inhibit NF- κ B-mediated signaling through multiple receptor mediated pathways.

For this reason, the activity of a series of IRAK4/IRAK1 inhibitors was examined in AML cells. This allowed for a study of the effect of adding in additional inhibitory activity at IRAK1 on the background of high potency IRAK4 inhibitors. Using two reference compounds with varying IRAK4:IRAK1 potency, the relative ability of these two compounds to inhibit TLR-agonist or IL-1 β -agonist stimulated NF-kB activity in AML was compared. Compound 15 has an IRAK4:IRAK1 potency ratio of 36 whereas Compound 14 has an IRAK4:IRAK1 potency ratio of 100. Unlike what was observed with the IRAK4-selective antagonists, both compounds can completely suppress NF-kB signaling through IL-1 β , with relative potencies apparently determined by their activity at IRAK1: (IC₅₀ vs. Pam3CSK4 = 6.3 and 73.8 nM for Compound 15 and Compound 14, respectively); (IC₅₀ vs. IL-1 β = 9.3 and 227 nM for Compound 15 and Compound 14, respectively).

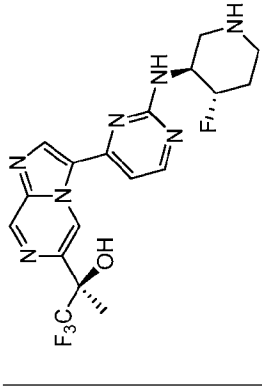
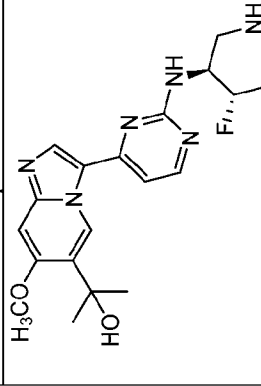
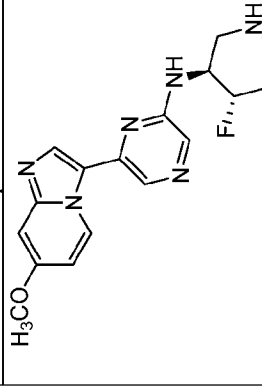
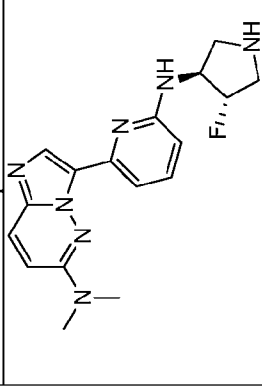
Finally, the correlation between potency in the biochemical kinase assay at IRAK1 or IRAK4, activity in the NF-kB reporter assay, and leukemic progenitor cell activity in the colony forming assay was examined for a series of compounds. A correlation was found between kinase activity for both IRAK1 and IRAK4 and NF-kB activity that extends to the leukemia colony forming assays. This suggests that NF-kB signaling contributes to leukemia progenitor cell function and that optimal inhibition requires potent antagonism of both IRAK1 and IRAK4 in the setting of MDS and AML.

See FIGS. 1-7 and Table 1 for the data described in Example 1.

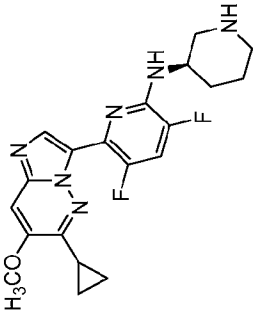
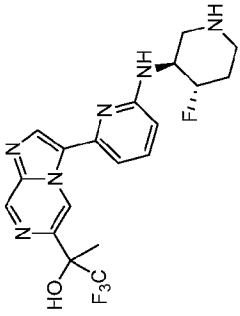
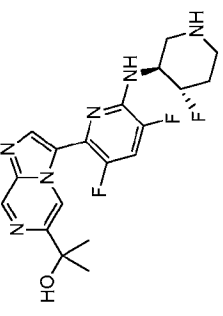
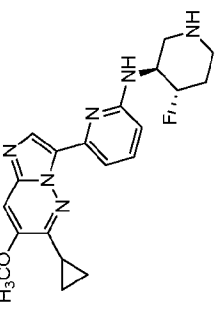
Table 1.

Compound	Reaction Bio		THP-1 NFκB		LOG(IRAK1)	LOG(IRAK4)	LOG(PAM)	LOG(IL1B)
	IRAK1 IC50	IRAK4 IC50	PAM IC50	IL1B IC50				
 Compound 1	52.8	1.350	242	209	1.72	0.13	2.38	2.32
 Compound 2	21.3	1.300	79.2	63.5	1.33	0.11	1.90	1.80
 Compound 3	62.6	4.400	317	316	1.80	0.64	2.50	2.50

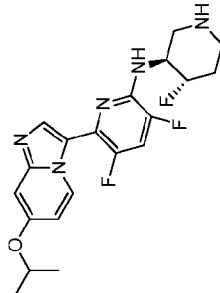
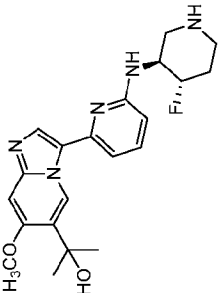
130364-5012-WO

 Compound 4	6.96	2.200	17.3	73.3	0.84	0.34	1.24	1.87
 Compound 5	3.84	0.609	10.5	25	0.58	-0.22	1.02	1.40
 Compound 6	40.4	0.898	27.6	33.6	1.61	-0.05	1.44	1.53
 Compound 7	1.54	0.637	3.3	15.1	0.19	-0.20	0.52	1.18

130364-5012-WO

Compound 7		27.2	1.540	62.9	58.7	1.43	0.19	1.80	1.77
Compound 8		21	0.500	14.2	25.9	1.32	-0.30	1.15	1.41
Compound 9		33	1.490	17.3	87.5	1.52	0.17	1.24	1.94
Compound 10		220	1.670	280	419	2.34	0.22	2.45	2.62
Compound 11									

130364-5012-WO

 Compound 12	14.7	1.060	12.2	48.8	1.17	0.03	1.09	1.69
 Compound 13	10.4	0.727	13.6	15.4	1.02	-0.14	1.13	1.19
CA-4948 (Emavusertib)	1757	31.2	307	580	3.24	1.49	2.49	2.76
BAY1834845	NA	10.7	150	81.2		1.02938378	2.18	1.91
PF-06650833	NA	0.2	496	678		-0.69897	2.70	2.83

Example 2: IRAK1 Contributes to IRAK4 Inhibitor Resistance Via Non-Canonical Signaling Mechanisms in MDS/AML

Herein, the mechanisms of resistance to IRAK4-selective inhibitors were explored in MDS/AML. The findings uncovered non-canonical IRAK1/4 signaling paradigms driving leukemic stem and progenitor cells (LSPC) and yielded novel therapeutic strategies for MDS/AML.

Consistent with the initial observations from the clinical trials, inhibition or deletion of IRAK4 in a panel of MDS/AML cell lines and patient samples resulted in incomplete suppression of LSPCs and a corresponding activation of innate immune pathways. Given the evolutionary conserved redundancy of IRAK-dependent pathways, the expression of IRAK paralogs was first examined. In IRAK4 knockout (KO) MDS/AML cells, only overexpression and activation of the IRAK4 paralog, IRAK1 was observed. IRAK4 kinase inhibitors or PROTACs resulted in a similar compensatory activation of IRAK1 in MDS/AML. To validate the compensation of IRAK1, IRAK1 was deleted in MDS/AML cells and it was found that concomitant suppression of IRAK1 led to a significant reduction of LSPC function in IRAK4-KO MDS/AML cells. Co-deletion of IRAK1 and IRAK4 similarly reduced leukemic engraftment and extended survival in an AML xenograft model. Hence, IRAK1 mitigates the efficacy of IRAK4-inhibitors in MDS/AML.

Canonical IRAK signaling depends on recruitment of MyD88 and IRAK4 to activated receptors, which results in the subsequent recruitment and activation of IRAK1. Based on this canonical model, IRAK1 and IRAK4 are thus independently essential for signaling. Since dual inhibition of IRAK1/4 is obligatory for suppression of LSPCs, it was posited that conventional IRAK signaling is not sufficient nor essential in MDS/AML. Therefore, the role of proximal upstream (MyD88) and downstream (TRAF6) effectors of IRAK1/4 was first examined.

Deletion of TRAF6 resulted in suppression of LSPCs as observed upon inhibition of IRAK1/4. In contrast, MyD88-KO AML cells did not exhibit a functional defect but did retain sensitivity to deletion of IRAK1 and IRAK4, indicating canonical MyD88-dependent signaling is not operational in MDS/AML. To investigate non-canonical IRAK1/4 signaling RNA- and ATAC-seq was performed and identified gene expression programs dependent on IRAK1 and/or IRAK4, yet independent of MyD88. IRAK1/4 deletion correlated with dysregulation of transcription factors involved in stem cell maintenance and myeloid differentiation. The

requirement for IRAK1/4 in preserving an undifferentiated LSPC state was corroborated by morphological assessment of IRAK1/4-KO MDS/AML cells. To delineate the signaling mechanisms by which IRAK1/4 governs stem programs, mass spectrometry proteomics was performed which identified unique IRAK4- and IRAK1-interacting proteins. Integration of the proteomic and transcriptomic studies identified pathways (HIF1A, STAT3/IRFs, E2F4) implicated in stem cell and undifferentiated states as effectors of IRAK1 and IRAK4.

To extend these studies to improve the efficacy of IRAK4-targeted therapy in MDS/AML, a novel series of structurally related inhibitors were developed targeting IRAK1 and IRAK4 (Compound 15: IRAK1 IC_{50} = 32 nM; IRAK4 IC_{50} = 0.9 nM) or IRAK4 alone (Compound 14: IRAK1 IC_{50} = >500 nM; IRAK4 IC_{50} = 5 nM). In human AML cell lines and patient samples, the dual IRAK1/4 inhibitor was significantly more effective at inducing cell death and differentiation, and attenuating LSPC function as compared to the IRAK4 inhibitor. Thus, the mandate for targeting both IRAK1 and IRAK4 established in these genetic studies translates to pharmacologic interventions.

Overall, it was demonstrated that compensation by IRAK1 is a barrier to IRAK4-directed therapy and revealed that dual IRAK1/4 inhibitors are needed for achieving optimal clinical response in MDS/AML. In the process, novel and non-canonical signaling paradigms governing the oncogenic role of IRAK1/4 were also uncovered.

Example 3: IRAK1 and IRAK4 Are Required for Leukemic Stem and Progenitor Cells Via Myd88-Independent Mechanisms in Myeloid Malignancies

Dysregulation of innate immune signaling is a hallmark of hematologic malignancies. Recent therapeutic efforts to subvert aberrant innate immune signaling in MDS and AML have focused on the kinase IRAK4. IRAK4 inhibitors have achieved promising, though moderate, responses in pre-clinical studies and in clinical trials for MDS and AML. The reasons underlying the limited responses to IRAK4 inhibitors remain unknown. Herein, it was revealed that inhibiting IRAK4 in leukemic cells elicits functional complementation and compensation by its paralog, IRAK1. Using genetic approaches, it was demonstrated that co-targeting IRAK1 and IRAK4 is required to suppress leukemic stem/progenitor cell (LSPC) function and induce differentiation in cell lines and patient-derived cells. While IRAK1 and IRAK4 are presumed to require the adaptor MyD88 for signaling, it was found that complimentary and compensatory IRAK1 and IRAK4 dependencies in MDS/AML occur via non-canonical MyD88-independent

pathways. Genomic and proteomic analyses revealed that IRAK1 and IRAK4 preserve the undifferentiated state of MDS/AML LSPCs by coordinating a network of pathways, including ones that converge on the PRC2 complex and interferon signaling. To translate these findings, a structure-based design of a potent and selective dual IRAK1 and IRAK4 inhibitor, Compound 15, was implemented. MDS/AML cell lines and patient-derived samples showed a significant suppression of LSPC function and viability when treated with Compound 15 as compared to selective IRAK4 inhibitors. The results provide a mechanistic basis and rationale for co-targeting IRAK1 and IRAK4 for the treatment of cancers, including MDS/AML.

Material and Methods

Compounds and materials

PF-06650833 (PZ0327-5MG) were Sigma-Aldrich. CA-4948 and IRAK4 degrader-1 was purchased from ChemExpress. Compound 14 and Compound 15 were obtained from Kurome Therapeutics.

Kinome screens

Dissociation constants (K_d) were measured at DiscoverX using the KINOMEscan Profiling Service. Kinase inhibition (IC_{50}) was measured at Reaction Biology using the Kinase Assay service.

Cell lines and patient-derived samples

THP1, OCI-AML3, and TF1 were purchased from the American Type Culture Collection. MDSL cells were provided by K. Tohyama (Kawasaki Medical School, Okayama, Japan). THP1 were cultured in RPMI-1640 medium with 10% FBS and 1% penicillin–streptomycin. MDSL and TF1 cell lines were cultured with complete RPMI supplemented with 10 ng ml⁻¹ recombinant human IL-3 (Stem Cell Technologies). OCIAML3 were cultured with Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS and 1% penicillin–streptomycin.

Bone marrow (BM) and peripheral blood samples from patients with AML at initial diagnosis were obtained with written informed consent and approved by the institutional review board of Cincinnati Children's Hospital Medical Center and University of Cincinnati, or from the Eastern Cooperative Oncology Group (ECOG). These samples had been obtained within the framework of routine diagnostic BM aspirations after written informed consent in accordance with the Declaration of Helsinki. De-identified leukemic cells from peripheral blood and BM of patients with AML were obtained at CCHMC following consent under the IRB approved Study ID

#2008-0021. To obtain sufficient cell numbers for functional studies, the AML samples were first expanded in immunocompromised mice. Patient samples were RBC lysed and coated with OKT3 antibody (UCHT1, BioXCell). Primary NSGS mice were given a single 30 mg/kg intraperitoneal dose of busulfan 24 hrs prior to intravenous or intrafemoral injection of the OKT3-coated cell preparations. After ~60 days (median 56 days, average 70 days) in xenografted mice, single cell spleen preparations were isolated and cultured in IMDM, 20% FBS, and 10 ng/mL of cytokines (SCF, TPO, FLT3L, IL3, IL-6). AML samples capable of indefinite expansion in liquid culture were selected for use in this study: AML(1714) and AML(1294).

Generation of CRISPR/Cas9 mutant cells

The THP1 IRAK4^{KO} clone was generated from a pre-derived WT THP1 clone. To generate the THP1 IRAK1^{KO} and IRAK1/4^{dkO}, the WT and IRAK4^{KO} clone were suspended in buffer R with Cas9-NLS and a modified synthetic gRNA targeting exon 1 of IRAK1 (Synthego) and electroporated (1700 mV x 20 ms x 1 pulse) using the Neon Transfection system (Invitrogen). Transfected cells were recovered for 48 hours in antibiotic-free RPMI-1640 with 1% FBS. Following recovery, transfected cells were plated in 96 well plates at a target density of 0.25 cells/well to isolate single clones. Clones were expanded and screened for IRAK1 deletion by immunoblotting. Deletion was confirmed by PCR amplification of the PAM site for Sanger sequencing. MDSL, TF-1, OCIAML3, AML(1714) and AML(1294) IRAK4^{KO} clones were generated from parental populations following the protocol outlined above using a synthetic gRNA targeting Exon 1 of IRAK4. WT clones were derived in parallel by plating parental cells in single-cell suspensions and expanding clones. MDSL and THP1 MyD88^{KO} and TRAF6^{KO} clones were generated from parental populations following the protocol outlined above using a synthetic gRNA targeting Exon 1 of MyD88 and Exon 1 of TRAF6, respectively.

Clonogenic assays

Clonogenic progenitor frequencies were determined by plating cell lines or patient samples in Methocult H4434 (Stem Cell Technologies) at a density of 500 cells per ml in SmartDish meniscus-free 6-well plates. Plates were kept in humidified chambers and colonies were imaged and manually scored after 9-14 days using the STEMvision counter (Stem Cell). For inhibitor treatments, cells were plated in methylcellulose (StemCell technologies H4236) at

the indicated concentrations of inhibitors. Cells were incubated at 37°C and 5% CO₂. Colonies were scored after ~10 days in culture.

Xenografts

Animals were bred and housed in an Association for Assessment and Accreditation of Laboratory Animal Care-accredited animal facility. WT, IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells were suspended in PBS and injected via tail vein into NOD-scid IL2R^{gnull}-3/GM/SF (NSGS) mice at a dose of 2.5×10^5 cells per mouse. Moribund mice were sacrificed and assessed for leukemic burden measurements. Briefly, mice were euthanized with carbon dioxide following the AVMA Guidelines for the Euthanasia of Animals and BM cells were immediately extracted by breaking the femurs with a mortar and pestle. BM cells were frozen in FBS with 10% DMSO until time of analysis. BM was analyzed for huCD45 (BDPharmingen, 555485) and huCD33 (BDPharmingen, 555450) expression by flow cytometry using a BD LSRFortessa (BD Biosciences). For staining, 1×10^6 cells from each BM sample were incubated with antibodies diluted 1:100 in a solution of PBS, 0.2% FBS for 30 minutes on ice in the dark. Cells were washed once with PBS, resuspended in PBS with 0.2% FBS, and immediately analyzed by flow cytometry. Spleens and livers from sacrificed were photographed and preserved in 10% phosphate buffered formalin for histological assessment of leukemic infiltration. For survival analysis, time of death was recorded, and Kaplan Meier survival analysis was performed using GraphPad Prism version 9 for Mac (GraphPad Software).

Immunoblotting

Protein lysates were made by lysing cells in cold RIPA lysis buffer (50 mM Tris-HCl, 150 mM NaCl, 1 mM ethylenediaminetetraacetic acid (EDTA), 1% Triton X-100, and 0.1% sodium dodecyl sulfate (SDS)) in the presence of sodium orthovanadate, phenylmethylsulfonyl fluoride (PMSF), and protease and phosphatase inhibitors. Protein concentration was quantified using bicinchoninic acid (BCA) assay (Pierce, Cat#23225). Protein lysates were separated by SDS-polyacrylamide gel electrophoresis (BIO-RAD), transferred to nitrocellulose membranes (BIO-RAD, Cat#1620112), and immunoblotted. The following antibodies were used for western blot analysis: GAPDH (Cell Signaling, Cat#D16H11, 1:1000 milk), Vinculin (Cell Signaling, Cat# 13901, 1:1000 BSA), IRAK4 (Cell Signaling, Cat#4363, 1:1000 BSA), IRAK1 (Santa Cruz, Cat#sc-5288, 1:1000 milk), phospho-IRAK1 (T209) (Assay Biotech, Cat#A1074, 1:500 BSA), phospho-SAPK/JNK (Thr183/Tyr185) (Cell Signaling, Cat#4668, 1:500 BSA), phospho-

p38 MAPK (Thr180/Tyr182) (Cell Signaling, Cat#4631, 1:500 BSA), phospho-p44/42 MAPK (ERK1/2, Thr202/Tyr204) (Cell signaling, Cat#4377, 1:1000 BSA), phospho-IKKa/b (Ser176/180) (Cell Signaling, Cat#2697, 1:500 BSA), MyD88 (Cell Signaling, Cat#4283, 1:1000 BSA, TRAF6 (Santa Cruz, Cat#sc-7221, 1:1000 milk), IRAK2 (Cell Signaling, Cat#4367, 1:1000 BSA), peroxidase-conjugated AffiniPure goat anti-rabbit IgG (Jackson ImmunoResearch Laboratories, Inc., Cat#111-035-003, 1:10000 milk), peroxidase-conjugated AffiniPure goat anti-mouse IgG (Jackson ImmunoResearch Laboratories, inc., Cat#115-035-003, 1:10000 milk). Blots were visualized using ECL Western Blotting Substrate (Pierce, Cat#32106) or SuperSignal West Femto Substrate (Thermo Scientific, Cat#34096) and imaged on a BIO-RAD ChemiDoc Touch Imaging system.

NF- κ B activation reporter

THP1-Blue NF- κ B SEAP reporter cells were grown in a 96-well plate in triplicate with the indicated inhibitor for 24 hours. In a new 96-well plate, 20 μ l of cell supernatant was added to 180 μ l of QuantiBlue Reagent (Invivogen, Cat#rep-qbs2) and incubated at 37 °C for 30 minutes. Absorbance was read at 630 nm.

RNA sequencing

WT, MyD88^{KO}, IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells were plated in triplicate at a uniform density of 5×10^5 cells per ml of complete media 24 hours prior to RNA collection. For inhibitor studies, cells lines were cultured at a density of 5×10^5 cell/mL in the presence of IRAK4 inhibitors for 24 hours. Inhibitor studies were performed in duplicate. RNA from IRAK KO and inhibitor-treated cell lines was isolated with the RNeasy Mini Kit (Qiagen). RNA quality was assessed with the Agilent 2100 Bioanalyzer. Sequencing libraries were prepared and sequenced at an average depth of 30M paired-end 100 nucleotide reads. FASTA files were used for alignment to the human genome (GRCh37) with the STAR software to generate BAM files. After the quality of reads was examined using FastQC, paired-end reads were aligned against the UCSC/hg38 genome using HISAT2 (v2.0.5). The raw gene counts were calculated using featureCounts (v1.5.2) and normalized using edgeR. Differentially expressed genes were predicted using limma/voom (v3.30.6).

Assay for Transposase-Accessible Chromatin (ATAC) sequencing

ATAC-sequencing was performed using a slightly modified version of the OMNI protocol. Briefly, nuclei were isolated by collecting 50,000 cells per sample and lysing in 10

mM Tris-HCl, pH 7.5/10 mM NaCl/3 mM MgCl₂ supplemented with 0.1% Tween-20, 0.1% NP-40 and 0.01% digitonin. Samples from each condition were collected in triplicate. The Illumina Tagment DNA TDE1 Enzyme kit (Illumina) was used for the transposition and tagmentation of open chromatin regions under the conditions specified by the OMNI protocol. DNA was next purified using the Qiagen MinElute Reaction Clean-up kit, per manufacturer's instructions. For library preparation, tagmented DNA was PCR amplified with the NEBNext High-Fidelity 2X PCR Master Mix using the Nextera i5 common adapter and i7 index adaptors. The amplified library was purified by size-selective precipitation with AMPure XP magnetic beads. Library concentrations were determined with the Qubit fluorometer and the dsDNA HS Assay Kit.

Library quality was assessed by running a portion of each sample on an agarose gel with SYBR Safe to visualize nucleosome banding. ATAC libraries were paired-end sequenced at 150 nucleotides per end on an Illumina NovaSeq 6000. After the quality of reads was examined using FastQC, adapters in paired-end reads were trimmed using Trim Galore (v0.6.6). Trimmed reads were aligned against the UCSC/hg38 genome using Bowtie2 (v2.4.2). Duplicated and multi-mapped reads (MAPQ cutoff = 30) reads were removed using PICARD (v2.18.22) and Samtools (v1.13.0), respectively. HOMER (v4.11) was used to predict and annotate differential peaks with the following parameters (-size 75 -mDist 50 -style factor -FDR 0.05). Differential peaks with FDR < 0.05 were considered as statistically significant.

Growth curves

For growth curves with IRAK4 inhibitors, cells were initially plated at a uniform density in 12-well plates with media containing designated concentrations of drug. Cells were counted every other day, at which point cultures were spun down to completely replace the media with fresh media and drug. Cells were split to maintain appropriate confluency, and dilution factors were recorded to adjust cell counts.

APEX affinity purification

The cDNA sequences for IRAK4 and IRAK1 were optimized using the IDT Codon Optimization tool. To produce N-terminal fusions, gBlocks encoding 5'-APEX2-spacer-V5 tag-IRAK1/4 cDNA-3' with overhangs for Gibson assembly were obtained from IDT. Due to the large size of IRAK1, the IRAK1 sequence was split into two gBlocks. NEBuilder HiFi DNA Assembly master mix was used to Gibson assemble the IRAK4 and IRAK1 gBlocks into the pCW57.1-eGFP plasmid, which was linearized by digestion with NheI and MluI. pCW57.1-

eGFP was generated from Addgene #41393 by substituting the puromycin cassette for eGFP. Assembled APEX2 vectors were transformed into One Shot™ Stbl3™ E. coli and individual colonies were expanded. APEX2 vectors were maxi-prepped and sequenced to confirm the fidelity of the inserts and then transfected into HEK-293T with 3rd generation lentiviral helper plasmids. IRAK4-APEX2, IRAK1-APEX2, and empty vector viral supernatants were collected and used to transduce IRAK4^{KO} and IRAK1^{KO} THP1. Transduced cells were sorted on GFP expression to obtain pure populations. Inducible expression of fusion proteins and functional rescue of canonical signaling was confirmed by immunoblot. To perform the proximity labeling, 2x10⁷ Dox-induced (0.5 mg/ml, 48 hrs) and uninduced cells were plated in 1 ml of pre-warmed media in quadruplicate. Cells were preloaded by incubating with 500 μM biotin phenol for 30 minutes at 37 °C. The APEX2 enzyme was then activated by adding H₂O₂ at a final concentration of 1 mM and gently agitating for 45 seconds. The reaction was immediately quenched by adding quenching buffer (PBS with 10 mM sodium azide, 10 mM sodium ascorbate, 5 mM Trolox). Cells were washed with quenching buffer two additional times and then lysed and sonicated in 500 uL RIPA containing protease inhibitor and quenchers. Lysates were rotated overnight with Sera-Mag blocked streptavidin SpeedBeads to precipitate biotinylated proteins. Beads were washed and stored at -80 °C prior to protein identification by mass spectrometry. Beads from one replicate each of the uninduced controls and dox-induced samples were eluted with sample buffer containing 20 mM DTT. Eluents were run on an SDS gel which was stained with imperial stain to ensure capture of biotinylated proteins above background in the dox-induced samples.

Statistical analysis

The number of animals, cells, and experimental/biological replicates can be found in the figure legends. Differences among multiple groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison posttest for all possible combinations. Comparison of two group was performed using the Mann-Whitney test or the Student's *t* test (unpaired, two tailed) when sample size allowed. Unless otherwise specified, results are depicted as the mean ± standard deviation or standard error of the mean. A normal distribution of data was assessed for data sets >30. For correlation analysis, Pearson correlation coefficient (*r*) was calculated. For Kaplan-Meier analysis, Mantel-Cox test was used. All graphs

and analysis were generated using GraphPad Prism software or using the package ggplot2 from R.

Results

IRAK4 inhibition or deletion results in compensatory activation of IRAK1 in MDS/AML

To interrogate the role of IRAK4 in HR-MDS/AML, a panel of cell lines and patient-derived samples was treated with two clinical-stage IRAK4 inhibitors, PF-06650833 (“PF-066”) and CA-4948 (Table 14), and cell viability and LSPC function was evaluated in methylcellulose. As expected, both IRAK4 inhibitors suppressed TLR-mediated NF- κ B activation at sub-micromolar concentrations (PF-06650833, IC_{50} = 7 nM; CA-4948, IC_{50} = 500 nM) (FIG. 8A).

Next, the effect of IRAK4 inhibitors on in vitro hematopoietic progenitor cell-mediated colony formation was evaluated in methylcellulose, a surrogate assay to assess LSPC properties. Consistent with previous reports, emavusertib (CA-4948) treatment resulted in a dose-dependent, yet incomplete, inhibition of colony formation in a subset of MDS/AML cell lines (MDSL and TF1) and patient-derived AML samples (AML1714 and AML1294) (FIGS. 9A-9N). PF-06650833 also resulted in inhibition of colony formation by MDSL and TF1 cells but was less effective at suppressing the patient-derived AML samples (FIG. 8B). The proliferation and cell survival of MDS (MDSL) and AML (THP1) cells was only modestly suppressed following treatment with CA-4948 (FIG. 8C), suggesting that IRAK4 inhibition is not cytotoxic but rather suppresses LSPC function. To confirm that the effects observed with the IRAK4 inhibitors were mediated by targeting IRAK4, a panel of IRAK4-deficient isogenic cell lines (IRAK4^{KO}) was generated using CRISPR/Cas9 (FIG. 9B). Generally consistent with the effects observed with the IRAK4 inhibitors, deletion of IRAK4 resulted in a significant, although moderate, reduction in leukemic progenitor cell colonies in a subset of MDS/AML cell lines (FIG. 9C). For OCIAML3 and AML(1294), pharmacologic or genetic targeting of IRAK4 did not result in suppression of colony formation, suggesting that inhibition of IRAK4 alone in these samples is not sufficient to suppress LSPC function. As observed with the IRAK4 inhibitor studies above, deletion of IRAK4 did not significantly affect MDS or AML cell survival (data not shown). Collectively, IRAK4 inhibition incompletely suppresses MDS/AML LSPC function in a subset of evaluated samples, recapitulating the observations from the single-agent clinical trials for HR-MDS and AML.

Table 14. Cell lines and patient-derived samples

Specimen	Diagnosis	IRAK4-L*	Relevant mutations/cytogenetics
AML(1714) (2017-114)	AML	Yes	MLL-AF10, PTPN11, del(11)(q21q23)
AML(1294)(2017-94)	AML	Yes	CDKN2A, CDKN2B
AML(64519)	AML	ND	TET2, EZH2, ASXL1, CEBPA, JAK2
AML(08)	AML	ND	Del(5), -3, del(17), +8, -15,
AML(0169)(2016-9)	AML	ND	EGFR, FLT3, FLT3-ITD, MLL-MLLT4, HOOK3-MYST3
MDS(76960)	MDS-RCMD	ND	ETV6
MDS(3328)	MDS	ND	U2AF1
THP1	AML (M5)	Yes	MLL-AF9, ATM, FANCD2, NRAS, TP73
MDSL	HR-MDS	Yes	CEBPA, NRAS, TET2, TP53, del(5q)
TF1	AML (M6)	Yes	MAP3K1, NRAS, SF3B1, TP53
OCIAML3	AML (M4)	Yes	NPM1, NRAS

To explore potential mechanisms for the moderate and incomplete responses to IRAK4 inhibitors in MDS/AML, gene expression changes in AML cells upon deletion or inhibition of IRAK4 were examined. RNA sequencing was performed on THP1 cells treated with the IRAK4 inhibitors (CA-4948, PF-06650833) or a PROTAC (IRAK4 degrader-1), and isogenic wild-type (WT) and IRAK4^{KO} THP1 cells. To identify potential compensatory pathways activated upon either IRAK4 kinase inhibition or IRAK4 degradation, the analysis was initially focused on upregulated genes (Log₂ FC > 1.5, q value > 0.05) (FIG. 9D and Tables 2-5 in Appendix A). There were 91 common upregulated genes following treatment with CA-4948 and PF-06650833 relative to vehicle-treated cells (FIGS. 9E and 9F). In THP1 cells following genetic deletion (IRAK4^{KO}) or pharmacologic degradation with a PROTAC (IRAK4 degrader-1) of IRAK4, 68 common upregulated genes were identified relative to the respective control cells (FIG. 9E and FIG. 9G). Unexpectedly, pathway analysis of the overlapping upregulated genes corresponded with significant enrichment for “TLR signaling” (P = 0.027) upon IRAK4 kinase inhibition (FIG. 9H) and “Inflammatory response” (P = 0.0006) and IL-6/JAK/STAT3 signaling” (P = 0.035) upon IRAK4 deletion (FIG. 9I). Since inflammatory-related signaling pathways were paradoxically activated in IRAK4-inhibited and -deleted AML cells, it was posited that compensatory signaling via the MyD88 complex may contribute to the limited efficacy of

IRAK4 inhibitors in leukemic cells. The proximal upstream (MyD88) and downstream (IRAK1, IRAK2, and TRAF6) effectors of canonical IRAK4 signaling were then focused on (FIG. 9J). IRAK1, IRAK2 and IRAK4 are also closely related paralogs with shared structural and functional elements. Immunoblotting of MDS/AML cell lines and patient-derived AML samples revealed increased protein expression of IRAK1 and TRAF6, but not MyD88 nor IRAK2, in IRAK4^{KO} MDS/AML cells as compared to control cells (FIG. 9K). Importantly, IRAK1 phosphorylation, which is an indication of its activation state, was also increased upon deletion of IRAK4 in the MDS/AML cells (FIG. 9L). To determine whether IRAK4 kinase inhibition similarly results in IRAK1 activation, immunoblotting of MDS/AML cell lines and patient-derived AML samples treated with the IRAK4 inhibitors or the IRAK4 PROTAC (IRAK4 degrader-1) was performed. Treatment with IRAK4 degrader-1 resulted in a dose-dependent decrease in IRAK4 protein expression and a reciprocal increase in IRAK1 phosphorylation (FIG. 9M). Similarly, CA-4948 resulted in increased IRAK1 phosphorylation in MDS/AML cells and in a patient-derived AML sample (FIG. 9N). Although the IRAK4 PROTAC and kinase inhibitors both induced IRAK1 activation, they did not result in increased total IRAK1 proteins. This discrepancy with the IRAK4^{KO} MDS/AML cells is likely due to the differences in duration of the experimental conditions. Nevertheless, IRAK4 deficiency or kinase inhibition corresponds with IRAK1 activation in MDS/AML cells.

Co-targeting IRAK1 and IRAK4 is required for maximal suppression of LSPCs

Since IRAK1 is activated upon inhibition or deletion of IRAK4, it was speculated that targeting IRAK1 would complement IRAK4 inhibitor treatment in MDS/AML. Using CRISPR/Cas9, IRAK1-deficient (IRAK1^{KO}) THP1 and MDS/AML cell lines were generated (FIG. 10A). IRAK1^{KO} MDS/AML cells exhibited similar growth kinetics and leukemic progenitor cell colony formation as WT THP1 and MDS/AML (FIGS. 11A-11B). However, IRAK1^{KO} MDS/AML cells were more sensitive to treatment with IRAK4 inhibitors (CA-4948) or the PROTAC (IRAK4 degrader-1) (FIGS. 11B-11C). A similar effect was also observed on IRAK1^{KO} MDS/AML cells treated with PF-06650833 (FIG. 10B). To confirm these observations with orthogonal approaches, IRAK1 was first knocked down using shRNAs expressed from lentiviral vectors in the isogenic WT and IRAK4^{KO} MDS/AML cell lines and patient-derived AML samples (FIG. 11D). While OCIAML3 remained less sensitive to deletion of IRAK1 and IRAK4, combined deficiency of IRAK1 and IRAK4 in THP1, MDS/AML, and AML(1294) resulted

in a significant reduction in leukemic progenitor cell colonies as compared to deficiency of either IRAK4 or IRAK1 alone (FIGS. 11E-11F). CRISPR/Cas9 was next used to generate isogenic double IRAK1 and IRAK4 deficient (IRAK1/4^{dKO}) THP1 cells (FIG. 11G). IRAK1/4^{dKO} THP1 cells expanded at a moderately slower rate in liquid culture as compared to IRAK1^{KO} or IRAK4^{KO} cells (FIG. 10C). However, IRAK1/4^{dKO} THP1 cells formed significantly fewer leukemic progenitor cell colonies as compared to IRAK1^{KO} or IRAK4^{KO} cells in the initial plating (FIG. 11H) as well as a secondary replating assay (FIG. 22A). To assess the consequences of combined IRAK1/4 deficiency on leukemia development *in vivo*, WT, IRAK4^{KO}, IRAK1^{KO}, and IRAK1/4^{dKO} THP1 cells were xenografted into NOD-scid IL2R^{null}-3/GM/SF (NSGS) mice. Mice engrafted with IRAK1/4^{dKO} THP1 cells survived longer than mice engrafted with either WT (P = 0.004), IRAK1^{KO} (P = 0.0002), or IRAK4^{KO} cells (P = 0.0022) (FIG. 11I and FIG. 22B). Histology samples collected at time of death revealed significantly reduced leukemia cell infiltration of IRAK1/4^{dKO} THP1 cells in the bone marrow (BM) (huCD33+CD15+) and liver (presence of nodules) as compared mice engrafted with WT, IRAK1^{KO}, or IRAK4^{KO} cells (FIGS. 11J-11K and FIG. 23). Thus, concomitant targeting of IRAK1 elicits an exaggerated LSPC defect in IRAK4-deficient MDS/AML models.

IRAK1 and IRAK4 dependency in MDS/AML is independent of canonical MyD88 signaling

IRAK1 and IRAK4 are presumed to transduce canonical MyD88-dependent signaling in a mutually dependent manner, wherein IRAK4 requires IRAK1 as a downstream effector upon MyD88 activation (FIG. 9J). Thus, singular loss of either kinase should be sufficient to abrogate signaling. However, this paradigm is inconsistent with the observed exaggerated defect of leukemic cells upon concomitant targeting of IRAK1 and IRAK4. Based on these observations, it was hypothesized that IRAK1 and IRAK4 exhibit a degree of functional redundancy downstream of MyD88 signaling in leukemic cells. To test this possibility, the consequences of IRAK1 and IRAK4 deletion on IL1R and TLR2 activation in THP1 cells was examined. As previously reported, deletion of either IRAK4 or IRAK1 was sufficient to prevent activation of NF-κB (pIKKb) upon stimulation with IL-1b (via IL-1R) (FIG. 10D). As a notable exception, phosphorylation of IKKb upon TLR2 stimulation with PAM3CSK4 was partially reduced in IRAK4^{KO} and IRAK1^{KO} THP1 cells, but completely ablated in the IRAK1/4^{dKO} cells (FIG. 10D). IRAK4 deletion was also sufficient to block phosphorylation of JNK and p38 upon TLR2 stimulation with PAM3CSK4 (FIG. 10E). In addition, it was observed that activation of MAPK

was increased at baseline in IRAK4^{KO} THP1 cells, which is consistent with the observed enrichment of inflammatory signatures in the gene expression analysis. Similar signaling dependencies on IRAK1 and IRAK4 were observed in MDSL cells (FIG. 10F). The role of MyD88 in MDS and AML cells was next explored. Deletion of MyD88 in THP1 and MDSL cells using CRISPR/Cas9 confirmed that downstream NF- κ B and MAPK pathway activation was terminated in MyD88^{KO} THP1 and MDSL cells upon IL1R or TLR2 stimulation (FIG. 12A), reaffirming an absolute requirement for MyD88 during canonical signaling.

If compromised canonical MyD88-dependent signaling underlies the IRAK1/4^{dKO} phenotype, deletion of MyD88 should phenocopy IRAK1/4^{dKO} MDS/AML cells. Surprisingly, MyD88^{KO} THP1 or MDSL cells formed equivalent number of colonies as compared to WT cells, indicating that MyD88 is dispensable for leukemic progenitor cell function (FIGS. 12B-12C). The dependency of MyD88^{KO} AML cells to loss of IRAK1/4 was next assessed. Knockdown of IRAK4 using shRNAs expressed from lentiviral vectors in isogenic WT and MyD88^{KO} THP1 and MDSL cell lines resulted in a significant reduction of leukemic progenitor cell function (FIGS. 12B-12D). Thus, IRAK1 and IRAK4 exhibit functions that are uncoupled from canonical MyD88 signaling in MDS/AML cells. Since it was observed that TRAF6, the proximal downstream effector of IRAK1/4 signaling (FIG. 9J), is upregulated upon deletion of IRAK4 in MDS/AML cells (FIG. 9K), it was next discerned whether TRAF6 remains relevant to MyD88-independent IRAK1/4 signaling. Deletion of TRAF6 in THP1 and MDSL cells using CRISPR/Cas9 resulted in a significant reduction in leukemic progenitor cell colonies (FIGS. 13A-13C), suggesting that MyD88-independent IRAK1/4 signaling requires TRAF6 as an effector. Collectively, these findings demonstrate that IRAK1 and IRAK4 mediate MyD88-independent functions that are critical for MDS and AML LSPC function.

Non-canonical IRAK1/4 signaling is essential for maintaining LSPC states in MDS/AML

To delineate the gene expression programs that are regulated by non-canonical MyD88-independent IRAK1/4 signaling in leukemic cells, a gene expression analysis was performed in isogenic WT, MYD88^{KO}, IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells. The replicates from each isogenic cell line clustered together and affirmed distinct gene expression programs (FIG. 14A). To focus on MyD88-independent gene expression programs, all differentially expressed genes that overlapped with the MyD88^{KO} cells were excluded from subsequent analyses (FIGS. 15A-15B and Table 6 in Appendix A). Deletion of IRAK1 or IRAK4 resulted

in 129 and 548 repressed genes, respectively, and 98 and 636 overexpressed genes, respectively, versus WT cells (>2-fold change; P value < 0.05) (Fig. 14B). Combined deletion of IRAK1 and IRAK4 resulted in 614 downregulated and 720 upregulated genes (FIG. 14B). Examination of the differentially expressed genes (DEGs) revealed a subset of genes unique to IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} cells (FIGS. 14C-14D and Table 7 in Appendix A). The DEG in the IRAK1/4^{dKO} THP1 cells mostly overlapped with the IRAK4^{KO} THP1 cells, with small subsets of genes that were coordinated by IRAK1 (FIGS. 14C-14D). Correspondingly, KEGG and PANTHER pathway analysis of the DEG in the isogenic cell lines corresponded with enrichment of dysregulated pathways in IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} AML cells (FIG. 14E). For example, down regulated genes in IRAK1^{KO} THP1 cells exhibit enrichment of pathways related HIF1a, metabolism, and inflammatory signaling; IRAK4^{KO} THP1 cells exhibit enrichment of pathways related TLR and WNT signaling, and glycolysis; and IRAK1/4^{dKO} THP1 cells exhibit enrichment of pathways related AMPK activation, HIF1a signaling, inflammation, and hematopoietic stem cells (FIG. 14E). MyD88^{KO} THP1 did not exhibit enrichment of these pathways, further supporting the observations that IRAK1/4 signaling can function independent of canonical MyD88 (Fig. 15C). Gene set enrichment analysis (GSEA) revealed that upregulated genes in IRAK1/4^{dKO} cells are associated with loss of HSC states and suppression of MLL-rearranged leukemia, as well as genes that are associated with neutrophil activation and RUNX1-mediated myeloid differentiation (FIG. 14F). A such, targeting of IRAK1 and IRAK4 results in gene expression programs associated with LSPC differentiation.

To determine whether IRAK1 and IRAK4 signaling in LSPCs is required for preserving an undifferentiated cell state of LSPCs, morphological changes of MDS and AML cells were examined upon deletion of IRAK1 and IRAK4. Wright-Giemsa staining of isogenic cell lines and patient-derived samples that are proficient (WT) or deficient for IRAK1 and IRAK4 (IRAK4^{KO};shIRAK1) was performed. As expected, WT MDS/AML cells exhibited uniform morphologies and low cytoplasmic to nuclear ratios (FIG. 14G). In contrast, IRAK1/4 dual-deficient MDS/AML cells had heterogeneous morphologies and size and exhibited increased cytoplasmic to nuclear ratios (FIG. 14G) and decreased expression of CD34 (FIG. 24). Such morphological changes are congruent with myeloid differentiation of leukemic cells. The single IRAK1 or IRAK4 deficient MDS/AML cells also exhibited evidence of morphological changes congruent with differentiation of leukemic cells but not to the magnitude observed upon

combined deficient of IRAK1 and IRAK4 (data not shown). Moreover, aberrant myeloid cell differentiation was not observed in MyD88^{KO} MDS and AML cells (Fig. 15D), suggesting that the observed morphological changes of leukemic cells upon deletion of IRAK1 and IRAK4 are uncoupled from canonical MyD88 signaling. These findings suggest that IRAK1 and IRAK4 mediate MyD88-independent functions that are critical for LSPC function by preserving an immature cell state.

IRAK1 and IRAK4 interactomes reveal non-canonical signaling networks associated with LSPC states.

It was found that IRAK1 and IRAK4 coordinate complimentary gene expression programs implicated in maintaining the undifferentiated state of LSPCs; however, the non-canonical signaling mechanisms and key effectors by which IRAK1/4 regulate these programs remains unknown. As such, to map out the IRAK1 and IRAK4 interactome in AML proximity labeling was performed followed by mass spectrometry analysis using APEX2. In the presence of biotin-phenol and hydrogen peroxide, APEX2 labels proteins with biotin in a 20 nm radius. APEX2 was fused to the N-terminal domains of V5-tagged IRAK1 and IRAK4 and expressed individually under the control of a doxycycline-inducible promoter (pCW57.1GFP) in IRAK1^{KO} and IRAK4^{KO} THP1 cells, respectively (Fig. 16A). Doxycycline-induced expression of IRAK1- and IRAK4-APEX2 fusion constructs was confirmed in IRAK1^{KO} (IRAK1^{KO};APEX2-IRAK1) and IRAK4^{KO} (IRAK4^{KO};APEX2-IRAK4) THP1 cells by immunoblotting with antibodies against V5 and either IRAK1 or IRAK4 (Fig. 17A). It was also confirmed that APEX2-IRAK1 and APEX2-IRAK4 retained their normal functions as they rescued the NF- κ B signaling defect in IRAK1^{KO} and IRAK4^{KO} THP1 cells, respectively (FIG. 17A). Proximity protein labeling was performed by inducing the APEX2 fusion proteins in IRAK1^{KO};APEX2-IRAK1 and IRAK4^{KO};APEX2-IRAK4 THP1 with doxycycline, incubating with biotin-phenol, and activating the APEX2 enzyme with hydrogen peroxide (FIG. 17B). Biotin tagged proteins from lysed cells were precipitated for identification and quantitative analysis on the LTQ-Orbitrap Elite Mass Spectrometer. Unique peptides that were >2-fold enriched in the doxycycline-treated samples (false discovery rate adjusted label-free quantification P value < 0.05) were pursued. Based on this criterion, 311 proteins proximal to IRAK4 and 142 proteins proximal to IRAK1 were identified in THP1 cells (FIG. 16B and Tables 8 and 9 in Appendix A). Two hundred ninety-two

proteins were unique to IRAK4 and 123 were unique to IRAK1 (FIG. 16B), while 19 proteins were common to IRAK1 and IRAK4 (FIG. 16B).

Canonical IRAK1/4 signaling activates members of the NF- κ B and MAPK pathways. As expected, several proteins implicated in functions associated with canonical IRAK1/4 signaling were identified, such as IKKb (IKBKB), RELB, p100/NF κ B2, and ERK (MAPK1) (FIG. 16B).

To uncover novel IRAK1/4 signaling networks in AML, an ontology pathway analysis was performed with Metascape using the list of IRAK1 (n = 142) and IRAK4 (n = 311) proximal proteins. The pathway analysis revealed that proximal IRAK4 proteins include effectors of multiple signaling pathways, such PI3K/AKT (GRB2, ERK1/2, GRB2, CBL), MAPK (ERK1 and ERK2), and RHO/GTPases (RAC1, VAV1, CDC42, and ROCK1) (FIG. 16C). Importantly, the dysregulated genes observed in IRAK4^{KO} AML (FIG. 14E) are enriched for several pathways, such as signaling related to integrins, inflammation, and TLRs, that can be directly explained by the aforementioned IRAK4 proximal proteins. Proximal IRAK1 proteins were significantly enriched for effectors of interferon and antiviral signaling (RIG-1, MX1, MX2, OAS1, STAT1 and STAT3) (FIG. 16D). Since STAT3 cooperates with HIF-1a in mediating target gene expression, STAT1/3 regulation by IRAK1 may therefore provide a mechanistic basis for the observed dysregulation of HIF-1a target genes in IRAK1^{KO} AML (FIG. 14E). There were also proteins that were found proximal to both IRAK1 and IRAK4, which include effectors of interferon/viral, VEGFR signaling and mRNA metabolism (FIG. 16B and FIG. 16E).

The enriched pathways among IRAK1 and IRAK4 proximal proteins are predicted to form physical interactions as demonstrated by a protein-protein interaction enrichment analysis using STRING (FIGS. 16F-16G). The IRAK1 and IRAK4 proximal proteins were next focused on as well as pathways that may provide a mechanistic explanation for the aberrant expression of genes that contribute to LSPC differentiation upon targeting of IRAK1/4. Integration of the enriched pathways derived from the gene expression analysis (FIGS. 16A-16H) and the interactome analysis highlighted the potential convergence of IRAK1 on interferon-related signaling and IRAK4 on the heteromeric polycomb repressive complex 2 (PRC2) (FIG. 16H).

As indicated above, several IRAK1 proximal proteins were identified that were directly implicated in interferon receptor and JAK-STAT signaling (Fig. 16H). Additionally, several members of the PRC2 core (EZH2, EED, CTBP1, VAV1) were identified among the top-ranking IRAK4 proximal proteins (FIG. 16H). SUZ12, EED, and EZH2 are part of the core heteromeric

PRC2 complex, a chromatin regulator that is responsible for repression of target genes by methylating H3K27. JAK-STAT and PRC2 function, including activating EZH2 mutations, are well-defined in AML LSPCs by regulating genes that promote cellular differentiation. Since the predicated IRAK1 and IRAK4 interactions are with nuclear proteins, the cellular localization of IRAK1 and IRAK4 in leukemic cells was examined. IRAK4 localized to the cytoplasm and nucleus of MDS and AML cells (FIG. 25A). In contrast, IRAK1 was primarily localized to the cytoplasm in these cells. To determine whether IRAK4 directly associates with the PRC2 complex, co-immunoprecipitation experiments were performed in AML cells. It was found that EZH2 co-immunoprecipitated with IRAK4 in THP1 cells (FIG. 25B), suggesting that nuclear IRAK4 can directly associate with the PRC2 complex in AML. To further interrogate this proposed IRAK1-IRAK4 network, it was also determined whether deletion of IRAK4 results in a corresponding increase in IRAK1-dependent JAK-STAT signaling. IRAK4^{KO} cells exhibited increased phosphorylated STAT5 as compared to WT cells, while IRAK1^{KO} cells expressed phosphorylated STAT5 below the levels observed in WT cells (FIG. 25C). Moreover, IRAK4^{KO} THP1 cells were sensitive to a STAT inhibitor (BBi608) as compared to IRAK1^{KO}, MyD88^{KO}, or WT cells (FIG. 25D). Collectively, these findings reveal extensive IRAK1 and IRAK4 signaling networks implicated in maintaining LSPCs and that extend beyond canonical MyD88-dependent signaling.

IRAK1/4 maintains undifferentiated leukemic cell states through chromatin and transcription factor networks

Next, studies were performed to gain further insight into the regulatory effectors downstream of non-canonical IRAK1/4 signaling that are required for maintaining LSPC states. Although the proteomic and transcriptomic analyses implicated several relevant pathways in MDS/AML, how IRAK1/4 signaling may coordinate chromatin and transcriptional factor networks was the focus. The PRC2 complex was nominated as one of the top-ranking hits among the IRAK4 proximal proteins and is responsible for transcriptional gene regulation in LSPCs via H3K27 tri-methylation (me3) at select genomic locations. One consequence of PRC2-mediated H3K27me3 is compaction of chromatin and loss of transcriptional factor accessibility at select gene loci, as such, chromatin accessibility was studied by performing Transposase-Accessible Chromatin using sequencing (ATAC-seq) and mapped global changes in chromatin accessibility in isogenic WT, MYD88^{KO}, IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO}

THP1 cells (FIG. 18A). To prioritize MyD88-independent pathways, as above, all differential chromatin peaks identified in MYD88^{KO} THP1 cells were excluded (Table 10 in Appendix A). IRAK1^{KO} (n = 657), IRAK4^{KO} (n = 1083), and IRAK1/4^{dKO} (n = 1224) THP1 cells displayed a similar number of closed peaks (FIG. 18B and Table 11 in Appendix A). However, IRAK1^{KO} THP1 cells exhibited significantly fewer open peaks (n = 23) as compared to IRAK4^{KO} (n = 2051) and IRAK1/4^{dKO} (n = 2184) THP1 cells (FIG. 18B). Upon examination of gene loci proximal to the differential chromatin peaks (<1 Mbp; P < 0.01), genes associated with increased chromatin accessibility peaks were identified (IRAK1 = 21, IRAK4 = 1524, and IRAK1/4 = 1705), as well as genes associated with loss of accessibility peaks (IRAK1 = 525, IRAK4 = 792, and IRAK1/4 = 824) in IRAK1^{KO}, IRAK4^{KO}, and IRAK1/4^{dKO} THP1 cells (FIG. 18C). IRAK4-regulated chromatin accessibility peaks are preserved in IRAK1/4^{dKO} THP1 cells, while the effects of IRAK1 on chromatin accessibility is minimal (FIG. 18C). Of the 525 genes associated with loss of chromatin peaks in IRAK1^{KO} THP1 cells, only 9 genes were significantly downregulated in the RNA sequencing data set (FIG. 18C), which are predicted targets of STAT1 (P = 0.002) (FIG. 18D).

To identify IRAK4-regulated factors that drive the IRAK1/4^{dKO} AML cell phenotype, genes that are both downregulated and associated with loss of chromatin accessibility in IRAK4^{KO} and IRAK1/4^{dKO} THP1 cells were first assessed (FIG. 18C). Significant overlap of genes that are repressed in IRAK4^{KO} and IRAK1/4^{dKO} THP1 cells was identified, which are enriched as targets of CREB Binding Protein (CBP) (P = 2.1x10⁻²¹) and E2F Transcription Factor 4 (E2F4) (P = 8.3x10⁻¹¹) (FIG. 18D). CBP and E2F4 are both implicated in maintaining LSPCs^{34,35}. Next, genes associated with open chromatin peaks and upregulated expression that are conserved in IRAK4^{KO} and IRAK1/4^{dKO} THP1 cells were examined (FIG. 18C). This set of genes were enriched for regulatory targets of SUZ12 (P = 1.4x10⁻⁵), EZH2 (P = 0.04), STAT3 (P = 0.01), and NANOG (P = 0.006) (FIG. 18E). Notably, SUZ12 and EZH2 are core members of the PRC2 complex. Thus, based on the transcriptomic and proteomic analyses, deletion of IRAK1 and IRAK4 is associated with loss of JAK-STAT signaling and PRC2-mediated function, and consequently expression of genes that mediate myeloid leukemia cell differentiation. These findings suggest that IRAK4 regulates a broad network of transcription factors and gene expression programs, while IRAK1 impacts a distinct and restricted gene regulatory network, that collectively preserve LSPC function. These observations also support

the concept that IRAK1 and IRAK4 function in a non-redundant mechanism independent of MyD88 signaling.

IRAK1/4 signaling programs define a subset of MDS and AML patients

To establish whether the core IRAK1/4 signaling program is operational in AML patients, an unsupervised hierarchical clustering analysis of RNA sequencing data from the BEAT AML trial for differential expression of the defined IRAK1/4-associated genes was performed. The set of 51 genes that were downregulated and associated with loss of chromatin accessibility in IRAK1/4^{dKO} THP1 cells was utilized. The list of genes was restricted to ones that were also differentially expressed in AML versus healthy controls (> 2-fold change; $P < 0.05$) (n = 27 genes; Table 12 in Appendix A). Patients with AML from the BEAT AML data set revealed 3 groups characterized by the distinct expression of the IRAK1/4-associated genes at diagnosis (FIG. 18F). Group 1 consists of AML patients with elevated expression of the IRAK1/4-associated genes (“IRAK1/4^{High}”), whereas Group 2 and 3 consists of AML patients with decreased and/or variable expression of these genes (“IRAK1/4^{Int/Low}”) (FIG. 18F). IRAK1/4^{High} AML were enriched for mutations in BCOR ($P = 0.007$), SRSF2 ($P = 0.0019$), JAK2 ($P = 0.029$), TET2 ($P = 0.03$), RUNX1 ($P = 0.07$), EZH2 ($P = 0.27$) as determined by Hypergeometric testing (FIG. 18G). In contrast, the same cohort of IRAK1/4^{High} AML patients were significantly underrepresented for mutations in CEBPA ($P = 0.006$), NPM1 ($P = 0.019$), FLT3 ($P = 0.034$), GATA2 ($P = 0.048$) and PTPN11 mutations ($P = 0.22$) (FIG. 18G). These enrichment mutation profiles are consistent with altered chromatin assembly via the PRC1/2 complex (BCOR, SRSF2, EZH2) and JAK-STAT signaling (JAK2). Independent analysis of the IRAK1/4-associated gene signature in additional adult (TCGA) and pediatric (TARGET) AML populations and MDS CD34+ cells also divided the patients into groups based on high and intermediate/low expression of IRAK1/4-associated genes (FIGS. 19B-19D). Although the IRAK1/4-associated gene signature did not have prognostic value nor did it correlate with age, the IRAK1/4 signature did correlate with myelomonocytic subtypes (M4 FAB) of AML in adult ($P = 3.28 \times 10^{-5}$) and pediatric patients ($P = 0.013$) and with an antecedent MDS (Supplemental FIG. 19D). These findings reveal that IRAK1/4 signaling programs are operational in MDS/AML and could define a subset of adult and pediatric patients with a greater dependency on IRAK1/4.

IRAK1/4 deficiency can be rescued by reactivation of stem cell programs and leukemia-associated transcriptional programs

To gain insight into the cellular processes that contribute to attrition of LSPCs following IRAK1/4 inhibition, a genome-scale CRISPR activation (CRISPRa) screen was performed to identify genes that restore the growth ability of IRAK1/4-deficient AML cells. IRAK1/4^{dKO} THP1 cells were selected for the screen as they exhibit a growth defect that correlates with impaired LSPC function in vitro and in vivo. WT and IRAK1/4^{dKO} THP1 cells were transduced with a CRISPRa single-guide RNA (sgRNA) library consisting of sgRNAs activating 18,000 coding isoforms (FIG. 18H). The transduced cells were grown for 3 weeks and then the sgRNA library was deep-sequenced. MAGECK was performed on the independent replicates to identify candidate genes that were enriched in IRAK1/4^{dKO} relative to WT cells (FIG. 18I and Table 13 in the Appendix). Several candidate genes have been previously shown to mediate leukemic activity, such as ETV5, TEAD1, CDC42, AKT1/2, and WNT10A. Pathway analysis on the candidate genes (top 438 based on fold change and P value) identified in IRAK1/4^{dKO} cells revealed significant enrichment of pathways implicated in stem cell activity (NES, 30.5; P value = 0.0032; Adjusted P value = 0.07) and cancer-related pathways (FIG. 18K). These overexpressed genes are predicted to be transcription targets of ATF3, USF1, E2F1, and MYC (FIG. 18J), which are directly implicated in LSPC function. Moreover, STAT3 target genes enriched in IRAK1/4^{dKO} cells were identified, supporting the earlier observations that loss of STAT signaling contributes to the impairment of IRAK1/4-deficient AML cells (FIG. 18J). This analysis highlighted that IRAK1/4 inhibition can be rescued by reactivation of stem cell programs and leukemia-associated transcriptional programs.

A dual IRAK1/4 inhibitor is effective at suppressing MDS/AML LSPCs

The complimentary and compensatory nature of IRAK1 and IRAK4 activation in AML cells necessitates concomitant inhibition of both targets to maximize therapeutic efficacy. Therefore, a small-molecule inhibitor was desired that simultaneously targeted the IRAK1 and IRAK4 kinase functions. IRAK1 and IRAK4 retain a high degree of structural homology, enabling the generation of dual selective compounds. NCGC1481, derived from a 3-(pyridine-2-yl)imidazole[1,2-a]pyridines backbone with inhibitory activity against IRAK1 and IRAK4, was utilized as a chemical starting point for further optimization of a dual IRAK1/4 inhibitor. Structure activity relationship exploration of this core scaffold yielded a series of small

molecules that potently targeted IRAK1 and IRAK4. In functional biochemical assays, Compound 15 exhibited high affinity binding (dissociation constant, K_d) and potent inhibition (inhibitory constant, IC_{50}) of both IRAK1 ($K_d = 2.2$ nM; $IC_{50} = 32$ nM) and IRAK4 ($K_d = 0.2$ nM; $IC_{50} = 0.9$ nM) (FIG. 20A). A structurally similar derivative was also identified (Compound 14) with selectivity for IRAK4 ($K_d = 5$ nM; $IC_{50} = 5$ nM), but not IRAK1 ($K_d = 150$ nM; $IC_{50} > 500$ nM) (FIG. 20A). Whereas Compound 14 and Compound 15 were equipotent IRAK4 inhibitors, their differential potency against IRAK1 allowed for the evaluation of the additional therapeutic benefit of targeting IRAK1. It was first confirmed that the small molecules inhibit canonical IRAK1/4-mediated signaling in AML cells upon TLR stimulation. TLR2-mediated activation of NF- κ B was selected as a readout as it was previously found that combined deletion of IRAK1 and IRAK4 is needed to completely inhibit NF- κ B activation (FIG. 10E). The dual IRAK1/4 inhibitor Compound 15 ($IC_{50} = 4.5$ nM) was significantly more effective at suppressing TLR2-mediated activation of NF- κ B in THP1 cells as compared to the IRAK4 inhibitor Compound 14 ($IC_{50} = 155$ nM) (FIG. 20B). Moreover, Compound 15 completely suppressed TLR2-mediated activation of NF- κ B at 100 nM while Compound 14 achieved only ~80% suppression of the pathway at 5 μ M (FIG. 20B). As expected, Compound 15 also inhibited auto-phosphorylation of IRAK1 in THP1 and MDSL cells, while Compound 14 did not affect phosphorylation of IRAK1 (FIG. 20C). These findings indicate that Compound 15 is more effective at suppressing canonical signaling via TLR2 due to combined targeting of IRAK1 and IRAK4 as compared to the selective IRAK4 inhibitor Compound 14.

The gene expression changes were next compared in AML cells treated with the dual IRAK1/4 inhibitor Compound 15 and the IRAK4 inhibitor Compound 14. As expected, there were a set of common genes downregulated (“IRAK4-dependent genes”) following treatment with both inhibitors relative to vehicle-treated cells (FIG. 20D). These genes were enriched in MAPK/AP1, ATF4, IGFBP, and EGFR signaling (FIG. 21A). However, treatment with the dual IRAK1/4 inhibitor Compound 15 also resulted in downregulated genes that remained expressed in cells treated with Compound 14 (“IRAK1-dependent genes”) (FIG. 20D). Consistent with the observation that IRAK1 mediates JAK/STAT/interferon signaling (FIGS. 14A-14G, 16A-16H, and 18A-18G), the genes selectively suppressed by the dual IRAK1/4 inhibitor Compound 15, but not the IRAK4 inhibitor Compound 14, are highly enriched in interferon-related pathways (FIG. 21B). The effectiveness of the IRAK1/4 and IRAK4 inhibitors at suppressing the core

“IRAK1/4 AML signature” was also examined (FIG. 18B). The dual IRAK1/4 inhibitor Compound 15 suppressed most genes (~65%) associated with the “IRAK1/4 AML signature,” while the IRAK4 inhibitor Compound 14 had an unremarkable effect on these genes (FIG. 20D). As such, targeting the kinase function of IRAK1 and IRAK4 results in suppression of gene expression programs that are insufficiently inhibited upon targeting IRAK4 alone.

Lastly, it was tested whether dual IRAK1/4 inhibition is more effective than selective IRAK4 inhibition at suppressing LSPCs by evaluating the activity of Compound 14 and Compound 15 on a panel of MDS/AML cell lines and patient-derived samples (FIG. 20E). The IRAK4 inhibitor Compound 14 resulted in an approximately 75% reduction in leukemia progenitor cell colony formation of all MDS/AML cell lines (60-75%) and patient-derived AML samples evaluated (80-85%) (FIG. 20E). The variation in efficacy of the IRAK4 inhibitors Compound 14, CA-4948, and PF-06650833 at suppressing MDS/AML LSPCs is likely due to the unique physical properties and polypharmacology of each chemical structure. As expected, Compound 15 was more effective at inhibiting leukemia progenitor cell colony formation of the MDS/AML cell lines and patient-derived AML samples (FIG. 20E). At these concentrations, Compound 15 treatment of healthy donor CD34+ cells only modestly inhibited myeloid cell colonies yet increased erythroid colony formation (FIG. 21C). In all samples (except for THP1 cells), Compound 15 resulted in complete suppression of leukemia progenitor cell colony formation (FIG. 20E). Compound 15 was also more effective than Compound 14 at mediating apoptosis of the AML cell lines and patient-derived samples (FIG. 20F). Wright-Giemsa staining was performed on MDS/AML cell lines and patient-derived samples treated Compound 14 and Compound 15 for 12 days. Dual inhibition of IRAK1/4 with Compound 15 coincided with heterogeneous morphologies and size and increased cytoplasmic to nuclear ratios, suggestive of aberrant differentiation (FIG. 20G). These morphological changes were more prominent in leukemic cells treated with Compound 15 relative to Compound 14. Consistent with the morphological changes, Compound 15 treatment resulted in a greater expression of CD38, a glycoprotein expressed on mature immune cells, as compared to Compound 14 or vehicle (FIG. 21D).

A dual IRAK1/4 inhibitor suppresses MDS/AML in xenografted mice

Impaired cellular differentiation is a hallmark of MDS and AML and treatment approaches that promote differentiation are curative in certain subtypes of AML. Therefore, to confirm that the

differentiated state of the leukemic cells upon IRAK1/4 inhibition correlates with suppression of LSPCs in vivo, first the leukemic potential of patient-derived AML cells that were exposed to either the dual IRAK1/4 or selective IRAK4 inhibitor for 21 days in vitro were evaluated (FIG. 20I). Exposure of patient-derived AML cells to Compound 15 corresponded with significantly diminished colony formation in vitro (FIG. 21E) and complete loss of leukemic engraftment and AML development in vivo (FIGS. 20J and 20K). In contrast, targeting IRAK4 alone with Compound 14 only partially suppressed LSPCs in vitro and in vivo. These findings suggest that IRAK1/4 is important for preserving the leukemia-propagating cells, and that targeting IRAK1/4 can induce differentiation and suppress LSPC function and AML development.

To evaluate the therapeutic potential of targeting IRAK1/4 in vivo, xenograft studies were also performed using patient-derived AML and MDS samples. Immunocompromised mice were engrafted with leukemic cells from patients with AML or MDS for two weeks and then treated with vehicle, Compound 14, or Compound 15 daily for up to 48 days (FIG. 20L). Leukemic cell engraftment in the PB was significantly reduced with the dual IRAK1/4 inhibitor for AML(64519)($P = 0.007$; FIG. 20M), AML(0169)($P = 0.04$; FIG. 20N), or MDS(76960) ($P = 0.004$; FIG. 20O) as compared to vehicle treated mice. However, the IRAK4 inhibitor Compound 14 did not significantly suppress leukemic cell engraftment during the same time (FIGS. 20M-20O). Collectively, these findings suggest that dual IRAK1 and IRAK4 inhibition is required for maximal suppression of signaling and LSPC function (FIG. 20H). To determine whether the reduced leukemic cell engraftment impacts overall survival, mice engrafted with AML(0169) were monitored. Mice treated with the vehicle or Compound 14 achieved a median survival of 29 and 33 days, respectively (FIG. 20P). In contrast, mice treated with Compound 15 survived significantly longer (median of 40 days) (FIG. 20P). Although not wishing to be limited by theory, these findings suggest that dual IRAK1 and IRAK4 inhibition more effectively suppresses AML as compared to targeting IRAK4 alone.

Discussion

Cell-intrinsic dysregulation of innate immune and inflammatory-related pathways as well as systemic inflammation have been implicated in myeloid malignancies, including MDS and AML. Specifically, LSPCs exhibit extensive dysregulation of immune and inflammatory pathways, many of which converge on IRAK4 signaling. As such, IRAK1 and IRAK4 have been both independently studied in the context of MDS and AML biology; however, their

interdependent and complimentary functions have not been sufficiently explored. Based on the central dogma that targeting IRAK4 is sufficient to suppress IRAK1-dependent signaling, several IRAK4 inhibitors and PROTACs are currently being investigated as therapeutic agents for inflammatory diseases and hematologic malignancies. Initial data from clinical trials evaluating IRAK4 inhibitors in HR-MDS and AML revealed encouraging responses in patients with spliceosome mutations that are known to induce hypermorphic IRAK4 isoforms. A subset of patients without spliceosome mutations also exhibited responses to IRAK4 inhibitors, suggesting that IRAK4 signaling is operational in other subtypes of HR-MDS and AML. Based on the initial clinical data as well as pre-clinical studies, IRAK4 therapies are likely inadequate as monotherapies for hematologic malignancies. Furthermore, despite that signaling redundancy is an evolutionarily conserved feature of the mammalian immune system, insufficient attention has been given to the possibility that the IRAK4 paralog, IRAK1, may functionally compensate and/or compliment IRAK4 deficiency in leukemic cells. Such models of functional compensation or complementation by proximal effectors in signaling pathways are common mechanisms underlying therapy resistance and limited therapeutic efficacy in cancer. Treatment of RAS-mutant cancers with MEK inhibitors, for instance, results in upregulation of other mediators of the MAPK pathway to restore signaling. Similarly, P53 can be inactivated by interaction with either MDM2 or its paralog MDMX; while therapeutic efforts have focused on inhibiting the interaction with MDM2, a recently developed MDM2/MDMX dual-inhibitor achieves superior efficacy in suppressing LSPC function in preclinical AML models. Herein, it was demonstrated that deficiency or inhibition of IRAK4 paradoxically elicits inflammatory signaling pathways, including JAK/STAT/interferon signaling, via upregulation and/or activation of IRAK1 (FIG. 20H). Leveraging genetic and pharmaceutical interventions, it was found that this phenomenon translates to a robust LSPC defect when simultaneously targeting IRAK1 and IRAK4.

Interrogating the physiologic underpinning for the requirement for IRAK1 and IRAK4 in AML, MyD88-independent IRAK1/4 signaling functions were also uncovered. Though IRAK1 and IRAK4 are subject of broad study as central effectors of innate immune responses and recruitment of adaptive immunity, mechanistic dissection of IRAK1/4 functions in myeloid malignancies are lacking. Therapeutic efforts to target IRAK1/4 signaling for these diseases have conveniently adopted paradigms formed in studies of innate immunology that are based

exclusively on models of acute receptor stimulation, wherein the adaptor MyD88 nucleates a complex with IRAK4 to activate IRAK1 and initiate signaling through the NF- κ B and MAPK pathways. Consequently, IRAK4, as the proximal effector of MyD88-dependent signaling, has been the exclusive focus of therapeutic interventions without consideration for the possibility that IRAK1 and IRAK4 may execute distinct and/or compensatory functions in malignant cells. Here, it was shown that MyD88 is indeed dispensable for MDS/AML LSPC function, while MyD88-deficient LSPCs remain dependent on IRAK1/4 signaling. Through transcriptional and chromatin studies, it was found that MyD88-independent IRAK1/4 signaling is required to preserve the undifferentiated state of LSPCs and that a MyD88-independent “IRAK1/4 signature” is present in a subset of MDS and AML patients. Proximity labelling to characterize the unique and overlapping interactomes of IRAK1 and IRAK4 did identify components of NF- κ B and MAPK signaling as interactors of IRAK1 and IRAK4, however, the majority of proximal proteins mapped to MyD88-independent pathways. For instance, high-confidence interactions were identified between IRAK4 and core constituents of the PRC2 complex, an epigenetic regulator that is requisite for the maintenance of LSPCs. The interaction with the PRC2 complex is consistent with the differentiated phenotype observed upon deletion or inhibition of IRAK4 in AML and corresponding alterations in chromatin accessibility at PRC2-regulated genomic loci. These findings are further corroborated by the enrichment of BCOR and SRSF2 mutations in AML patients with the “IRAK1/4 signature.” BCOR is a component of the PRC1 complex, which is recruited by PRC2 to genomic loci, while SRSF2 mutations cause mis-splicing of the PRC2 component EZH2 and are mutually exclusive with EZH2 mutations in some hematologic malignancies. Collectively, these data argue that the PRC2 complex is a disease-relevant substrate of IRAK4 signaling in MDS/AML.

The IRAK4 interactome also included mediators of AKT signaling and core machinery of receptor tyrosine kinase signaling (GRB2, ERK1, ERK2, RAC1), indicating a role for IRAK4 in growth factor signal transduction. Thus, IRAK4 is far more dynamic than is ascribed by models of acute TLR stimulation. It was found that high-confidence IRAK1 interactions mapped to mediators of JAK/STAT/interferon signaling, which could account for the induction of a JAK/STAT/interferon signaling observed upon genetic or pharmaceutical deficiency of IRAK4. While excessive interferon signaling can suppress normal and malignant hematopoiesis, recent reports indicate a requirement for tonic, sterile interferon signaling in LSPC maintenance.

Notably, activating JAK2 mutations are also significantly enriched in AML patients with the “IRAK1/4 signature,” further suggesting that IRAK1 coordinates JAK/STAT/interferon signaling. Collectively, these studies resolve novel MyD88-independent signaling mechanisms for IRAK1 and IRAK4 and present a model wherein (1) IRAK4 regulates epigenetic machinery and signaling pathways that mediate a differentiation block in leukemic cells, and (2) targeting of IRAK4 upregulates IRAK1 to activate complimentary signaling pathways, including the JAK/STAT/interferon axis (FIG. 20H).

As this model presents a rational basis for the design of dual IRAK1/4 targeted therapy, a set of structurally similar small molecule inhibitors were developed with selectivity for IRAK4 (Compound 14) or dual-selectivity for IRAK1 and IRAK4 (Compound 15). In line with genetic models, the dual IRAK1/4 inhibitor induced differentiation and suppressed the function of LSPCs more effectively than the IRAK4-selective inhibitor. Furthermore, it was found that genes that are downregulated upon treatment with the dual IRAK1/4 inhibitor, but not the IRAK4-selective inhibitor, are significantly enriched for JAK/STAT/interferon signatures. This finding confirms that activation of JAK/STAT/interferon signaling by IRAK1 can be suppressed by pharmacological inhibition and suggests that this may underly a therapeutic advantage for dual IRAK1/4 therapy.

Although AML was relied on as a model system, it is anticipated that the MyD88-independent complimentary functions of IRAK1 and IRAK4 can be extended to other pathologies and perhaps normal immunobiology. Both IRAK1 and IRAK4 are implicated as effectors of pathogenesis, stemness, and chemoresistance in numerous solid tissue tumors. Thus, IRAK1/4-targeted therapies may gain traction for malignancies of diverse tissue types, lending greater importance to the optimization of treatment strategies. Whether the roles of IRAK1 and IRAK4 in solid tissue tumors are attributable to MyD88-independent signaling, and whether IRAK1 and IRAK4 complement each other in these contexts remains unknown. Addressing these questions will be critical in determining if a therapeutic mandate for targeting of IRAK1 and IRAK4 is broadly applicable. Collectively, it was demonstrated that IRAK1 and IRAK4 mediate compensatory and complementary MyD88-independent functions that underly a need for dual IRAK1/4 inhibitors. The findings also reveal that IRAK1 and IRAK4 signaling is dynamic with wide-ranging implications for treating malignancies and inflammatory disease.

References

1. Cazzola, M. Myelodysplastic Syndromes. *N Engl J Med* 383, 1358-1374 (2020).
2. Kantarjian, H., et al. Acute myeloid leukemia: current progress and future directions. *Blood Cancer J* 11, 41 (2021).
- 5 3. Pandolfi, A., Barreyro, L. & Steidl, U. Concise review: preleukemic stem cells: molecular biology and clinical implications of the precursors to leukemia stem cells. *Stem Cells Transl Med* 2, 143-150 (2013).
4. Shastri, A., Will, B., Steidl, U. & Verma, A. Stem and progenitor cell alterations in myelodysplastic syndromes. *Blood* 129, 1586-1594 (2017).
- 10 5. Stauber, J., Grealley, J.M. & Steidl, U. Preleukemic and leukemic evolution at the stem cell level. *Blood* 137, 1013-1018 (2021).
6. Daver, N., et al. New directions for emerging therapies in acute myeloid leukemia: the next chapter. *Blood Cancer J* 10, 107 (2020).
7. Krivtsov, A.V., et al. A Menin-MLL Inhibitor Induces Specific Chromatin Changes and
15 Eradicates Disease in Models of MLL-Rearranged Leukemia. *Cancer Cell* 36, 660-673 e611 (2019).
8. Lane, S.W. & Gilliland, D.G. Leukemia stem cells. *Semin Cancer Biol* 20, 71-76 (2010).
9. Barreyro, L., et al. Blocking UBE2N abrogates oncogenic immune signaling in acute myeloid leukemia. *Sci Transl Med* 14, eabb7695 (2022).
- 20 10. Trowbridge, J.J. & Starczynowski, D.T. Innate immune pathways and inflammation in hematopoietic aging, clonal hematopoiesis, and MDS. *J Exp Med* 218(2021).
11. Sallman, D.A. & List, A. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. *Blood* 133, 1039-1048 (2019).
12. Varney, M.E., et al. Deconstructing innate immune signaling in myelodysplastic
25 syndromes. *Exp Hematol* 43, 587-598 (2015).
13. Starczynowski, D.T. & Karsan, A. Innate immune signaling in the myelodysplastic syndromes. *Hematol Oncol Clin North Am* 24, 343-359 (2010).
14. Barreyro, L., Chlon, T.M. & Starczynowski, D.T. Chronic immune response dysregulation in MDS pathogenesis. *Blood* 132, 1553-1560 (2018).
- 30 15. Monlish, D.A., Bhatt, S.T. & Schuettelpelz, L.G. The Role of Toll-Like Receptors in Hematopoietic Malignancies. *Front Immunol* 7, 390 (2016).

16. Gañán-Gómez, I., et al. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. *Leukemia* 29, 1458 (2015).
17. Bennett, J. & Starczynowski, D.T. IRAK1 and IRAK4 as emerging therapeutic targets in hematologic malignancies. *Curr Opin Hematol* 29, 8-19 (2022).
- 5 18. Fitzgerald, K.A. & Kagan, J.C. Toll-like Receptors and the Control of Immunity. *Cell* 180, 1044-1066 (2020).
19. Yu, X., et al. MYD88 L265P Mutation in Lymphoid Malignancies. *Cancer research* 78, 2457-2462 (2018).
20. Winkler, A., et al. The Interleukin-1 Receptor-Associated Kinase 4 Inhibitor PF-
10 06650833 Blocks Inflammation in Preclinical Models of Rheumatic Disease and in Humans Enrolled in a Randomized Clinical Trial. *Arthritis Rheumatol* 73, 2206-2218 (2021).
21. Gummadi, V.R., et al. Discovery of CA-4948, an Orally Bioavailable IRAK4 Inhibitor for Treatment of Hematologic Malignancies. *ACS Med Chem Lett* 11, 2374-2381 (2020).
22. Stevens, D., et al. Phase 1 Study of KT-413, a Targeted Protein Degradator of IRAK4 and
15 IMiD Substrates, in Adult Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma. in ASCO (2022).
23. Eric Kuhn, et al. Discovery and targeted mass spectrometry-based proteomics: Enabling technologies advancing IRAK4 protein degrader along the drug discovery pipeline into the clinic. in ASMS (2022).
- 20 24. Garcia-Manero, G., et al. Takeaim Leukemia- A Phase 1/2a Study Of The IRAK4 Inhibitor Emavusertib (Ca-4948) as Monotherapy or in Combination with Azacitidine or Venetoclax in Relapsed/Refractory AML or MDS. In EHA (ed. HemaSphere) (2022).
25. Choudhary, G.S., et al. Activation of targetable inflammatory immune signaling is seen in myelodysplastic syndromes with SF3B1 mutations. *Elife* 11(2022).
- 25 26. Smith, M.A., et al. U2AF1 mutations induce oncogenic IRAK4 isoforms and activate innate immune pathways in myeloid malignancies. *Nat Cell Biol* 21, 640-650 (2019).
27. Lam, S.S., et al. Directed evolution of APEX2 for electron microscopy and proximity labeling. *Nat Methods* 12, 51-54 (2015).
28. Zhou, Y., et al. Metascape provides a biologist-oriented resource for the analysis of
30 systems-level datasets. *Nat Commun* 10, 1523 (2019).

29. Pawlus, M.R., Wang, L. & Hu, C.J. STAT3 and HIF1alpha cooperatively activate HIF1 target genes in MDA-MB-231 and RCC4 cells. *Oncogene* 33, 1670-1679 (2014).
30. Szklarczyk, D., et al. The STRING database in 2021: customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Res* 49, D605-D612 (2021).
31. Iwama, A. Polycomb repressive complexes in hematological malignancies. *Blood* 130, 23-29 (2017).
32. Wingelhofer, B., et al. Implications of STAT3 and STAT5 signaling on gene regulation and chromatin remodeling in hematopoietic cancer. *Leukemia* 32, 1713-1726 (2018).
33. Chi, P., Allis, C.D. & Wang, G.G. Covalent histone modifications--miswritten, misinterpreted and mis-erased in human cancers. *Nat Rev Cancer* 10, 457-469 (2010).
34. Giotopoulos, G., et al. The epigenetic regulators CBP and p300 facilitate leukemogenesis and represent therapeutic targets in acute myeloid leukemia. *Oncogene* 35, 279-289 (2016).
35. Feng, Y., Li, L., Du, Y., Peng, X. & Chen, F. E2F4 functions as a tumour suppressor in acute myeloid leukaemia via inhibition of the MAPK signalling pathway by binding to EZH2. *J Cell Mol Med* 24, 2157-2168 (2020).
36. Tyner, J.W., et al. Functional genomic landscape of acute myeloid leukaemia. *Nature* 562, 526-531 (2018).
37. Melgar, K., et al. Overcoming adaptive therapy resistance in AML by targeting immune response pathways. *Sci Transl Med* 11(2019).
38. Jones, L.M., et al. Targeting AML-associated FLT3 mutations with a type I kinase inhibitor. *J Clin Invest* 130, 2017-2023 (2020).
39. Rhyasen, G.W., Bolanos, L. & Starczynowski, D.T. Differential IRAK signaling in hematologic malignancies. *Exp Hematol* 41, 1005-1007 (2013).
40. Rhyasen, G.W., et al. Targeting IRAK1 as a therapeutic approach for myelodysplastic syndrome. *Cancer Cell* 24, 90-104 (2013).
41. Hosseini, M.M., et al. Inhibition of interleukin-1 receptor-associated kinase-1 is a therapeutic strategy for acute myeloid leukemia subtypes. *Leukemia* 32, 2374-2387 (2018).
42. Stoner, S.A., et al. Hippo kinase loss contributes to del(20q) hematologic malignancies through chronic innate immune activation. *Blood* 134, 1730-1744 (2019).

43. Liang, K., et al. Therapeutic Targeting of MLL Degradation Pathways in MLL-Rearranged Leukemia. *Cell* 168, 59-72 e13 (2017).
44. Nish, S. & Medzhitov, R. Host defense pathways: role of redundancy and compensation in infectious disease phenotypes. *Immunity* 34, 629-636 (2011).
- 5 45. Kun, E., Tsang, Y.T.M., Ng, C.W., Gershenson, D.M. & Wong, K.K. MEK inhibitor resistance mechanisms and recent developments in combination trials. *Cancer Treat Rev* 92, 102137 (2021).
46. Carvajal, L.A., et al. Dual inhibition of MDMX and MDM2 as a therapeutic strategy in leukemia. *Sci Transl Med* 10(2018).
- 10 47. Kawasaki, T. & Kawai, T. Toll-like receptor signaling pathways. *Front Immunol* 5, 461 (2014).
48. Aujla, A., Linder, K., Iragavarapu, C., Karass, M. & Liu, D. SRSF2 mutations in myelodysplasia/myeloproliferative neoplasms. *Biomark Res* 6, 29 (2018).
49. Kim, E., et al. SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific
15 Effects on Exon Recognition. *Cancer Cell* 27, 617-630 (2015).
50. Musella, M., et al. Type I IFNs promote cancer cell stemness by triggering the epigenetic regulator KDM1B. *Nat Immunol* 23, 1379-1392 (2022).
51. Zhang, D., et al. Tumor-Stroma IL1beta-IRAK4 Feedforward Circuitry Drives Tumor
20 Fibrosis, Chemoresistance, and Poor Prognosis in Pancreatic Cancer. *Cancer research* 78, 1700-1712 (2018).
52. Li, Q., et al. IRAK4 mediates colitis-induced tumorigenesis and chemoresistance in colorectal cancer. *JCI Insight* 4(2019).
53. Liu, L., et al. Targeting the IRAK1-S100A9 Axis Overcomes Resistance to Paclitaxel in Nasopharyngeal Carcinoma. *Cancer research* 81, 1413-1425 (2021).
- 25 54. Adams, A.K., et al. IRAK1 is a novel DEK transcriptional target and is essential for head and neck cancer cell survival. *Oncotarget* 6, 43395-43407 (2015).
55. Wee, Z.N., et al. IRAK1 is a therapeutic target that drives breast cancer metastasis and resistance to paclitaxel. *Nat Commun* 6, 8746 (2015).
56. Cheng, B.Y., et al. IRAK1 Augments Cancer Stemness and Drug Resistance via the AP-1/AKR1B10 Signaling Cascade in Hepatocellular Carcinoma. *Cancer research* 78, 2332-2342
30 (2018).

57. Hu, Q., et al. miR-146a promotes cervical cancer cell viability via targeting IRAK1 and TRAF6. *Oncol Rep* 39, 3015-3024 (2018).

58. Wickham, H. *Ggplot2: Elegant Graphics for Data Analysis*, (2009).

Example 4:

5 All AML patients become resistant/refractory to existing therapies. The leukemic cells of these patients exhibit dysregulation of innate immune signaling pathways upon diagnosis, wherein these pathways become further activated in drug resistance. The IRAK1/IRAK4 kinase complex is part of a critical signaling node that becomes activated in these dysregulated pathways. Multiple genetic alterations in MDS/AML result in activation of IRAK1/4 pathways.
10 IRAK1/4 regulates genes involved in cancer cell survival, self-renewal, and stress response via the NF- κ B, MAPK, and potentially, the inflammasome pathways. IRAK1/4 is involved in cancer cell dependencies and adaptive resistance mechanisms. IRAK4 exists as 2 major isoforms: IRAK4-L (“hyperactive”) and IRAK4-S (“less active”). IRAK1 is overexpressed and activated in myeloid malignancies. The IRAK1/4 inhibitors of the present disclosure work by
15 targeting key cancer survival pathways and thereby increase overall survival (OS) of patients with hematopoietic and solid tumors, prolong remission rates, and/or increase the success of a stem cell transplant (HSCT). The IRAK 1/4 inhibitors of the present disclosure also synergize with Venetoclax and are thus positioned to treat cancers such as AML with a higher potency than other targeted therapies that are currently available.

20 Dual IRAK1/4 inhibition was found to be required to drive maximal efficacy (FIGS. 20E-20F). Specifically, it was discovered that: 1) IRAK1 is activated in response to IRAK4 inhibition or degradation, 2) the complete inhibition of NF- κ B-derived signaling through multiple receptors requires inhibition of both IRAK1 and IRAK4 (FIG. 28), and 3) genetic ablation of both IRAK1 and IRAK4 is more effective in promoting survival in AML xenograft
25 models than is deletion of either kinase alone (FIGS. 11H-11I). IRAK1 and IRAK4 mediate distinct and overlapping signaling pathways in AML. In leukemia, IRAK1 compensates for IRAK4 inhibition and therefore IRAK4 inhibition is insufficient for full efficacy. Targeting IRAK4 was found to result in compensation by IRAK1 wherein IRAK1 is upregulated and activated upon IRAK4 deletion (FIG. 26). Similar results were also obtained with IRAK4
30 inhibitors or degraders. FIG. 27 depicts that complete antagonism of signaling through both receptor pathways is only seen with an IRAK1/4 inhibitor of the present disclosure while the

irreversible IRAK1 inhibitor JH-X-119-01 does not inhibit signaling through either receptor and the IRAK4 selective inhibitors do not completely inhibit signaling through IL1R. Furthermore, an IRAK1/4 inhibitor of the present disclosure was found to provide enhanced survival in xenograft mice compared to emavusertib (CA-4948) and gilteritinib (FIG. 28).

5 The *in vitro* and *in vivo* studies were used to develop an IRAK1/4 signature in patients (FIGS. 29A-29B). Based on the development of the IRAK1/4 signature (see Example 3), the data suggest:

1) the IRAK1/4 signature is present in AML patients throughout the BEAT-AML, TCGA, and TARGET databases indicating that IRAK1/4 signaling is operational in a significant
10 cohort of pediatric and adult AMLs,

2) the highest levels occur in 24.8%, 43.4% of adult and 44.4% of pediatric AML patients,

3) the highest levels of expression are found in the monocytic-like (M4) AML patients (adult and pediatric), and

15 4) since the monocytic-like AML patients are also those who are resistant to hypomethylating agents/venetoclax (HMA/VEN), the data suggest that the population most likely to respond to an IRAK1/4 inhibitor will be the HMA/VEN resistant population.

While the commercially available IRAK4 inhibitor emavusertib (CA-4948) shows early efficacy in relapsed/refractory (R/R) MDS/AML patients previously treated with HMA/VEN,
20 this efficacy is only seen in a sub-population of HMA/VEN R/R patients (spliceosome-mutant patients) which have been found to have increased expression of activated IRAK4. Therefore, the highest efficacy is seen in MDS patients, where the incidence of spliceosome mutations is higher and lower efficacy is seen in AML (as predicted by the comparative data herein). This further demonstrates the need for dual IRAK1/4 inhibition in AML patients. The dual IRAK1/4
25 inhibitors disclosed herein have been demonstrated to have superior efficacy vs. IRAK4 inhibitors in multiple orthogonal assays. Furthermore, the IRAK1/4 signature suggests that a clinical effect will be observed in a large proportion of AML/MDS patients treated with an IRAK1/4 inhibitor of the present disclosure, including the HMA/VEN R/R population.

30 It is noted that terms like “preferably,” “commonly,” and “typically” are not used herein to limit the scope of the claimed disclosure or to imply that certain features are critical, essential, or even important to the structure or function of the claimed disclosure. Rather, these terms are

merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the present disclosure.

The various methods and techniques described above provide a number of ways to carry out the disclosure. Of course, it is to be understood that not necessarily all objectives or advantages described can be achieved in accordance with any particular embodiment described herein. Thus, for example, those skilled in the art will recognize that the methods can be performed in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objectives or advantages as taught or suggested herein. A variety of alternatives are mentioned herein. It is to be understood that some preferred embodiments specifically include one, another, or several features, while others specifically exclude one, another, or several features, while still others mitigate a particular feature by inclusion of one, another, or several advantageous features.

Furthermore, the skilled artisan will recognize the applicability of various features from different embodiments. Similarly, the various elements, features and steps discussed above, as well as other known equivalents for each such element, feature or step, can be employed in various combinations by one of ordinary skill in this art to perform methods in accordance with the principles described herein. Among the various elements, features, and steps some will be specifically included and others specifically excluded in diverse embodiments.

Although the application has been disclosed in the context of certain embodiments and examples, it will be understood by those skilled in the art that the embodiments of the disclosure extend beyond the specifically disclosed embodiments to other alternative embodiments and/or uses and modifications and equivalents thereof.

In some embodiments, the numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth, used to describe and claim certain embodiments of the application are to be understood as being modified in some instances by the term “about.” Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. In some embodiments, the numerical parameters should be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of some embodiments of the application are

approximations, the numerical values set forth in the specific examples are reported as precisely as practicable.

In some embodiments, the terms “a” and “an” and “the” and similar references used in the context of describing a particular embodiment of the application (especially in the context of certain of the following claims) can be construed to cover both the singular and the plural. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (for example, “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate the application and does not pose a limitation on the scope of the application otherwise claimed. As used in the disclosure or claims, “another” means at least a second or more, unless otherwise specified. As used in the disclosure, the phrases “such as,” “for example,” and “e.g.” mean “for example, but not limited to” in that the list following the term (“such as,” “for example,” or “e.g.”) provides some examples but the list is not necessarily a fully inclusive list. The word “comprising” means that the items following the word “comprising” may include additional unrecited elements or steps; that is, “comprising” does not exclude additional unrecited steps or elements. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the application.

In certain instances, sequences disclosed herein are included in publicly available databases, such as GENBANK[®] and SWISSPROT. Unless otherwise indicated or apparent the references to such publicly available databases are references to the most recent version of the database as of the filing date of this Application.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently disclosed subject matter. As used herein, the term “about,” when referring to a value or to an

amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations of in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed method.

Preferred embodiments of this application are described herein. Variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. It is contemplated that skilled artisans can employ such variations as appropriate, and the application can be practiced otherwise than specifically described herein.

Accordingly, many embodiments of this application include all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the application unless otherwise indicated herein or otherwise clearly contradicted by context.

Appendix A

Table 2. Differentially expressed genes with CA-4948 vs DMSO in THP1 cells

Gene	Log(FC)	P Value	Adj P Value
CRABP2	3.095	5.57E-08	5.57E-08
TNXB	1.806	5.79E-10	5.79E-10
EFCAB12	1.697	8.48E-09	8.48E-09
FLJ45513	1.668	2.14E-06	2.14E-06
NPIPA3	1.643	0.0004833	0.0004833
COL7A1	1.605	1.38E-08	1.38E-08
WNK4	1.507	2.94E-09	2.94E-09
SMIM11	1.485	0.03161	0.03161
LOC102724409	1.429	0.003556	0.003556
LOC102723975	1.408	9.25E-06	9.25E-06
GNMT	1.408	2.24E-05	2.24E-05
ZDHHC11	1.406	2.62E-06	2.62E-06
DND1	1.389	3.35E-05	3.35E-05
SCART1	1.38	9.59E-05	9.59E-05
GUCA1B	1.348	2.21E-05	2.21E-05
BZRAP1	1.334	4.00E-10	4.00E-10
CPT1B	1.318	0.007755	0.007755
LOC101927910	1.281	0.0002476	0.0002476
ASIC3	1.28	0.0001091	0.0001091
DCST2	1.278	0.0007274	0.0007274
SPTBN5	1.272	4.22E-09	4.22E-09
PRR22	1.272	2.11E-08	2.11E-08
LOC100507424	1.26	0.0008331	0.0008331
CEACAM19	1.259	5.73E-08	5.73E-08
ITIH4	1.233	2.41E-08	2.41E-08
LOC100129083	1.194	1.63E-06	1.63E-06
LINC01133	1.19	2.63E-09	2.63E-09
C1R	1.188	0.001884	0.001884
UCN	1.177	2.18E-06	2.18E-06
SPATC1	1.175	0.0001674	0.0001674
FCRLB	1.162	0.0004631	0.0004631
CMTM1	1.158	6.22E-07	6.22E-07
PIP5KL1	1.154	2.27E-08	2.27E-08
PRSS57	1.151	1.71E-05	1.71E-05
FBXO39	1.15	0.0003452	0.0003452

SLC23A3	1.148	0.0002647	0.0002647
AOC2	1.143	0.0003823	0.0003823
SLC25A34	1.141	1.53E-05	1.53E-05
TMEM249	1.14	8.22E-07	8.22E-07
TREML1	1.14	1.20E-06	1.20E-06
ZNF205-AS1	1.14	0.001593	0.001593
MIR3187	1.121	0.004933	0.004933
LOC100506548	1.108	2.85E-17	2.85E-17
DCAF4L1	1.097	0.0004582	0.0004582
MYLK-AS1	1.091	0.003903	0.003903
DNHD1	1.083	1.80E-12	1.80E-12
CLK1	1.08	1.80E-16	1.80E-16
LHPP	1.078	0.000127	0.000127
POTEE	1.077	0.01333	0.01333
MIR570	1.064	0.0003682	0.0003682
SNORD30	1.062	0.001393	0.001393
C1orf51	1.033	7.31E-05	7.31E-05
CTRL	1.027	5.78E-05	5.78E-05
YJEFN3	1.024	2.47E-09	2.47E-09
ADCY4	1.023	2.42E-07	2.42E-07
LOC100129924	1.019	0.003331	0.003331
POLN	1.016	0.0002137	0.0002137
DNASE1L2	1.008	1.64E-06	1.64E-06
IL9R	1.002	0.01654	0.01654
TMEM145	0.9943	0.0003413	0.0003413
LOC100128494	0.9913	0.002477	0.002477
LOC102723959	0.9881	7.52E-05	7.52E-05
RUFY4	0.9698	1.92E-06	1.92E-06
CCDC183	0.9658	2.33E-05	2.33E-05
SAP25	0.962	3.86E-08	3.86E-08
HSPA7	0.9538	0.0001058	0.0001058
CNIH2	0.9526	0.0015	0.0015
IGFBP7-AS1	0.9516	0.003228	0.003228
FAM57B	0.9462	7.12E-07	7.12E-07
ZP3	0.9339	4.20E-05	4.20E-05
CLK3	0.9323	4.28E-17	4.28E-17
ZSWIM8-AS1	0.9316	0.0005395	0.0005395
ANKRD34A	0.9288	0.0008014	0.0008014
CNKSR1	0.9226	0.003884	0.003884
RPS18P9	0.9157	0.000963	0.000963

QRICH2	0.9066	0.0002348	0.0002348
CGN	0.9021	0.004276	0.004276
DRP2	0.9019	0.0002334	0.0002334
CCDC109B	0.8991	0.001084	0.001084
CILP2	0.8989	0.002546	0.002546
LOC100506100	0.8985	0.000907	0.000907
EGFR	0.882	0.01651	0.01651
LOC101928038	0.8781	0.005726	0.005726
TMEM9B-AS1	0.8758	0.001738	0.001738
ARID3C	0.8751	0.008951	0.008951
SCXB	0.8721	1.46E-05	1.46E-05
C15orf62	0.8673	0.007947	0.007947
VWA7	0.8656	0.001993	0.001993
LOC101928055	0.8595	0.000212	0.000212
STX18-AS1	0.8594	0.005636	0.005636
CHN2	0.8531	0.000282	0.000282
LOC102724545	0.8513	0.003253	0.003253
FAM229A	0.8452	0.002954	0.002954
LOC100130705	0.845	0.003108	0.003108
LOC100134868	0.8444	0.02866	0.02866
MROH6	0.8417	2.51E-10	2.51E-10
LOC101929264	0.8417	0.001338	0.001338
PAPPA2	0.8397	0.003118	0.003118
LOC284889	0.8366	3.31E-05	3.31E-05
TEKT4P2	0.8324	0.01705	0.01705
LINC00641	0.8241	1.47E-09	1.47E-09
SLC7A5P2	0.8202	0.001087	0.001087
NPIPA8	0.8183	0.01717	0.01717
LOC102723589	0.8153	0.02702	0.02702
LOC100506083	0.8144	0.008399	0.008399
CLK4	0.8127	1.43E-10	1.43E-10
PDE5A	0.8121	0.01982	0.01982
NGFR	0.8097	0.005778	0.005778
GPR135	0.8057	0.003204	0.003204
TXLNB	0.8051	0.0002951	0.0002951
UNC5CL	0.8031	0.01038	0.01038
GP9	0.8031	0.01726	0.01726
ELMO3	0.7963	2.35E-05	2.35E-05
CCDC154	0.7952	0.0004243	0.0004243
LOC101929280	0.7936	0.04057	0.04057

ATP2B3	0.7931	0.0003836	0.0003836
SLC22A20	0.7923	0.008079	0.008079
LINC00959	0.7922	0.004591	0.004591
PRSS53	0.79	5.15E-05	5.15E-05
SCN8A	0.7836	0.006734	0.006734
AC093391.2	0.7835	0.006881	0.006881
SARM1	0.783	0.0001099	0.0001099
HHLA3	0.7796	6.30E-06	6.30E-06
KIAA1324	0.7793	0.0008591	0.0008591
AMH	0.7789	0.002083	0.002083
LOC100507373	0.7784	1.58E-05	1.58E-05
LOC100506518	0.7779	7.18E-06	7.18E-06
M1AP	0.7754	0.007768	0.007768
ZNF491	0.7713	0.007561	0.007561
LOC100505771	0.7704	0.0008818	0.0008818
GSDMB	0.7698	0.001682	0.001682
LOC101927974	0.7679	0.0007673	0.0007673
TMEM254-AS1	0.767	0.004141	0.004141
LTB4R2	0.7655	1.99E-06	1.99E-06
LOC100506472	0.7649	0.001022	0.001022
LOC101929243	0.7647	0.002408	0.002408
LOC101928830	0.7631	0.01618	0.01618
GPR113	0.7578	0.005797	0.005797
LDLRAD4	0.7569	4.77E-07	4.77E-07
CLEC12B	0.7555	0.01879	0.01879
C5orf56	0.7488	0.009988	0.009988
PDPN	0.7486	0.03511	0.03511
GSTM2	0.7484	0.003808	0.003808
LOC101929661	0.748	0.0032	0.0032
EIF3CL	0.7466	0.003876	0.003876
ENHO	0.7452	0.0004327	0.0004327
LOC102724235	0.7375	0.003857	0.003857
LINC00893	0.737	0.01581	0.01581
APOLD1	0.7365	0.0001127	0.0001127
SEC31B	0.7359	5.72E-06	5.72E-06
CACTIN-AS1	0.7321	0.004634	0.004634
MDGA1	0.7307	0.002473	0.002473
SIGLEC16	0.7305	0.0007117	0.0007117
LOC102467073	0.73	0.02379	0.02379
IPO9-AS1	0.7271	0.02734	0.02734

LOC102724169	0.726	0.002057	0.002057
LPAR2	0.7255	4.77E-09	4.77E-09
SYTL2	0.7254	0.003306	0.003306
TESPA1	0.724	0.002913	0.002913
LOC728752	0.7225	0.003079	0.003079
AP3B2	0.7192	0.0398	0.0398
TP53I3	0.7187	4.41E-06	4.41E-06
AP000330.8	0.7147	0.004826	0.004826
LOC102723616	0.7122	0.03423	0.03423
RP11-344E13.3	0.712	7.85E-13	7.85E-13
TLR5	0.7065	0.01408	0.01408
SLFNL1-AS1	0.7053	5.76E-06	5.76E-06
GJC2	0.7031	0.04664	0.04664
TPD52L1	0.7014	0.01284	0.01284
CPNE5	0.7008	0.01143	0.01143
LOC100507462	0.6976	0.01246	0.01246
UCP3	0.6963	0.001122	0.001122
SEMA3B	0.6963	0.02005	0.02005
GDPD3	0.695	0.01034	0.01034
BTBD19	0.6939	0.02825	0.02825
LOC100288069	0.6928	0.005851	0.005851
DCAKD	0.6901	1.03E-09	1.03E-09
ID3	0.6893	0.0004751	0.0004751
ADAM8	0.6886	8.35E-05	8.35E-05
PITX2	0.6882	0.003134	0.003134
ARTN	0.6881	3.65E-06	3.65E-06
LOC102724217	0.6865	0.001358	0.001358
LAMC3	0.6855	0.002075	0.002075
ABCC2	0.6855	0.009668	0.009668
ORM1	0.6834	0.008792	0.008792
TMEM191A	0.6824	0.01585	0.01585
LOC101929046	0.6794	0.007944	0.007944
RP3-476K8.3	0.6781	0.0433	0.0433
LOC102723714	0.6674	0.02358	0.02358
TCAM1P	0.6669	0.002562	0.002562
CCDC155	0.6645	0.01486	0.01486
TMPRSS13	0.6639	0.005115	0.005115
BRICD5	0.6636	2.29E-05	2.29E-05
NPFF	0.6633	0.01125	0.01125
WDFY3-AS2	0.6617	0.01072	0.01072

PPP1R13L	0.6598	7.29E-05	7.29E-05
TMEM175	0.6594	1.27E-08	1.27E-08
RNU86	0.6578	0.01054	0.01054
STXBP5-AS1	0.6561	0.01142	0.01142
SNX32	0.6555	0.001315	0.001315
LOC102724248	0.652	0.003291	0.003291
CDC42EP2	0.6518	0.003912	0.003912
DEGS2	0.6503	0.02278	0.02278
TMEM86B	0.6481	5.29E-07	5.29E-07
RCN3	0.6431	1.56E-05	1.56E-05
LOC101927119	0.6408	0.02294	0.02294
NOL3	0.6401	0.001321	0.001321
LOC728715	0.6401	0.0204	0.0204
WT1-AS	0.6396	3.18E-06	3.18E-06
VAMP5	0.6392	0.01861	0.01861
CLDN15	0.6387	3.39E-07	3.39E-07
LOC101927895	0.6379	0.04179	0.04179
GALR2	0.6354	0.01227	0.01227
C16orf86	0.6351	0.0002384	0.0002384
LOC155060	0.6346	0.0001873	0.0001873
DMPK	0.6345	0.0005548	0.0005548
RARRES3	0.6342	0.03888	0.03888
APOE	0.6335	2.01E-06	2.01E-06
LINC00337	0.6329	0.02314	0.02314
AURKB	0.6324	2.14E-09	2.14E-09
ARL17B	0.6318	0.0209	0.0209
METTL12	0.6315	0.0008087	0.0008087
MIR1244-1	0.6309	0.0159	0.0159
DNAJC27-AS1	0.6304	0.03354	0.03354
PROB1	0.6297	0.0008142	0.0008142
MAMDC4	0.628	4.07E-05	4.07E-05
PPIEL	0.6279	0.008493	0.008493
PAQR6	0.6274	0.0001796	0.0001796
RP11-307C12.11	0.6268	0.0004513	0.0004513
HPD	0.6253	0.03002	0.03002
PSMG3-AS1	0.6249	4.09E-07	4.09E-07
LOC644961	0.6222	0.00201	0.00201
PTGER1	0.6218	0.01002	0.01002
GIPR	0.6177	0.01276	0.01276
SPATA41	0.6171	0.03953	0.03953

CLEC10A	0.6157	0.01863	0.01863
CATSPER3	0.6152	0.0194	0.0194
ANKFN1	0.6129	0.002676	0.002676
LOC101929747	0.6127	0.009365	0.009365
RAPGEFL1	0.6118	4.27E-05	4.27E-05
C9orf37	0.6108	4.05E-09	4.05E-09
IL10RB-AS1	0.6103	0.001636	0.001636
MYO7B	0.6068	0.002185	0.002185
C2orf48	0.606	0.004042	0.004042
GAS6-AS1	0.6025	0.0001122	0.0001122
CD302	0.6021	0.03042	0.03042
DNAH1	0.6015	2.15E-08	2.15E-08
MFI2-AS1	0.5997	0.003165	0.003165
LOC101929112	0.5992	0.02087	0.02087
SLFNL1	0.599	0.0305	0.0305
ADAM19	0.5984	0.04367	0.04367
HLA-F-AS1	0.5961	0.01589	0.01589
MGC16142	0.5952	0.03968	0.03968
TRIM72	0.5946	0.006274	0.006274
BVES-AS1	0.5945	0.0179	0.0179
SLC2A14	0.5944	0.01741	0.01741
PCBP3	0.5937	0.003672	0.003672
KCND1	0.5935	0.001082	0.001082
TUBA1A	0.5916	0.000171	0.000171
FFAR4	0.5911	0.01248	0.01248
PPP1R32	0.5902	0.01888	0.01888
LOC101928710	0.5901	0.02826	0.02826
CD101	0.5897	0.02758	0.02758
LOC101929054	0.589	0.04092	0.04092
DDB2	0.5883	9.92E-11	9.92E-11
RP11-454P21.1	0.5869	0.03268	0.03268
AC016629.8	0.586	2.85E-05	2.85E-05
SNORD79	0.5858	0.01589	0.01589
TSPEAR-AS1	0.5855	0.005867	0.005867
LOC100133091	0.5851	0.001316	0.001316
TMEM255A	-0.5904	0.001517	0.001517
GPR3	-0.5921	0.006117	0.006117
CD163	-0.5952	0.01736	0.01736
FBXO15	-0.5977	0.01129	0.01129
SLC25A5-AS1	-0.5981	0.01961	0.01961

ZNF284	-0.5982	0.008629	0.008629
LOC100288102	-0.6006	0.02688	0.02688
GPR158	-0.6058	0.0002466	0.0002466
CCDC103	-0.6115	0.00229	0.00229
KCNH2	-0.6125	0.003693	0.003693
MBLAC1	-0.6134	0.02149	0.02149
KCNIP3	-0.6151	0.02074	0.02074
SEMG1	-0.6203	0.002619	0.002619
SERPINB2	-0.6225	7.50E-13	7.50E-13
ST13P4	-0.623	0.03648	0.03648
SYDE2	-0.6236	0.0003263	0.0003263
SPRED1	-0.6296	0.009698	0.009698
TTC4	-0.6304	0.002673	0.002673
SMA4	-0.6311	0.04294	0.04294
LOC102724098	-0.6399	1.48E-05	1.48E-05
TSKU	-0.6402	0.009829	0.009829
SAMD13	-0.6418	0.0007131	0.0007131
PCOLCE2	-0.6424	0.008973	0.008973
RASSF8-AS1	-0.6459	0.03274	0.03274
RN7SL1	-0.6652	0.004629	0.004629
PAX8	-0.6687	0.002062	0.002062
SEMA3C	-0.6821	0.01336	0.01336
RIMS2	-0.6856	0.01222	0.01222
LOC101927085	-0.6948	0.002305	0.002305
RPSAP9	-0.6976	0.01868	0.01868
SAMD5	-0.6977	0.02336	0.02336
SLCO2B1	-0.6999	0.0029	0.0029
IL8	-0.7139	0.003093	0.003093
RNU105A	-0.7199	0.02246	0.02246
ZCWPW2	-0.722	0.002292	0.002292
RP11-261C10.3	-0.7243	0.04782	0.04782
RN7SK	-0.7805	0.04651	0.04651
ZNF891	-0.7965	0.002573	0.002573
TMEM150A	-0.8108	0.0003505	0.0003505
KRBA2	-0.8123	0.009637	0.009637
RP11-540A21.2	-0.8218	0.0008734	0.0008734
LOC101929814	-0.8463	0.004974	0.004974
LOC102724528	-0.8481	3.02E-06	3.02E-06
SIM1	-0.8741	1.04E-05	1.04E-05
MGC12916	-0.9124	0.0002149	0.0002149

ULK4P1	-0.9282	0.03746	0.03746
CHRFAM7A	-0.9429	0.004936	0.004936
FLJ31945	-0.9544	0.0005693	0.0005693
IGFBP3	-0.9606	0.001251	0.001251
SLC7A11	-0.9711	2.18E-10	2.18E-10
LOC100130698	-1.064	0.0002141	0.0002141
SNORD3A	-1.579	0.002427	0.002427
TNFAIP8L2-SCNM1	-1.749	0.0001107	0.0001107
RPPH1	-1.864	0.002257	0.002257
RNU2-2P	-3.126	0.001517	0.001517

Table 3. Differentially expressed genes with PF-06650833 vs DMSO in THP1 cells

Gene	Log(FC)	P Value	Adj P Value
CCL4	3.289	1.24E-07	1.24E-07
IGFBP5	2.575	7.86E-08	7.86E-08
CRABP2	2.494	4.22E-06	4.22E-06
STC2	2.439	5.30E-08	5.30E-08
COLEC12	2.26	1.28E-06	1.28E-06
EGR2	2.256	1.16E-05	1.16E-05
GFRA2	2.227	5.99E-10	5.99E-10
SLC6A9	2.152	9.98E-07	9.98E-07
EGR3	2.039	5.74E-09	5.74E-09
C1QC	2.005	1.06E-05	1.06E-05
NTRK1	1.984	9.16E-08	9.16E-08
LOC101927030	1.964	8.18E-06	8.18E-06
GBP1	1.918	1.09E-06	1.09E-06
LGMN	1.841	2.28E-07	2.28E-07
NR4A3	1.811	1.73E-05	1.73E-05
PLXNA4	1.673	6.14E-10	6.14E-10
CLEC7A	1.667	1.05E-06	1.05E-06
LOC100507424	1.616	0.0001903	0.0001903
FERMT2	1.604	2.43E-05	2.43E-05
ADM2	1.566	3.88E-09	3.88E-09
PIP5KL1	1.553	4.42E-09	4.42E-09
TNXB	1.526	9.02E-08	9.02E-08
IGFBP3	1.497	6.93E-07	6.93E-07
CCL3	1.486	7.30E-07	7.30E-07
ZNF205-AS1	1.477	0.0001292	0.0001292
GJC2	1.449	1.68E-05	1.68E-05

LRRC16B	1.408	5.96E-05	5.96E-05
CCDC176	1.4	6.43E-05	6.43E-05
CD14	1.387	1.38E-08	1.38E-08
SLC23A3	1.375	0.0002623	0.0002623
UCN	1.351	3.86E-06	3.86E-06
SPOCD1	1.344	0.001497	0.001497
LOC80154	1.337	0.0002532	0.0002532
TDO2	1.319	6.24E-05	6.24E-05
FSCN2	1.308	0.0001416	0.0001416
ZFP36L1	1.303	4.00E-08	4.00E-08
DMPK	1.303	1.07E-07	1.07E-07
C1QA	1.3	3.79E-05	3.79E-05
GUCA1B	1.299	0.0001859	0.0001859
SNX32	1.297	1.11E-07	1.11E-07
ADAMTS4	1.291	6.04E-08	6.04E-08
LILRB3	1.289	0.0003463	0.0003463
CCDC183	1.264	4.23E-06	4.23E-06
CXCL10	1.261	0.0001711	0.0001711
NPTX1	1.239	7.49E-14	7.49E-14
MMP9	1.236	3.51E-07	3.51E-07
XKR5	1.227	0.0006901	0.0006901
HSPA7	1.214	1.79E-05	1.79E-05
LINC00959	1.198	6.99E-05	6.99E-05
BZRAP1	1.197	4.14E-06	4.14E-06
ST7-AS1	1.195	7.28E-05	7.28E-05
CHAC1	1.187	3.06E-06	3.06E-06
TUFT1	1.185	1.99E-07	1.99E-07
MIR3187	1.178	0.004858	0.004858
LAMB2P1	1.171	0.0006961	0.0006961
DNAJC27-AS1	1.155	0.0007675	0.0007675
TMEM9B-AS1	1.148	0.0001979	0.0001979
LOC100134868	1.147	0.002577	0.002577
PAPPA2	1.135	0.0002675	0.0002675
FCRLB	1.123	0.0006238	0.0006238
ZP3	1.112	9.98E-06	9.98E-06
GIMAP4	1.106	0.002989	0.002989
RGS22	1.098	0.01446	0.01446
LOC101929661	1.096	2.37E-05	2.37E-05
ATP6V1B1	1.092	3.37E-05	3.37E-05
DDIT4	1.091	2.13E-10	2.13E-10

SPP1	1.09	2.56E-12	2.56E-12
DND1	1.089	0.0009627	0.0009627
OVGP1	1.087	0.0008256	0.0008256
SMAGP	1.085	0.0002803	0.0002803
SNORA16A	1.083	0.001672	0.001672
FCGR2B	1.077	1.67E-06	1.67E-06
CEACAM19	1.074	1.18E-05	1.18E-05
FAM86HP	1.074	4.08E-05	4.08E-05
BAIAP3	1.069	0.0008714	0.0008714
COL4A2	1.067	4.70E-05	4.70E-05
IL4I1	1.065	2.86E-08	2.86E-08
SULF2	1.061	7.23E-07	7.23E-07
C5AR1	1.057	8.07E-06	8.07E-06
NPIPA8	1.054	0.02254	0.02254
TNFAIP8L3	1.046	6.54E-05	6.54E-05
LINC00852	1.042	0.002944	0.002944
MERTK	1.04	7.43E-06	7.43E-06
RGPD5	1.034	0.01634	0.01634
RGS20	1.033	7.87E-06	7.87E-06
FBXO39	1.033	0.00132	0.00132
ITGA10	1.021	0.01994	0.01994
COL7A1	1.019	0.000471	0.000471
DMWD	1.01	3.67E-08	3.67E-08
LOC284561	1.008	0.0009719	0.0009719
TBX15	0.9995	3.82E-06	3.82E-06
LOC100129924	0.999	0.001094	0.001094
RGL1	0.9882	1.84E-05	1.84E-05
LOC101928055	0.9875	6.24E-05	6.24E-05
NPAS4	0.9873	0.0007027	0.0007027
MAF	0.9858	1.63E-06	1.63E-06
LOC102467073	0.9792	0.00192	0.00192
TNF	0.9769	9.38E-07	9.38E-07
MAEL	0.9722	0.003201	0.003201
LILRA6	0.9697	0.005032	0.005032
MIR6859-1	0.9679	0.0006825	0.0006825
DNHD1	0.9622	9.50E-07	9.50E-07
GMPR	0.9617	0.0002394	0.0002394
VCAN	0.9606	1.80E-12	1.80E-12
LPAR6	0.9586	5.72E-07	5.72E-07
ZNF660	0.9528	0.00693	0.00693

ODF3B	0.9517	3.42E-07	3.42E-07
MAFB	0.9482	4.70E-08	4.70E-08
DLEU1	0.9476	3.48E-10	3.48E-10
MIR1304	0.9441	0.003141	0.003141
NOG	0.9438	0.00126	0.00126
TG	0.9411	0.001149	0.001149
ARTN	0.94	3.99E-07	3.99E-07
SNX22	0.9328	0.02218	0.02218
C6orf164	0.9305	0.01886	0.01886
TYMP	0.9304	3.61E-13	3.61E-13
C15orf62	0.9266	0.003237	0.003237
KDM7A	0.9238	1.14E-05	1.14E-05
LOC102723539	0.9233	0.0111	0.0111
FCGR2C	0.9192	0.0006853	0.0006853
TSPAN2	0.9171	8.43E-05	8.43E-05
CCND1	0.9157	6.93E-07	6.93E-07
GPR135	0.9122	0.001059	0.001059
FAM229A	0.9084	0.0007076	0.0007076
CYBB	0.9082	2.30E-13	2.30E-13
SLC7A5P2	0.9068	0.0004882	0.0004882
VSIG4	0.9068	0.0006297	0.0006297
FBXL2	0.9045	0.03921	0.03921
PRSS57	0.9042	0.001051	0.001051
NDUFA4L2	0.9024	5.42E-06	5.42E-06
LINC01137	0.9012	0.001017	0.001017
SLC7A8	0.8957	1.84E-05	1.84E-05
CCDC17	0.8953	0.02421	0.02421
CYP27B1	0.8892	9.49E-05	9.49E-05
ASIC3	0.8892	0.01145	0.01145
FCER1G	0.8867	2.20E-15	2.20E-15
RPS6KA2	0.8831	2.86E-08	2.86E-08
MDGA1	0.8814	0.0002049	0.0002049
LOC100507403	0.878	0.002816	0.002816
WNK4	0.8768	0.0007319	0.0007319
ATP6AP1L	0.8753	0.004168	0.004168
HES4	0.8744	0.001723	0.001723
ARHGAP31	0.8738	8.80E-08	8.80E-08
GEM	0.8734	0.001983	0.001983
BSCL2	0.8729	0.001973	0.001973
IFI44L	0.87	1.34E-10	1.34E-10

PTPRF	0.869	3.26E-15	3.26E-15
LYRM9	0.8667	6.84E-05	6.84E-05
LOC102723975	0.8647	0.004304	0.004304
FMNL2	0.8614	7.84E-08	7.84E-08
LOC101928498	0.8614	4.48E-06	4.48E-06
LOC100506100	0.8612	0.001425	0.001425
FGD6	0.8584	0.02636	0.02636
MAPK8IP2	0.8582	0.01267	0.01267
MIR25	0.8562	0.006214	0.006214
TMEM136	0.8558	0.0002695	0.0002695
PAIP2B	0.8549	0.001256	0.001256
SNORD23	0.845	0.003847	0.003847
LOC101929887	0.8434	0.01538	0.01538
APOLD1	0.8405	8.73E-05	8.73E-05
LOC101929264	0.8399	0.001093	0.001093
LOC102723566	0.8345	0.01121	0.01121
LOC101928061	0.8344	0.01315	0.01315
MSTO2P	0.8326	4.97E-05	4.97E-05
PC	0.8297	2.17E-06	2.17E-06
AC011747.4	0.8271	0.000165	0.000165
ARID3C	0.8267	0.01059	0.01059
CNFN	0.8262	0.002023	0.002023
HS3ST3A1	0.825	0.006772	0.006772
DYSF	0.8249	0.0002721	0.0002721
KIF26A	0.8244	0.0008009	0.0008009
ELMO3	0.8236	1.90E-05	1.90E-05
SLC29A2	0.8234	0.004801	0.004801
AP3B2	0.8215	0.01752	0.01752
FLJ38668	0.8194	0.00233	0.00233
TM6SF1	0.8176	0.003407	0.003407
BAI2	0.8125	0.004657	0.004657
LOC100506548	0.8113	1.08E-11	1.08E-11
WWTR1	0.8094	0.0003533	0.0003533
TMEM249	0.8078	0.0003653	0.0003653
AKR1C1	0.8022	2.15E-07	2.15E-07
PPM1J	0.8006	0.02053	0.02053
RND3	0.799	0.0002383	0.0002383
TGFB1I1	0.7986	6.41E-06	6.41E-06
KDM4A	0.7984	4.72E-15	4.72E-15
ITIH4	0.7974	0.000136	0.000136

NRP1	0.7956	1.08E-07	1.08E-07
ADCY4	0.7949	3.97E-05	3.97E-05
CCDC157	0.7949	0.0002938	0.0002938
GCAT	0.7929	3.78E-10	3.78E-10
RUFY4	0.7909	0.0002859	0.0002859
PPP1R32	0.7889	0.003896	0.003896
DUSP6	0.7884	6.10E-11	6.10E-11
FABP4	0.7874	0.00816	0.00816
CSNK1E	0.7843	5.28E-13	5.28E-13
SLC25A34	0.7822	0.002542	0.002542
AC009501.4	0.781	6.20E-07	6.20E-07
ARHGEF33	0.7807	0.04726	0.04726
TMOD2	0.7766	0.004161	0.004161
MVK	0.7763	4.29E-08	4.29E-08
WDR63	0.7756	5.48E-08	5.48E-08
GVINP1	0.7752	0.001471	0.001471
C5orf56	0.7688	0.003978	0.003978
DNAH6	0.7671	0.001252	0.001252
IQCD	0.7669	0.0004106	0.0004106
RP1-234P15.4	0.7666	0.01162	0.01162
LOC101928291	0.765	0.02055	0.02055
POLN	0.7629	0.00433	0.00433
BAI3	0.76	0.00198	0.00198
KLHL25	0.7591	0.001089	0.001089
HAVCR2	0.7577	0.001538	0.001538
FLJ32255	0.7549	5.30E-10	5.30E-10
LOC101929540	0.7548	0.02358	0.02358
ZDHHC1	0.7524	4.31E-05	4.31E-05
RAB43	0.7504	0.002726	0.002726
CATSPER2	0.749	0.003116	0.003116
KHDRBS3	0.748	0.005767	0.005767
GOLGA8I	0.7478	0.0009563	0.0009563
EFR3B	0.7477	0.004828	0.004828
MSMO1	0.7474	6.65E-11	6.65E-11
GOLGA8M	0.7431	1.11E-05	1.11E-05
LOC101928236	0.7402	0.006828	0.006828
ATF3	0.7392	0.0003015	0.0003015
EPB41L3	0.7326	6.44E-05	6.44E-05
MACROD2	0.732	0.04097	0.04097
B4GALT3	0.7299	1.68E-13	1.68E-13

LINC01133	0.7293	2.14E-05	2.14E-05
VAMP5	0.7262	0.007717	0.007717
CCDC168	0.726	0.02725	0.02725
ADAMTS13	0.7258	0.0001203	0.0001203
RAB30	0.7249	0.01874	0.01874
WDR78	0.7248	0.0009827	0.0009827
SNHG9	0.7207	0.0004372	0.0004372
LOC100506127	0.7206	0.01007	0.01007
PRSS53	0.7204	0.0002843	0.0002843
TGFB3	0.716	0.001062	0.001062
HHLA3	0.7146	5.04E-05	5.04E-05
FAM106A	0.7126	0.02782	0.02782
ALDH1L2	0.7092	4.27E-10	4.27E-10
ASNS	0.7091	1.35E-08	1.35E-08
CADM4	0.7086	0.01509	0.01509
DLL1	0.7074	2.59E-06	2.59E-06
GSDMB	0.706	0.006157	0.006157
GOLGA8S	0.7043	0.001743	0.001743
ABCC3	0.7039	0.005012	0.005012
SLAMF8	0.7036	0.001235	0.001235
ANKFN1	0.7003	0.001028	0.001028
CCDC109B	0.7003	0.0155	0.0155
MYL9	0.7	2.77E-13	2.77E-13
SERPINE2	0.6973	8.17E-06	8.17E-06
HFM1	0.6957	0.00182	0.00182
RNF150	0.6949	0.003711	0.003711
LOC100507373	0.6923	0.0001831	0.0001831
EGR4	0.6895	0.04072	0.04072
TBC1D4	0.6891	7.07E-05	7.07E-05
ZMYND12	0.6875	0.0004466	0.0004466
TMEM191B	0.6858	0.02669	0.02669
ANXA2R	0.684	1.67E-06	1.67E-06
CLK1	0.6825	7.40E-10	7.40E-10
FAM117A	0.6817	6.87E-11	6.87E-11
ULBP1	0.6817	0.001966	0.001966
ARMC9	0.6809	2.54E-05	2.54E-05
KDM4A-AS1	0.6797	1.13E-08	1.13E-08
BRICD5	0.6785	2.10E-05	2.10E-05
LOC100507316	0.6752	0.00374	0.00374
ZNF837	0.6746	0.0003729	0.0003729

DYRK1B	0.674	0.000372	0.000372
DSE	0.6739	0.0001542	0.0001542
RPS18P9	0.6739	0.005679	0.005679
LOC101928891	0.6706	1.85E-05	1.85E-05
MYCBPAP	0.6704	0.0001176	0.0001176
DUSP8	0.6703	0.004321	0.004321
EFCAB12	0.6683	0.009862	0.009862
CNIH3	0.6672	0.01	0.01
SAP25	0.6664	0.0004155	0.0004155
LIME1	0.6643	2.32E-06	2.32E-06
EPSTI1	0.6635	3.73E-06	3.73E-06
LOC644961	0.6627	0.001475	0.001475
RABL2A	0.662	7.94E-07	7.94E-07
GYPC	0.6616	3.02E-11	3.02E-11
LOC100128494	0.6601	0.01518	0.01518
RAB7B	0.6594	3.26E-11	3.26E-11
FBXO36	0.6581	0.008048	0.008048
PDGFA	0.658	0.0001519	0.0001519
CMTM1	0.6576	0.0004042	0.0004042
DEFB1	0.6573	4.35E-07	4.35E-07
MGC16142	0.6573	0.02766	0.02766
HOXA10-AS	0.6571	2.44E-07	2.44E-07
SLC4A5	0.6567	0.02946	0.02946
SEC31B	0.6526	0.000611	0.000611
FAM86B3P	0.652	0.0002163	0.0002163
PHGDH	0.6517	3.35E-11	3.35E-11
LOC102724169	0.6507	0.002849	0.002849
CDH15	0.6506	0.01514	0.01514
DTX4	0.6489	1.19E-08	1.19E-08
LOC102724200	0.6477	0.0002363	0.0002363
TMEM120B	0.647	2.00E-07	2.00E-07
LY6E	0.6468	1.03E-09	1.03E-09
FBXW9	0.6445	5.11E-07	5.11E-07
SUGT1P1	0.6445	0.01143	0.01143
CBS	0.6442	0.0003749	0.0003749
BPHL	0.6436	0.001821	0.001821
MAPK8IP3	0.6418	3.53E-09	3.53E-09
WNT11	0.6411	0.018	0.018
LOC101060264	0.6408	0.008278	0.008278
LOC100996255	0.6406	6.04E-05	6.04E-05

HEXDC	0.6399	4.40E-08	4.40E-08
DRP2	0.6398	0.005272	0.005272
OGDHL	0.638	0.0006565	0.0006565
SEMA3B	0.638	0.02725	0.02725
OAS3	0.6367	1.31E-10	1.31E-10
CAPS	0.6367	0.002033	0.002033
POU6F1	0.6362	0.0003754	0.0003754
HOXA11-AS	0.6352	1.13E-07	1.13E-07
WIPI1	0.6348	0.01021	0.01021
BEX1	0.6345	4.59E-11	4.59E-11
ECEL1	0.634	0.002337	0.002337
HIP1R	0.6336	1.60E-06	1.60E-06
EFHC1	0.6331	6.68E-05	6.68E-05
AJAP1	0.6325	3.38E-06	3.38E-06
ZNF491	0.6315	0.03485	0.03485
SPTBN5	0.6308	0.0004272	0.0004272
MVD	0.6304	1.59E-10	1.59E-10
DHCR7	0.6274	3.58E-09	3.58E-09
LOC284889	0.6273	0.0009566	0.0009566
CSNK1D	0.6268	2.55E-12	2.55E-12
NUTM2D	0.6255	0.009197	0.009197
LOC155060	0.6248	0.000533	0.000533
LOC100133091	0.624	0.001533	0.001533
MROH6	0.623	0.0001424	0.0001424
KDELC1	0.6226	1.16E-07	1.16E-07
VMAC	0.6223	2.60E-05	2.60E-05
AMH	0.6216	0.01002	0.01002
KCNMB1	0.6206	3.05E-09	3.05E-09
ZNF862	0.6201	1.81E-08	1.81E-08
POMC	0.6194	2.47E-05	2.47E-05
LOC101928069	0.6192	0.03161	0.03161
SLCO2B1	0.6179	0.00231	0.00231
EPPK1	0.6174	0.001133	0.001133
LTB4R2	0.6156	6.22E-05	6.22E-05
LINC00923	0.6156	0.0392	0.0392
SNORD47	0.6141	0.0001853	0.0001853
CLK4	0.614	2.48E-07	2.48E-07
FAM195B	0.6137	3.78E-09	3.78E-09
PPIEL	0.6131	0.009004	0.009004
YTHDF3-AS1	0.6129	0.01483	0.01483

KCNJ2	0.6121	0.01611	0.01611
SH3BP5	0.612	1.33E-08	1.33E-08
KCND1	0.6111	0.001184	0.001184
HMOX1	0.6105	3.59E-05	3.59E-05
WDR31	0.6097	0.0002511	0.0002511
MTSS1	0.6091	0.002149	0.002149
C11orf96	0.609	0.001221	0.001221
P2RY11	0.6089	0.0003097	0.0003097
THBS1	0.6067	0.002686	0.002686
LINC00936	0.6067	0.01834	0.01834
TBC1D16	0.6053	6.59E-09	6.59E-09
RRNAD1	0.6046	1.44E-09	1.44E-09
PSMG3-AS1	0.6046	6.89E-07	6.89E-07
MIRLET7BHG	0.6031	0.000963	0.000963
PLEKHO1	0.6026	8.60E-10	8.60E-10
ARHGAP39	0.6023	0.0009057	0.0009057
FAM86JP	0.6016	0.002215	0.002215
BEND6	0.6013	0.0001593	0.0001593
VEGFA	0.6012	2.00E-09	2.00E-09
FHL2	0.6008	2.29E-07	2.29E-07
FLJ23867	0.6003	2.69E-07	2.69E-07
C14orf79	0.5996	1.31E-05	1.31E-05
CYR61	0.5968	0.003388	0.003388
TMEM243	0.5958	0.0004383	0.0004383
ZNF880	0.5954	0.0175	0.0175
SNORA61	0.5952	0.006134	0.006134
RHPN1	0.5949	2.31E-06	2.31E-06
ZKSCAN7	0.5948	0.0004542	0.0004542
YJEFN3	0.5945	0.0002329	0.0002329
RP11-890B15.2	0.5938	0.000124	0.000124
BDNF-AS	0.5938	0.001856	0.001856
TSGA10	0.5927	0.006394	0.006394
LOC100652768	0.5921	0.03597	0.03597
MSH5-SAPCD1	0.5918	0.03224	0.03224
NOTUM	0.5915	0.0001975	0.0001975
GOLGA8K	0.5909	0.001288	0.001288
HELZ2	0.5883	2.47E-09	2.47E-09
AQP1	0.5878	0.02184	0.02184
SGSH	0.5856	0.008507	0.008507
LOC102724256	-0.5851	1.74E-05	1.74E-05

C1orf186	-0.5855	4.08E-05	4.08E-05
EVA1C	-0.5859	0.01363	0.01363
ANKRD35	-0.5869	5.53E-07	5.53E-07
FAM150A	-0.5871	0.004085	0.004085
LOC100129203	-0.5871	0.009145	0.009145
VIM-AS1	-0.5879	0.0009357	0.0009357
SLC17A5	-0.5886	1.26E-09	1.26E-09
PROX2	-0.5893	0.01732	0.01732
ARHGAP25	-0.5895	1.33E-07	1.33E-07
LOC101929545	-0.5904	0.005401	0.005401
TMEM45A	-0.5913	0.0001047	0.0001047
IQGAP2	-0.5919	1.22E-07	1.22E-07
SYTL1	-0.5922	0.0001249	0.0001249
MPZ	-0.5945	0.0002494	0.0002494
LOC102723883	-0.5967	0.02617	0.02617
CD300LB	-0.5972	0.0005345	0.0005345
FOS	-0.5974	2.52E-06	2.52E-06
C1QL4	-0.5987	0.02055	0.02055
ARRDC3-AS1	-0.5996	0.01169	0.01169
NCALD	-0.6	1.38E-06	1.38E-06
FAM161B	-0.6003	0.000525	0.000525
TACC2	-0.6004	5.64E-06	5.64E-06
HSPA1L	-0.6007	0.0004268	0.0004268
SWT1	-0.6012	0.006825	0.006825
LHFPL2	-0.6019	2.06E-05	2.06E-05
CCDC78	-0.6022	8.66E-05	8.66E-05
GAPT	-0.6025	6.01E-10	6.01E-10
C1orf226	-0.604	1.82E-06	1.82E-06
SYN3	-0.6041	0.005724	0.005724
CACNA2D3	-0.6049	1.26E-08	1.26E-08
SLC2A3	-0.6056	0.0006029	0.0006029
ZNF836	-0.606	0.0006991	0.0006991
PDCD4	-0.6069	7.27E-11	7.27E-11
GIPC3	-0.6076	1.00E-09	1.00E-09
LOC81691	-0.6095	7.27E-09	7.27E-09
RPSAP9	-0.6104	0.03111	0.03111
SIM1	-0.6107	0.0004076	0.0004076
HYDIN2	-0.6113	0.02136	0.02136
LOC101929119	-0.6138	0.03086	0.03086
TMEM238	-0.6139	0.04929	0.04929

SERPINA1	-0.615	0.0004516	0.0004516
FOSL1	-0.6175	1.52E-06	1.52E-06
DGKG	-0.6202	4.66E-08	4.66E-08
BMP8B	-0.6206	2.17E-13	2.17E-13
SNX10	-0.6217	1.75E-08	1.75E-08
SNORA73A	-0.6228	0.0167	0.0167
RGS3	-0.6231	0.001326	0.001326
PSTPIP1	-0.6238	1.12E-08	1.12E-08
KREMEN2	-0.6258	0.001855	0.001855
RSP01	-0.6269	0.01096	0.01096
ZNF630	-0.6307	0.01635	0.01635
SCIMP	-0.6308	0.003438	0.003438
ASGR2	-0.631	0.0001283	0.0001283
LOC100093631	-0.631	0.0004864	0.0004864
LOC101927841	-0.6312	0.0001154	0.0001154
MPO	-0.6316	0.0001052	0.0001052
SLC6A11	-0.6327	0.00349	0.00349
C1orf228	-0.634	2.89E-10	2.89E-10
PCED1B-AS1	-0.6355	3.29E-06	3.29E-06
MUC19	-0.6358	0.001935	0.001935
EVI2B	-0.6362	3.17E-12	3.17E-12
TLR1	-0.6365	0.0009513	0.0009513
NHSL2	-0.639	1.40E-08	1.40E-08
FMO5	-0.639	4.09E-05	4.09E-05
BPI	-0.6416	0.04729	0.04729
AQP3	-0.6432	2.37E-05	2.37E-05
C19orf59	-0.6476	1.28E-09	1.28E-09
S1PR3	-0.6476	1.48E-07	1.48E-07
LDOC1	-0.6494	0.001256	0.001256
APOBR	-0.6497	4.45E-11	4.45E-11
S1PR5	-0.6503	0.0001619	0.0001619
LOC100507642	-0.6508	4.51E-06	4.51E-06
SLC9A7	-0.6539	1.54E-05	1.54E-05
LOC339862	-0.6552	0.007553	0.007553
CALHM2	-0.6575	8.40E-05	8.40E-05
NHLRC3	-0.66	5.18E-07	5.18E-07
C3	-0.6607	4.52E-12	4.52E-12
GPR35	-0.6621	8.54E-05	8.54E-05
KLHL30	-0.6632	0.0002329	0.0002329
GNG12	-0.6632	0.003494	0.003494

FAM111B	-0.6646	7.41E-11	7.41E-11
PODNL1	-0.6661	0.0132	0.0132
IL16	-0.667	3.14E-07	3.14E-07
ADPGK-AS1	-0.6683	0.003957	0.003957
TREM1	-0.6699	0.00879	0.00879
APOC1	-0.67	1.43E-08	1.43E-08
CENPH	-0.6701	1.21E-09	1.21E-09
MTMR11	-0.6705	1.38E-06	1.38E-06
ALDH1A3	-0.6705	0.009436	0.009436
SETBP1	-0.6709	0.0001633	0.0001633
ACVR1C	-0.6723	0.001876	0.001876
TRIM72	-0.6733	0.005988	0.005988
CCL23	-0.6739	3.19E-07	3.19E-07
PAX8	-0.674	0.002641	0.002641
C19orf35	-0.675	0.0001515	0.0001515
KCNA3	-0.6759	1.74E-08	1.74E-08
LINC01094	-0.6762	0.01506	0.01506
PRTN3	-0.6776	3.69E-11	3.69E-11
THBS4	-0.6785	7.11E-07	7.11E-07
NMNAT2	-0.6786	0.01318	0.01318
FAS	-0.6791	0.005757	0.005757
TNFSF10	-0.6794	1.32E-07	1.32E-07
IL1R1	-0.6855	0.004712	0.004712
MPEG1	-0.6879	8.63E-11	8.63E-11
KIF21B	-0.6912	2.75E-10	2.75E-10
FAT4	-0.6913	0.03983	0.03983
C20orf197	-0.6914	0.0002667	0.0002667
TNS1	-0.6915	5.01E-09	5.01E-09
HOXA4	-0.6934	0.01335	0.01335
ZNF385A	-0.6954	5.44E-13	5.44E-13
TXNDC5	-0.6972	0.003239	0.003239
MIR223	-0.6973	0.007621	0.007621
DBNDD1	-0.7011	0.008893	0.008893
ARHGAP42	-0.7014	0.003632	0.003632
EMILIN1	-0.7021	0.0004212	0.0004212
SLC29A4	-0.7026	4.28E-07	4.28E-07
C20orf112	-0.7028	5.80E-10	5.80E-10
SYT11	-0.7029	0.002233	0.002233
CORO2A	-0.7032	1.44E-08	1.44E-08
TNNT1	-0.7036	8.01E-10	8.01E-10

PTPRO	-0.7068	4.32E-09	4.32E-09
HK3	-0.7069	2.21E-09	2.21E-09
AGT	-0.7076	5.29E-12	5.29E-12
NPAS1	-0.7099	0.0005322	0.0005322
COL15A1	-0.7101	0.0001607	0.0001607
GUCY1A2	-0.7109	0.01957	0.01957
DISC1	-0.711	0.008048	0.008048
BLNK	-0.7123	0.005472	0.005472
PPP1R3G	-0.7143	3.77E-09	3.77E-09
LOC101929017	-0.7157	0.004197	0.004197
ROM1	-0.7161	0.002756	0.002756
ITGA7	-0.7201	1.20E-05	1.20E-05
EPHB6	-0.7205	9.99E-08	9.99E-08
NLRC4	-0.7207	0.0001096	0.0001096
HIVEP1	-0.721	0.0002165	0.0002165
TCN2	-0.7222	0.003808	0.003808
DYNC1I1	-0.7256	0.02718	0.02718
ZDHHC2	-0.7271	1.99E-10	1.99E-10
LINC00977	-0.7277	0.0001526	0.0001526
JADE2	-0.7279	3.25E-12	3.25E-12
AOAH	-0.7284	7.53E-06	7.53E-06
ZRANB2	-0.7305	6.36E-10	6.36E-10
CCDC103	-0.7315	0.0007288	0.0007288
SPTB	-0.7316	0.00909	0.00909
MAPK13	-0.732	6.22E-06	6.22E-06
CIB3	-0.7332	0.01446	0.01446
MAP3K12	-0.7385	0.005251	0.005251
MRVI1	-0.7407	0.003672	0.003672
HVCN1	-0.7409	9.13E-08	9.13E-08
ST13P4	-0.746	0.00448	0.00448
RRM2	-0.7461	2.95E-13	2.95E-13
SAMD15	-0.7474	0.005549	0.005549
ZNF804A	-0.7477	2.61E-09	2.61E-09
POU2F2	-0.7486	2.76E-08	2.76E-08
SLAMF6	-0.7493	2.12E-05	2.12E-05
LINC01140	-0.7494	0.0004332	0.0004332
FAM171A1	-0.7497	0.0006271	0.0006271
TMEM38A	-0.7514	0.00062	0.00062
ANK1	-0.7531	0.004581	0.004581
FLT3	-0.7537	5.66E-12	5.66E-12

NAIP	-0.756	1.18E-06	1.18E-06
KCNN1	-0.7562	0.005132	0.005132
DKK2	-0.7603	9.45E-07	9.45E-07
PINLYP	-0.7608	0.0001727	0.0001727
HAPLN3	-0.761	0.008535	0.008535
PDE7B	-0.7615	1.88E-08	1.88E-08
LYZ	-0.7629	1.85E-14	1.85E-14
PPFIA4	-0.7651	6.67E-07	6.67E-07
FAM83B	-0.7654	0.001277	0.001277
RP11-344B5.2	-0.7679	0.005385	0.005385
TEC	-0.7683	4.90E-11	4.90E-11
ATL1	-0.7704	0.002434	0.002434
PDGFD	-0.7728	1.93E-08	1.93E-08
SOX1	-0.7735	0.005021	0.005021
SSPO	-0.7746	0.0004629	0.0004629
RP11-12A2.3	-0.7755	0.002975	0.002975
CXCR2	-0.7757	3.66E-10	3.66E-10
LOC102723375	-0.7777	0.01399	0.01399
NAPSB	-0.7786	1.09E-11	1.09E-11
SUCNR1	-0.7829	0.004753	0.004753
C1orf200	-0.7835	1.82E-06	1.82E-06
SIGLEC7	-0.7835	0.00623	0.00623
TGFBR1	-0.7837	1.39E-12	1.39E-12
LOC441081	-0.7841	0.01311	0.01311
LOC101926967	-0.7845	0.005217	0.005217
CAMSAP2	-0.7856	1.74E-09	1.74E-09
EPS8L3	-0.7859	0.001515	0.001515
TTBK1	-0.7874	0.005246	0.005246
ARAP3	-0.7895	3.88E-05	3.88E-05
ZSCAN5A	-0.7934	6.21E-07	6.21E-07
TEAD3	-0.7971	5.93E-07	5.93E-07
ANK3	-0.7983	0.002059	0.002059
LOC102724740	-0.7986	0.0001148	0.0001148
ST8SIA5	-0.7999	0.001964	0.001964
FAM212A	-0.8011	2.95E-06	2.95E-06
PPP1R1C	-0.8015	0.005555	0.005555
STAP1	-0.8025	0.0005231	0.0005231
C19orf38	-0.8036	1.59E-06	1.59E-06
CDA	-0.8048	0.00027	0.00027
SLA2	-0.8054	0.001515	0.001515

CD84	-0.806	3.86E-13	3.86E-13
TMC8	-0.8072	2.07E-10	2.07E-10
FCGR1C	-0.8082	1.80E-05	1.80E-05
GPA33	-0.8087	1.24E-10	1.24E-10
RIMS2	-0.8103	0.01082	0.01082
MPP7	-0.8145	0.0001462	0.0001462
SCAMP5	-0.8149	9.11E-11	9.11E-11
ACY3	-0.8185	0.01955	0.01955
IPCEF1	-0.8187	1.20E-12	1.20E-12
LOC101927402	-0.8192	3.66E-06	3.66E-06
LOXHD1	-0.8198	4.49E-06	4.49E-06
PDCD4-AS1	-0.822	0.002122	0.002122
FXYD6	-0.8254	0.0009757	0.0009757
TBXA2R	-0.8265	0.0005963	0.0005963
NLRC3	-0.8267	3.14E-05	3.14E-05
CDC42EP4	-0.828	1.96E-08	1.96E-08
SYNC	-0.8315	0.0001209	0.0001209
TNFSF14	-0.8321	8.11E-09	8.11E-09
LOC101927727	-0.8344	5.29E-05	5.29E-05
HERC2P3	-0.8359	0.0009494	0.0009494
LMTK3	-0.8375	1.17E-05	1.17E-05
FCGR1A	-0.8405	4.97E-13	4.97E-13
PCDH12	-0.8428	4.85E-05	4.85E-05
CASS4	-0.8445	5.60E-06	5.60E-06
TBC1D10C	-0.8446	0.005701	0.005701
ZNF280A	-0.8461	0.01084	0.01084
NUAK1	-0.8471	0.003439	0.003439
ST3GAL6	-0.8472	8.57E-10	8.57E-10
UTF1	-0.8522	0.0004818	0.0004818
ZNF467	-0.8564	6.61E-08	6.61E-08
PLEKHA7	-0.8616	0.001675	0.001675
HGF	-0.8618	7.88E-06	7.88E-06
C1orf54	-0.8667	7.66E-10	7.66E-10
GALNT3	-0.8672	0.00297	0.00297
CD244	-0.8676	4.90E-10	4.90E-10
KIAA1644	-0.8707	6.06E-05	6.06E-05
PTAFR	-0.876	3.23E-08	3.23E-08
PANX2	-0.8769	0.0001463	0.0001463
ADRB2	-0.8797	4.36E-05	4.36E-05
TMEM156	-0.8837	0.001552	0.001552

RNU105A	-0.889	0.01168	0.01168
COL24A1	-0.8894	0.0001137	0.0001137
ADAMDEC1	-0.8915	0.0004552	0.0004552
SPNS3	-0.8934	5.02E-09	5.02E-09
ITGAL	-0.8979	6.60E-13	6.60E-13
MILR1	-0.9008	2.84E-09	2.84E-09
TNFSF13	-0.9069	4.70E-05	4.70E-05
GPNMB	-0.9098	1.07E-12	1.07E-12
MMP19	-0.9114	0.001211	0.001211
TSPAN32	-0.9149	2.64E-07	2.64E-07
TNNI2	-0.9152	0.001752	0.001752
RAB37	-0.9156	5.57E-06	5.57E-06
LOC102724017	-0.9194	0.00284	0.00284
HSPB7	-0.9221	6.71E-08	6.71E-08
KCNIP3	-0.9234	0.002365	0.002365
TAF9B	-0.9236	6.12E-10	6.12E-10
GPR18	-0.9263	8.56E-09	8.56E-09
PNOC	-0.9344	0.001406	0.001406
IL12RB1	-0.9377	2.39E-08	2.39E-08
ZNF536	-0.9396	0.00355	0.00355
SLPI	-0.9448	3.71E-10	3.71E-10
METTL7A	-0.9471	5.92E-08	5.92E-08
MCTP1	-0.9488	2.40E-10	2.40E-10
ARHGAP24	-0.9524	0.0001124	0.0001124
AIM1	-0.9582	9.57E-13	9.57E-13
CLEC12A	-0.9606	6.16E-07	6.16E-07
LOC101928429	-0.9638	2.78E-11	2.78E-11
ARID5B	-0.9649	8.35E-06	8.35E-06
IKZF3	-0.9658	0.0005995	0.0005995
LOC100653515	-0.9658	0.002789	0.002789
ANXA1	-0.9704	6.27E-14	6.27E-14
MYBPH	-0.9733	2.43E-12	2.43E-12
SLAMF1	-0.9814	0.0002577	0.0002577
SIRPD	-0.9825	8.69E-06	8.69E-06
PRAM1	-0.9831	3.00E-08	3.00E-08
LOC101928841	-0.9836	0.0008729	0.0008729
CD101	-0.9851	0.004417	0.004417
IGSF9	-0.9853	0.0008233	0.0008233
SLC22A4	-0.9885	4.78E-07	4.78E-07
LOC102723894	-0.9952	5.57E-05	5.57E-05

MARCO	-0.997	0.000231	0.000231
OR2A1-AS1	-0.997	0.003193	0.003193
EPHA1-AS1	-0.998	0.001485	0.001485
LRRK2	-1.001	3.55E-06	3.55E-06
SERHL2	-1.003	0.0008259	0.0008259
ACOX2	-1.008	0.00447	0.00447
IL2RB	-1.011	8.34E-05	8.34E-05
TMEM229B	-1.014	6.86E-11	6.86E-11
ASB2	-1.021	1.33E-05	1.33E-05
SEMA3A	-1.021	4.63E-05	4.63E-05
PTGER3	-1.021	0.0002156	0.0002156
FCAMR	-1.024	0.009561	0.009561
CD36	-1.033	1.32E-12	1.32E-12
LOC101929174	-1.039	0.0001858	0.0001858
SIGLEC12	-1.04	6.53E-09	6.53E-09
VIT	-1.043	7.78E-08	7.78E-08
EGR1	-1.043	1.02E-05	1.02E-05
PADI2	-1.045	1.02E-07	1.02E-07
PTPN22	-1.046	1.92E-10	1.92E-10
LPAR4	-1.047	8.88E-08	8.88E-08
MOXD1	-1.048	1.08E-08	1.08E-08
SLCO4C1	-1.071	6.55E-08	6.55E-08
FRMD3	-1.074	3.88E-09	3.88E-09
SYNPO	-1.079	1.87E-06	1.87E-06
CSGALNACT1	-1.079	5.05E-06	5.05E-06
IL3RA	-1.081	3.49E-09	3.49E-09
SPIB	-1.088	6.80E-07	6.80E-07
C1orf127	-1.091	6.99E-06	6.99E-06
DDR2	-1.094	9.10E-05	9.10E-05
LAMA2	-1.103	5.24E-05	5.24E-05
TLR6	-1.109	3.26E-08	3.26E-08
LOC102724661	-1.11	0.001586	0.001586
IL8	-1.117	0.0001554	0.0001554
CLSTN2	-1.129	6.27E-13	6.27E-13
C1S	-1.133	3.71E-06	3.71E-06
CIITA	-1.143	0.0001472	0.0001472
PTCRA	-1.143	0.00412	0.00412
EPHA1	-1.149	5.60E-06	5.60E-06
HRC	-1.149	0.001155	0.001155
HAL	-1.151	4.33E-12	4.33E-12

FYB	-1.152	1.37E-11	1.37E-11
SH2D3C	-1.159	1.71E-07	1.71E-07
GPR133	-1.171	2.23E-05	2.23E-05
C10orf91	-1.173	3.27E-13	3.27E-13
SOCS1	-1.196	0.0004241	0.0004241
GABBR2	-1.215	6.23E-07	6.23E-07
CMYA5	-1.22	2.55E-10	2.55E-10
FCGR1B	-1.221	2.23E-11	2.23E-11
METTL7B	-1.224	5.08E-15	5.08E-15
ANXA8	-1.224	7.86E-09	7.86E-09
CUX2	-1.225	3.81E-07	3.81E-07
PNPLA1	-1.233	3.22E-06	3.22E-06
ANKRD55	-1.27	2.06E-07	2.06E-07
MYOZ1	-1.292	1.69E-07	1.69E-07
LINC00968	-1.305	0.0004354	0.0004354
RGS18	-1.313	6.84E-12	6.84E-12
NFE2	-1.357	6.54E-13	6.54E-13
SH3TC2	-1.362	3.10E-06	3.10E-06
NKG7	-1.379	4.76E-08	4.76E-08
FBXO15	-1.382	2.14E-05	2.14E-05
CSPG4	-1.396	8.53E-10	8.53E-10
SHISA8	-1.407	0.0001636	0.0001636
DUSP27	-1.409	9.77E-09	9.77E-09
PRLR	-1.416	3.02E-12	3.02E-12
RP11-330A16.1	-1.416	9.49E-06	9.49E-06
IGSF6	-1.417	5.53E-10	5.53E-10
C10orf10	-1.438	6.15E-06	6.15E-06
GPR141	-1.441	9.59E-07	9.59E-07
SEMG1	-1.446	5.26E-06	5.26E-06
HSD11B1	-1.447	8.43E-13	8.43E-13
ULK4P1	-1.452	0.006578	0.006578
LGALS12	-1.455	1.31E-08	1.31E-08
CLIC5	-1.459	2.70E-05	2.70E-05
IL31RA	-1.47	2.95E-08	2.95E-08
ANXA8L1	-1.473	5.86E-06	5.86E-06
SIGLEC6	-1.489	2.59E-10	2.59E-10
KCNF1	-1.511	6.58E-06	6.58E-06
CD180	-1.512	7.64E-11	7.64E-11
KMO	-1.531	2.92E-08	2.92E-08
TGM5	-1.532	7.96E-10	7.96E-10

LOC101927934	-1.533	7.89E-05	7.89E-05
LOC100130698	-1.545	2.56E-05	2.56E-05
HMCN1	-1.57	1.68E-05	1.68E-05
CAMK4	-1.571	5.12E-06	5.12E-06
FAM135B	-1.606	1.91E-09	1.91E-09
ROS1	-1.612	3.49E-10	3.49E-10
KCNS1	-1.651	9.49E-07	9.49E-07
TGM4	-1.665	7.08E-08	7.08E-08
LOC101928109	-1.668	8.08E-07	8.08E-07
DLGAP1-AS3	-1.678	1.76E-05	1.76E-05
NRG4	-1.74	9.85E-08	9.85E-08
RNU2-2P	-1.742	0.03418	0.03418
LOC101926956	-1.765	5.41E-07	5.41E-07
HHLA2	-1.793	3.22E-08	3.22E-08
GRIN3A	-2.04	2.09E-06	2.09E-06
LINC00211	-2.08	3.90E-08	3.90E-08
HP	-2.224	3.92E-08	3.92E-08

Table 4. Differentially expressed genes with IRAK4 degrader vs DMSO in THP1 cells

Gene	Log(FC)	P Value	Adj P Value
DGCR6	3.809	0.009345	0.009345
PPFIA2	2.06	2.01E-05	2.01E-05
OSBPL10	2.025	1.18E-05	1.18E-05
ADAM12	1.84	0.0001329	0.0001329
TREML1	1.81	8.05E-07	8.05E-07
OSMR	1.809	4.07E-05	4.07E-05
GPX8	1.746	1.41E-08	1.41E-08
FAM157C	1.726	0.005339	0.005339
PDGFRL	1.679	0.001351	0.001351
SYDE1	1.594	9.01E-05	9.01E-05
ACOXL	1.573	0.0002067	0.0002067
CLEC10A	1.547	6.72E-06	6.72E-06
ST7-AS1	1.53	1.36E-05	1.36E-05
CTSK	1.499	1.43E-08	1.43E-08
ZFHX4	1.419	9.13E-05	9.13E-05
IL17RE	1.412	1.15E-06	1.15E-06
VSIG4	1.395	0.0001535	0.0001535
SLAMP8	1.389	1.68E-05	1.68E-05
MEOX2	1.385	2.84E-05	2.84E-05

KIAA1324	1.342	1.44E-05	1.44E-05
PARVA	1.34	6.95E-10	6.95E-10
PDE11A	1.234	0.0006406	0.0006406
TGFB111	1.225	6.10E-06	6.10E-06
EPB41L1	1.221	1.32E-05	1.32E-05
SCN8A	1.211	0.002232	0.002232
TEAD2	1.209	0.0001149	0.0001149
DCST2	1.209	0.0005518	0.0005518
EMP2	1.206	6.21E-07	6.21E-07
ARHGAP31	1.186	8.84E-07	8.84E-07
NRP2	1.182	1.10E-05	1.10E-05
LOC100129083	1.179	0.000173	0.000173
CGN	1.172	0.001115	0.001115
COL7A1	1.17	0.00351	0.00351
C1orf51	1.168	0.0004074	0.0004074
ACE	1.151	1.92E-06	1.92E-06
LOC101927119	1.145	0.0008609	0.0008609
TNXB	1.131	7.70E-05	7.70E-05
LOC101928038	1.128	0.001865	0.001865
ADORA1	1.124	0.003859	0.003859
ELFN2	1.12	0.002394	0.002394
CNRIP1	1.112	5.37E-06	5.37E-06
PALLD	1.109	7.19E-06	7.19E-06
FLJ45513	1.095	0.001537	0.001537
SIGLEC11	1.081	9.79E-06	9.79E-06
ABCC3	1.075	0.000747	0.000747
ITIH4	1.07	0.0003538	0.0003538
CTRL	1.065	0.0002332	0.0002332
FAM57B	1.057	2.83E-05	2.83E-05
TMEM145	1.053	0.0005918	0.0005918
ZNF703	1.039	3.04E-06	3.04E-06
CXCL10	1.039	0.004186	0.004186
CD6	1.035	0.0003271	0.0003271
ETV7	1.033	0.001047	0.001047
ESAM	1.029	0.0005568	0.0005568
FMN1	1.023	0.0003309	0.0003309
DRP2	1.021	0.0004556	0.0004556
WLS	1.018	6.19E-07	6.19E-07
TREM2	1.015	5.53E-08	5.53E-08
LOC101927759	1.008	0.001649	0.001649

TMEM132A	1.007	0.001164	0.001164
MTMR9LP	1.005	0.002096	0.002096
PRTFDC1	0.9999	5.97E-05	5.97E-05
CYP19A1	0.9982	6.15E-05	6.15E-05
TENC1	0.9976	1.25E-05	1.25E-05
FBXO39	0.9949	0.004449	0.004449
SLC23A3	0.9786	0.01089	0.01089
DND1	0.9739	0.006522	0.006522
CLEC5A	0.9722	0.0007795	0.0007795
RCN3	0.9655	0.0002108	0.0002108
SIGLEC1	0.9624	3.08E-08	3.08E-08
DPF3	0.9551	1.30E-05	1.30E-05
C3AR1	0.9486	1.06E-05	1.06E-05
PCGF2	0.9426	4.35E-06	4.35E-06
SH3D19	0.9398	5.51E-06	5.51E-06
KIFC3	0.9383	3.01E-08	3.01E-08
LOC728715	0.9371	0.006749	0.006749
DLGAP1-AS3	0.9343	0.003231	0.003231
PDPN	0.934	0.0135	0.0135
SPTBN5	0.9333	0.0004318	0.0004318
LOC100507424	0.9213	0.03029	0.03029
TP53I3	0.9165	0.0003618	0.0003618
STON2	0.9074	0.0002017	0.0002017
ACY3	0.9004	0.00569	0.00569
WNK4	0.8958	0.001176	0.001176
LOC100130705	0.8931	0.01584	0.01584
LINC01140	0.8923	0.0001283	0.0001283
COL12A1	0.8907	0.000228	0.000228
FRMD4A	0.8857	3.35E-06	3.35E-06
ASIC3	0.8853	0.008545	0.008545
NUP62CL	0.8845	0.0033	0.0033
RAB13	0.8838	7.87E-09	7.87E-09
GPR68	0.8786	0.01129	0.01129
DNM1P35	0.8768	0.00413	0.00413
EPHB1	0.8762	4.92E-08	4.92E-08
HFE	0.8753	0.006761	0.006761
CNKSR1	0.8752	0.0262	0.0262
SLC25A34	0.8676	0.0008293	0.0008293
OAS3	0.8644	5.14E-08	5.14E-08
CEACAM19	0.8599	0.0001513	0.0001513

C1QC	0.8531	0.03751	0.03751
GPR141	0.8504	0.0001626	0.0001626
ZDHHC11	0.8496	0.001132	0.001132
MIR1304	0.848	0.01285	0.01285
MAEL	0.8478	0.01712	0.01712
WDFY3-AS2	0.8469	0.002496	0.002496
TMEM86A	0.8452	0.001029	0.001029
SLC17A7	0.8444	0.0004026	0.0004026
PPP1R13L	0.8416	7.58E-05	7.58E-05
CMTM1	0.8404	0.0003617	0.0003617
KCP	0.8372	0.0006037	0.0006037
UCP3	0.8346	0.0006094	0.0006094
NHS	0.8343	0.02638	0.02638
CCDC168	0.833	0.0248	0.0248
C15orf62	0.832	0.01743	0.01743
CCDC103	0.8305	0.000111	0.000111
SAMD14	0.8275	0.001003	0.001003
TLX1	0.8267	0.0004001	0.0004001
RASA4B	0.8256	0.002978	0.002978
PIP5KL1	0.8222	0.0001107	0.0001107
TNFAIP8L3	0.8214	0.001828	0.001828
STXBP5-AS1	0.8147	0.004513	0.004513
TMEM9B-AS1	0.8128	0.003187	0.003187
AP000330.8	0.8121	0.007586	0.007586
TNF	0.8082	0.0002992	0.0002992
SULT1A2	0.8036	0.04001	0.04001
ACSS3	0.8011	5.43E-06	5.43E-06
MYOZ1	0.7996	9.89E-06	9.89E-06
MAFB	0.7995	1.19E-05	1.19E-05
ZNF462	0.7988	0.002408	0.002408
LOC100506083	0.7987	0.009823	0.009823
EMR4P	0.792	0.001349	0.001349
GNG12	0.7908	0.000786	0.000786
SLC6A11	0.7889	0.0005212	0.0005212
LINC01094	0.7883	0.001385	0.001385
ASIC1	0.7864	1.68E-06	1.68E-06
ST6GALNAC2	0.7857	0.001085	0.001085
SAP25	0.7837	0.003548	0.003548
ERVMER34-1	0.783	0.000567	0.000567
SIGLEC16	0.7817	0.001478	0.001478

ALDH7A1	0.7814	0.0004313	0.0004313
SLC7A5P2	0.7784	0.007366	0.007366
FOXF1	0.7783	0.0005357	0.0005357
FSTL1	0.7768	7.52E-06	7.52E-06
RDM1	0.7755	0.002135	0.002135
ITGA7	0.7751	0.0002095	0.0002095
NXPH4	0.7731	0.01052	0.01052
BZRAP1	0.77	0.002838	0.002838
AASS	0.7689	0.001218	0.001218
TTC9	0.7631	0.01821	0.01821
EFCAB4A	0.7605	0.0007022	0.0007022
CBWD3	0.7604	0.03521	0.03521
DUSP27	0.7571	3.80E-05	3.80E-05
MDGA1	0.7551	0.0009009	0.0009009
NGFR	0.7531	0.009821	0.009821
HSPA7	0.7529	0.01421	0.01421
CCDC154	0.7503	0.01697	0.01697
IPO9-AS1	0.7483	0.04274	0.04274
UCN	0.748	0.003772	0.003772
SLC7A7	0.7473	7.00E-07	7.00E-07
ZNF692	0.747	2.79E-06	2.79E-06
PTPN14	0.7468	1.16E-05	1.16E-05
PKD1L3	0.7459	0.003647	0.003647
IL17RC	0.7449	0.0003498	0.0003498
RASGRP3	0.7449	0.003997	0.003997
ADAM19	0.7416	0.01334	0.01334
PRR22	0.7408	0.001105	0.001105
TTLL3	0.7397	0.006413	0.006413
TMEM255B	0.7394	0.002404	0.002404
PYROXD2	0.7385	6.06E-05	6.06E-05
GNMT	0.7369	0.0343	0.0343
CSPG4	0.7368	5.49E-06	5.49E-06
ST5	0.7363	0.008974	0.008974
ATP8B1	0.7357	3.01E-05	3.01E-05
CCDC183	0.7354	0.001773	0.001773
GJC2	0.7345	0.01838	0.01838
LOC101928055	0.7325	0.006065	0.006065
LINC00663	0.7322	0.03076	0.03076
ADAMTS15	0.7281	4.84E-06	4.84E-06
LOC101929112	0.7273	0.004874	0.004874

PLA2G4C	0.7272	0.0001224	0.0001224
GAS6-AS2	0.7271	0.0004976	0.0004976
EPHA1	0.7244	0.0002962	0.0002962
IGFBP4	0.723	1.97E-07	1.97E-07
SPHK1	0.7228	0.0001541	0.0001541
SEC31B	0.7222	0.00177	0.00177
ADAMTS17	0.7209	0.0007844	0.0007844
SEMA6B	0.72	3.49E-05	3.49E-05
DOK4	0.7192	0.0001361	0.0001361
YJEFN3	0.7187	0.0008396	0.0008396
BIN1	0.7172	3.85E-06	3.85E-06
EFCAB12	0.717	0.007817	0.007817
SEMA3D	0.716	0.01923	0.01923
SCML1	0.711	0.01977	0.01977
CLDN7	0.7103	0.002722	0.002722
RP11-15A1.7	0.7096	0.01305	0.01305
NPAS4	0.7093	0.0151	0.0151
RAI14	0.7085	3.27E-07	3.27E-07
AMOTL2	0.7081	7.21E-05	7.21E-05
MOB3B	0.7081	0.00972	0.00972
ZNF491	0.7057	0.01952	0.01952
RP5-1180C10.2	0.7048	0.001957	0.001957
FAM83B	0.7036	0.0006643	0.0006643
SGK1	0.7027	0.001916	0.001916
ZFHX2	0.7007	0.002393	0.002393
C1RL-AS1	0.7006	0.003501	0.003501
SNTB2	0.7004	0.0002471	0.0002471
RPS18P9	0.6993	0.008565	0.008565
ZNF487	0.6987	0.01634	0.01634
SERPINH1	0.696	3.85E-07	3.85E-07
ARMCX5-GPRASP2	0.6881	0.01107	0.01107
GSTM2	0.6815	0.03953	0.03953
TEAD3	0.6802	5.29E-05	5.29E-05
LTB4R2	0.6791	0.0003389	0.0003389
KLRAP1	0.6778	0.03904	0.03904
MIR570	0.6767	0.03771	0.03771
LRRC4B	0.6766	6.89E-05	6.89E-05
MANEA-AS1	0.6759	0.03958	0.03958
RP11-307C12.11	0.675	0.001382	0.001382
ARAP3	0.6734	0.0001437	0.0001437

PXDC1	0.6721	0.003061	0.003061
TBC1D9	0.6706	5.22E-05	5.22E-05
DNHD1	0.667	0.0003086	0.0003086
CCDC155	0.6658	0.0269	0.0269
PLEKHA4	0.6652	0.0001923	0.0001923
STXBP6	0.6645	8.24E-05	8.24E-05
CCDC27	0.6611	0.002215	0.002215
ITGB2-AS1	0.6608	0.02077	0.02077
LINC00337	0.6601	0.03059	0.03059
MROH6	0.6588	0.00252	0.00252
CALHM2	0.6574	9.82E-05	9.82E-05
QRICH2	0.6567	0.007838	0.007838
IFIT3	0.6563	6.47E-06	6.47E-06
SEMA3B	0.6545	0.03474	0.03474
BLNK	0.654	0.002566	0.002566
HGD	0.6528	0.0005552	0.0005552
RP3-399L15.3	0.6516	0.0001035	0.0001035
REC8	0.651	0.007974	0.007974
MGC16142	0.6505	0.04274	0.04274
FBXL8	0.6504	0.001621	0.001621
ATP2B3	0.6497	0.006879	0.006879
RND3	0.6494	0.002165	0.002165
LOC100505771	0.6492	0.01974	0.01974
NRP1	0.6479	0.0001242	0.0001242
PIPOX	0.6465	4.46E-05	4.46E-05
ADCY4	0.644	0.03089	0.03089
BTN2A3P	0.6432	0.005706	0.005706
USH1C	0.6382	0.003174	0.003174
MLXIPL	0.6377	0.007901	0.007901
CLK1	0.6367	2.06E-06	2.06E-06
NR1H3	0.6367	1.26E-05	1.26E-05
KCNJ5	0.6358	0.007752	0.007752
VAX2	0.6346	0.006492	0.006492
CD1C	0.6342	0.02268	0.02268
AC007038.7	0.6314	0.01056	0.01056
DHRS3	0.6307	0.005189	0.005189
DAB2	0.6294	2.10E-05	2.10E-05
TBX15	0.6293	0.001029	0.001029
PRSS53	0.6281	0.001429	0.001429
DUSP4	0.6271	0.0002337	0.0002337

CUEDC1	0.6243	2.22E-05	2.22E-05
ASMTL-AS1	0.6242	0.01732	0.01732
QPCT	0.624	0.00212	0.00212
TTLL7	0.623	0.01612	0.01612
LOC101927321	0.6228	0.02817	0.02817
CEACAM4	0.6227	0.00696	0.00696
FFAR4	0.6221	0.00907	0.00907
NUPR1	0.6201	0.01145	0.01145
TTC23	0.6179	4.07E-06	4.07E-06
DPYD	0.6177	1.26E-07	1.26E-07
EGR3	0.6175	0.01362	0.01362
CROCCP3	0.6154	0.004248	0.004248
ADAMTS4	0.6146	0.003386	0.003386
GPR84	0.6139	0.002879	0.002879
NEAT1	0.6129	0.004838	0.004838
LOC101926956	0.6127	0.006163	0.006163
AURKC	0.6123	0.01388	0.01388
GPR113	0.6105	0.02041	0.02041
LOC100506548	0.6092	1.91E-06	1.91E-06
GDPD3	0.6082	0.01922	0.01922
SIPA1L1	0.6081	3.97E-05	3.97E-05
PPP1R1C	0.6074	0.01131	0.01131
LAX1	0.6066	0.01031	0.01031
TLR5	0.6066	0.04147	0.04147
PCDHGA12	0.6055	0.005677	0.005677
EPSTI1	0.6007	0.0001589	0.0001589
CACTIN-AS1	0.5982	0.01303	0.01303
ANK1	0.5978	0.01365	0.01365
RASGRF1	0.5973	0.002775	0.002775
VAMP5	0.5964	0.04627	0.04627
LINC00877	0.5956	0.03995	0.03995
CBX6	0.5943	4.61E-07	4.61E-07
BACE1	0.5942	6.12E-08	6.12E-08
CTGF	0.591	0.00699	0.00699
ZNF665	0.5908	0.03949	0.03949
PAQR6	0.5901	0.003754	0.003754
TTC21A	0.5886	0.02085	0.02085
SPTB	0.5877	0.008665	0.008665
CD14	0.5874	0.01658	0.01658
LOC102724217	0.5853	0.007105	0.007105

CIITA	-0.5914	0.03258	0.03258
EPHX4	-0.5929	0.01281	0.01281
NLRC3	-0.5939	0.001443	0.001443
SLC7A2	-0.5943	0.001	0.001
CXCR4	-0.5961	2.57E-07	2.57E-07
CLUHP3	-0.5966	0.04581	0.04581
SHISA7	-0.6063	0.0003919	0.0003919
PXK	-0.6096	1.04E-07	1.04E-07
CAV1	-0.6103	0.0005454	0.0005454
PRG2	-0.6148	0.007062	0.007062
HGF	-0.6155	0.0007808	0.0007808
KCNA3	-0.617	6.54E-05	6.54E-05
NRG4	-0.619	0.005312	0.005312
ANKRD55	-0.6194	0.0007287	0.0007287
DBNDD1	-0.6216	0.008926	0.008926
SLA2	-0.6218	0.007374	0.007374
TRPV3	-0.6266	0.04907	0.04907
ST6GALNAC3	-0.6268	0.007342	0.007342
EMR1	-0.6277	0.008108	0.008108
FAM69B	-0.6279	5.15E-06	5.15E-06
C17orf64	-0.635	0.03323	0.03323
CD84	-0.6436	2.22E-07	2.22E-07
SEMA3A	-0.6449	0.00526	0.00526
MPZL1	-0.6451	5.41E-05	5.41E-05
IL20RB	-0.6457	0.01414	0.01414
SYNPO2	-0.6472	2.42E-06	2.42E-06
TMEM150A	-0.6474	0.008799	0.008799
VASN	-0.6475	0.007328	0.007328
ZNF891	-0.6524	0.01175	0.01175
ZMYND10	-0.6531	0.02976	0.02976
MLC1	-0.6577	3.48E-07	3.48E-07
CUX2	-0.6584	0.00311	0.00311
LOC728819	-0.6633	0.01192	0.01192
PTAFR	-0.6643	2.27E-05	2.27E-05
GPM6B	-0.6692	0.004281	0.004281
GOLGA8EP	-0.6799	0.04995	0.04995
CCNB3	-0.6872	0.02893	0.02893
PLXNA4	-0.6889	0.00329	0.00329
ZCWPW2	-0.6945	0.03201	0.03201
FAM46B	-0.6967	0.004989	0.004989

SORBS1	-0.7035	0.01427	0.01427
FCER2	-0.7125	3.21E-05	3.21E-05
NKD2	-0.7164	1.85E-06	1.85E-06
TMEM176B	-0.7176	0.0005188	0.0005188
NPAS1	-0.718	0.002538	0.002538
AKAP7	-0.719	1.76E-05	1.76E-05
TERT	-0.7203	0.0002245	0.0002245
CORO2A	-0.7299	5.36E-06	5.36E-06
EBF3	-0.7345	4.93E-06	4.93E-06
CST7	-0.7412	0.001926	0.001926
PLAC8	-0.7588	1.60E-08	1.60E-08
C6orf223	-0.7674	2.49E-05	2.49E-05
HSH2D	-0.7767	2.13E-06	2.13E-06
PPP1R27	-0.7803	1.52E-06	1.52E-06
LOC102724005	-0.7847	0.01254	0.01254
SLC4A3	-0.791	0.00801	0.00801
SERPINB2	-0.7957	6.09E-06	6.09E-06
CHRFAM7A	-0.7978	0.03433	0.03433
MRAP2	-0.8016	0.0004844	0.0004844
SAMD13	-0.815	0.0007667	0.0007667
IL31RA	-0.816	0.0003034	0.0003034
MXN1-AS1	-0.8198	0.005986	0.005986
PMEPA1	-0.8346	0.002697	0.002697
AIF1L	-0.9276	0.006215	0.006215
GPR158	-0.9326	0.0001847	0.0001847
LOC100996717	-0.9425	0.0004041	0.0004041
TNFAIP8L2-SCNM1	-0.9742	0.008369	0.008369
SEMG1	-0.9769	0.001761	0.001761
ARL4C	-1.01	0.0006149	0.0006149
ELOVL3	-1.016	8.56E-05	8.56E-05
CIB3	-1.023	0.004862	0.004862
CSGALNACT1	-1.159	4.84E-05	4.84E-05
FAM157A	-1.186	0.0005428	0.0005428
SEMA3C	-1.247	0.003467	0.003467

Table 5. Differentially expressed genes in IRAK4-KO vs WT THP1 cells

Gene	Log(FC)	P Value	Adj P Value
ZBED6CL	8.385	1.56E-11	8.78E-09
PDE9A	6.886	9.68E-09	3.25E-07

BHLHE22	6.81	1.86E-14	8.43E-11
SPATA31C1	6.337	1.95E-09	1.11E-07
WIPF3	6.247	1.05E-07	1.77E-06
GNLY	5.453	5.89E-08	1.16E-06
SHROOM2	5.282	1.76E-06	1.61E-05
SSC5D	5.271	1.53E-06	1.44E-05
LINC00599	5.256	8.06E-06	5.28E-05
TSPAN18	4.949	3.64E-07	4.74E-06
C14orf132	4.829	8.18E-07	8.90E-06
CYP27A1	4.818	1.51E-10	2.50E-08
MOCS1	4.807	1.48E-06	1.40E-05
LOC284240	4.776	2.35E-05	0.0001222
SPP1	4.756	9.83E-13	1.67E-09
DEFA4	4.719	1.92E-08	5.34E-07
ZNF334	4.657	7.57E-08	1.38E-06
TCEA3	4.6	4.40E-06	3.34E-05
UNC5C	4.51	4.42E-11	1.28E-08
GP9	4.496	3.83E-08	8.55E-07
KRT17	4.464	2.64E-07	3.65E-06
LOC401463	4.429	3.58E-09	1.58E-07
IGSF9	4.367	2.65E-11	1.13E-08
ITGA1	4.343	2.75E-07	3.76E-06
ERICH2	4.321	1.19E-05	7.20E-05
AQP1	4.305	9.21E-11	1.96E-08
TCEAL2	4.255	1.32E-05	7.77E-05
CYP11A1	4.236	2.06E-08	5.63E-07
MCTP2	4.235	1.64E-07	2.50E-06
SLC22A17	4.159	3.98E-08	8.77E-07
CYP1B1	4.122	6.94E-15	4.71E-11
IGLON5	4.044	4.06E-07	5.13E-06
SERPINB9	4.038	7.20E-06	4.86E-05
CCL4	3.994	6.25E-08	1.21E-06
SLAMF8	3.943	1.35E-09	9.05E-08
BACH2	3.933	1.09E-06	1.11E-05
PTGER2	3.901	4.81E-07	5.83E-06
CST7	3.812	3.61E-10	3.86E-08
ALDH1A2	3.767	1.07E-07	1.80E-06
CLEC5A	3.731	1.04E-09	7.81E-08
LOC101927070	3.714	7.25E-09	2.63E-07
AACSP1	3.697	2.34E-08	6.14E-07

TMEM52B	3.658	2.48E-06	2.11E-05
PDPN	3.607	1.23E-09	8.69E-08
EPB41L3	3.604	8.08E-11	1.77E-08
MGAM	3.576	5.76E-08	1.14E-06
PTCRA	3.568	1.74E-09	1.03E-07
CCL4L1	3.531	3.89E-07	4.97E-06
SIGLEC7	3.483	1.53E-08	4.49E-07
ZSWIM5	3.481	9.19E-08	1.60E-06
SCN11A	3.475	6.53E-08	1.24E-06
POU4F2	3.462	1.21E-12	1.83E-09
RHOH	3.46	6.64E-07	7.51E-06
ACSM5	3.452	2.98E-07	4.03E-06
SLC2A10	3.438	2.41E-09	1.23E-07
PRG2	3.404	5.60E-09	2.21E-07
PTGDS	3.393	5.06E-10	4.99E-08
NRP2	3.372	2.07E-07	3.01E-06
CTSW	3.357	1.14E-09	8.27E-08
FCAR	3.312	2.25E-07	3.21E-06
TREML2	3.299	2.48E-08	6.40E-07
ZNF542	3.276	9.40E-07	9.98E-06
LOC101928581	3.264	1.18E-08	3.74E-07
CCDC120	3.241	5.13E-09	2.08E-07
SOWAHC	3.229	1.20E-08	3.79E-07
FLT1	3.223	1.59E-05	8.97E-05
NBEA	3.21	1.40E-07	2.23E-06
MFAP4	3.191	2.89E-07	3.92E-06
SPOCD1	3.174	5.10E-06	3.75E-05
KCNJ2	3.106	1.34E-06	1.30E-05
RASGRF1	3.105	1.98E-08	5.47E-07
VANGL2	3.086	2.58E-05	0.0001315
CR1	3.081	3.72E-05	0.000177
COL12A1	3.067	5.35E-08	1.09E-06
EFCC1	3.062	7.69E-06	5.09E-05
COL4A2	2.963	3.88E-09	1.69E-07
PRKCDBP	2.962	1.23E-07	2.00E-06
ADRA2B	2.956	9.92E-08	1.69E-06
POPDC3	2.95	1.31E-07	2.11E-06
RGS1	2.946	1.34E-05	7.84E-05
CTSF	2.93	5.42E-10	5.16E-08
LOC102724908	2.92	2.90E-10	3.58E-08

LOC102723741	2.92	3.72E-06	2.93E-05
RGS20	2.916	5.61E-10	5.22E-08
ITGAL	2.915	2.63E-13	8.92E-10
FPR2	2.905	2.81E-08	6.93E-07
SYT17	2.882	2.56E-07	3.56E-06
CDKL5	2.87	8.46E-09	2.95E-07
GLIS3	2.861	6.18E-05	0.000266
TRO	2.823	9.69E-10	7.48E-08
TMEM176B	2.816	3.50E-09	1.57E-07
KCNJ15	2.795	2.01E-06	1.78E-05
FABP4	2.786	5.26E-06	3.84E-05
ADAM19	2.777	2.84E-08	6.96E-07
FAM163A	2.762	9.91E-10	7.61E-08
ANGPTL6	2.73	9.97E-07	1.04E-05
MLLT4	2.729	1.45E-09	9.27E-08
SVEP1	2.729	2.14E-08	5.75E-07
NLRP2	2.725	1.94E-05	0.0001048
TIAM2	2.707	3.31E-06	2.67E-05
FAM46A	2.698	5.13E-13	1.36E-09
PDGFRL	2.686	9.37E-06	5.94E-05
LOC729737	2.681	9.50E-08	1.63E-06
LINC00452	2.681	4.45E-07	5.48E-06
FLJ36000	2.673	1.19E-08	3.76E-07
SERPINA1	2.669	1.33E-08	4.09E-07
CYP46A1	2.664	3.01E-08	7.23E-07
LOC101927732	2.662	0.000136	0.0005043
LOC101928173	2.643	9.64E-06	6.09E-05
ALOX15	2.637	1.18E-06	1.18E-05
SORT1	2.631	1.51E-11	8.78E-09
MYO7B	2.627	5.56E-08	1.12E-06
ORM1	2.626	8.57E-10	6.95E-08
NEO1	2.603	4.89E-11	1.30E-08
IGFBP3	2.601	1.81E-08	5.11E-07
AKAP12	2.596	1.06E-08	3.46E-07
GSG1L	2.595	1.48E-06	1.40E-05
LOC101926956	2.583	1.19E-07	1.96E-06
PLEKHN1	2.56	1.66E-06	1.54E-05
NLRP1	2.558	4.01E-08	8.80E-07
FN1	2.544	1.39E-06	1.35E-05
ADAM12	2.543	4.44E-06	3.36E-05

AOC1	2.515	3.48E-12	4.29E-09
SNCAIP	2.5	1.21E-05	7.27E-05
ABCC3	2.498	1.93E-08	5.34E-07
DMRT3	2.486	6.11E-08	1.19E-06
DLG3	2.484	2.32E-06	1.99E-05
TREM1	2.462	3.89E-08	8.62E-07
MTSS1	2.454	1.30E-08	4.03E-07
KIAA1211L	2.438	2.93E-08	7.11E-07
MGC57346	2.435	2.91E-06	2.42E-05
MYO5C	2.412	5.18E-07	6.19E-06
TNFAIP8L3	2.41	1.39E-08	4.21E-07
C8orf47	2.402	2.31E-06	1.99E-05
DACT1	2.399	3.98E-05	0.0001869
DYSF	2.395	5.06E-06	3.73E-05
SPRY4	2.377	2.62E-07	3.63E-06
MGLL	2.363	1.13E-08	3.61E-07
LYG2	2.35	7.58E-05	0.0003143
PEX5L	2.347	1.87E-11	9.06E-09
TGFB2	2.337	7.63E-07	8.42E-06
SIT1	2.329	1.28E-05	7.56E-05
IL8	2.31	7.69E-06	5.09E-05
DTX3	2.291	1.60E-05	9.02E-05
MEOX2	2.287	4.71E-07	5.72E-06
TRIB2	2.281	1.27E-08	3.97E-07
CCL2	2.281	8.55E-08	1.52E-06
DDIT4L	2.278	2.73E-07	3.75E-06
ANTXR1	2.276	2.75E-10	3.46E-08
ABI3	2.267	5.85E-05	0.0002543
CCND1	2.26	5.35E-10	5.16E-08
GPR27	2.25	4.98E-08	1.03E-06
WWTR1	2.247	2.88E-08	6.99E-07
AZU1	2.244	3.16E-11	1.13E-08
PLCB4	2.235	6.94E-05	0.0002917
GAS6-AS2	2.234	2.42E-10	3.22E-08
SOGA3	2.227	1.68E-06	1.55E-05
LPL	2.226	7.00E-13	1.36E-09
ABLIM3	2.217	9.68E-06	6.11E-05
ROS1	2.215	9.71E-09	3.25E-07
HOXC10	2.214	2.22E-06	1.93E-05
LINC00565	2.213	4.22E-05	0.0001949

SPOCK1	2.21	2.10E-08	5.69E-07
ADAMTS15	2.202	1.01E-10	2.05E-08
DLL4	2.199	6.81E-09	2.52E-07
TM6SF1	2.198	3.79E-07	4.87E-06
FAIM3	2.194	2.72E-05	0.000137
CYP2J2	2.193	4.34E-05	0.0001995
TJP3	2.191	8.30E-07	8.98E-06
APOC1	2.188	2.30E-10	3.10E-08
TUB	2.177	3.68E-07	4.77E-06
SCUBE2	2.176	0.000467	0.001396
EPHA7	2.175	1.24E-05	7.36E-05
SYT6	2.16	1.11E-06	1.13E-05
NLRC3	2.154	7.88E-10	6.66E-08
HP	2.153	1.64E-08	4.74E-07
TREML1	2.149	6.69E-09	2.48E-07
TENM3	2.141	6.35E-08	1.22E-06
KY	2.131	1.54E-06	1.45E-05
HMCN1	2.128	1.98E-07	2.92E-06
CKAP4	2.126	6.20E-12	5.26E-09
KIT	2.126	8.14E-10	6.78E-08
IGFBP2	2.124	2.89E-11	1.13E-08
KIAA1147	2.122	8.67E-08	1.53E-06
RP11-356I2.4	2.122	7.76E-07	8.52E-06
DYRK3	2.12	0.0001669	0.0005948
CLSTN2	2.116	9.76E-09	3.26E-07
CD101	2.102	7.88E-07	8.62E-06
FBXO15	2.101	1.23E-06	1.22E-05
NUAK2	2.101	0.0001873	0.0006528
TMEM200A	2.099	8.19E-06	5.35E-05
C1orf186	2.098	3.22E-08	7.59E-07
CPNE5	2.098	9.12E-06	5.82E-05
VCAN	2.096	6.25E-09	2.36E-07
LOC100128374	2.095	1.07E-05	6.62E-05
NMNAT2	2.084	4.38E-07	5.45E-06
MFNG	2.08	9.45E-12	7.13E-09
PCOLCE2	2.08	5.94E-10	5.45E-08
S100A12	2.079	0.0001443	0.0005299
C17orf100	2.078	1.53E-05	8.74E-05
ADAMTS6	2.078	7.80E-05	0.0003204
CAPN6	2.076	2.99E-05	0.000148

MMP2	2.073	3.95E-11	1.22E-08
SLC44A2	2.069	5.32E-07	6.34E-06
ALDH7A1	2.069	1.82E-06	1.66E-05
ABHD4	2.067	1.94E-07	2.86E-06
DSC3	2.065	2.60E-09	1.28E-07
LSP1	2.062	4.95E-10	4.98E-08
ACSS1	2.042	1.56E-10	2.50E-08
ACP6	2.028	4.51E-08	9.63E-07
ABCB4	2.028	4.41E-08	9.50E-07
TCN2	2.017	6.79E-07	7.66E-06
ALDH1A1	2.017	1.92E-06	1.72E-05
CEACAM6	2.015	2.54E-10	3.31E-08
A2M	2.015	2.48E-09	1.24E-07
GPR176	2.008	2.30E-05	0.0001202
IL2RB	2.006	6.82E-06	4.69E-05
LOC100130093	2.001	6.54E-06	4.54E-05
FAM135B	1.999	4.62E-08	9.84E-07
MAML2	1.997	2.30E-06	1.98E-05
CLEC7A	1.994	1.05E-05	6.50E-05
TCF23	1.99	7.21E-08	1.34E-06
ANPEP	1.987	4.74E-11	1.30E-08
ABCG1	1.987	2.09E-05	0.0001116
MARCO	1.985	1.79E-07	2.68E-06
C3AR1	1.982	1.30E-08	4.03E-07
MYH10	1.979	6.51E-09	2.43E-07
ERVMER34-1	1.979	4.00E-07	5.08E-06
PRR18	1.976	1.01E-05	6.33E-05
IL12RB2	1.975	4.08E-10	4.30E-08
PRDM13	1.971	1.11E-06	1.13E-05
KIAA1244	1.961	6.84E-07	7.69E-06
TFAP2C	1.956	1.01E-05	6.32E-05
TBC1D4	1.952	2.31E-07	3.29E-06
PARK2	1.947	1.41E-05	8.19E-05
S100A9	1.937	1.69E-10	2.64E-08
APOE	1.936	2.24E-09	1.17E-07
EIF4E3	1.936	4.46E-08	9.59E-07
AGT	1.933	2.65E-11	1.13E-08
FERMT2	1.929	1.77E-05	9.72E-05
SIGLEC16	1.925	1.14E-07	1.88E-06
ITGB5	1.922	1.37E-09	9.05E-08

SLPI	1.919	2.68E-10	3.44E-08
CPXM1	1.915	2.16E-06	1.89E-05
SEZ6L2	1.909	4.60E-11	1.30E-08
NKG7	1.909	3.75E-08	8.45E-07
C16orf45	1.902	1.81E-05	9.88E-05
MYO7A	1.898	2.72E-07	3.75E-06
COL15A1	1.897	2.08E-08	5.64E-07
KIF13A	1.896	4.05E-06	3.12E-05
LONRF2	1.884	0.0004156	0.001266
KCNN1	1.874	4.73E-05	0.0002138
TSHZ3	1.871	5.17E-08	1.06E-06
LIPG	1.866	1.12E-07	1.85E-06
GJA3	1.862	1.50E-07	2.33E-06
ADAMTS17	1.858	5.45E-06	3.94E-05
GPR68	1.85	6.90E-06	4.72E-05
CTSG	1.845	2.11E-10	3.00E-08
NT5E	1.845	2.22E-09	1.17E-07
EPHB1	1.843	1.91E-09	1.10E-07
SLC16A10	1.841	6.17E-06	4.35E-05
GBP2	1.839	7.29E-08	1.35E-06
CD14	1.838	2.30E-08	6.09E-07
CXCL1	1.828	7.54E-05	0.000313
FBLN1	1.823	3.06E-08	7.30E-07
EPHA1	1.823	5.66E-08	1.13E-06
MST1	1.814	7.25E-08	1.34E-06
CCL3	1.812	9.67E-07	1.02E-05
EGR2	1.807	0.0006606	0.001866
LOC100130872	1.806	3.64E-06	2.88E-05
SLC29A2	1.797	3.99E-07	5.07E-06
VWF	1.792	0.000105	0.0004084
SLCO2B1	1.79	1.16E-05	7.04E-05
PPP1R14C	1.789	6.09E-09	2.34E-07
LDLRAD3	1.786	7.35E-08	1.35E-06
TMEM136	1.786	8.99E-07	9.60E-06
IFITM10	1.784	2.84E-07	3.87E-06
CLEC10A	1.782	1.62E-05	9.11E-05
POU4F1	1.777	4.67E-08	9.89E-07
RP11-66B24.1	1.772	9.96E-05	0.000391
F2RL3	1.759	2.97E-06	2.45E-05
CLU	1.758	6.18E-07	7.09E-06

IL2RG	1.757	1.22E-05	7.28E-05
BCL2A1	1.753	2.64E-06	2.22E-05
LTBP1	1.752	4.22E-06	3.23E-05
ABCA6	1.751	4.37E-05	0.0002006
EPPK1	1.749	4.15E-07	5.22E-06
HSD11B1	1.748	1.41E-10	2.46E-08
SH3BGRL2	1.745	1.52E-07	2.35E-06
SIGLEC11	1.739	2.17E-09	1.17E-07
GRM1	1.737	0.0002518	0.0008371
DOCK9	1.736	6.12E-07	7.06E-06
STXBP6	1.733	4.86E-08	1.01E-06
EHD2	1.732	1.11E-08	3.59E-07
ST5	1.727	1.23E-05	7.33E-05
PLEKHA6	1.72	9.46E-07	1.00E-05
SLC26A11	1.719	3.35E-05	0.0001617
SASH1	1.717	1.48E-10	2.50E-08
ATP6V0E2-AS1	1.714	2.43E-05	0.0001255
CDON	1.711	5.73E-08	1.14E-06
SLAMF7	1.708	8.86E-06	5.68E-05
DHX32	1.705	1.23E-07	2.00E-06
CEACAM4	1.702	1.10E-07	1.83E-06
SCN8A	1.7	2.66E-05	0.0001347
TCF24	1.699	8.54E-06	5.53E-05
SLC35F1	1.699	1.09E-05	6.71E-05
CYP19A1	1.699	0.0001514	0.0005508
SLFN5	1.689	1.97E-06	1.75E-05
SLC1A7	1.684	1.37E-05	8.01E-05
SFRP1	1.681	2.20E-11	1.03E-08
PALLD	1.678	1.68E-05	9.37E-05
TREM2	1.676	5.44E-11	1.39E-08
ZFHX2	1.675	1.95E-05	0.0001051
ARAP3	1.671	2.73E-08	6.81E-07
RBP4	1.67	5.24E-05	0.0002325
MAP3K9	1.67	0.0003543	0.001111
NPTX1	1.662	4.12E-11	1.24E-08
MAP7	1.662	2.11E-07	3.05E-06
SORCS2	1.655	6.21E-07	7.12E-06
INHBA-AS1	1.653	7.62E-05	0.0003151
RAB37	1.652	2.76E-08	6.84E-07
CTSD	1.645	1.00E-10	2.05E-08

MAPK13	1.645	7.28E-08	1.35E-06
GPRIN3	1.644	0.0002848	0.0009261
ITGB7	1.643	2.51E-10	3.31E-08
C1orf115	1.643	8.63E-08	1.52E-06
SDS	1.642	1.44E-05	8.34E-05
TNIK	1.641	1.39E-07	2.21E-06
CHI3L1	1.64	5.99E-11	1.51E-08
ALOX5AP	1.64	1.16E-10	2.20E-08
PCDHGB4	1.64	6.26E-08	1.21E-06
GJD3	1.639	8.65E-10	6.95E-08
ELANE	1.635	3.09E-10	3.68E-08
LOXHD1	1.633	1.16E-06	1.17E-05
CIB2	1.63	8.68E-05	0.00035
KIF5C	1.629	0.0001169	0.0004456
GPR84	1.627	2.60E-06	2.20E-05
COL1A1	1.626	0.001886	0.004534
LOC93432	1.623	0.002678	0.006112
P2RX1	1.621	1.87E-10	2.79E-08
SIGLEC9	1.621	9.12E-05	0.0003646
LOC101927686	1.618	7.84E-05	0.0003217
PAQR9	1.618	0.0001114	0.000428
TMEM176A	1.618	0.0002111	0.000722
CSF1	1.614	3.54E-06	2.82E-05
SLC37A2	1.612	3.00E-11	1.13E-08
ATP2B3	1.612	3.74E-07	4.82E-06
SPTB	1.612	3.65E-06	2.89E-05
LOC654342	1.604	0.0001543	0.0005588
SLC11A1	1.6	4.72E-10	4.85E-08
PTPN14	1.6	1.62E-08	4.67E-07
THSD4	1.598	1.01E-05	6.32E-05
MLNR	1.591	9.73E-07	1.03E-05
LRRC3B	1.589	5.36E-08	1.09E-06
CPVL	1.588	3.31E-10	3.75E-08
SYNPO	1.587	1.20E-07	1.97E-06
OAF	1.585	3.89E-11	1.22E-08
FOLR2	1.58	3.29E-07	4.36E-06
C3	1.575	2.19E-10	3.00E-08
ID3	1.573	5.49E-08	1.11E-06
STAG3	1.572	1.75E-07	2.64E-06
TOB2P1	1.568	3.70E-06	2.91E-05

VSIG4	1.568	1.48E-05	8.50E-05
FLRT2	1.564	1.93E-05	0.0001041
AMDHD1	1.562	0.0002881	0.0009341
DLGAP1-AS3	1.561	3.14E-06	2.56E-05
RASGRP3	1.559	1.74E-05	9.58E-05
RHOBTB3	1.558	2.19E-08	5.87E-07
GLT1D1	1.558	2.29E-06	1.98E-05
EDARADD	1.557	6.43E-06	4.50E-05
LOC100289533	1.554	0.0001803	0.0006338
FEZ1	1.553	1.06E-06	1.09E-05
HIST1H2BK	1.552	1.84E-08	5.16E-07
ARHGAP31	1.551	4.41E-07	5.45E-06
ANKRD29	1.551	0.000253	0.0008401
ITGA2	1.548	1.83E-06	1.66E-05
DLEU7	1.546	8.72E-06	5.62E-05
CD5	1.546	0.0002249	0.000761
SNAP91	1.543	9.82E-05	0.0003867
CAMK4	1.539	9.75E-06	6.15E-05
TBC1D10C	1.538	4.40E-07	5.45E-06
NR2F2	1.537	4.91E-05	0.0002203
C5AR1	1.532	3.14E-06	2.56E-05
BHLHB9	1.524	8.93E-06	5.72E-05
HTR1B	1.524	9.82E-06	6.19E-05
ARHGEF3	1.523	5.86E-09	2.28E-07
ZNF358	1.523	2.40E-07	3.40E-06
PAIP2B	1.511	0.000183	0.0006409
GREB1	1.509	1.94E-05	0.0001048
FGF2	1.509	0.001609	0.003961
RAB7B	1.508	2.10E-10	3.00E-08
CCL3L3	1.505	1.29E-05	7.63E-05
FXVD5	1.504	4.39E-09	1.85E-07
APCDD1	1.503	5.48E-07	6.46E-06
MYO1B	1.503	1.65E-05	9.25E-05
LOC101929523	1.502	3.40E-07	4.48E-06
BTBD19	1.5	0.0006669	0.00188
MFGE8	1.499	2.36E-07	3.35E-06
PPARG	1.498	5.42E-10	5.16E-08
TMC5	1.498	1.97E-05	0.0001063
ENOX1	1.497	0.0002732	0.000894
GABRR2	1.497	0.001443	0.003605

PCNXL2	1.496	2.76E-08	6.84E-07
RNASE3	1.494	2.51E-08	6.41E-07
CACFD1	1.493	1.54E-07	2.37E-06
GLIDR	1.493	0.0004812	0.001432
ATP9A	1.492	2.29E-08	6.09E-07
ATP7B	1.491	1.21E-05	7.28E-05
GPR37	1.491	0.0001293	0.0004836
PRAM1	1.489	3.28E-10	3.74E-08
ENAH	1.486	1.57E-06	1.46E-05
CXCL16	1.485	7.28E-06	4.90E-05
OSMR	1.485	0.0009989	0.002639
SLC9A7	1.483	6.46E-08	1.23E-06
MTUS1	1.48	4.71E-06	3.52E-05
LOXL4	1.475	1.85E-05	0.0001006
SLC44A3	1.474	5.22E-05	0.0002322
LOC101928319	1.473	0.0004236	0.001286
PNOC	1.472	1.57E-05	8.86E-05
MPO	1.469	8.52E-08	1.52E-06
SCN5A	1.469	2.77E-05	0.0001388
TMIE	1.469	5.64E-05	0.0002461
RABAC1	1.466	1.36E-08	4.14E-07
MLC1	1.465	1.29E-10	2.36E-08
DKK2	1.465	1.41E-08	4.25E-07
REPS2	1.465	1.81E-05	9.90E-05
CHST6	1.462	1.72E-07	2.60E-06
TRPM8	1.462	4.66E-05	0.0002114
MAML3	1.461	2.04E-06	1.80E-05
LOC102724476	1.461	0.000778	0.002137
ZNF215	1.457	5.28E-06	3.85E-05
SAMD5	1.457	0.0001175	0.0004468
TMEM255B	1.456	2.30E-05	0.0001202
LRP1	1.455	2.46E-07	3.46E-06
STXBP5	1.452	3.55E-10	3.83E-08
PADI2	1.452	5.69E-08	1.13E-06
DPF3	1.451	6.32E-07	7.21E-06
NKX2-4	1.45	3.81E-08	8.52E-07
SLAMF9	1.449	1.19E-07	1.96E-06
XKR5	1.448	9.95E-05	0.000391
PDGFA	1.444	2.62E-07	3.63E-06
HLA-H	1.443	0.0007573	0.002089

GOLGA6L9	1.442	0.004426	0.009394
GAS6	1.439	3.72E-10	3.95E-08
IL16	1.438	1.38E-09	9.05E-08
ADAMTS5	1.436	0.0006533	0.001848
STXBP5-AS1	1.435	1.35E-05	7.90E-05
PTK7	1.433	7.75E-07	8.52E-06
FCGRT	1.43	7.90E-10	6.66E-08
CEBPE	1.429	3.91E-08	8.65E-07
CEACAM21	1.426	6.77E-08	1.28E-06
FLJ36777	1.42	0.0009528	0.002539
TTC9	1.418	0.0001865	0.0006504
CUX2	1.417	8.43E-07	9.09E-06
ADAMTS10	1.417	4.15E-06	3.19E-05
GRN	1.415	2.09E-09	1.16E-07
TMC8	1.413	5.04E-10	4.99E-08
WIPI1	1.413	2.84E-05	0.0001415
HAVCR2	1.412	9.37E-06	5.94E-05
LPO	1.411	4.21E-05	0.0001947
KIAA0355	1.406	1.55E-06	1.45E-05
SCG3	1.406	0.0001179	0.0004481
LOC101927532	1.403	0.0001461	0.000535
LOC102724571	1.401	9.86E-05	0.0003879
LINC01094	1.399	9.47E-05	0.000376
L1CAM	1.399	0.0009662	0.002568
SIAE	1.398	1.11E-09	8.19E-08
TESC	1.396	9.84E-08	1.68E-06
EMR4P	1.396	2.53E-05	0.0001294
TLR1	1.395	5.02E-07	6.03E-06
PAQR5	1.395	5.51E-07	6.49E-06
ZSWIM4	1.395	7.94E-06	5.23E-05
TGM2	1.393	1.28E-06	1.26E-05
PFN2	1.391	4.09E-05	0.0001906
LINC00883	1.391	0.001198	0.003072
VIT	1.389	1.36E-09	9.05E-08
APBB1	1.389	3.84E-07	4.92E-06
SERPINF2	1.387	0.0002316	0.0007798
MYO3B	1.385	0.0005477	0.001596
DLL3	1.385	0.001184	0.003041
PCDHGB7	1.383	0.0003918	0.001207
TDO2	1.382	9.80E-05	0.0003864

KCNK2	1.38	0.001094	0.002843
MST1L	1.379	0.001537	0.003805
LOX	1.376	0.0008275	0.002253
ITGA3	1.375	4.93E-07	5.94E-06
ECSCR	1.375	0.0008299	0.002258
DEFB1	1.374	2.56E-08	6.53E-07
FAM198B	1.374	7.61E-05	0.0003149
HEXA	1.372	1.33E-10	2.38E-08
CSF1R	1.372	7.14E-10	6.22E-08
TNN	1.371	4.26E-09	1.82E-07
C1S	1.371	2.74E-07	3.76E-06
PTCH2	1.37	0.0001081	0.000418
CORO2A	1.368	8.94E-10	7.02E-08
ACAP1	1.368	1.61E-06	1.50E-05
NRN1	1.365	8.70E-09	3.00E-07
KLHL30	1.362	3.32E-08	7.77E-07
CRYBB1	1.36	4.45E-07	5.48E-06
RP11-426L16.8	1.36	0.0001007	0.0003945
EPHA1-AS1	1.359	3.60E-05	0.0001722
TLR5	1.358	1.28E-06	1.26E-05
C11orf63	1.352	1.46E-07	2.28E-06
ITGB2	1.349	3.50E-10	3.83E-08
CRISPLD2	1.349	0.001008	0.002661
FHL3	1.347	1.19E-06	1.19E-05
SYNGR1	1.341	1.21E-08	3.81E-07
AC147651.4	1.339	5.72E-08	1.14E-06
PCDHGA11	1.337	5.90E-06	4.20E-05
MAP3K15	1.337	5.86E-05	0.0002543
TMOD2	1.335	0.0007551	0.002084
HCST	1.333	5.83E-08	1.15E-06
ADAMTS1	1.33	2.55E-09	1.27E-07
PK4	1.33	7.32E-06	4.92E-05
LOC101927085	1.33	4.59E-05	0.000209
SCRN1	1.329	6.97E-08	1.31E-06
CHST2	1.329	1.26E-06	1.24E-05
ARHGAP20	1.322	1.03E-05	6.41E-05
MEX3B	1.321	0.001737	0.004224
CD300LG	1.321	0.001838	0.00444
GAA	1.319	2.83E-10	3.52E-08
CD52	1.318	2.07E-08	5.63E-07

ZMYND12	1.318	3.04E-06	2.50E-05
PDE6G	1.316	0.0001232	0.0004655
MRVI1	1.316	0.0001275	0.0004783
SMPD5	1.316	0.0005198	0.001527
ALOX5	1.315	3.52E-09	1.57E-07
TNXB	1.313	1.54E-05	8.75E-05
ANKDD1A	1.313	0.0002039	0.0007014
PMEL	1.312	0.0009432	0.002518
VASH1	1.31	1.73E-10	2.64E-08
PLCB1	1.304	0.0006114	0.001748
TGFBI	1.3	2.75E-10	3.46E-08
PLD4	1.299	7.57E-10	6.51E-08
ADORA3	1.299	8.47E-07	9.12E-06
HTRA3	1.297	5.06E-05	0.000226
CAMKV	1.296	4.95E-06	3.66E-05
SPTBN1	1.295	4.49E-08	9.62E-07
NUAK1	1.295	0.0001362	0.0005048
PDIA5	1.294	5.61E-10	5.22E-08
KLHL29	1.292	1.31E-07	2.11E-06
NDRG2	1.291	9.52E-09	3.22E-07
TPP1	1.287	1.07E-09	7.98E-08
DERL3	1.287	6.26E-07	7.15E-06
LOC101929151	1.287	0.001847	0.004457
IGSF1	1.285	2.67E-08	6.71E-07
ARRDC4	1.284	8.52E-10	6.95E-08
CAV1	1.284	9.08E-08	1.59E-06
CD247	1.281	0.000882	0.002376
NAV1	1.28	3.82E-07	4.90E-06
PIP5K1B	1.279	1.24E-07	2.01E-06
GPR133	1.279	3.13E-06	2.56E-05
NFE2	1.277	7.49E-09	2.71E-07
LOC101929667	1.277	1.63E-05	9.13E-05
C2	1.274	1.57E-08	4.58E-07
PSMG3-AS1	1.274	3.97E-08	8.75E-07
CMAHP	1.274	0.000189	0.0006577
C1orf95	1.273	0.0002889	0.0009359
FITM2	1.272	1.41E-05	8.19E-05
CRLF2	1.272	2.83E-05	0.0001414
LOC101928101	1.272	5.50E-05	0.0002417
RAPGEF4	1.271	0.0009337	0.002496

ARHGAP24	1.269	1.27E-05	7.55E-05
S100A8	1.269	1.00E-05	6.30E-05
C1orf200	1.268	4.83E-07	5.85E-06
TMEM86A	1.267	2.06E-06	1.81E-05
IFI30	1.266	2.74E-09	1.35E-07
ARAP2	1.266	5.65E-06	4.06E-05
RAB38	1.265	0.0004025	0.001233
RAB17	1.262	0.0001079	0.0004172
SLC16A2	1.261	2.66E-05	0.0001347
SGSH	1.26	2.49E-05	0.0001281
SPATC1	1.26	0.00127	0.00323
SMPD1	1.258	2.12E-09	1.17E-07
OLIG1	1.256	4.66E-07	5.67E-06
ZNF536	1.256	9.48E-05	0.0003763
FAM26F	1.256	0.0002577	0.0008532
ITGAX	1.254	8.38E-09	2.93E-07
IL1RN	1.251	2.11E-08	5.70E-07
CETP	1.249	0.000423	0.001285
TCHH	1.248	6.09E-08	1.19E-06
FBXO25	1.246	5.20E-08	1.07E-06
CASS4	1.245	2.02E-06	1.78E-05
TSPAN6	1.243	0.0005114	0.001506
NWD1	1.241	0.007163	0.01431
CDK20	1.237	1.04E-08	3.42E-07
KLF15	1.237	1.48E-06	1.40E-05
FHDC1	1.237	1.20E-05	7.24E-05
NOMO3	1.232	2.21E-07	3.15E-06
KIAA1324L	1.232	1.85E-06	1.68E-05
FOXO3B	1.231	0.0001646	0.0005885
ELFN2	1.23	2.75E-05	0.000138
QPCT	1.229	5.66E-07	6.61E-06
MRC2	1.228	8.79E-10	6.98E-08
FAM150A	1.228	7.20E-05	0.0003002
IGFBPL1	1.227	3.95E-09	1.71E-07
LOC101929014	1.227	0.0003783	0.001172
DZIP1	1.226	3.18E-08	7.55E-07
TPBG	1.224	2.14E-09	1.17E-07
ALPK3	1.223	8.22E-08	1.48E-06
FAM229B	1.222	1.57E-05	8.89E-05
FBXO32	1.22	0.0003136	0.001005

VWA7	1.22	0.001659	0.00406
CILP2	1.219	0.0001243	0.0004686
HHLA3	1.218	1.78E-05	9.76E-05
FCAMR	1.217	1.21E-05	7.27E-05
TBXAS1	1.216	1.91E-06	1.72E-05
MGAT4A	1.215	2.79E-09	1.36E-07
SPN	1.215	1.26E-08	3.92E-07
SLC22A4	1.214	1.18E-08	3.74E-07
COLGALT2	1.213	8.47E-08	1.51E-06
RASAL2-AS1	1.213	0.0006738	0.001897
LOC100507316	1.212	3.02E-05	0.0001489
P4HA3	1.211	0.0006099	0.001745
HLA-L	1.208	1.27E-06	1.25E-05
PRRT4	1.202	7.78E-07	8.52E-06
CCDC64	1.201	8.92E-10	7.02E-08
LBH	1.2	1.73E-06	1.58E-05
DAAM1	1.2	2.54E-06	2.15E-05
ARL4C	1.2	1.52E-05	8.67E-05
C4orf19	1.2	7.79E-05	0.0003204
PLEKHA8	1.197	6.22E-08	1.20E-06
TSGA10	1.197	9.69E-05	0.000383
NFAM1	1.195	6.02E-09	2.32E-07
TSPEAR-AS1	1.194	4.36E-05	0.0002004
MKLN1-AS	1.192	0.000241	0.0008054
SOGA2	1.186	1.25E-07	2.03E-06
SYN2	1.186	2.65E-05	0.0001345
CFP	1.185	3.99E-08	8.77E-07
CCDC103	1.185	1.05E-06	1.09E-05
LINC00886	1.185	6.39E-05	0.0002726
FAM174B	1.184	1.16E-06	1.17E-05
FUZ	1.184	0.002052	0.004871
FMN1	1.183	2.39E-05	0.0001238
NOMO1	1.182	1.98E-09	1.12E-07
EFNA5	1.178	0.0004033	0.001235
CUL7	1.177	4.63E-09	1.94E-07
ZNF219	1.177	2.99E-06	2.47E-05
TMEM71	1.176	2.01E-05	0.0001082
LURAP1L	1.176	0.0003713	0.001153
CAV2	1.171	2.49E-05	0.0001278
DNAH6	1.171	0.0001715	0.0006084

PLEKHA7	1.171	0.0003709	0.001153
HLX-AS1	1.171	0.0006684	0.001883
SCPEP1	1.17	1.91E-09	1.10E-07
ERG	1.168	2.82E-05	0.0001411
ABCB11	1.168	0.001081	0.002817
RASAL3	1.167	4.46E-08	9.59E-07
PNCK	1.167	8.04E-05	0.0003284
CSPG4	1.166	6.17E-07	7.08E-06
CLIP4	1.166	0.0001964	0.0006804
HLA-G	1.165	0.0004363	0.001318
TGM5	1.162	5.56E-09	2.21E-07
SYTL1	1.162	1.20E-07	1.98E-06
KIF9-AS1	1.161	0.001227	0.003135
CNKSR3	1.16	8.29E-07	8.98E-06
TMEM150A	1.159	2.54E-05	0.0001299
SLC51A	1.159	0.0001005	0.000394
ARSA	1.158	2.99E-09	1.40E-07
C9orf9	1.157	0.0004112	0.001256
EGR4	1.157	0.001401	0.003513
CACNB1	1.155	3.84E-07	4.92E-06
NOMO2	1.149	6.59E-08	1.25E-06
RNF32	1.148	2.17E-05	0.0001152
NPM2	1.147	3.29E-06	2.66E-05
EDEM2	1.146	6.20E-09	2.36E-07
LOC101927594	1.144	0.001773	0.004297
LOC100129917	1.142	0.0001481	0.0005409
GSPT2	1.141	7.36E-07	8.17E-06
LINC00654	1.14	0.0001046	0.0004066
ATP6V0A1	1.139	3.13E-08	7.46E-07
MAGED1	1.139	2.18E-07	3.13E-06
COL6A1	1.138	3.06E-09	1.42E-07
PPP1R13B	1.137	2.09E-05	0.0001114
RNF135	1.136	8.80E-09	3.03E-07
HIST2H2BE	1.136	7.25E-05	0.0003022
SBK1	1.135	0.0111	0.02092
CD180	1.134	2.84E-07	3.87E-06
MSC	1.133	6.96E-07	7.79E-06
SAMD15	1.133	6.95E-05	0.000292
CNIH3	1.131	3.70E-05	0.0001761
WASF1	1.13	9.16E-09	3.13E-07

DST	1.13	2.25E-06	1.96E-05
TCTN1	1.129	5.47E-07	6.45E-06
PIGT	1.128	4.60E-08	9.81E-07
PLOD3	1.127	3.77E-09	1.65E-07
WDR35	1.126	1.42E-06	1.36E-05
KCP	1.126	1.18E-05	7.12E-05
AGPAT9	1.126	2.49E-05	0.0001281
KCNK13	1.126	0.0002343	0.0007869
TTC28	1.125	3.87E-06	3.01E-05
CNRIP1	1.124	4.03E-06	3.12E-05
PAN3-AS1	1.123	0.0001011	0.0003955
PKIG	1.123	0.0001401	0.0005167
SIRPB1	1.122	1.53E-07	2.37E-06
IRAK2	1.122	6.90E-06	4.72E-05
CGNL1	1.122	1.35E-05	7.91E-05
GPR161	1.122	0.0003287	0.001044
HLA-DMA	1.119	3.12E-06	2.55E-05
DKKL1	1.119	0.002296	0.005346
HSPB7	1.118	6.01E-09	2.32E-07
RAP1GAP2	1.117	8.58E-08	1.52E-06
NHLRC1	1.116	7.56E-05	0.0003135
MYO1E	1.115	5.30E-08	1.08E-06
FKBP9	1.114	9.57E-09	3.22E-07
PC	1.114	1.71E-06	1.57E-05
PTPN21	1.114	0.000369	0.001147
SYDE2	1.111	2.04E-06	1.80E-05
GRIN3A	1.111	2.55E-05	0.0001302
ELFN1	1.111	0.003294	0.007294
FBP1	1.11	4.84E-09	2.00E-07
PDGFD	1.11	8.13E-09	2.86E-07
MORC2-AS1	1.11	3.28E-05	0.0001587
NRXN2	1.109	0.001538	0.003805
TIMP1	1.105	4.85E-08	1.01E-06
ULBP3	1.105	4.25E-05	0.0001959
EPHB3	1.105	6.52E-05	0.000277
ANXA8L1	1.105	0.0004254	0.00129
PNPLA1	1.104	1.13E-05	6.89E-05
RIMS2	1.099	0.001208	0.003092
SIX4	1.096	0.003141	0.007012
ZCCHC5	1.095	0.002459	0.005676

EBI3	1.095	0.005767	0.01184
CTSA	1.094	1.04E-08	3.43E-07
GGT7	1.094	4.30E-07	5.37E-06
NEB	1.094	1.20E-05	7.24E-05
VIPR1	1.094	0.0001939	0.0006725
NDST1	1.092	4.34E-08	9.39E-07
OSBP2	1.091	0.0001994	0.0006891
LOC101927200	1.091	0.001452	0.003625
IL21R	1.09	1.40E-07	2.22E-06
C6orf132	1.09	0.0007519	0.002077
RNASET2	1.088	4.79E-09	1.99E-07
PTPRU	1.085	6.11E-07	7.05E-06
TNFSF14	1.083	7.73E-08	1.41E-06
TDRKH	1.083	2.86E-06	2.38E-05
POMC	1.082	3.49E-07	4.58E-06
LOC101929131	1.08	0.01364	0.02498
DUSP4	1.079	1.57E-06	1.47E-05
FBLL1	1.078	0.0002888	0.0009356
HLA-DQB1	1.077	2.45E-08	6.37E-07
CNTNAP3B	1.077	4.32E-07	5.38E-06
LOC100505771	1.077	1.13E-05	6.90E-05
HVCN1	1.076	7.57E-08	1.38E-06
TFAP2A	1.076	0.0006245	0.001781
FXVD6	1.075	0.0002344	0.0007873
TBL1X	1.073	8.50E-08	1.52E-06
HLA-DRB1	1.07	2.57E-09	1.27E-07
PLBD2	1.07	6.75E-07	7.61E-06
HLA-DRB6	1.07	0.0002624	0.0008656
PPP1R13L	1.069	8.15E-05	0.0003323
FRMD3	1.068	7.34E-08	1.35E-06
ATP1A3	1.068	4.99E-06	3.68E-05
PFKM	1.068	2.82E-05	0.000141
FAT4	1.067	0.008338	0.0163
CALCRL	1.066	0.001272	0.003233
TMEM150C	1.065	8.59E-05	0.0003468
GRIK2	1.062	0.002893	0.006533
LOC100129461	1.061	0.005584	0.01152
HHAT	1.06	3.77E-06	2.96E-05
ANXA8	1.058	4.68E-06	3.50E-05
C21orf90	1.055	0.001237	0.003158

LOC101928291	1.055	0.001397	0.003505
LOC283887	1.055	0.004301	0.009174
QPR1	1.054	2.94E-09	1.40E-07
ATP6V1C2	1.054	1.70E-05	9.43E-05
AK9	1.054	4.59E-05	0.0002092
TXLNB	1.054	0.004728	0.009938
PLEC	1.053	5.81E-07	6.75E-06
CPE	1.052	1.60E-07	2.45E-06
IL1B	1.051	0.0004219	0.001282
LRRC39	1.051	0.01146	0.0215
HEXB	1.05	2.37E-09	1.22E-07
ACRBP	1.049	2.92E-06	2.42E-05
SYNE1	1.049	3.60E-06	2.86E-05
HLX	1.048	8.09E-08	1.46E-06
RAB3IL1	1.047	5.27E-08	1.08E-06
KIAA1024	1.047	6.10E-05	0.0002631
EXOC6B	1.046	8.65E-07	9.30E-06
LRRC6	1.046	0.0004897	0.001454
PCDHGA8	1.046	0.0006794	0.00191
MX2	1.042	1.12E-08	3.59E-07
HIST1H1C	1.042	1.60E-05	9.02E-05
C20orf197	1.042	3.21E-05	0.0001564
IL1R1	1.04	0.000112	0.00043
CLUHP3	1.039	0.002371	0.005496
NEU1	1.038	4.92E-09	2.02E-07
PDE7B	1.038	7.85E-08	1.43E-06
PGR	1.038	9.19E-08	1.60E-06
GLDC	1.038	0.0002754	0.0008998
PHC1	1.036	1.57E-05	8.86E-05
TBC1D9	1.035	2.56E-07	3.56E-06
NUDT16P1	1.033	2.21E-05	0.0001165
DNAJC6	1.033	0.0003498	0.0011
LOC101928143	1.033	0.0008433	0.002287
FBXO27	1.032	6.26E-05	0.0002683
SLC1A4	1.031	2.96E-08	7.15E-07
OLFML3	1.03	1.23E-07	2.00E-06
SHH	1.03	0.01058	0.02005
KCND1	1.028	0.0003542	0.001111
FAM159A	1.028	0.001986	0.004736
RGS22	1.027	0.002406	0.005569

TMEM9B-AS1	1.026	0.0007017	0.00196
UGDH-AS1	1.026	0.001501	0.003727
RUNDC3A	1.026	0.001846	0.004455
GANAB	1.025	3.73E-09	1.65E-07
TBX3	1.025	2.34E-06	2.01E-05
TMEM45A	1.022	1.42E-07	2.24E-06
ASIC1	1.021	1.20E-07	1.97E-06
PRKCSH	1.019	1.41E-08	4.25E-07
BEX4	1.019	8.59E-05	0.0003468
ABCC5	1.018	2.72E-06	2.28E-05
TNFRSF10C	1.018	0.001453	0.003627
HLA-DMB	1.017	0.0005502	0.001602
DPYD	1.016	2.46E-09	1.24E-07
QSOX1	1.015	1.35E-08	4.13E-07
MIR4477B	1.014	0.003358	0.00741
LOC101929004	1.013	0.001202	0.00308
TUBA1A	1.013	0.007814	0.01542
RAB11FIP4	1.012	1.61E-06	1.49E-05
NEK8	1.011	1.23E-06	1.22E-05
HYDIN2	1.01	0.001678	0.0041
HTATSF1P2	1.009	6.15E-06	4.35E-05
PMFBP1	1.009	0.0004869	0.001446
SRCIN1	1.009	0.000787	0.002158
CSF3R	1.008	1.24E-09	8.69E-08
ENG	1.008	1.31E-07	2.11E-06
RAB3C	1.008	0.0002441	0.0008149
TRPM2	1.006	1.15E-09	8.27E-08
NCALD	1.006	5.53E-08	1.11E-06
SMO	1.006	0.0001045	0.0004066
GABRB2	1.006	0.0001497	0.0005459
SCAMP5	1.004	2.25E-08	6.01E-07
LOC100507507	1.004	6.23E-07	7.13E-06
ST6GALNAC2	1.004	1.54E-05	8.78E-05
LOC101927578	1.003	0.003271	0.007257
FMNL2	1.002	1.96E-06	1.74E-05
ARMC2	1.002	2.60E-05	0.0001323
RNASE6	1.001	0.0002159	0.0007353
PSMC6	-1.001	5.23E-05	0.0002325
SAR1A	-1.003	5.90E-09	2.29E-07
CERS1	-1.003	1.45E-05	8.35E-05

ARID2	-1.004	6.86E-08	1.29E-06
LGI2	-1.004	0.0004711	0.001406
C5orf51	-1.005	7.67E-09	2.74E-07
ZFP14	-1.006	7.43E-06	4.98E-05
NLGN2	-1.007	0.0008716	0.002352
RP11-344B5.2	-1.007	0.001565	0.003863
LY6G5C	-1.007	0.002878	0.006506
PPP2R2D	-1.008	1.33E-08	4.09E-07
PPAP2A	-1.008	0.0009595	0.002552
CCT5	-1.009	3.47E-09	1.57E-07
IKZF5	-1.009	4.29E-08	9.33E-07
RBM39	-1.009	5.20E-07	6.21E-06
USP18	-1.009	3.32E-06	2.67E-05
EDRF1	-1.01	3.77E-08	8.47E-07
CRYZ	-1.012	1.46E-06	1.40E-05
PYROXD2	-1.012	2.28E-05	0.0001198
NFKB2	-1.014	4.81E-08	1.01E-06
FAM111B	-1.014	6.15E-08	1.19E-06
UBTD1	-1.014	9.90E-08	1.69E-06
ZSCAN12	-1.014	3.60E-05	0.0001721
KRCC1	-1.015	2.77E-05	0.0001389
NHLRC2	-1.017	1.49E-06	1.41E-05
OSBPL8	-1.018	4.36E-07	5.43E-06
PAPD7	-1.019	2.88E-08	6.99E-07
RBM17	-1.02	2.48E-09	1.24E-07
LOC101928092	-1.021	0.0001068	0.0004139
VDAC2	-1.023	3.79E-08	8.50E-07
ZNF492	-1.023	2.46E-06	2.10E-05
ZNF682	-1.023	1.11E-05	6.77E-05
NCKAP1	-1.023	0.0003293	0.001045
CALM2	-1.025	1.73E-05	9.57E-05
PGAM4	-1.025	4.19E-05	0.0001943
DUSP5P1	-1.026	8.59E-05	0.0003468
LIPJ	-1.026	0.0001661	0.0005925
SCD5	-1.027	1.91E-06	1.72E-05
PDCD4	-1.028	1.09E-08	3.56E-07
NAP1L1	-1.029	6.16E-09	2.36E-07
COQ3	-1.03	1.13E-06	1.14E-05
EIF3E	-1.03	7.06E-05	0.0002955
SRRM3	-1.031	7.92E-05	0.0003244

GALR2	-1.031	0.001288	0.003266
MYNN	-1.032	1.35E-05	7.93E-05
LOC102724002	-1.032	8.06E-05	0.0003292
LGR4	-1.033	3.76E-09	1.65E-07
ZNF845	-1.033	1.56E-06	1.46E-05
MLLT10	-1.034	3.09E-09	1.43E-07
FAM21C	-1.037	5.17E-09	2.08E-07
ZNF254	-1.037	5.42E-06	3.93E-05
TIAL1	-1.038	1.28E-09	8.89E-08
AVPI1	-1.038	0.0001709	0.0006068
NUP37	-1.04	3.75E-07	4.83E-06
SGOL2	-1.04	3.15E-06	2.56E-05
TRMT10C	-1.04	7.20E-06	4.86E-05
VIM-AS1	-1.04	1.56E-05	8.85E-05
DPM1	-1.04	3.52E-05	0.000169
ADO	-1.041	8.71E-09	3.00E-07
VPS29	-1.041	1.52E-06	1.43E-05
NDUFAF7	-1.041	1.15E-05	6.99E-05
FBXO4	-1.042	1.47E-06	1.40E-05
CYSLTR1	-1.043	1.86E-06	1.68E-05
DDX11-AS1	-1.043	0.0006734	0.001896
AGAP6	-1.044	1.64E-05	9.21E-05
SDHAP3	-1.045	2.81E-06	2.34E-05
NDUFS4	-1.046	2.48E-05	0.0001275
ZNF239	-1.047	6.91E-07	7.75E-06
MATR3	-1.047	5.41E-07	6.40E-06
MRPS28	-1.048	2.54E-07	3.54E-06
NET1	-1.049	7.01E-09	2.57E-07
FAM175A	-1.049	3.93E-06	3.05E-05
JKAMP	-1.05	2.01E-06	1.78E-05
KIF18A	-1.05	2.35E-05	0.0001222
RPL41	-1.051	7.20E-08	1.34E-06
CKS2	-1.051	1.55E-06	1.46E-05
FCGR2C	-1.051	0.0003092	0.0009929
CETN3	-1.052	6.52E-06	4.53E-05
CASP3	-1.052	1.05E-05	6.53E-05
SRGN	-1.053	2.28E-06	1.98E-05
SFXN2	-1.054	1.75E-08	4.97E-07
SNORA81	-1.054	0.0008529	0.002309
TMC4	-1.054	0.001881	0.004526

ZNF37BP	-1.057	0.0001557	0.0005628
PDCD6	-1.059	5.63E-09	2.21E-07
TMEM180	-1.059	2.75E-06	2.30E-05
SEPHS1	-1.063	3.28E-09	1.50E-07
GIMAP2	-1.063	2.54E-06	2.15E-05
DNAAF3	-1.063	0.000751	0.002075
METRNL	-1.066	1.64E-06	1.52E-05
TCF7	-1.067	1.12E-06	1.14E-05
HIF1AN	-1.068	7.55E-09	2.72E-07
GLUD1	-1.069	1.41E-09	9.16E-08
ZCRB1	-1.069	2.12E-08	5.72E-07
SEC31B	-1.069	0.001401	0.003513
BDH2	-1.07	2.75E-07	3.76E-06
BMI1	-1.072	2.38E-06	2.04E-05
LKAAEAR1	-1.074	0.006881	0.01383
NUTM2B	-1.074	0.008797	0.01704
IPO8	-1.076	4.34E-09	1.85E-07
LRRC20	-1.076	1.27E-07	2.06E-06
HPS6	-1.077	2.43E-08	6.35E-07
LOC101928000	-1.078	2.77E-05	0.0001388
FBXL15	-1.079	1.75E-07	2.64E-06
RUFY4	-1.079	0.0003461	0.001092
HOXB13	-1.083	0.003352	0.007397
TVP23B	-1.084	7.69E-05	0.0003174
LOC101929021	-1.086	1.12E-06	1.14E-05
BEND4	-1.086	4.28E-06	3.27E-05
MAP3K8	-1.087	2.74E-05	0.0001376
XPNPEP1	-1.088	1.87E-09	1.09E-07
ZNF100	-1.088	4.01E-08	8.79E-07
LOC283683	-1.09	0.0007195	0.002001
IRF7	-1.091	8.61E-08	1.52E-06
ECHDC3	-1.091	1.03E-05	6.43E-05
ABCC2	-1.092	0.002229	0.005217
ABI1	-1.093	2.47E-09	1.24E-07
ESF1	-1.093	1.70E-05	9.44E-05
CDK17	-1.094	1.48E-08	4.38E-07
PARG	-1.094	1.82E-08	5.14E-07
ASB13	-1.094	9.15E-08	1.60E-06
RABGGTB	-1.094	2.27E-06	1.97E-05
ZNF184	-1.095	4.30E-07	5.37E-06

UGCG	-1.095	2.48E-06	2.11E-05
PPFIBP1	-1.096	9.27E-08	1.60E-06
FUOM	-1.097	2.60E-09	1.28E-07
TOMM40L	-1.098	4.06E-09	1.75E-07
OASL	-1.099	4.40E-06	3.34E-05
ATE1	-1.101	2.29E-08	6.09E-07
ARRDC3	-1.101	5.63E-07	6.58E-06
BEND6	-1.101	2.48E-05	0.0001276
GSTO1	-1.102	4.48E-08	9.62E-07
HMGCS1	-1.102	8.74E-08	1.54E-06
MSX1	-1.102	6.56E-06	4.55E-05
PCED1B	-1.102	5.92E-05	0.0002565
DDX21	-1.103	1.11E-09	8.19E-08
ZNF622	-1.103	9.81E-09	3.27E-07
NDUFA5	-1.103	6.63E-05	0.0002813
METTL18	-1.104	2.87E-05	0.0001431
NUP107	-1.106	2.93E-09	1.40E-07
AP1S2	-1.106	1.81E-07	2.70E-06
CENPE	-1.106	3.67E-06	2.90E-05
PRIM1	-1.107	8.23E-07	8.94E-06
LINC01165	-1.107	0.006718	0.01353
CCPG1	-1.108	7.79E-07	8.53E-06
ZSCAN26	-1.109	3.99E-06	3.09E-05
MIR155HG	-1.109	0.0001358	0.0005036
NEUROG3	-1.111	2.50E-06	2.12E-05
ITGB1	-1.112	5.84E-10	5.40E-08
ZNF138	-1.112	4.88E-06	3.61E-05
LLPH	-1.113	7.93E-09	2.82E-07
BIK	-1.113	1.82E-08	5.14E-07
BLZF1	-1.113	7.21E-07	8.02E-06
ZNF257	-1.113	2.41E-06	2.07E-05
CCDC6	-1.114	7.57E-09	2.72E-07
FAM188A	-1.115	6.55E-07	7.44E-06
HMMR	-1.115	2.84E-06	2.37E-05
MRPS30	-1.117	1.97E-09	1.12E-07
DNAJB4	-1.117	8.77E-06	5.64E-05
CCDC58	-1.117	3.24E-05	0.0001573
SNORA32	-1.119	0.0006375	0.00181
CCL28	-1.12	1.04E-07	1.75E-06
SERPINB10	-1.12	1.23E-06	1.22E-05

SNHG8	-1.121	1.02E-06	1.06E-05
EIF3C	-1.121	3.02E-05	0.0001489
FAM173B	-1.122	2.11E-07	3.05E-06
TMEM255A	-1.123	1.47E-05	8.49E-05
GTPBP4	-1.126	1.88E-09	1.09E-07
MCM10	-1.128	2.01E-09	1.13E-07
EPSTI1	-1.129	3.97E-06	3.08E-05
TIGD3	-1.13	0.0004915	0.001458
CAPRIN2	-1.131	1.86E-05	0.0001008
SLA2	-1.132	2.65E-05	0.0001346
DDAH2	-1.133	5.40E-08	1.10E-06
MNS1	-1.133	4.49E-06	3.39E-05
MGAT4C	-1.133	0.01342	0.02462
ARHGAP19	-1.134	3.53E-09	1.57E-07
PHYH	-1.134	1.99E-08	5.47E-07
MRPL42	-1.135	2.81E-06	2.34E-05
PAOX	-1.135	1.56E-05	8.83E-05
UPF2	-1.137	4.88E-09	2.01E-07
HSP90AA1	-1.137	7.48E-07	8.27E-06
NCAM2	-1.138	5.44E-10	5.16E-08
RP11-119F19.2	-1.138	1.35E-05	7.91E-05
TNKS2	-1.14	1.54E-09	9.52E-08
PGAM1	-1.14	1.72E-09	1.03E-07
ALDOC	-1.14	8.44E-06	5.48E-05
THAP9	-1.14	3.83E-05	0.0001811
ASCC1	-1.141	2.31E-08	6.09E-07
HERC4	-1.142	1.15E-09	8.27E-08
RICTOR	-1.142	1.00E-07	1.71E-06
PRTFDC1	-1.142	6.36E-05	0.0002714
LOC100506901	-1.143	0.004126	0.008845
TMEM191C	-1.143	0.01557	0.02805
FRS2	-1.144	3.34E-08	7.78E-07
ZNF439	-1.145	7.25E-08	1.34E-06
NUF2	-1.145	6.51E-06	4.53E-05
ULK2	-1.146	1.17E-06	1.18E-05
DNAJC1	-1.148	2.89E-09	1.40E-07
ZNF33A	-1.15	8.53E-08	1.52E-06
MUC19	-1.15	0.004287	0.009145
FRAT2	-1.151	8.25E-10	6.83E-08
ARL6	-1.151	3.80E-06	2.97E-05

PPP1R2P3	-1.151	0.002065	0.004894
C10orf76	-1.152	5.12E-09	2.08E-07
SNHG3	-1.152	1.42E-08	4.28E-07
LARP7	-1.152	1.83E-05	9.98E-05
CDHR1	-1.153	0.001108	0.002876
EGFR	-1.154	0.004619	0.00974
ZNF267	-1.155	2.52E-06	2.14E-05
LINC01085	-1.155	0.0005412	0.00158
ADK	-1.157	2.91E-09	1.40E-07
FAM105A	-1.159	2.19E-09	1.17E-07
FAM84B	-1.16	6.89E-07	7.74E-06
LOC102723616	-1.16	0.001835	0.004433
PPA1	-1.161	3.87E-09	1.69E-07
NUDCD1	-1.161	1.72E-06	1.58E-05
RAD1	-1.162	1.51E-09	9.51E-08
ZNF816	-1.162	3.89E-07	4.97E-06
FAM178A	-1.164	2.96E-09	1.40E-07
CIITA	-1.165	8.76E-05	0.0003524
WHAMMP2	-1.166	4.44E-07	5.47E-06
C5orf34	-1.166	1.90E-06	1.71E-05
PANK1	-1.168	5.60E-08	1.12E-06
LINC00843	-1.168	5.44E-07	6.42E-06
ZNF441	-1.171	5.40E-07	6.40E-06
FZD8	-1.174	7.35E-05	0.0003059
ANKRD46	-1.177	3.10E-06	2.54E-05
NXT2	-1.177	3.20E-06	2.60E-05
TUBA8	-1.178	6.39E-06	4.47E-05
GDI2	-1.18	1.74E-09	1.03E-07
ZMYND11	-1.18	2.42E-09	1.23E-07
ACBD5	-1.181	8.59E-09	2.98E-07
LEPREL2	-1.181	0.0001328	0.0004945
MAPK8	-1.183	1.43E-08	4.28E-07
C15orf38	-1.184	5.83E-08	1.15E-06
LINC00938	-1.184	2.38E-07	3.36E-06
SIRT1	-1.185	4.83E-09	2.00E-07
BLNK	-1.185	0.0003809	0.001178
DUSP8	-1.185	0.0005816	0.00168
ZNF91	-1.186	9.33E-08	1.61E-06
ARHGAP22	-1.186	0.0005596	0.001625
MSRB3	-1.187	2.98E-09	1.40E-07

NELL2	-1.187	8.34E-06	5.43E-05
PPP3CB	-1.188	2.13E-09	1.17E-07
EPC1	-1.188	5.43E-09	2.17E-07
FCGR2B	-1.188	0.0003221	0.001027
ZNF675	-1.19	2.05E-07	3.00E-06
CHST3	-1.191	3.35E-07	4.43E-06
SLC35G1	-1.191	2.26E-05	0.0001187
SNORD5	-1.191	0.0002453	0.0008186
LOC339862	-1.192	0.0001269	0.0004769
SNORA8	-1.193	0.0002001	0.0006908
FRA10AC1	-1.194	6.68E-08	1.26E-06
OSCAR	-1.194	5.72E-07	6.66E-06
SHISA7	-1.194	4.79E-05	0.000216
MPPED1	-1.195	0.003465	0.007609
RALGPS2	-1.196	1.06E-07	1.78E-06
WAPAL	-1.198	1.57E-09	9.68E-08
UTF1	-1.198	0.008533	0.01662
SNORD22	-1.199	9.19E-05	0.0003666
RMRP	-1.199	0.001875	0.004514
BUB3	-1.203	3.35E-10	3.76E-08
C8orf88	-1.204	2.13E-07	3.07E-06
DACH1	-1.205	1.53E-09	9.52E-08
CDC123	-1.206	2.18E-09	1.17E-07
ARL14EP	-1.209	8.34E-06	5.43E-05
PAIP1	-1.21	2.38E-09	1.22E-07
DENND1B	-1.21	1.33E-07	2.14E-06
RASSF9	-1.21	0.000825	0.002248
SDC2	-1.212	2.51E-09	1.25E-07
KAZALD1	-1.212	5.90E-06	4.20E-05
VEGFA	-1.215	2.63E-07	3.64E-06
SECTM1	-1.215	4.93E-06	3.65E-05
KIF5B	-1.216	1.83E-10	2.76E-08
GIN1	-1.22	1.50E-05	8.58E-05
MCMBP	-1.222	2.07E-10	3.00E-08
RPP38	-1.223	2.19E-08	5.87E-07
ZNF724P	-1.225	5.08E-05	0.0002268
SMNDC1	-1.228	1.87E-09	1.09E-07
AHNAK2	-1.229	4.94E-06	3.65E-05
ANKRD26P3	-1.23	0.0002994	0.0009658
SUMO1P3	-1.23	0.0003051	0.0009816

ZNF487	-1.23	0.00046	0.001379
NUTM2D	-1.23	0.01303	0.02403
TEX30	-1.231	3.48E-07	4.57E-06
MMP11	-1.231	0.0001617	0.0005802
ZDHHC6	-1.232	1.83E-09	1.08E-07
ZWINT	-1.234	3.18E-10	3.70E-08
FAM53B	-1.235	9.59E-09	3.23E-07
FAIM	-1.235	1.13E-06	1.14E-05
LRRC40	-1.235	1.11E-05	6.81E-05
FGL2	-1.236	6.58E-06	4.56E-05
CREM	-1.238	2.75E-07	3.76E-06
HDHD3	-1.24	2.40E-08	6.26E-07
ZNF14	-1.243	5.66E-07	6.62E-06
NNT-AS1	-1.244	1.11E-08	3.59E-07
ITPR3	-1.244	2.85E-08	6.97E-07
ZNF432	-1.245	9.04E-06	5.78E-05
MAGEB2	-1.246	2.22E-09	1.17E-07
AGAP9	-1.246	6.66E-06	4.59E-05
ARTN	-1.246	1.03E-05	6.44E-05
ZNF568	-1.247	8.25E-06	5.39E-05
PRDX3	-1.249	3.54E-09	1.57E-07
CES3	-1.249	1.61E-07	2.45E-06
P2RX7	-1.252	6.69E-05	0.0002831
SNORD44	-1.253	0.01001	0.0191
WBP1L	-1.254	4.39E-10	4.59E-08
FAM175B	-1.254	9.03E-10	7.05E-08
CEP55	-1.255	2.57E-10	3.33E-08
FAM160B1	-1.255	9.76E-08	1.67E-06
WBP5	-1.255	3.65E-06	2.88E-05
LZTS2	-1.256	3.11E-10	3.68E-08
KIAA1586	-1.257	1.44E-06	1.38E-05
ARL3	-1.258	3.63E-08	8.26E-07
CCT2	-1.259	1.20E-08	3.79E-07
IFIT3	-1.259	1.99E-07	2.92E-06
FAM60A	-1.26	1.20E-09	8.51E-08
BNIP3	-1.26	1.93E-08	5.34E-07
AIMP1	-1.26	4.92E-07	5.94E-06
ELMOD2	-1.26	3.77E-06	2.96E-05
LPCAT1	-1.261	6.46E-10	5.74E-08
GLRX3	-1.261	9.12E-09	3.12E-07

ZNF737	-1.261	9.87E-07	1.03E-05
GXYLT1	-1.263	2.85E-09	1.38E-07
TARS	-1.264	3.06E-10	3.68E-08
INPP5F	-1.265	3.15E-07	4.22E-06
SFMBT2	-1.266	8.11E-09	2.86E-07
TBK1	-1.267	2.04E-07	2.99E-06
QRICH2	-1.269	0.0002054	0.0007051
LOC101060181	-1.273	0.0005085	0.001499
BMS1P6	-1.274	0.001323	0.003339
GRIA3	-1.275	2.28E-06	1.98E-05
OTUD6B	-1.277	2.66E-06	2.24E-05
KCNS1	-1.277	0.0005475	0.001596
LOC100288152	-1.279	1.37E-05	8.03E-05
MRPS16	-1.281	1.93E-09	1.10E-07
HES4	-1.282	0.0003976	0.00122
FLJ37201	-1.282	0.006494	0.01313
SFXN4	-1.285	2.31E-08	6.09E-07
DCLRE1C	-1.286	4.90E-10	4.97E-08
IDE	-1.29	1.18E-09	8.46E-08
DCLRE1A	-1.29	1.25E-07	2.03E-06
TLE6	-1.291	7.99E-06	5.26E-05
RP11-454P21.1	-1.291	0.0003444	0.001088
SUV39H2	-1.296	1.45E-08	4.30E-07
ZFAND4	-1.297	6.16E-07	7.08E-06
KITLG	-1.298	1.66E-08	4.76E-07
ADAMTS14	-1.298	0.002214	0.005183
FAM45A	-1.301	4.40E-09	1.85E-07
ALG10	-1.301	2.46E-07	3.46E-06
ZNF680	-1.302	6.91E-07	7.75E-06
CUL2	-1.303	1.33E-09	9.04E-08
ARHGAP12	-1.303	7.63E-09	2.74E-07
SLITRK5	-1.304	3.74E-08	8.45E-07
RAD54B	-1.305	1.11E-07	1.85E-06
SEC14L2	-1.307	4.77E-05	0.0002157
LOC101927104	-1.31	0.0001735	0.000614
TM9SF3	-1.311	2.17E-10	3.00E-08
LOC101928913	-1.311	0.0006498	0.001839
SMC3	-1.312	9.74E-11	2.04E-08
HELLS	-1.313	1.99E-08	5.47E-07
BMPR1A	-1.314	3.46E-07	4.56E-06

MRPL36	-1.315	6.23E-09	2.36E-07
HLA-DPA1	-1.316	0.0003633	0.001133
RPP30	-1.318	5.82E-09	2.27E-07
ZNF503-AS2	-1.318	2.25E-05	0.0001185
MEIS3	-1.319	0.0002859	0.0009283
PRPF18	-1.323	3.05E-09	1.42E-07
SNORA24	-1.324	0.001313	0.003319
ULK4P2	-1.324	0.003413	0.00751
LRRC10B	-1.327	8.19E-05	0.0003335
KCNK1	-1.327	0.0003484	0.001097
ZNF506	-1.328	6.56E-09	2.44E-07
FOXF1	-1.328	1.55E-06	1.45E-05
DNAJC9	-1.33	8.61E-10	6.95E-08
PCGF5	-1.331	7.87E-08	1.43E-06
LOC728407	-1.331	0.0007165	0.001994
ALG10B	-1.336	1.72E-06	1.58E-05
PLEKHA8P1	-1.337	1.10E-07	1.83E-06
CLIC5	-1.337	0.001485	0.003692
MNAT1	-1.341	7.93E-08	1.44E-06
BCAT1	-1.343	2.90E-09	1.40E-07
ANAPC16	-1.345	6.93E-09	2.56E-07
RNLS	-1.348	8.82E-07	9.47E-06
ENTPD1-AS1	-1.348	5.33E-05	0.0002355
CADM1	-1.349	1.46E-06	1.39E-05
ZNF92	-1.351	1.37E-06	1.34E-05
AP1S3	-1.352	3.24E-10	3.73E-08
HECTD2	-1.352	7.68E-06	5.09E-05
RP11-96H19.1	-1.354	5.63E-06	4.05E-05
SNORA25	-1.354	0.00018	0.0006332
IL31RA	-1.356	1.97E-06	1.75E-05
LOC100507487	-1.357	0.0001818	0.0006381
USP6NL-IT1	-1.357	0.0002521	0.0008374
BTA1F1	-1.358	1.47E-07	2.28E-06
EBF3	-1.36	7.24E-09	2.63E-07
C12orf29	-1.36	1.77E-06	1.61E-05
NKD2	-1.361	4.41E-09	1.85E-07
TMEM117	-1.361	3.98E-07	5.07E-06
LYSMD1	-1.363	0.000107	0.0004145
RPL22L1	-1.364	4.29E-07	5.37E-06
PXDC1	-1.364	2.36E-05	0.0001225

COMMD3	-1.366	2.33E-07	3.31E-06
GHITM	-1.367	1.42E-09	9.21E-08
CEP290	-1.37	9.25E-08	1.60E-06
ACTR6	-1.37	1.55E-06	1.45E-05
TFEC	-1.372	5.18E-06	3.79E-05
UBE2D1	-1.374	2.26E-07	3.23E-06
DEPDC4	-1.374	7.00E-06	4.76E-05
BLOC1S2	-1.375	9.24E-08	1.60E-06
LOC101928524	-1.377	8.57E-05	0.0003465
RP11-12A2.3	-1.378	5.33E-05	0.0002355
FSD1L	-1.385	5.97E-06	4.24E-05
C2CD4C	-1.387	0.0001417	0.0005217
DPCD	-1.388	7.48E-06	5.00E-05
CES4A	-1.388	0.0008601	0.002324
LCOR	-1.392	2.30E-08	6.09E-07
KIAA1324	-1.394	4.11E-05	0.0001912
KIN	-1.396	5.60E-09	2.21E-07
C1QTNF3	-1.398	2.50E-06	2.12E-05
BBIP1	-1.399	1.63E-07	2.48E-06
C2CD5	-1.4	1.63E-09	9.93E-08
TLX3	-1.402	4.50E-06	3.40E-05
LMBRD2	-1.406	2.73E-07	3.75E-06
LRRC17	-1.407	4.20E-05	0.0001944
TFAM	-1.409	5.27E-09	2.12E-07
NFYB	-1.41	8.24E-07	8.94E-06
NCOA4	-1.411	5.32E-11	1.39E-08
C10orf55	-1.411	0.00014	0.0005165
SNORD47	-1.413	0.0001106	0.0004256
ARL5B	-1.418	3.52E-07	4.62E-06
TIMM23	-1.419	3.47E-10	3.83E-08
ZNF33B	-1.419	1.06E-08	3.46E-07
PSTPIP2	-1.42	7.97E-10	6.68E-08
GOLT1B	-1.421	2.14E-08	5.77E-07
PPP1R3F	-1.424	3.33E-06	2.68E-05
NUDT13	-1.424	4.02E-05	0.0001883
OXCT1	-1.426	8.30E-11	1.79E-08
CAMK1D	-1.426	1.43E-08	4.28E-07
RGS10	-1.427	2.79E-09	1.36E-07
RPL37	-1.428	2.84E-08	6.96E-07
DNAJC21	-1.429	1.15E-10	2.20E-08

METTLL10	-1.435	1.63E-09	9.93E-08
CCDC7	-1.437	2.07E-05	0.0001106
NEURL1	-1.441	4.80E-08	1.01E-06
TMTC3	-1.441	1.47E-07	2.28E-06
JMJD1C	-1.442	4.41E-09	1.85E-07
AMN1	-1.442	1.71E-07	2.60E-06
KRR1	-1.443	1.94E-07	2.87E-06
PTPRO	-1.448	1.32E-09	9.04E-08
SNHG12	-1.448	5.47E-07	6.45E-06
OGDHL	-1.449	3.88E-05	0.0001828
SLC38A2	-1.45	4.39E-11	1.28E-08
ANO6	-1.45	2.16E-10	3.00E-08
SAMD11	-1.45	6.94E-05	0.0002918
IL17RB	-1.453	2.88E-05	0.0001432
CWF19L1	-1.454	4.86E-10	4.97E-08
IDI1	-1.455	4.47E-07	5.50E-06
ZNF85	-1.455	6.05E-07	6.99E-06
PTER	-1.463	1.34E-09	9.04E-08
LRRC27	-1.463	1.40E-06	1.35E-05
CCDC177	-1.465	0.002963	0.006665
EXOC6	-1.469	2.25E-09	1.17E-07
SYCP2	-1.47	0.0005772	0.001669
ZNF726	-1.473	7.62E-05	0.0003151
DNA2	-1.474	3.37E-09	1.53E-07
SNORD104	-1.475	0.0001337	0.0004976
ANKRD26	-1.476	3.46E-08	7.97E-07
SHISA3	-1.477	4.03E-07	5.10E-06
ZNF438	-1.479	7.15E-11	1.65E-08
AGAP4	-1.481	3.31E-06	2.67E-05
VPS26A	-1.483	7.51E-11	1.70E-08
CLCF1	-1.485	0.0003625	0.001131
RNF175	-1.488	3.54E-08	8.11E-07
GNG11	-1.495	2.74E-05	0.0001375
LINC00477	-1.507	3.24E-06	2.62E-05
HSPA14	-1.509	1.31E-09	9.04E-08
SAMD8	-1.509	6.36E-08	1.22E-06
DENND5B	-1.509	6.36E-08	1.22E-06
TYSND1	-1.51	1.50E-09	9.51E-08
LAT	-1.511	2.81E-08	6.93E-07
BCCIP	-1.515	2.18E-09	1.17E-07

RAB18	-1.515	5.78E-09	2.26E-07
METTL20	-1.521	5.51E-05	0.0002419
FAM35A	-1.524	4.84E-09	2.00E-07
ZNF518A	-1.524	9.48E-09	3.22E-07
UNC80	-1.524	9.00E-05	0.0003605
CPNE8	-1.529	8.01E-09	2.84E-07
TRUB1	-1.53	1.38E-09	9.05E-08
CAPS2	-1.53	0.00192	0.004596
USMG5	-1.533	1.77E-08	5.02E-07
CEP70	-1.534	1.46E-07	2.28E-06
ZNF32	-1.536	1.22E-08	3.81E-07
FAM45B	-1.536	2.97E-08	7.16E-07
IPMK	-1.538	8.45E-10	6.95E-08
SNX16	-1.538	5.15E-06	3.78E-05
TM7SF3	-1.541	1.81E-11	9.06E-09
NEXN	-1.542	3.20E-06	2.60E-05
THAP2	-1.543	6.94E-07	7.77E-06
PPHLN1	-1.547	2.17E-10	3.00E-08
LOC100130992	-1.547	2.01E-06	1.78E-05
ZNF503	-1.551	9.43E-09	3.21E-07
SNORA61	-1.552	0.0001016	0.0003971
SCAF11	-1.558	1.06E-10	2.09E-08
FAM204A	-1.558	1.61E-09	9.91E-08
ZFR	-1.56	7.07E-08	1.32E-06
BRIX1	-1.561	6.94E-10	6.08E-08
INPP5A	-1.561	1.02E-09	7.71E-08
ZNF131	-1.562	5.47E-10	5.16E-08
DDX11	-1.563	4.59E-10	4.76E-08
HHEX	-1.563	1.48E-09	9.43E-08
TUBB3	-1.565	6.75E-05	0.0002849
NOC3L	-1.566	2.35E-09	1.21E-07
HTR7	-1.566	4.32E-08	9.37E-07
SLC4A11	-1.566	1.01E-06	1.05E-05
GPX8	-1.568	1.28E-07	2.07E-06
ADM	-1.568	0.0001005	0.000394
SHOC2	-1.571	6.19E-11	1.52E-08
YAF2	-1.584	6.23E-09	2.36E-07
SNORD87	-1.584	0.001157	0.002982
ZNF98	-1.589	3.96E-08	8.75E-07
ASUN	-1.59	1.51E-10	2.50E-08

FLJ37035	-1.598	6.03E-05	0.0002607
KIF11	-1.603	2.80E-11	1.13E-08
ATAD1	-1.603	4.12E-09	1.77E-07
SNORD76	-1.606	0.0002649	0.0008721
PARPBP	-1.607	8.32E-09	2.92E-07
P4HA1	-1.607	2.82E-08	6.93E-07
SEPP1	-1.607	0.0005001	0.001479
LOC647859	-1.613	0.0004781	0.001426
ZNF25	-1.614	1.00E-09	7.64E-08
SLK	-1.614	1.51E-09	9.51E-08
SEC61A2	-1.614	4.50E-06	3.40E-05
CHUK	-1.62	6.41E-10	5.73E-08
ZNF485	-1.622	9.39E-08	1.62E-06
SLC16A9	-1.623	1.59E-08	4.61E-07
CASC5	-1.626	2.15E-09	1.17E-07
ZNF511	-1.627	8.04E-11	1.77E-08
ARNTL2	-1.63	8.79E-10	6.98E-08
SLC7A11	-1.63	3.31E-09	1.50E-07
CISD1	-1.638	4.16E-08	9.08E-07
PDSS1	-1.642	2.29E-10	3.10E-08
IFIT2	-1.647	8.57E-08	1.52E-06
NEGR1	-1.647	4.58E-07	5.60E-06
CHCHD1	-1.651	1.44E-08	4.29E-07
C1QA	-1.652	2.92E-05	0.0001453
KLHL42	-1.658	3.49E-11	1.18E-08
CRABP1	-1.663	8.64E-09	2.99E-07
ZNF22	-1.665	6.11E-09	2.34E-07
RPS24	-1.665	8.75E-08	1.54E-06
DNM1L	-1.667	2.60E-11	1.13E-08
C10orf32	-1.667	7.29E-09	2.64E-07
LOC728819	-1.669	3.24E-05	0.0001574
ARSG	-1.671	4.63E-07	5.65E-06
OAT	-1.672	3.19E-10	3.70E-08
SMAD9	-1.676	0.001001	0.002644
ABCC6P1	-1.687	9.32E-05	0.0003709
PAPSS2	-1.688	1.84E-09	1.08E-07
CUTC	-1.69	1.26E-09	8.85E-08
NSMCE4A	-1.701	3.04E-08	7.28E-07
CYP2B7P	-1.701	0.0004275	0.001295
PCGF6	-1.703	9.22E-10	7.16E-08

LDHB	-1.706	3.18E-09	1.46E-07
SLC2A13	-1.707	7.10E-09	2.59E-07
EPS8L2	-1.707	0.0008933	0.002403
MASTL	-1.709	6.25E-10	5.62E-08
KIF20B	-1.709	1.01E-09	7.67E-08
TRDMT1	-1.711	5.52E-08	1.11E-06
NKX6-3	-1.713	1.14E-05	6.94E-05
CMA5	-1.716	1.61E-11	8.78E-09
TEX15	-1.725	3.35E-08	7.78E-07
RUFY2	-1.73	5.57E-07	6.54E-06
DDX50	-1.733	6.19E-10	5.61E-08
PEAR1	-1.737	0.000203	0.0006989
RNF208	-1.747	5.62E-05	0.0002457
KIAA1551	-1.748	3.03E-11	1.13E-08
RASSF8	-1.754	2.95E-08	7.13E-07
NCAM1	-1.761	6.98E-09	2.57E-07
SFR1	-1.768	1.84E-08	5.16E-07
YARS2	-1.77	1.70E-10	2.64E-08
SPEF2	-1.772	1.52E-09	9.51E-08
SLC16A6	-1.773	0.0004402	0.001328
STK38L	-1.774	1.55E-10	2.50E-08
CTBP2	-1.779	1.58E-11	8.78E-09
RECQL	-1.785	1.44E-09	9.27E-08
EGR1	-1.785	0.004835	0.01013
KCNS3	-1.789	4.59E-05	0.0002092
VIM	-1.791	3.99E-12	4.50E-09
PTENP1	-1.798	9.92E-05	0.0003899
SOCS2	-1.804	6.17E-07	7.08E-06
PAWR	-1.805	8.45E-07	9.11E-06
SNORA73A	-1.807	0.0004286	0.001298
ATP5C1	-1.81	8.96E-09	3.08E-07
CTNNA3	-1.811	0.001171	0.003014
SIGLEC1	-1.816	1.72E-10	2.64E-08
PUS7L	-1.827	3.41E-08	7.89E-07
KREMEN2	-1.829	1.06E-06	1.09E-05
ANK3	-1.83	0.0001689	0.000601
HOXB6	-1.832	8.88E-06	5.69E-05
DPY19L2	-1.838	0.0004262	0.001292
CD209	-1.869	4.86E-11	1.30E-08
EPHB4	-1.875	9.95E-09	3.31E-07

MRPS35	-1.902	3.12E-11	1.13E-08
VAT1L	-1.908	1.65E-09	9.98E-08
LTK	-1.911	7.76E-10	6.63E-08
SHISA8	-1.914	1.84E-05	0.0001003
C5orf28	-1.919	4.65E-08	9.87E-07
SLC12A7	-1.921	6.53E-10	5.76E-08
SUB1	-1.922	5.89E-08	1.16E-06
CCDC91	-1.933	3.10E-10	3.68E-08
METTL12	-1.943	5.83E-06	4.16E-05
ETNK1	-1.946	1.13E-09	8.23E-08
LYRM5	-1.953	5.48E-08	1.11E-06
PCDHGA12	-1.981	4.42E-06	3.35E-05
KRAS	-1.982	6.64E-12	5.31E-09
RP11-996F15.2	-1.984	8.81E-06	5.66E-05
FAM35BP	-1.987	5.40E-06	3.91E-05
KCNQ5	-1.995	1.39E-09	9.05E-08
GUCY1B3	-1.997	8.16E-06	5.34E-05
ACPP	-2.006	4.76E-12	4.50E-09
IFITM1	-2.008	6.20E-10	5.61E-08
PLEKHO1	-2.01	1.06E-10	2.09E-08
LOC100506688	-2.012	3.84E-09	1.68E-07
SPRED1	-2.012	7.01E-05	0.000294
LOC100506374	-2.023	3.91E-06	3.04E-05
LRMP	-2.038	1.18E-11	8.44E-09
SOX1	-2.056	1.99E-05	0.000107
LOC101927646	-2.067	3.09E-05	0.000152
TWF1	-2.069	1.38E-08	4.18E-07
SETD6	-2.078	2.47E-06	2.10E-05
AKR1C3	-2.08	3.83E-08	8.55E-07
IFI44	-2.092	2.51E-08	6.41E-07
LOC102724472	-2.093	1.40E-05	8.18E-05
IFIT5	-2.099	2.11E-07	3.05E-06
FCER2	-2.106	1.89E-10	2.79E-08
AASS	-2.116	3.29E-05	0.0001593
MED21	-2.118	3.31E-09	1.50E-07
CDK1	-2.135	5.80E-08	1.15E-06
ERGIC2	-2.139	1.68E-08	4.82E-07
LOC101927799	-2.144	7.45E-06	4.99E-05
UGT3A2	-2.153	2.25E-09	1.17E-07
SOX5	-2.164	1.22E-06	1.22E-05

LOC284600	-2.179	0.000259	0.0008566
CDH2	-2.197	3.00E-09	1.41E-07
FGD4	-2.208	9.99E-09	3.31E-07
PYROXD1	-2.213	2.34E-09	1.21E-07
TGFBR3L	-2.215	1.87E-07	2.78E-06
GLIS2	-2.222	1.33E-06	1.30E-05
MCF2L2	-2.251	0.0009547	0.002543
TTC33	-2.259	1.34E-08	4.12E-07
PCED1B-AS1	-2.26	7.85E-09	2.80E-07
GPC6	-2.27	6.93E-06	4.73E-05
ABCD2	-2.272	1.10E-06	1.13E-05
ZNF43	-2.282	5.07E-10	4.99E-08
OVOL2	-2.284	3.63E-08	8.26E-07
TRIM22	-2.293	5.28E-10	5.16E-08
MDGA2	-2.307	8.94E-05	0.0003584
FGFR1OP2	-2.323	1.33E-09	9.04E-08
TOM1L1	-2.338	1.12E-08	3.59E-07
LOC441666	-2.342	1.84E-08	5.16E-07
PCDHB14	-2.385	6.65E-06	4.59E-05
RPAP3	-2.431	1.84E-11	9.06E-09
GRTP1	-2.438	1.19E-05	7.16E-05
MX1	-2.44	1.17E-10	2.20E-08
RHBDL3	-2.443	8.49E-05	0.0003439
HMX2	-2.444	2.46E-08	6.37E-07
LGALS3BP	-2.457	1.37E-08	4.17E-07
SHANK3	-2.457	3.11E-08	7.40E-07
DDIT4	-2.473	3.03E-10	3.68E-08
COL27A1	-2.475	1.55E-10	2.50E-08
LOC100506691	-2.496	2.59E-08	6.59E-07
CA3	-2.517	3.58E-07	4.68E-06
GUSBP5	-2.549	3.12E-06	2.55E-05
DAPK2	-2.559	1.29E-08	4.01E-07
PCSK5	-2.565	1.04E-06	1.07E-05
MT1G	-2.606	2.21E-09	1.17E-07
GAS1	-2.652	1.69E-09	1.02E-07
AGAP7	-2.657	8.75E-06	5.63E-05
SNORA1	-2.672	1.84E-06	1.66E-05
ZNF829	-2.701	9.61E-08	1.65E-06
PCDHB13	-2.716	2.73E-08	6.81E-07
ZNF572	-2.716	6.35E-08	1.22E-06

RP11-53O19.1	-2.739	2.87E-08	6.99E-07
IFIT1	-2.744	5.39E-09	2.16E-07
AKR1E2	-2.746	3.10E-07	4.17E-06
HSH2D	-2.747	1.49E-11	8.78E-09
KIF26A	-2.785	8.35E-09	2.92E-07
IRAK4	-2.835	4.39E-12	4.50E-09
ZNF320	-2.849	3.65E-11	1.19E-08
RGL3	-2.85	7.06E-06	4.79E-05
FIGN	-2.85	6.64E-05	0.0002819
ELK1	-2.872	1.62E-11	8.78E-09
ZNF99	-2.909	2.21E-07	3.15E-06
LINC00461	-2.95	4.88E-05	0.0002193
LOC100996425	-2.991	2.91E-06	2.42E-05
HLA-DRA	-2.999	1.28E-10	2.36E-08
HSD17B8	-3.064	1.46E-07	2.28E-06
CSMD3	-3.101	0.0002328	0.000783
C6orf223	-3.102	3.67E-11	1.19E-08
TLX1	-3.134	1.93E-06	1.73E-05
ALX1	-3.176	3.41E-10	3.80E-08
RP11-184I16.4	-3.222	4.97E-12	4.50E-09
C10orf10	-3.28	4.27E-07	5.35E-06
DYNC1I1	-3.29	2.20E-06	1.92E-05
NES	-3.346	7.38E-08	1.36E-06
TNNI3	-3.386	2.29E-08	6.09E-07
PTEN	-3.416	5.45E-15	4.71E-11
IFI44L	-3.425	1.52E-10	2.50E-08
CPS1	-3.432	1.72E-06	1.58E-05
SV2A	-3.448	1.41E-07	2.23E-06
CADPS2	-3.448	1.42E-06	1.37E-05
IFI27	-3.451	2.20E-09	1.17E-07
ZNF662	-3.591	4.79E-08	1.01E-06
MPPED2	-3.635	1.31E-06	1.28E-05
PVRL3	-3.73	5.81E-07	6.75E-06
SMAD1	-3.734	7.07E-11	1.65E-08
RTN1	-3.897	1.38E-08	4.19E-07
SLFN12	-3.902	9.53E-09	3.22E-07
HMX3	-3.973	7.07E-09	2.59E-07
AIF1L	-3.981	1.47E-07	2.29E-06
TPTEP1	-4.027	6.56E-09	2.44E-07
YPEL3	-4.027	1.10E-07	1.84E-06

C3orf18	-4.112	4.71E-08	9.97E-07
INPP5J	-4.166	3.52E-08	8.11E-07
PAX5	-4.211	1.12E-09	8.20E-08
TRIM72	-4.298	2.11E-07	3.05E-06
VENTX	-4.317	3.75E-05	0.0001781
TMEM63C	-4.504	7.11E-08	1.33E-06
HLA-F	-4.589	1.76E-07	2.64E-06
PI15	-4.746	3.23E-07	4.30E-06
C1QC	-4.893	1.91E-07	2.83E-06
UNC13D	-5.014	6.21E-13	1.36E-09
SIDT1	-5.08	5.71E-07	6.66E-06
CXorf57	-5.085	3.38E-11	1.18E-08
PAK6	-5.381	6.33E-09	2.37E-07
AKR1C2	-5.484	1.43E-12	1.95E-09
IL17RC	-5.534	5.17E-06	3.79E-05
MAGEA4	-5.651	1.06E-08	3.47E-07
LDOC1	-5.769	1.72E-08	4.92E-07
ZNF404	-5.785	1.11E-07	1.85E-06
MT1L	-5.912	1.71E-09	1.03E-07
PKIA	-5.97	2.01E-09	1.13E-07
ANKFN1	-5.991	4.30E-08	9.34E-07
LOC100653233	-6.247	3.54E-10	3.83E-08
COL4A5	-6.267	7.20E-10	6.23E-08
CNTN1	-6.719	1.41E-10	2.46E-08
GYPE	-7.245	1.33E-10	2.38E-08
BEX5	-7.505	6.82E-11	1.63E-08
AKR1C1	-7.68	1.34E-09	9.04E-08
ADAMTS9	-9.535	6.25E-11	1.52E-08

Table 6. Differentially expressed genes in MyD88-KO vs WT THP1 cells

Gene	Log(FC)	P Value	Adj P Value
IFI27	5.004	1.11E-11	1.11E-11
PCSK5	4.205	3.27E-10	3.27E-10
WIPF3	3.104	4.25E-06	4.25E-06
ANKRD19P	2.834	2.16E-05	2.16E-05
TAL1	2.767	4.27E-05	4.27E-05
PGM5P3-AS1	2.718	1.36E-05	1.36E-05
PTPN13	2.55	0.0008288	0.0008288
SPON1	2.501	0.001977	0.001977

GABRA4	2.304	1.40E-05	1.40E-05
BDNF	2.274	0.0004115	0.0004115
RAB38	2.123	8.81E-05	8.81E-05
TIAM2	2.086	0.000142	0.000142
SCRN1	2.032	2.09E-09	2.09E-09
LOC729737	2.032	0.0004831	0.0004831
DLEU7-AS1	1.968	8.62E-08	8.62E-08
LONRF2	1.941	0.0004953	0.0004953
RNU4-1	1.925	0.1368	0.1368
IFI44L	1.92	1.05E-05	1.05E-05
CCDC120	1.855	1.38E-06	1.38E-06
PPP1R36	1.809	0.01049	0.01049
RFK	1.777	3.99E-10	3.99E-10
DMD	1.758	0.0002615	0.0002615
HFE	1.741	0.0001211	0.0001211
FIGN	1.724	2.02E-05	2.02E-05
HOXB13	1.722	7.85E-05	7.85E-05
HOXB6	1.719	4.02E-07	4.02E-07
ROBO4	1.719	0.008999	0.008999
BTNL9	1.718	0.0003396	0.0003396
SLC6A9	1.701	2.01E-05	2.01E-05
LOC645166	1.672	0.0002332	0.0002332
MTMR7	1.631	0.001032	0.001032
LSR	1.624	0.0005328	0.0005328
APOLD1	1.613	2.65E-07	2.65E-07
RUFY4	1.61	4.21E-05	4.21E-05
TFPI	1.588	0.0005722	0.0005722
VAT1L	1.56	7.06E-09	7.06E-09
ZNF827	1.551	0.0004303	0.0004303
RN7SK	1.544	0.1016	0.1016
EPSTI1	1.538	7.25E-06	7.25E-06
FIRRE	1.536	0.011	0.011
LAMA2	1.525	4.37E-07	4.37E-07
NAPSA	1.509	0.001484	0.001484
DLL1	1.487	1.16E-06	1.16E-06
CCND1	1.487	5.05E-06	5.05E-06
SARM1	1.459	8.01E-05	8.01E-05
HFM1	1.422	0.008283	0.008283
LINC01356	1.417	0.002198	0.002198
SLC47A1	1.403	0.005899	0.005899

LAMB2P1	1.395	0.006539	0.006539
PLBD1	1.385	7.13E-06	7.13E-06
VENTX	1.375	2.64E-05	2.64E-05
RMRP	1.375	0.1139	0.1139
RNA18S5	1.358	0.05323	0.05323
PPP1R32	1.355	0.0003128	0.0003128
ZNF462	1.345	1.66E-05	1.66E-05
PGM5	1.344	0.00357	0.00357
SIGLEC1	1.333	1.77E-06	1.77E-06
CDC42BPA	1.331	3.97E-07	3.97E-07
PCDHGA8	1.327	0.001193	0.001193
MX1	1.299	2.09E-08	2.09E-08
MIR2052HG	1.298	0.005069	0.005069
GABRD	1.293	0.000356	0.000356
SLC22A23	1.287	0.002727	0.002727
LOC101929415	1.277	0.004777	0.004777
A2M	1.269	5.47E-07	5.47E-07
ASIC3	1.269	0.002579	0.002579
NPR2	1.25	0.001993	0.001993
IFI44	1.248	6.10E-05	6.10E-05
TMEM63C	1.247	0.0001438	0.0001438
IFI6	1.245	9.85E-08	9.85E-08
SARDH	1.245	0.0006221	0.0006221
CNKSR1	1.245	0.002316	0.002316
CNIH3	1.22	0.001653	0.001653
POLR2J3	1.204	0.0002499	0.0002499
CAPN6	1.186	0.0001565	0.0001565
GMPR	1.182	0.004771	0.004771
ASPRV1	1.174	0.009129	0.009129
ZNF630	1.172	0.0004312	0.0004312
TRIM22	1.165	2.43E-06	2.43E-06
COL4A5	1.164	6.41E-06	6.41E-06
GNG7	1.163	7.36E-07	7.36E-07
DMC1	1.154	0.002323	0.002323
NEXN	1.152	1.51E-05	1.51E-05
LARP6	1.149	0.002797	0.002797
SLC35F3	1.132	0.01293	0.01293
HYDIN2	1.126	0.0006369	0.0006369
HOXB7	1.125	0.001243	0.001243
LPAR6	1.125	0.01413	0.01413

PRAC2	1.12	0.001021	0.001021
PFN2	1.119	0.0007115	0.0007115
MAEL	1.117	0.008775	0.008775
RNU4-2	1.115	0.4748	0.4748
VLDLR-AS1	1.114	1.74E-05	1.74E-05
CFAP70	1.111	0.003466	0.003466
SYT11	1.109	0.0001933	0.0001933
FAM171A1	1.102	0.002471	0.002471
GRTP1	1.101	0.001091	0.001091
LIPN	1.098	0.001701	0.001701
OAS3	1.094	6.61E-09	6.61E-09
LOC101929592	1.094	2.20E-07	2.20E-07
PII5	1.083	0.0008236	0.0008236
FLJ32255	1.081	1.26E-08	1.26E-08
CNTN1	1.081	0.0008388	0.0008388
LINC01169	1.077	0.00114	0.00114
KIF9-AS1	1.075	0.005	0.005
OVOL2	1.071	9.45E-06	9.45E-06
TBC1D3P1-DHX40P1	1.071	0.05772	0.05772
PNMA2	1.07	0.002867	0.002867
MSR1	1.066	0.002334	0.002334
NBPF9	1.057	0.0003286	0.0003286
CGN	1.055	0.0002051	0.0002051
MEGF6	1.046	6.84E-05	6.84E-05
MIR7641-2	1.044	0.228	0.228
DLX3	1.043	1.30E-05	1.30E-05
OTUD1	1.043	1.24E-05	1.24E-05
RPS6KA2	1.043	3.93E-05	3.93E-05
PCDHB12	1.037	0.02716	0.02716
TMEM254-AS1	1.036	0.01687	0.01687
OAS1	1.035	6.85E-07	6.85E-07
RNA28S5	1.032	0.004217	0.004217
SYTL3	1.031	0.0006695	0.0006695
KIRREL	1.028	0.001776	0.001776
PMEPA1	1.025	0.003844	0.003844
SCN8A	1.023	0.004269	0.004269
GNAL	1.023	0.008918	0.008918
LINC01270	1.022	0.02285	0.02285
ITGA2	1.021	0.0001891	0.0001891
OAS2	1.02	1.49E-08	1.49E-08

ARFGEF3	1.018	9.72E-05	9.72E-05
CBS	1.017	0.0361	0.0361
ABLIM2	1.014	0.0004158	0.0004158
TMEM221	1.014	0.004114	0.004114
CBWD3	1.003	0.01803	0.01803
ADAMTS9	-9.776	1.87E-11	1.87E-11
MFNG	-9.746	2.79E-10	2.79E-10
ELOVL3	-7.35	6.64E-10	6.64E-10
ALPK3	-7.059	9.97E-11	9.97E-11
ZNF37A	-6.359	1.36E-07	1.36E-07
ANKFN1	-6.277	1.04E-08	1.04E-08
KCNK1	-6.189	9.78E-09	9.78E-09
ZNF662	-5.935	8.93E-08	8.93E-08
CNTNAP4	-5.859	2.19E-08	2.19E-08
MT1L	-5.789	2.30E-08	2.30E-08
VWA1	-5.707	2.57E-08	2.57E-08
LINC01446	-5.707	2.57E-08	2.57E-08
MAGED1	-5.675	1.02E-07	1.02E-07
ZNF829	-5.528	1.11E-07	1.11E-07
LINC00654	-5.197	5.10E-07	5.10E-07
LDOC1	-5.067	2.59E-06	2.59E-06
PLEKHB1	-4.983	8.69E-07	8.69E-07
LRRC8E	-4.878	4.18E-06	4.18E-06
MT1G	-4.865	2.65E-09	2.65E-09
GNG11	-4.777	7.80E-06	7.80E-06
LOC102724661	-4.651	2.00E-06	2.00E-06
CADPS2	-4.61	3.66E-07	3.66E-07
SLFN12	-4.431	1.22E-07	1.22E-07
MAGEB2	-4.408	1.26E-11	1.26E-11
PINLYP	-4.318	1.74E-05	1.74E-05
ZNF536	-4.274	5.55E-07	5.55E-07
UNCX	-4.224	0.0001804	0.0001804
CCRL2	-4.14	9.39E-07	9.39E-07
AKR1C2	-4.135	1.37E-10	1.37E-10
IL12RB2	-3.951	3.12E-11	3.12E-11
RGL3	-3.872	0.000209	0.000209
PNCK	-3.862	7.77E-07	7.77E-07
NUDT16P1	-3.804	1.24E-07	1.24E-07
TOM1L1	-3.708	5.28E-09	5.28E-09
DYNC1H1	-3.708	3.07E-06	3.07E-06

CD93	-3.526	8.36E-14	8.36E-14
CKM	-3.523	5.39E-08	5.39E-08
PRSS30P	-3.46	1.78E-05	1.78E-05
SIX3	-3.422	1.66E-06	1.66E-06
POU4F2	-2.998	2.72E-08	2.72E-08
EPS8L2	-2.856	0.0001462	0.0001462
CNTN5	-2.81	4.00E-05	4.00E-05
PCDHGA12	-2.714	3.30E-06	3.30E-06
CYP27A1	-2.714	4.08E-05	4.08E-05
PAK6	-2.654	1.78E-07	1.78E-07
NES	-2.632	2.24E-06	2.24E-06
KDELC1	-2.596	1.10E-06	1.10E-06
FRMD4A	-2.58	1.89E-08	1.89E-08
C2	-2.565	5.89E-08	5.89E-08
RGS16	-2.557	6.88E-10	6.88E-10
LIPG	-2.403	1.39E-06	1.39E-06
IL17RC	-2.371	2.27E-06	2.27E-06
SELM	-2.35	1.67E-05	1.67E-05
SMO	-2.339	1.28E-05	1.28E-05
SPRED1	-2.318	3.01E-05	3.01E-05
N4BP3	-2.318	3.45E-05	3.45E-05
C1orf186	-2.239	1.27E-07	1.27E-07
TEX41	-2.209	7.61E-06	7.61E-06
CTSW	-2.209	3.98E-05	3.98E-05
FAM46C	-2.2	2.28E-05	2.28E-05
TPTEP1	-2.163	4.09E-07	4.09E-07
CKAP4	-2.139	1.82E-10	1.82E-10
FAM163A	-2.094	7.18E-07	7.18E-07
HSPA1A	-2.065	1.67E-09	1.67E-09
SV2A	-2.055	6.05E-06	6.05E-06
ST8SIA6	-2.048	0.0001081	0.0001081
NCAM1	-2.045	4.82E-09	4.82E-09
PAQR5	-2.031	8.70E-05	8.70E-05
NAV3	-2.001	7.01E-10	7.01E-10
GPX8	-1.992	3.38E-07	3.38E-07
PDE11A	-1.933	0.0003522	0.0003522
ZNF568	-1.915	2.09E-05	2.09E-05
SPAG16	-1.902	0.001127	0.001127
BHLHE22	-1.899	2.10E-06	2.10E-06
AJAP1	-1.898	4.40E-06	4.40E-06

PSMD5-AS1	-1.87	2.87E-05	2.87E-05
SERPINA1	-1.869	5.74E-05	5.74E-05
HTRA3	-1.818	0.000177	0.000177
CARD11	-1.797	2.56E-06	2.56E-06
GPR35	-1.791	3.60E-07	3.60E-07
SLAMF1	-1.777	0.0001023	0.0001023
ALX1	-1.76	1.71E-08	1.71E-08
SULF2	-1.755	2.12E-07	2.12E-07
KCNK10	-1.751	1.07E-05	1.07E-05
ANKLE1	-1.748	1.64E-08	1.64E-08
PTENP1	-1.723	9.81E-06	9.81E-06
AHNAK2	-1.722	2.06E-07	2.06E-07
BCAM	-1.712	2.71E-06	2.71E-06
G0S2	-1.688	5.62E-07	5.62E-07
LINC01088	-1.68	1.06E-06	1.06E-06
ANXA8L1	-1.667	0.001985	0.001985
CAMKV	-1.663	0.0001651	0.0001651
DEFB1	-1.642	4.35E-07	4.35E-07
TESC	-1.63	3.06E-06	3.06E-06
SIGLEC6	-1.619	5.01E-06	5.01E-06
TSPAN15	-1.613	1.38E-05	1.38E-05
MYO7A	-1.61	0.001237	0.001237
LPAR5	-1.595	7.84E-07	7.84E-07
ETNK2	-1.566	0.0002664	0.0002664
PAX5	-1.546	4.30E-08	4.30E-08
HMCN1	-1.529	0.0009012	0.0009012
MS4A3	-1.522	3.51E-08	3.51E-08
SEMG1	-1.515	2.32E-05	2.32E-05
CEBPE	-1.503	1.72E-06	1.72E-06
POLR2J2	-1.491	0.002487	0.002487
DPEP1	-1.486	5.62E-05	5.62E-05
AKR1C1	-1.483	1.00E-05	1.00E-05
AKR1C3	-1.482	1.24E-05	1.24E-05
FCAMR	-1.476	0.001059	0.001059
PLD3	-1.47	1.83E-10	1.83E-10
SEPT5-GP1BB	-1.461	0.001132	0.001132
FBXO15	-1.45	9.74E-05	9.74E-05
DNAH8	-1.445	0.0006908	0.0006908
TSPEAR-AS2	-1.433	0.01173	0.01173
SAMD14	-1.426	0.002199	0.002199

FBLN1	-1.425	3.15E-05	3.15E-05
NUDT11	-1.4	0.001135	0.001135
FUZ	-1.398	0.01073	0.01073
GALR2	-1.397	1.04E-05	1.04E-05
PCGF2	-1.387	9.30E-06	9.30E-06
TLR9	-1.373	0.001235	0.001235
TUBA8	-1.35	3.29E-05	3.29E-05
CD52	-1.348	4.36E-05	4.36E-05
CFP	-1.342	6.28E-07	6.28E-07
ARRDC4	-1.339	2.64E-07	2.64E-07
CIITA	-1.335	0.0003352	0.0003352
PRAM1	-1.33	6.08E-07	6.08E-07
C6orf223	-1.325	9.93E-08	9.93E-08
FAM135B	-1.321	0.0001931	0.0001931
C3AR1	-1.311	0.008129	0.008129
CXCL8	-1.308	0.0001412	0.0001412
AGK	-1.3	1.06E-07	1.06E-07
SYN3	-1.299	0.0009512	0.0009512
DRC7	-1.293	0.0009396	0.0009396
SIGLEC10	-1.289	2.16E-05	2.16E-05
LRRC25	-1.287	0.0003791	0.0003791
APOC1	-1.282	1.50E-07	1.50E-07
TSPEAR-AS1	-1.277	9.93E-05	9.93E-05
GAS6-AS2	-1.269	0.005078	0.005078
PLTP	-1.267	1.21E-08	1.21E-08
FEV	-1.263	0.005341	0.005341
PLEKHA6	-1.256	0.0002187	0.0002187
SPOCK1	-1.25	0.0007964	0.0007964
TIFAB	-1.249	4.52E-08	4.52E-08
HLA-DRA	-1.246	7.79E-06	7.79E-06
FAM150A	-1.245	0.0003636	0.0003636
TIMP3	-1.238	1.17E-09	1.17E-09
SLAMF9	-1.237	0.001371	0.001371
FAM46A	-1.235	2.28E-09	2.28E-09
DLL4	-1.23	0.001169	0.001169
ANXA8	-1.228	5.13E-05	5.13E-05
PTAFR	-1.223	0.0005927	0.0005927
SOX18	-1.221	0.002136	0.002136
ARHGAP22	-1.219	0.001064	0.001064
OLIG1	-1.218	9.42E-06	9.42E-06

PCDH7	-1.217	1.77E-05	1.77E-05
S100A8	-1.216	1.20E-05	1.20E-05
TNFSF4	-1.214	0.007379	0.007379
EHD2	-1.211	9.63E-07	9.63E-07
NFE2	-1.209	5.99E-08	5.99E-08
SPRY4	-1.202	0.0001361	0.0001361
MIP	-1.196	0.002865	0.002865
PTPN14	-1.186	7.50E-06	7.50E-06
TEX30	-1.183	4.62E-07	4.62E-07
DCHS1	-1.181	9.73E-06	9.73E-06
TMEM37	-1.179	0.0001138	0.0001138
NID1	-1.178	4.70E-09	4.70E-09
SCIMP	-1.173	0.0002844	0.0002844
TMEM261	-1.171	7.89E-07	7.89E-07
ATP1B1	-1.167	3.26E-06	3.26E-06
IRS2	-1.165	4.88E-09	4.88E-09
SLC2A10	-1.164	0.001733	0.001733
EGR3	-1.164	0.005139	0.005139
TMIGD3	-1.161	0.002304	0.002304
PTEN	-1.159	4.70E-09	4.70E-09
RGS20	-1.158	0.001548	0.001548
ARHGAP44	-1.155	1.16E-05	1.16E-05
ABI3	-1.155	0.01236	0.01236
ANXA6	-1.15	2.27E-09	2.27E-09
CDHR1	-1.143	0.000761	0.000761
STMN3	-1.141	1.42E-06	1.42E-06
ZNF358	-1.14	0.001154	0.001154
CTDSPL	-1.134	2.32E-07	2.32E-07
EGR4	-1.132	0.001224	0.001224
ACPP	-1.125	5.08E-09	5.08E-09
S100A9	-1.121	1.27E-07	1.27E-07
MARCKS	-1.121	1.49E-07	1.49E-07
SYNGR3	-1.12	0.01674	0.01674
PGR	-1.119	2.33E-05	2.33E-05
EFEMP2	-1.115	6.47E-06	6.47E-06
SGSH	-1.114	0.0141	0.0141
NCF1B	-1.112	1.14E-05	1.14E-05
PEAR1	-1.111	0.001386	0.001386
RASL11A	-1.108	0.0002425	0.0002425
HOXC10	-1.095	0.02029	0.02029

ZRANB3	-1.09	6.35E-06	6.35E-06
B3GNT9	-1.088	0.0001692	0.0001692
HSD11B1	-1.079	4.12E-08	4.12E-08
OLIG2	-1.078	1.21E-05	1.21E-05
MYO7B	-1.074	0.005325	0.005325
ATP2B3	-1.067	0.001907	0.001907
GGT1	-1.058	4.40E-08	4.40E-08
LYNX1	-1.049	0.006992	0.006992
PTCRA	-1.045	0.003054	0.003054
LOC101929771	-1.044	0.006373	0.006373
LOC102467222	-1.043	0.02166	0.02166
FMO4	-1.041	4.20E-05	4.20E-05
RAB7B	-1.038	7.48E-08	7.48E-08
WNT7B	-1.032	1.12E-07	1.12E-07
UNC5C	-1.032	0.000101	0.000101
THBS1	-1.03	0.003111	0.003111
OAF	-1.026	6.79E-09	6.79E-09
CLIC5	-1.026	0.003755	0.003755
ROPN1L	-1.025	0.004848	0.004848
EPPK1	-1.023	0.00705	0.00705
MPZ	-1.019	3.10E-05	3.10E-05
HIST1H1C	-1.017	0.000323	0.000323
TUBB3	-1.016	0.001204	0.001204
KIF26A	-1.014	0.0005932	0.0005932
DZIP1	-1.013	4.23E-06	4.23E-06
PPAPDC3	-1.008	0.0002983	0.0002983
DCANP1	-1.004	1.36E-06	1.36E-06

Table 7. Differentially expressed genes in IRAK1-KO, IRAK4-KO, and IRAK1/4-dKO vs WT THP1 cells

IRAK1-KO (- MyD88KO) vs WT	IRAK4-KO (- MyD88KO) vs WT	IRAK1/4-dKO (- MyD88KO) vs WT
SLC2A10	FOXF1	PLS3
DMTN	LOC339862	HSBP1L1
LOC101926931	LYSMD1	CDC42BPA
RLTPR	MSRB3	PPP2R3A
ATP10A	PPP1R3F	GNG12
IRAK1	SNORA24	PENK
CNTN4	SNORD22	STC2
UST	SNORD76	DNAJC22

RNF165	ZNF320	SH3D19
PLEKHG5	ZNF572	GABRD
ITGB2-AS1	PCDHGA12	RAVER2
NCF1C	IFIT1	ARHGEF26
ANKRD37	SEPP1	APBB2
MARCH9	TRIM22	BAI2
LY9	RNF175	DPEP1
NGEF	EGR1	LGI2
TBX15	SETD6	PIP5K1A
SNORD116-4	TTC33	SOX18
RP5-1057J7.6	SNORA73A	BMP4
HIVEP1	IFITM1	TMC4
NTN1	FAM35BP	KCNIP3
TBX1	IFIT5	CCNO
DLEU7-AS1	PYROXD1	ULK4P2
KIAA1147	MED21	FAM57A
THBS1	FGFR1OP2	SCARA3
CDO1	RP11-996F15.2	CERS1
MEGF6	LOC441666	BEND5
NCF1	ERGIC2	HAPLN3
TG	LDHB	DNMBP
DLL1	PAWR	KIAA1522
GJC1	CDK1	PIR
IPW	KCNS1	GTF3C5
ZFP92	IFIT2	ECHDC3
IL4I1	SIGLEC1	ICAM1
RAB33A	TWF1	RAB3A
ADAMTS4	STK38L	SDHA
MYLIP	PTPRO	C9orf116
WNT10B	RP11-12A2.3	MKI67
RIMKLA	CUTC	LMTK3
TTC30A	RUFY2	MCM10
FHL3	ZNF485	ADM2
CD300A	ATP5C1	HSD17B14
AP000330.8	RECQL	LOC102724002
C17orf96	ETNK1	KCNH2
CAND2	MEIS3	PRAME
TNFAIP3	OAT	KIAA1279
NMUR1	BMI1	LOC101929974
PTK7	DDX50	ARHGAP21

FOXF1	LOC728819	SULT2B1
LOC339862	UNC80	ADCY6
LYSMD1	FLJ37035	GBF1
MSRB3	SUB1	TUBGCP2
PPP1R3F	LOC728407	CD19
SNORA24	CHCHD1	SPIRE2
SNORD22	LOC100130992	SH3PXD2B
SNORD76	PDSS1	AADAT
ANXA4	NSMCE4A	FOXC1
APLN	CCDC91	ZBED3
C1QL4	LOC101928524	TSKU
CCDC102A	C5orf28	NRARP
CHDH	PPHLN1	AMIGO2
EGLN3	KIAA1551	PCBD1
ENO2	RNLS	TCAM1P
FADS2	NEXN	FAM57B
HK2	TRDMT1	LOC101929021
HSPA7	SDC2	PCK2
IL17RB	RPS24	CCDC127
KLF2	CWF19L1	MGMT
LAMC3	CASC5	C6orf147
LINC00263	HHEX	TGFB1I1
LOC101928092	RASSF8	DPP4
LOC102724908	TIMM23	ALX4
MIR210HG	BMS1P6	TACC2
NRTN	HSPA14	WLS
PFKFB4	ZNF25	PACSIN3
SCD	CEP70	NAPA-AS1
SLC4A3	ZNF131	LINC00999
SLC6A8	MUC19	BAIAP3
ZNF215	LRRC17	ANKH
ZNF395	SNORD44	VDAC2
ADM	ZFR	TAF3
ALDOC	CCDC7	ECHS1
BNIP3	ZNF98	EFNA3
CA3	SLC2A13	CORO6
CD209	CPNE8	TCTN2
CSMD3	RPL37	HPS1
DDIT4	DNA2	DNAJB12
FCGR2B	NEGR1	SPIB

FCGR2C	ZNF32	SLC29A3
FIGN	FAM45B	PHGDH
GLIS2	ZNF33B	PTMS
SHISA8	CHUK	TMEM91
SOX5	PCGF6	SEC24C
TBC1D30	METTL10	HGD
TLE6	ZNF22	MSS51
TLX1	IPMK	TEAD3
VAT1L	PTER	LARP4B
VEGFA	IFIT3	ZCCHC24
	SLC7A11	ARHGEF16
	GHITM	FOXO6
	ATAD1	FBXO18
	BCCIP	PPRC1
	CRIP2	CCDC78
	CADM1	RHBDL1
	USMG5	SPINT1
	KIF20B	STON2
	ZFAND4	NUDT8
	C10orf55	NEBL
	SLC38A2	EPAS1
	ANKRD26P3	FAM178A
	DNAJC9	PI4K2A
	MRPL36	SNED1
	NELL2	STAM
	ENTPD1-AS1	PLOD2
	SLK	TM7SF2
	TIGD3	FGD1
	HPS6	PCDHB6
	RP11-454P21.1	CCNB3
	ARID2	MCMD2C2
	PARPBP	EDRF1
	DNAJC21	NRM
	GPER1	PPIF
	ARHGAP12	ATF5
	BBIP1	BRD9
	BMPR1A	B3GALT4
	KIN	NET1
	WBP1L	TMEM169
	TRUB1	RPH3AL

	SNHG19	DROSHA
	ZNF506	RBMS2
	ANKRD26	POLR3A
	SFXN4	TRIP13
	EPC1	LPHN1
	HTR7	ZMIZ1
	YAF2	RP11-344B5.2
	FBXL15	HNRNPF
	RGS10	HSD17B7P2
	RPL36A	SLIT1
	BRIX1	LOC648987
	COMMD3	ACTR1A
	SHOC2	CCT5
	C5orf34	S1PR5
	CEP55	WDFY4
	TOMM40L	GRK5
	PRPF18	SREBF1
	MAP3K8	STXBP5L
	PYROXD2	VAR52
	SLC35G1	GAB2
	AMN1	ZFP36L1
	CREM	CPNE7
	BIK	HSPA2
	ZNF439	NAT8L
	GDI2	DOK4
	LOC101060181	IGF1R
	ALG10	KHK
	RPL41	KIRREL2
	EXOSC1	COMTD1
	FAIM	ZNF488
	GLRX3	CASC10
	FAM35A	QRICH2
	LMBRD2	RBM17
	CDC123	LSS
	LOC102724168	PAX8
	BUB3	PKN3
	NCOA4	HELLS
	VPS26A	FN3K
	RP11-134O21.1	CDC42EP1
	NOC3L	NFIX

	SUMO1P3	BMS1
	EXOC6	STOX1
	UPF2	SEMA4B
	VIM-AS1	SUPV3L1
	FAM173B	FAM198A
	RPP30	RCOR2
	FAM160B1	PDCD4
	ZNF432	PPAP2A
	ZNF487	DDX12P
	LINC00843	ACY3
	BMS1P4	TSPAN10
	CUL2	NUP155
	MNAT1	RIBC2
	BLOC1S2	PLCXD1
	ANAPC16	TP53INP2
	AVPI1	GOLPH3
	METRNL	WDR70
	WHAMMP2	BTRC
	FRAT2	SVIL
	RAB18	DTX4
	CCL28	DUSP5
	LCOR	ECE1
	DACH1	MRPL43
	ARL3	SKP2
	SOX4	SNHG3
	TMEM117	MYRF
	GAL	ZFYVE27
	NFYB	H2AFY2
	ADK	NOLC1
	PRDX3	SLC25A28
	NUP107	WNK2
	WAPAL	NDUFS6
	DCLRE1C	SLC30A3
	SUV39H2	LOC642846
	ARL5B	NEURL1B
	FAR2	ARMC4
	HLA-DPA1	SFXN3
	ZNF37BP	VASH2
	RP11-119F19.2	NOTUM
	AGAP6	VCL

	ABI1	LOC100506901
	TNKS2	CSTF2T
	ACBD5	PRICKLE1
	DNAJC1	ZNF132
	EIF3C	GPR153
	NCKAP5L	ZMYND11
	GSTO1	DGCR5
	SMC3	OXER1
	PPOX	VTI1A
	TBK1	PCDHGC3
	NSUN6	MORC4
	ZNF816	EIF3A
	ADM	PDCD11
	ALDOC	SLC38A1
	BNIP3	MC1R
	CA3	CBS
	CD209	AC002454.1
	CSMD3	PDCD6
	DDIT4	B4GALNT1
	FCGR2B	RPP38
	FCGR2C	SUGT1P1
	FIGN	NEDD4L
	GLIS2	PROCA1
	SHISA8	SH3PXD2A
	SOX5	JAG2
	TBC1D30	FGFR3
	TLE6	TMEM191B
	TLX1	SEPHS1
	VAT1L	LOC100505761
	VEGFA	C21orf58
	AASS	FADS1
	ABCC6P1	TET1
	ABCD2	GBGT1
	ADAMTS14	KAT6B
	AGAP4	KIFC2
	AGAP9	TAF5
	AIFM2	CASP7
	AKR1C1	PELI3
	AKR1E2	PP7080
	ANK3	ATN1

	ANKRD33B	KIAA1598
	ANO6	FAM115A
	APBB1IP	NKX3-2
	ARHGAP19	CHCHD10
	ARNTL2	GPSM1
	ARSG	LRP4
	ARTN	CDT1
	ASCC1	EIF4EBP2
	ASUN	AASS
	BAG3	ABCC6P1
	BEND4	ABCD2
	BEX5	ADAMTS14
	BLNK	AGAP4
	BTAF1	AGAP9
	C10orf10	AIFM2
	C10orf12	AKR1C1
	C10orf76	AKR1E2
	C10orf91	ANK3
	C15orf38	ANKRD33B
	C2CD4C	ANO6
	C2CD5	APBB1IP
	C3orf18	ARHGAP19
	CALHM2	ARNTL2
	CAMK1D	ARSG
	CAPRIN2	ARTN
	CDH2	ASCC1
	CDHR1	ASUN
	CEL	BAG3
	CEP72	BEND4
	CES3	BEX5
	CES4A	BLNK
	CHST3	BTAF1
	CLIC5	C10orf10
	CMAS	C10orf12
	CNNM2	C10orf76
	CNTN1	C10orf91
	COL27A1	C15orf38
	COL4A5	C2CD4C
	CPS1	C2CD5
	CRABP1	C3orf18

	CTBP2	CALHM2
	CUEDC2	CAMK1D
	CXorf57	CAPRIN2
	DAPK2	CDH2
	DDAH2	CDHR1
	DDX11	CEL
	DDX11-AS1	CEP72
	DENND5B	CES3
	DHTKD1	CES4A
	DNM1L	CHST3
	DPCD	CLIC5
	DPY19L2	CMAS
	DUSP5P1	CNNM2
	EBF3	CNTN1
	EFEMP2	COL27A1
	EGFR	COL4A5
	ELK1	CPS1
	EPHB4	CRABP1
	FAM155B	CTBP2
	FAM175B	CUEDC2
	FAM21C	CXorf57
	FAM45A	DAPK2
	FAM53B	DDAH2
	FAM84B	DDX11
	FCER2	DDX11-AS1
	FGD4	DENND5B
	FOXL2	DHTKD1
	FZD8	DNM1L
	GAS1	DPCD
	GPC6	DPY19L2
	GRIA3	DUSP5P1
	GUCY1B3	EBF3
	GYPE	EFEMP2
	HDHD3	EGFR
	HES4	ELK1
	HIF1AN	EPHB4
	HMGCS1	FAM155B
	HMX2	FAM175B
	HMX3	FAM21C
	HOXB13	FAM45A

	HOXB6	FAM53B
	HSD17B8	FAM84B
	HSH2D	FCER2
	IDE	FGD4
	INPP5A	FOXL2
	INPP5F	FZD8
	INPP5J	GAS1
	IPO8	GPC6
	IRAK4	GRIA3
	ITPR2	GUCY1B3
	ITPR3	GYPE
	JMJD1C	HDHD3
	KAZALD1	HES4
	KCNQ5	HIF1AN
	KCNS3	HMGCS1
	KIAA1324	HMX2
	KIF11	HMX3
	KLHL42	HOXB13
	KLLN	HOXB6
	KRAS	HSD17B8
	KREMEN2	HSH2D
	LAT	IDE
	LDB1	INPP5A
	LGALS3BP	INPP5F
	LINC00477	INPP5J
	LIPE	IPO8
	LOC100288152	IRAK4
	LOC100506688	ITPR2
	LOC100506691	ITPR3
	LOC100507487	JMJD1C
	LOC101927104	KAZALD1
	LOC101927799	KCNQ5
	LOC101928913	KCNS3
	LOC102723337	KIAA1324
	LOC102724472	KIF11
	LPCAT1	KLHL42
	LRMP	KLLN
	LRRC10B	KRAS
	LRRC20	KREMEN2
	LRRC27	LAT

	LTK	LDB1
	LY6G5C	LGALS3BP
	LZTS2	LINC00477
	MAP2K6	LIPE
	MASTL	LOC100288152
	MCIDAS	LOC100506688
	MCMBP	LOC100506691
	MDGA2	LOC100507487
	METTL12	LOC101927104
	METTL20	LOC101927799
	MMS19	LOC101928913
	MPPED2	LOC102723337
	MRPS16	LOC102724472
	MRPS35	LPCAT1
	MSX1	LRMP
	MX1	LRRC10B
	NDUFB8	LRRC20
	NEURL1	LRRC27
	NEUROG3	LTK
	NFKB2	LY6G5C
	NIM1K	LZTS2
	NKD2	MAP2K6
	NLGN2	MASTL
	NNT	MCIDAS
	NNT-AS1	MCMBP
	NT5DC2	MDGA2
	NUDT13	METTL12
	OGDHL	METTL20
	OVOL2	MMS19
	OXCT1	MPPED2
	P2RX7	MRPS16
	P4HA1	MRPS35
	PABPC1L	MSX1
	PANK1	MX1
	PAOX	NDUFB8
	PAPD7	NEURL1
	PAPSS2	NEUROG3
	PCDHB13	NFKB2
	PCDHB14	NIM1K
	PCED1B	NKD2

	PCED1B-AS1	NLGN2
	PCSK5	NNT
	PDLIM1	NNT-AS1
	PEAR1	NT5DC2
	PFKP	NUDT13
	PGAM1	OGDHL
	PGAM4	OVOL2
	PI15	OXCT1
	PITX1	P2RX7
	PLEKHA8P1	P4HA1
	PLEKHO1	PABPC1L
	PPFIBP1	PANK1
	PPP2R2D	PAOX
	PPP3CB	PAPD7
	PRTFDC1	PAPSS2
	PSTPIP2	PCDHB13
	PTENP1	PCDHB14
	PVRL3	PCED1B
	PWWP2B	PCED1B-AS1
	PXDC1	PCSK5
	RNF208	PDLIM1
	ROBO1	PEAR1
	RP11-184I16.4	PFKP
	RP11-53O19.1	PGAM1
	RP11-96H19.1	PGAM4
	RPAP3	PI15
	RTN1	PITX1
	SAMD11	PLEKHA8P1
	SAMD8	PLEKHO1
	SCAF11	PPFIBP1
	SCD5	PPP2R2D
	SDHAP3	PPP3CB
	SEC14L2	PRTFDC1
	SEC31B	PSTPIP2
	SEC61A2	PTENP1
	SECTM1	PVRL3
	SFMBT2	PWWP2B
	SFXN2	PXDC1
	SHANK3	RNF208
	SHISA3	ROBO1

	SHISA7	RP11-184I16.4
	SIDT1	RP11-53O19.1
	SKIDA1	RP11-96H19.1
	SLA2	RPAP3
	SLC12A7	RTN1
	SLC16A6	SAMD11
	SLC16A9	SAMD8
	SLC4A11	SCAF11
	SLITRK5	SCD5
	SMAD1	SDHAP3
	SNHG12	SEC14L2
	SNORA61	SEC31B
	SNORD104	SEC61A2
	SOX1	SECTM1
	SPEF2	SFMBT2
	SRRM3	SFXN2
	SUFU	SHANK3
	TARS	SHISA3
	TCF7	SHISA7
	TEX15	SIDT1
	TGFBR3L	SKIDA1
	THBD	SLA2
	TIAL1	SLC12A7
	TLX3	SLC16A6
	TM7SF3	SLC16A9
	TMEM180	SLC4A11
	TMEM191C	SLITRK5
	TMEM255A	SMAD1
	TMEM63C	SNHG12
	TRIM72	SNORA61
	TUBB3	SNORD104
	TYSND1	SOX1
	UGT3A2	SPEF2
	ULK2	SRRM3
	UNC13D	SUFU
	USP54	TARS
	VENTX	TCF7
	VIM	TEX15
	XPNPEP1	TGFBR3L
	YARS2	THBD

	YPEL3	TIAL1
	ZDHHC16	TLX3
	ZDHHC6	TM7SF3
	ZNF43	TMEM180
	ZNF438	TMEM191C
	ZNF503	TMEM255A
	ZNF503-AS2	TMEM63C
	ZNF511	TRIM72
	ZNF574	TUBB3
	ZNF622	TYSND1
	ZNF726	UGT3A2
	ZNF99	ULK2
	ZWINT	UNC13D
		USP54
		VENTX
		VIM
		XPNPEP1
		YARS2
		YPEL3
		ZDHHC16
		ZDHHC6
		ZNF43
		ZNF438
		ZNF503
		ZNF503-AS2
		ZNF511
		ZNF574
		ZNF622
		ZNF726
		ZNF99
		ZWINT
		ADM
		ALDOC
		BNIP3
		CA3
		CD209
		CSMD3
		DDIT4
		FCGR2B
		FCGR2C

	FIGN
	GLIS2
	SHISA8
	SOX5
	TBC1D30
	TLE6
	TLX1
	VAT1L
	VEGFA
	ANXA4
	APLN
	C1QL4
	CCDC102A
	CHDH
	EGLN3
	ENO2
	FADS2
	HK2
	HSPA7
	IL17RB
	KLF2
	LAMC3
	LINC00263
	LOC101928092
	LOC102724908
	MIR210HG
	NRTN
	PFKFB4
	SCD
	SLC4A3
	SLC6A8
	ZNF215
	ZNF395

Table 8. IRAK1 proximity analysis

Accession	Gene Symbol	Abundance Ratio P-Value: (DOX) / (NO DOX)	Coverage %	# Peptides	# Unique Peptides	# AAs
Q9UNX3	RPL26L1	1E-17	45	12	1	145

Q9BZI7	UPF3B	1E-17	10	5	5	483
Q5F1R6	DNAJC21	1E-17	6	2	2	531
O15156	ZBTB7B	1E-17	10	2	2	539
P62745	RHOB	1E-17	17	2	1	196
Q9NRX1	PNO1	1E-17	13	2	2	252
P62316	SNRPD2	1E-17	17	2	2	118
Q9HCK8	CHD8	1E-17	2	3	3	2581
P12931	SRC	1E-17	13	6	5	536
Q12874	SF3A3	1E-17	4	2	2	501
O15294	OGT	1E-17	4	2	2	1046
Q03252	LMNB2	1E-17	7	5	1	620
Q9H0G5	NSRP1	1E-17	5	2	2	558
Q14213	EBI3	1E-17	8	2	2	229
P06400	RB1	1E-17	5	2	2	928
P52209	PGD	1E-17	8	3	3	483
Q8IY21	DDX60	1E-17	2	2	2	1712
Q86TB9	PATL1	1E-17	4	2	2	770
Q13325	IFIT5	1E-17	6	2	2	482
O15533	TAPBP	1E-17	7	3	3	448
A6NC98	CCDC88B	1E-17	2	2	2	1476
Q14847	LASP1	1E-17	10	2	2	261
P32456	GBP2	1E-17	5	2	1	591
Q9Y6W5	WASF2	1E-17	8	3	3	498
P34897	SHMT2	1E-17	4	2	2	504
P01859	IGHG2	1E-17	6	2	2	326
Q96C10	DHX58	1E-17	7	3	3	678
O43432	EIF4G3	1E-17	2	3	1	1585
P43304	GPD2	1E-17	3	2	2	727
O76031	CLPX	1E-17	4	2	2	633
Q01201	RELB	1E-17	10	3	3	579
Q8WYG1	RSAD2	1E-17	6	2	2	361
P67936	TPM4	1E-17	20	8	1	248
P09913	IFIT2	1E-17	15	5	5	472
Q16851	UGP2	1E-17	7	3	3	508
Q96PP9	GBP4	1E-17	5	2	2	640
P12273	PIP	1E-17	26	3	3	146
Q05209	PTPN12	1E-17	6	4	4	780
P35637	FUS	5.46331E-08	8	2	2	526
Q8IYM9	TRIM22	1.92275E-07	10	3	3	498
P61020	RAB5B	3.5903E-07	11	2	1	215

Q8TCB0	IFI44	1.89051E-11	9	3	3	444
P20839	IMPDH1	3.79633E-06	4	2	1	514
P13010	XRCC5	5.06599E-07	11	7	7	732
O15553	MEFV	7.96312E-06	8	4	4	781
O75934	BCAS2	4.01812E-05	24	3	3	225
P20592	MX2	8.82965E-09	39	23	20	715
Q9UHI6	DDX20	8.65309E-05	4	2	2	824
P05161	ISG15	5.43721E-08	37	6	6	165
O14776	TCERG1	0.000167061	3	3	3	1098
Q00653	NFKB2	4.3569E-07	19	11	11	900
Q16666	IFI16	3.01838E-07	27	18	18	785
P09914	IFIT1	4.72041E-07	46	21	21	478
O43290	SART1	1.2262E-06	47	32	32	800
P52630	STAT2	0.000799226	16	8	1	851
P20591	MX1	4.10551E-06	39	18	15	662
P04075	ALDOA	4.75671E-06	68	23	21	364
O95786	DDX58	1.02707E-06	9	5	5	925
Q9Y6K5	OAS3	1.61709E-05	31	29	29	1087
Q6ZUJ8	PIK3AP1	2.0602E-05	7	4	4	805
Q9UII4	HERC5	4.36447E-05	12	10	10	1024
P09972	ALDOC	3.24465E-05	23	6	4	364
P00973	OAS1	3.25013E-05	24	7	7	400
Q15646	OASL	6.29209E-05	41	16	16	514
P29728	OAS2	6.54454E-05	38	22	22	719
Q5EBM0	CMPK2	7.62999E-05	38	10	10	449
P14598	NCF1	7.74292E-05	48	14	14	390
O14933	UBE2L6	4.15319E-05	53	5	5	153
Q03169	TNFAIP2	5.10857E-05	13	5	5	654
P43490	NAMPT	0.000224384	27	9	9	491
Q9H3U1-2	UNC45A	0.010093224	5	3	3	929
Q13459	MYO9B	0.008865095	2	3	3	2157
P49005	POLD2	0.001568171	6	2	2	469
P29508	SERPINB3	0.008370477	10	4	2	390
P19474	TRIM21	0.000197083	9	4	4	475
Q96GA3	LTV1	0.000423566	27	12	12	475
P01889	HLA-B	0.000257974	20	5	3	362
Q9UGU5	HMGXB4	0.000344271	8	3	3	601
Q9UNM6	PSMD13	0.012034188	5	2	2	376
P42224	STAT1	0.000826917	48	35	35	750
Q96F86	EDC3	0.0183807	8	2	2	508

P61158	ACTR3	0.000548364	18	4	4	418
P06753-2	TPM3	0.001083333	46	15	8	248
Q8IXQ6	PARP9	0.000767085	13	8	8	854
O14602	EIF1AY	0.008309349	34	4	1	144
Q06830	PRDX1	0.001616614	76	18	14	199
P23381	WARS1	0.001448813	26	7	7	471
Q53G44	IFI44L	0.001911125	13	5	5	452
P32455	GBP1	0.002863221	10	4	3	592
P29692	EEF1D	0.002729569	33	7	7	281
P18615	NELFE	0.006030419	16	4	4	380
Q5K651	SAMD9	0.003578333	10	11	11	1589
Q8TDB6	DTX3L	0.003023628	17	10	10	740
P21127-2	CDK11B	0.004033685	38	37	4	782
P02042	HBD	0.005972218	18	2	2	147
P28838-2	LAP3	0.004820651	51	20	20	488
Q7Z417	NUFIP2	0.004491528	3	2	2	695
Q9Y2L1	DIS3	0.003198292	4	3	3	958
Q5JTH9	RRP12	0.005569554	33	33	33	1297
P32119	PRDX2	0.005593423	30	8	7	198
Q8IY81	FTSJ3	0.005673391	21	14	14	847
Q9UMW8	USP18	0.005063384	15	4	4	372
Q03518	TAP1	0.006299787	21	11	11	808
Q9ULV4	CORO1C	0.003578922	10	4	4	474
Q5TEJ8	THEMIS2	0.006840208	22	9	9	643
P19525	EIF2AK2	0.007435898	28	14	14	551
P55072	VCP	0.008147169	33	19	19	806
P40763	STAT3	0.009533038	15	8	8	770
Q969Q0	RPL36AL	0.009644425	45	9	2	106
P19878	NCF2	0.011737652	22	8	8	526
Q03519	TAP2	0.010916847	16	10	9	686
Q13263	TRIM28	0.008464859	6	2	2	835
P53004	BLVRA	0.01020831	26	6	6	296
Q63HN8	RNF213	0.012908625	15	60	60	5207
Q9NUQ6	SPATS2L	0.015785522	5	2	2	558
O95573	ACSL3	0.01823123	18	10	7	720
P52630-4	STAT2	0.014461363	16	8	1	847
P23469	PTPRE	0.010471086	7	4	4	700
P11021	HSPA5	0.01598158	42	26	24	654
Q8WWY3	PRPF31	0.010184287	6	2	2	499
Q9HB71	CACYBP	0.01733789	29	5	5	228

P62314	SNRPD1	0.017580861	28	3	3	119
P29466	CASP1	0.013091491	6	3	3	404
P55265	ADAR	0.02000974	7	7	7	1226
Q14498-2	RBM39	0.021078052	41	16	15	524
P08195	SLC3A2	0.027303718	4	2	2	630
Q6UN15	FIP1L1	0.025502679	35	15	15	594
P08621	SNRNP70	0.027868718	36	22	22	437
Q99459	CDC5L	0.028005395	44	29	29	802
P40121	CAPG	0.032783975	7	2	2	348
P12814	ACTN1	0.0325762	42	31	20	892
Q68CZ2	TNS3	0.027467904	5	4	4	1445
P47756-2	CAPZB	0.040814508	23	5	5	272
Q8WUM0	NUP133	0.045793019	3	3	3	1156
P78344	EIF4G2	0.037068288	5	4	4	907
Q66K74	MAP1S	0.027302343	6	4	4	1059
Q01518	CAP1	0.037763487	71	37	1	475
P08574	CYC1	0.041967876	4	2	2	325
Q14562	DHX8	0.039470256	31	28	27	1220
P09543	CNP	0.040997192	26	8	8	421
Q9ULA0	DNPEP	0.041163727	5	2	2	485
O43707	ACTN4	0.045025658	35	25	14	911
Q9P2R7	SUCLA2	0.036762317	7	3	3	463

Table 9. IRAK4 proximity analysis

Accession	Gene Symbol	Abundance Ratio P-Value: (DOX) / (NO DOX)	Coverage %	# Peptides	# Unique Peptides	# AAs
Q13509	TUBB3	1E-17	34	15	1	450
P35580	MYH10	1E-17	15	30	7	1976
Q58FF8	HSP90AB2P	1E-17	25	10	1	381
P63000	RAC1	1E-17	35	8	3	192
Q9H9B4	SFXN1	1E-17	26	6	5	322
Q9UBM7	DHCR7	1E-17	4	2	2	475
P29350-2	PTPN6	1E-17	58	29	1	556
P84085	ARF5	1E-17	22	3	2	180
P62633	CNBP	1E-17	20	3	3	177
P15311	EZR	1E-17	14	8	3	586
Q14166	TTL12	1E-17	12	5	5	644
P84095	RHOG	1E-17	52	7	6	191

P60953	CDC42	1E-17	20	3	2	191
P48047	ATP5PO	1E-17	16	3	3	213
Q13363	CTBP1	1E-17	19	5	5	440
Q14004	CDK13	1E-17	3	3	2	1512
Q00535	CDK5	1E-17	14	5	4	292
Q13630	GFUS	1E-17	8	2	2	321
P16402	H1-3	1E-17	12	2	2	221
P56192	MARS1	1E-17	4	3	3	900
Q14847	LASP1	1E-17	10	2	2	261
P19338	NCL	1E-17	5	3	3	710
Q15418	RPS6KA1	1E-17	7	5	5	735
P08754	GNAI3	1E-17	7	3	1	354
O94973	AP2A2	1E-17	13	11	3	939
Q14344	GNA13	1E-17	10	3	2	377
P54577	YARS1	1E-17	5	2	2	528
Q13057	COASY	1E-17	9	4	4	564
Q9BXW7	HDHD5	1E-17	10	3	3	423
Q9UMR2	DDX19B	1E-17	4	2	2	479
Q15149	PLEC	1E-17	3	10	10	4684
P49588	AARS1	1E-17	3	2	2	968
Q9Y3A5	SBDS	1E-17	7	2	2	250
Q92945	KHSRP	1E-17	3	2	2	711
Q13045	FLII	1E-17	13	13	1	1269
Q6XQN6	NAPRT	1E-17	6	3	3	538
P60981	DSTN	1E-17	15	3	1	165
Q9NVI7	ATAD3A	1E-17	7	4	4	634
O15260	SURF4	1E-17	19	4	4	269
Q9BU23	LMF2	1E-17	3	2	2	707
P54819	AK2	1E-17	7	2	2	239
P00966	ASS1	1E-17	16	6	6	412
O00148	DDX39A	1E-17	23	12	1	427
Q92608	DOCK2	1E-17	13	19	19	1830
P61006	RAB8A	1E-17	15	4	1	207
P46977	STT3A	1E-17	6	5	4	705
Q9BW92	TARS2	1E-17	5	3	2	718
P45880	VDAC2	1E-17	12	3	3	294
P07954	FH	1E-17	13	5	5	510
P11166	SLC2A1	1E-17	6	3	3	492
O00303	EIF3F	1E-17	18	5	5	357
O43396	TXNL1	1E-17	10	2	2	289

O00203	AP3B1	1E-17	15	15	15	1094
P52294	KPNA1	1E-17	7	3	2	538
O95758-1	PTBP3	1E-17	8	4	1	521
P62495	ETF1	1E-17	6	3	3	437
O14920	IKBKB	1E-17	6	4	4	756
Q7Z7A4	PXK	1E-17	10	4	4	578
Q709C8	VPS13C	1E-17	1	2	2	3753
Q9BUN8	DERL1	1E-17	8	2	2	251
P31689	DNAJA1	1E-17	12	4	4	397
Q8N766	EMC1	1E-17	3	2	2	993
Q9HCG8	CWC22	1E-17	17	15	15	908
O95232	LUC7L3	1E-17	29	10	10	432
Q9BQ39	DDX50	1E-17	12	6	5	737
Q96AA3	RFT1	1E-17	3	2	2	541
Q8IX19	MCEMP1	1E-17	11	2	2	187
P55884	EIF3B	1E-17	3	2	2	814
Q9BR76	CORO1B	1E-17	6	2	2	489
O95197	RTN3	1E-17	3	5	5	1032
Q9NPI1	BRD7	1E-17	13	4	4	651
Q9UGP8	SEC63	1E-17	14	10	10	760
Q8WVX9	FAR1	1E-17	7	3	3	515
A6NDG6	PGP	1E-17	10	3	3	321
O75683	SURF6	1E-17	10	3	3	361
Q9Y6V7	DDX49	1E-17	12	4	4	483
Q09161	NCBP1	1E-17	9	4	4	790
P13861	PRKAR2A	1E-17	7	2	2	404
P19784	CSNK2A2	1E-17	12	4	4	350
O95218	ZRANB2	1E-17	12	3	3	330
O75396		1E-17	16	3	3	215
Q02241	KIF23	1E-17	3	2	2	960
Q9Y265	RUVBL1	1E-17	12	4	4	456
Q8N3C0	ASCC3	1E-17	5	7	7	2202
P53992	SEC24C	1E-17	3	2	2	1094
P85037	FOXK1	1E-17	2	2	2	733
O00743	PPP6C	1E-17	11	3	3	305
Q7L2E3	DHX30	1E-17	18	16	16	1194
Q9UMS6	SYNPO2	1E-17	2	3	3	1093
Q9BUK6	MSTO1	1E-17	4	2	2	570
P08134	RHOC	1E-17	46	6	2	193
P27361	MAPK3	1E-17	6	2	2	379

Q9NW13	RBM28	1E-17	5	2	2	759
P22681	CBL	1E-17	12	8	8	906
Q9UNQ2	DIMT1	1E-17	14	3	3	313
Q9NQZ2	UTP3	1E-17	23	8	8	479
Q99447	PCYT2	1E-17	11	3	3	389
P43243	MATR3	1E-17	14	7	7	847
Q13206	DDX10	1E-17	7	5	5	875
Q96L92	SNX27	1E-17	3	2	2	541
Q13155	AIMP2	1E-17	5	2	2	320
O60762	DPM1	1E-17	19	3	3	260
P13498	CYBA	1E-17	13	2	2	195
P62993	GRB2	1E-17	17	2	2	217
Q9BXP5	SRRT	1E-17	2	2	2	876
Q5JVF3	PCID2	1E-17	9	2	2	399
Q14980	NUMA1	1E-17	3	4	4	2115
P36915	GNL1	1E-17	14	7	7	607
Q13464	ROCK1	1E-17	3	3	3	1354
P25398	RPS12	1E-17	36	3	3	132
Q05519	SRSF11	1E-17	15	5	5	484
P08574	CYC1	1E-17	4	2	2	325
O60315	ZEB2	1E-17	15	15	15	1214
P52907	CAPZA1	1E-17	14	3	3	286
Q99439	CNN2	1E-17	9	2	2	309
P28340	POLD1	1E-17	7	7	6	1107
Q16891	IMMT	1E-17	3	2	2	758
P62995	TRA2B	1E-17	27	6	6	288
Q9UJZ1	STOML2	1E-17	5	2	2	356
Q8N1F7	NUP93	1E-17	5	4	4	819
O14776	TCERG1	1E-17	3	4	4	1098
Q6PCB5	RSBN1L	1E-17	6	4	3	846
Q96JP5	ZFP91	1E-17	20	10	10	570
Q5T4S7	UBR4	1E-17	1	4	4	5183
O00186	STXBP3	1E-17	3	2	2	592
O95347	SMC2	1E-17	13	12	12	1197
Q9Y2T2	AP3M1	1E-17	15	5	5	418
P62195	PSMC5	1E-17	9	3	2	406
Q15382	RHEB	1E-17	13	2	2	184
O43809	NUDT21	1E-17	59	14	14	227
Q9P2R7	SUCLA2	1E-17	5	3	3	463
Q6P1X5	TAF2	1E-17	10	10	10	1199

P27105	STOM	1E-17	10	2	2	288
P78316	NOP14	1E-17	10	7	7	857
O95239	KIF4A	1E-17	2	3	3	1232
Q92769	HDAC2	1E-17	9	3	3	488
P49593	PPM1F	1E-17	8	2	2	454
Q9P0U4	CXXC1	1E-17	24	13	13	656
P63010	AP2B1	1E-17	9	6	4	937
Q14103	HNRNPD	1E-17	14	3	3	355
Q9NQ55	PPAN	1E-17	22	7	7	473
Q969V3	NCLN	1E-17	5	3	3	563
O15269	SPTLC1	1E-17	3	2	2	473
O60231	DHX16	1E-17	9	9	8	1041
Q15054	POLD3	1E-17	13	4	4	466
Q49A26	GLYR1	1E-17	9	4	4	553
Q96PU4	UHRF2	1E-17	5	3	2	802
Q8TEX9	IPO4	1E-17	5	3	3	1081
Q8TBB5	KLHDC4	1E-17	10	5	5	520
P52701	MSH6	1E-17	4	5	5	1360
Q99549	MPHOSPH8	1E-17	8	5	5	860
Q6P2Q9	PRPF8	1E-17	13	24	24	2335
O95373	IPO7	1E-17	8	6	6	1038
P62140	PPP1CB	1E-17	18	4	1	327
Q8WXX5	DNAJC9	1E-17	23	4	4	260
Q8WXA9-2	SREK1	1E-17	15	6	6	624
O95639	CPSF4	1E-17	23	4	4	269
Q9UBE0	SAE1	1E-17	10	2	2	346
Q9UNX4	WDR3	1E-17	12	7	7	943
Q9NQX3	GPHN	1E-17	3	2	2	736
Q93034	CUL5	1E-17	2	2	2	780
Q7L7X3	TAOK1	1E-17	18	16	11	1001
Q9NSD9	FARSB	1E-17	5	3	3	589
P36404	ARL2	1E-17	16	3	3	184
Q01433	AMPD2	1E-17	3	2	2	879
Q9Y2L1	DIS3	1E-17	5	4	4	958
Q9NVP1	DDX18	1E-17	19	9	9	670
P0DN79	CBS	1E-17	16	6	6	551
O75676	RPS6KA4	1E-17	2	2	2	772
O43491-4	EPB41L2	1E-17	13	8	7	852
Q12872	SFSWAP	1E-17	10	9	9	951
Q8IYB3	SRRM1	1E-17	15	12	12	904

O95352	ATG7	1E-17	8	5	5	703
Q92556	ELMO1	1E-17	3	2	1	727
P61962	DCAF7	1E-17	9	2	2	342
Q9Y383	LUC7L2	1E-17	44	18	12	392
O75534	CSDE1	1E-17	4	3	3	798
Q13111	CHAF1A	1E-17	15	9	9	956
Q9BQ70	TCF25	1E-17	8	3	3	676
Q8WUA2	PPIL4	1E-17	19	7	7	492
Q9UHI6	DDX20	1E-17	6	3	3	824
Q9H0C8	ILKAP	1E-17	15	4	4	392
O75694	NUP155	1E-17	4	4	4	1391
Q02880	TOP2B	1E-17	9	12	5	1626
Q86YP4	GATAD2A	1E-17	8	4	3	633
O15226	NKRF	1E-17	3	2	2	690
P26196	DDX6	1E-17	13	4	4	483
O00116	AGPS	1E-17	11	5	5	658
Q96KG9	SCYL1	1E-17	3	2	2	808
P11388	TOP2A	1E-17	19	24	17	1531
Q86VP6	CAND1	1E-17	10	9	9	1230
P46926	GNPDA1	1E-17	7	2	2	289
Q92620	DHX38	1E-17	22	22	22	1227
P27695	APEX1	1E-17	28	6	6	318
Q12769	NUP160	1E-17	2	2	2	1436
Q92621	NUP205	1E-17	5	5	5	2012
P51532	SMARCA4	1E-17	20	29	14	1647
Q5T280	SPOUT1	1E-17	22	6	6	376
Q4G0F5	VPS26B	1E-17	7	2	2	336
Q7Z2W4	ZC3HAV1	1E-17	21	14	14	902
Q14554	PDIA5	1E-17	14	6	6	519
Q9BY44	EIF2A	1E-17	12	6	6	585
Q1ED39	KNOP1	1E-17	5	2	2	458
P35998	PSMC2	1E-17	5	2	2	433
P19367	HK1	1E-17	3	2	2	917
P00390	GSR	1E-17	2	2	2	522
Q96EY4	TMA16	1E-17	26	5	5	203
Q9BRR9	ARHGAP9	1E-17	3	2	1	750
Q8N0V3	RBFA	1E-17	13	2	2	343
O43684	BUB3	1E-17	38	11	11	328
Q96AX1	VPS33A	1E-17	3	2	2	596
Q96GA3	LTV1	1E-17	24	10	10	475

Q9Y230	RUVBL2	1E-17	6	2	2	463
Q13131	PRKAA1	1E-17	3	2	2	559
Q2M2I8	AAK1	1E-17	8	5	4	961
Q13043	STK4	1E-17	5	2	2	487
P26639	TARS1	1E-17	7	4	3	723
Q13303	KCNAB2	1E-17	8	2	2	367
P28482	MAPK1	1E-17	7	2	2	360
Q9H2G2	SLK	1E-17	7	7	5	1235
Q9HD20	ATP13A1	1E-17	2	2	2	1204
P22234	PAICS	1E-17	14	5	5	425
P40121	CAPG	1E-17	11	3	3	348
Q5VWQ0	RSBN1	1E-17	6	5	4	802
P35236	PTPN7	1E-17	15	5	5	360
Q7LDG7	RASGRP2	1E-17	4	2	2	609
Q96T37	RBM15	1E-17	7	5	5	977
Q9ULA0	DNPEP	1E-17	5	2	2	485
P56182	RRP1	1E-17	25	10	10	461
Q13263	TRIM28	1E-17	2	2	2	835
P61160	ACTR2	1E-17	5	2	2	394
Q9ULV4	CORO1C	1E-17	7	3	3	474
Q13310	PABPC4	1E-17	6	4	4	644
Q16851	UGP2	1E-17	8	4	4	508
Q8WVM8	SCFD1	1E-17	9	4	4	642
Q5JTV8	TOR1AIP1	1E-17	15	7	7	583
P35232	PHB1	1E-17	12	3	3	272
Q96BI1	SLC22A18	1E-17	6	2	2	424
P19623	SRM	1E-17	8	2	2	302
Q9NTI5	PDS5B	1E-17	15	14	14	1447
P53999	SUB1	1E-17	19	2	2	127
Q9H2M9	RAB3GAP2	1E-17	2	3	3	1393
Q32MZ4	LRRFIP1	1E-17	8	6	6	808
Q12873	CHD3	1E-17	9	16	3	2000
P53618	COPB1	1E-17	15	10	10	953
Q10567		1E-17	6	4	2	949
P13807	GYS1	1E-17	5	3	3	737
P09543	CNP	1E-17	15	3	3	421
Q09666	AHNAK	1E-17	0	2	2	5890
O14980	XPO1	1E-17	3	3	3	1071
P29401	TKT	1E-17	6	3	3	623
Q15599	SLC9A3R2	1E-17	14	4	4	337

Q15910	EZH2	1E-17	5	4	4	746
P61009	SPCS3	1E-17	11	2	2	180
Q96AG4	LRRC59	1E-17	45	10	10	307
Q8WXF1	PSPC1	1E-17	8	2	2	523
Q9Y5L0	TNPO3	1E-17	8	5	5	923
Q9Y4W6	AFG3L2	1E-17	6	4	4	797
P54886	ALDH18A1	1E-17	7	4	4	795
Q14289	PTK2B	1E-17	4	3	3	1009
P32322	PYCR1	1E-17	31	6	5	319
Q92878	RAD50	1E-17	3	3	3	1312
P51148	RAB5C	1E-17	28	6	5	216
Q96GM8	TOE1	1E-17	12	4	4	510
Q9P2I0	CPSF2	1E-17	14	11	11	782
P50995	ANXA11	1E-17	3	2	2	505
A5YKK6	CNOT1	1E-17	1	2	2	2376
P0C7P4	UQCRFS1P1	1E-17	8	2	2	283
P30041	PRDX6	1E-17	40	8	8	224
P53004	BLVRA	1E-17	21	5	5	296
O95573	ACSL3	1E-17	5	2	1	720
O60488	ACSL4	1E-17	7	4	3	711
O75530	EED	1E-17	8	4	4	441
Q9BVJ6	UTP14A	1E-17	21	12	12	771
P54198	HIRA	1E-17	2	2	2	1017
Q96P47	AGAP3	1E-17	4	2	2	875
Q02447	SP3	1E-17	7	4	4	781
Q8TDN6	BRIX1	1E-17	16	4	4	353
Q9Y3D8	AK6	1E-17	20	3	3	172
P62136	PPP1CA	1E-17	22	5	2	330
Q15738	NSDHL	1E-17	6	2	2	373
Q9UBF2	COPG2	0.000125451	7	5	2	871
P04075	ALDOA	0.0001504	78	37	30	364
P47756	CAPZB	0.000935619	14	4	4	277
Q562R1	ACTBL2	0.006022582	28	12	2	376
O95819	MAP4K4	0.002133058	13	13	7	1239
P15498	VAV1	0.002357357	8	7	7	845
P62191	PSMC1	0.00283967	15	5	4	440
Q96GQ7	DDX27	0.009201485	22	19	19	796
Q15758	SLC1A5	0.016124136	4	2	2	541
P40763	STAT3	0.017905957	4	2	2	770
P31939	ATIC	0.005211795	19	8	8	592

Q13574	DGKZ	0.012216345	16	10	10	928
Q9UM00	TMCO1	0.007787056	15	3	3	239
Q8TCJ2	STT3B	0.009837064	17	14	13	826
Q9BSC4	NOL10	0.028620099	17	9	9	688
Q07955	SRSF1	0.013834443	31	6	6	248
Q13148	TARDBP	0.021125571	8	3	3	414
Q13151	HNRNPA0	0.016882416	17	3	3	305
P51531	SMARCA2	0.012775479	26	33	18	1590
P22694	PRKACB	0.019842981	9	3	3	351
Q9HB71	CACYBP	0.014701937	21	5	5	228
P62891	RPL39	0.015664591	24	2	2	51
Q9UG63	ABCF2	0.013275569	26	16	16	623
P19447	ERCC3	0.030161367	21	11	11	782
Q9H9T3	ELP3	0.049814787	12	6	6	547
P18085	ARF4	0.017307436	20	4	3	180
Q13557	CAMK2D	0.029339722	11	5	4	499
Q8NFC6	BOD1L1	0.033747268	2	5	5	3051
Q9Y6M1	IGF2BP2	0.024380007	17	7	7	599
Q9UKL3	CASP8AP2	0.037438365	3	5	5	1982
Q9NX58		0.043779567	44	20	20	379
P55160	NCKAP1L	0.039190631	6	5	5	1127
Q04917	YWHAH	0.041368367	13	4	1	246

Table 10. Differential ATAC-seq peaks in MyD88-KO vs WT THP1 cells

Genes near open peaks	Genes near closed peaks
HHAT	FLJ32255
DUSP12	LY6E
EXO1	ARID1B
CUX1	MIR153-2
CD93	MIR6071
SAXO1	EN2
ADAMTS9-AS2	VAV3
ANGPTL1	BMP4
TESC	MIR6774
NUDT16P1	C2orf48
CLNK	IFI27
TESC	LINC00870
BRINP2	LOC101927817
SEM1	GLDN

PLXNA2	RFK
ANKH	BRDT
CCDC60	
MIR3152	
LINC02422	
SLFN12	
IRF6	
ZNF536	
LINC01611	
SLC12A9	
ATP2B4	
MIR3124	
SHCBP1L	
HMX3	
PYY2	
SCN7A	
MIR548X2	
CNST	
PLXNA2	
XXYLT1-AS1	
HPS1	
TEX30	
LOC100131496	
SPAG16	
LINC02270	
TMCO5A	
LRRC52	
C11orf87	
ELOVL3	
MAF	
LOC100500773	
MIR326	
SOX17	
ST8SIA6	
ZIC4	
TENT5C	
ADAMTS9-AS2	
MIR4799	
CLDN10	
GPR148	

SMYD3	
ZNF536	
ZNF568	
DEGS1	
RGS1	
ZP3	
SPOCK1	
ZMAT4	
FMO1	
LINC02055	
GNB4	
UBASH3B	
LINC01395	
MIR802	
CD247	
CSMD3	
ADAMTS9	
MICA	
LOC285889	
ARL15	
SEC61G	
DGKI	
LOC101929882	
ZNF471	
OXR1	
FCGR2A	
HIF1AN	
LINC02032	
LOC101929331	
SEMA5B	
MTM1	
GTF3C4	
ZNF599	
GGT1	
MT1G	
ASMT	
LINC01370	
TAF4A1	
SMYD2	
LOC100379224	

DIXDC1	
FOXO6	
THRB	
ESYT3	
SLAMF6	
ARX	
RGS12	
LINC00971	
LINC01139	
STARD8	
TENT5A	
SMYD3	
ADAMTS9-AS1	
KCNJ10	
RBM46	
LOC339685	
MIR3654	
MIR9-3	
TEX30	
MYO16-AS1	
LOC100133091	
LOC101927082	
GNG4	
PROX1-AS1	
ZNF236-DT	
CHST15	
EQTN	
ANKFN1	
SPOCK1	
FBRSL1	
FAT1	
FAM49A	
GPBP1	
MIR548N	
LINC01435	
RBM47	
PLXNC1	
RPGRIP1	
ADAMTS9-AS1	
DACH2	

Table 11. Differential ATAC-seq peaks in IRAK1-KO, IRAK4-KO, and IRAK1/4-dKO vs WT THP1 cells

Down genes + Closed peaks			Up genes + Open peaks		
IRAK1-KO (- MyD88KO) vs WT	IRAK4-KO (- MyD88KO) vs WT	IRAK1/4-dKO (- MyD88KO) vs WT	IRAK1-KO (- MyD88KO) vs WT	IRAK4-KO (- MyD88KO) vs WT	IRAK1/4-dKO (- MyD88KO) vs WT
ANXA4	AKR1E2	ADAMTS14	CMBL	ABCC3	ABCC3
CA3	ALG10	AIFM2	SLC7A8	ABHD4	ADAMTS15
LOC339862	AMN1	AKR1E2	TMEM63C	ABI3	ALDH1A1
LY9	ANKRD33B	AMIGO2		ADAMTS15	ALOX5AP
PLEKHG5	ANO6	ANK3		ADRA2B	B3GNT5
RNF165	APBB1IP	ANKRD33B		ALDH1A1	BHLHE22
SLC2A10	ARID2	ANO6		AOC1	BMPER
UST	ARNTL2	ARHGAP21		ARAP2	C20orf197
ZFP92	ARSG	ARNTL2		ARHGAP24	CACFD1
	AVP11	ARSG		ARHGEF3	CBX3
	BAG3	BAG3		BHLHE22	CCL3L3
	BEX5	BEX5		C20orf197	CCT6B
	C2CD5	BRD9		C5AR1	CD14
	C3orf18	C10orf91		CACFD1	CD55
	CALHM2	C2CD5		CCDC120	CD82
	CAMK1D	C3orf18		CEACAM4	CDKL5
	CAPRIN2	CALHM2		CEBPE	CDON
	CCDC91	CAMK1D		CILP2	CEACAM4
	CCL28	CAPRIN2		CLIP4	CEBPE
	CDC123	CEP72		CORO2A	CILP2
	CES4A	CMA5		CRLF2	CKAP4
	CMA5	CNTN1		CST7	CLEC5A
	CNTN1	COL27A1		CTSG	CLIP4
	CPNE8	COL4A5		CYP19A1	CNR1

	CRABP1	COMTD1		CYP1B1	CPE
	CTBP2	CRABP1		CYP27A1	CRLF2
	CWF19L1	CTBP2		CYP46A1	CST7
	DACH1	DDIT4		CYP7B1	CTSG
	DAPK2	DDX11		DEFA4	CYP19A1
	DCLRE1C	DDX11-AS1		DMXL2	CYP1B1
	DDIT4	DENND5B		DYSF	CYP27A1
	DDX11	DNAJB12		EML1	CYP46A1
	DDX11-AS1	DNMIL		EPB41L3	DCAF13
	DENND5B	DNMBP		EPHB1	DMXL2
	DNAJC1	DPY19L2		ERG	EPB41L3
	DNAJC21	DUSP5		FBXO15	EPHA7
	DNMIL	ECHDC3		FBXO32	FAM135B
	EGR1	EIF3A		FRMD3	FAM49B
	ELK1	ELK1		GP9	FBXO15
	ETNK1	FGD4		GSG1L	FBXO32
	FAR2	FGFR3		IL12RB2	FCAR
	FGD4	GOLPH3		IL16	FZD6
	FGFR1OP2	GPC6		KIAA0355	G2E3
	GLRX3	GRK5		KIT	GADD45A
	GPC6	GTF3C5		KLF15	GP9
	GSTO1	HMX2		KLHL29	IL16
	HMX2	HNRNPF		KRT17	KIF5C
	HSD17B8	HSD17B8		KY	KIT
	HTR7	HSH2D		LDLRAD3	KPNA5
	IPO8	INPP5A		LINC00452	LCA5
	ITPR2	IPO8		LINC00565	LDLRAD3
	JMJD1C	ITPR2		LINC00654	LINC00211
	KCNS3	JMJD1C		LOC401463	LINC00654

130364-5012-WO

KIF11	KAZALD1	LPO	LOC100287896
KLHL42	KCNS3	LRRC6	LOC284240
KRAS	KLHL42	MARCO	LOC401463
LINC00477	KRAS	MFNG	LSP1
LOC100506688	LINC00477	MGAT4A	LURAP1L
LPCAT1	LOC100506688	MGLL	MARCO
LRMP	LOC648987	MITF	MERTK
LZTS2	LPCAT1	MTUS1	MFNG
MED21	LRMP	MX2	MGAT4A
MPED2	MCMD2C2	MYO7A	MPC1
MRPS35	MDGA2	NAV1	MS4A4A
MSX1	MPPED2	NLRC3	MX2
NCOA4	MRPL43	NLRP2	MYO7A
NELL2	MRPS35	NRP2	MYO7B
NNT	NIM1K	NT5E	NLRC3
NNT-AS1	NRARP	PAQR5	NMNAT2
NOC3L	OGDHL	PDE9A	NRP2
OAT	OXCT1	PDPN	NT5E
OGDHL	PABPC1L	PGR	NUAK1
OXCT1	PAOX	PNOC	NUDT16P1
PABPC1L	PCED1B	POU4F2	NWD1
PAWR	PCED1B-AS1	PPP1R13B	PDE4D
PCDHGA12	PDLIM1	PRDM13	PDE9A
PCED1B	PLEKHA8P1	PTCH2	PDPN
PCED1B-AS1	PPFIBP1	PTK7	PLCB4
PDSS1	PPP2R3A	RAB27B	POU4F2
PLEKHA8P1	PRICKLE1	RAB38	PPP1R14C
PLEKHO1	PSTPIP2	RGS20	PRDM13
PPFIBP1	PWWP2B	ROS1	PTCRA

	PPP2R2D	RPAP3		S100A9	RAB27B
	RASSF8	SCAF11		SASH1	RASGRF1
	RGS10	SCD		SCRNI	RGCC
	RNLS	SEPHS1		SH3BGRL2	RGS20
	RPAP3	SFMBT2		SLAMF9	RGS5
	SCAF11	SFXN3		SLC11A1	RHOH
	SDHAP3	SH3PXD2A		SLC2A10	ROS1
	SETD6	SHANK3		SLC44A1	S100A9
	SFMBT2	SKIDA1		SLCO2B1	SASH1
	SHANK3	SLC12A7		SOWAHC	SENP6
	SLC12A7	SLC29A3		SPATA31C1	SESN3
	SLC2A13	SLC38A1		SPOCK1	SH3BGRL2
	SLC35G1	SMAD1		STXBP5-AS1	SH3TC1
	SLC38A2	SOX1		STXBP6	SIGLEC7
	SMC3	SOX5		TBL1X	SLC11A1
	SOX1	STON2		TCEA3	SLC2A10
	SOX5	TACC2		TESC	SLC44A1
	SPEF2	TAF5		TFAP2C	SLC9A7P1
	STK38L	TARS		TIAM2	SMYD3
	TARS	TET1		TREML2	SNX10
	TLX1	TLX1		TSGA10	SOWAHC
	TM7SF3	TM7SF3		TSHZ3	STAT4
	UGT3A2	TUBGCP2		UNC5C	STX11
	UPF2	UGT3A2		WIPF3	STXBP5
	VENTX	VENTX		ZBTB18	STXBP5-AS1
	YARS2	WDR70		ZFHX2	SUCNR1
	ZFAND4	YARS2		ZNF334	TBC1D4
	ZNF22	ZFYVE27		ZNF536	TCTN1
	ZNF320	ZMIZ1		ZSWIM4	TENM3

	ZNF43	ZMYND11				TESC
	ZNF511	ZNF43				TLR4
	ZNF572	ZNF438				TLR5
	ZNF622	ZNF622				TMEM71
	ZNF99	ZNF99				TMTC2
						TREM1
						TRPM8
						TSGA10
						TSHZ3
						TSPAN18
						UACA
						UNC5C
						WIPF3
						ZBTB18
						ZNF334
						ZNF37A
						ZNF536

Table 12. IRAK1/4 signature

Gene name
KRAS
SOX5
HMX2
TACC2
AIFM2
ZNF438
FGD4
GRK5
ANK3
ZNF622
PWWP2B
SFXN3
SLC29A3
COL27A1
ARHGAP21
PDLIM1
CAMK1D
SCAF11
DNAJB12
TUBGCP2
DNMBP
JMJD1C
ELK1
SFMBT2
NRARP
DDIT4
DUSP5
INPP5A
BRD9
ZFYVE27
LRMP
SLC38A1
SLC12A7
ZMIZ1
ANO6
PRICKLE1
CALHM2
LINC00477

NIM1K
COMTD1
ECHDC3
PAOX
LPCAT1
ARSG
PSTPIP2
VENTX
AMIGO2
PCED1B
PCED1B-AS1
BAG3

Table 13. CRISPR activation screen in IRAK1/4^{dkO} THP1 cells

Gene ID	Score	P value	FDR	Fold change
CLEC14A	1.02E-05	3.70E-05	0.160891	4.7089
B3GNTL1	1.28E-05	4.53E-05	0.160891	4.5007
GHDC	2.13E-05	6.95E-05	0.160891	4.2536
PHGR1	1.40E-05	4.85E-05	0.160891	4.0855
PPP1R17	6.40E-05	0.0002021	0.346985	3.5241
GNPTAB	0.0001146	0.000352	0.385149	3.3594
KIFC3	0.0001608	0.0004904	0.385149	3.3503
ZNF808	0.0003436	0.0010277	0.412998	3.3302
GDF7	9.01E-05	0.0002718	0.36669	3.296
FSIP1	0.0001999	0.0005926	0.385149	3.2433
MAFF	0.0002174	0.0006513	0.385149	3.1419
CALCB	0.0002734	0.0008164	0.395405	3.1385
SPAG5	0.0002274	0.0006817	0.385149	3.0663
EQTN	0.0003259	0.0009732	0.412998	3.0443
TNFAIP3	0.000151	0.0004642	0.385149	3.0355
EML1	0.0010385	0.0029814	0.524551	3.0353
ZNF729	0.0009363	0.0026946	0.51538	3.0345
KDM4C	0.0007261	0.0021028	0.51538	3.0334
PNMA6A	2.17E-05	7.05E-05	0.160891	3.0142
DTYMK	0.0005913	0.0017296	0.490453	3.0106
UNC79	0.0009161	0.0026343	0.51538	3.0087
PGAP2	0.0001823	0.0005501	0.385149	2.9497
ESYT2	0.0007115	0.0020562	0.51538	2.9405
SCARF1	0.0015634	0.0044397	0.539071	2.9343

CYTH1	0.0007944	0.0022962	0.51538	2.9243
IGF2BP3	0.0014081	0.0039799	0.535455	2.9004
RNF212	0.0011748	0.0033645	0.524551	2.891
WNT10B	0.0009179	0.002638	0.51538	2.8872
KIAA0556	0.0002547	0.0007588	0.395405	2.8862
THPO	0.0004955	0.0014601	0.471807	2.8781
SCAMP3	0.0004996	0.001467	0.471807	2.8737
GMFB	0.0030379	0.0084781	0.6457	2.8689
WDR82	0.0002949	0.0008762	0.403646	2.8681
ATP5G3	0.0023939	0.006721	0.6126	2.8531
RPL24	2.23E-05	7.16E-05	0.160891	2.8252
TEX30	0.0089099	0.023961	0.777567	2.8217
VPS37B	0.0004431	0.0013181	0.467822	2.8195
TRIP6	0.0003688	0.0011021	0.425451	2.8161
THADA	0.0007164	0.002074	0.51538	2.8109
LRBA	0.0018278	0.005184	0.565988	2.8003
MAMLD1	0.0009567	0.0027491	0.51538	2.7956
MKNK2	0.0021819	0.0061407	0.606977	2.7872
CEP57	0.0014605	0.0041293	0.539071	2.7865
BMP1	0.0012588	0.0035831	0.525405	2.7834
LOC100130451	0.0010327	0.0029635	0.524551	2.756
NCAPG2	0.0008961	0.0025746	0.51538	2.7534
ESS2	0.0008835	0.0025379	0.51538	2.7509
MBLAC2	0.003114	0.0086799	0.648006	2.748
HMX1	0.023594	0.060282	0.867024	2.7249
TMC6	0.0006202	0.001814	0.490453	2.7239
DVL2	0.012503	0.033049	0.79022	2.7167
GIT1	0.000841	0.0024152	0.51538	2.7054
GOLGA5	0.0003864	0.0011488	0.425451	2.7042
BRAT1	0.002107	0.0059378	0.596561	2.6928
FCHO2	0.0011318	0.0032377	0.524551	2.6875
ATP6V1G1	0.0005884	0.0017196	0.490453	2.6867
ASMTL	0.000664	0.0019361	0.500949	2.6856
RBM15B	0.0012296	0.0035103	0.525405	2.6788
PIM3	0.0011624	0.003331	0.524551	2.6783
GPATCH2L	0.0001611	0.0004909	0.385149	2.6614
CNIH4	0.0011481	0.003287	0.524551	2.658
SMIM6	0.0030709	0.0085593	0.647923	2.6566
NHLRC2	0.014125	0.026486	0.777567	2.656
ENPP2	0.0047805	0.013208	0.706967	2.6495

REEP1	0.0009437	0.0027166	0.51538	2.6456
FRMPD2	0.0046784	0.012941	0.704383	2.6451
PTAR1	0.0003823	0.0011372	0.425451	2.6406
ESPL1	0.0028499	0.0079602	0.637083	2.6404
CENPS-CORT	0.0032283	0.0089745	0.649463	2.6402
C16orf87	0.0015681	0.0044502	0.539071	2.6365
UNKL	0.0001257	0.0003819	0.385149	2.6349
UBE2E2	0.0010857	0.0031218	0.524551	2.6342
PI4KA	0.033508	0.033445	0.795614	2.6267
ACAD9	0.0018873	0.0053465	0.577058	2.625
ATP6V0D1	0.0031407	0.008758	0.649463	2.6106
PTPRN2	0.0015657	0.0044449	0.539071	2.603
TRAF3IP1	0.0010897	0.0031308	0.524551	2.5981
MALSU1	0.0008184	0.0023597	0.51538	2.5967
DIAPH2	0.0020659	0.0058256	0.588421	2.5848
HIST1H4I	0.0013434	0.0038154	0.53381	2.5846
DCAF13	0.0014217	0.0040156	0.535455	2.5808
WDR73	0.0046338	0.012824	0.700037	2.5797
MEIS2	0.0001978	0.0005895	0.385149	2.579
PCGF2	0.0015515	0.0044009	0.539071	2.5783
ADGRL1	2.05E-05	6.74E-05	0.160891	2.5772
DCK	0.001472	0.0041618	0.539071	2.5726
SRSF7	0.0012248	0.0034956	0.525405	2.5706
AP2B1	0.0006455	0.0018842	0.500949	2.5697
SULT2B1	0.0092908	0.02497	0.777567	2.5621
ABHD5	0.0040845	0.011281	0.673127	2.5595
RAMP2	0.0001501	0.000461	0.385149	2.5537
C18orf25	0.0022449	0.0063173	0.608785	2.5512
TM2D1	0.0065734	0.017918	0.754444	2.5478
OR2T2	0.03053	0.030422	0.79022	2.5389
RAD23B	0.0013127	0.0037378	0.53082	2.5356
OR10X1	0.0061584	0.016843	0.745671	2.529
LRRC75A	0.0045573	0.012611	0.697803	2.5243
UBXN7	0.0073766	0.020021	0.77019	2.523
PELI3	0.0026987	0.0075419	0.634799	2.5188
UTP23	0.0089821	0.024157	0.777567	2.5149
POT1	0.0020415	0.0057669	0.586368	2.5123
GLB1L2	0.0020361	0.0057538	0.586368	2.5104
GTF2H1	2.61E-05	8.41E-05	0.160891	2.502
CALD1	0.011516	0.030604	0.79022	2.5011

DGAT1	0.0037675	0.010431	0.663716	2.4978
MAGEA1	0.0034629	0.0096004	0.654627	2.4952
ISLR2	0.0040466	0.01119	0.673127	2.4941
ZNF394	0.0007507	0.002171	0.51538	2.4938
KAT2A	0.014909	0.039073	0.819274	2.4887
RNF125	0.0010956	0.0031465	0.524551	2.4835
ALG1L2	0.0045093	0.012469	0.697624	2.4748
RPUSD4	0.0030116	0.0084068	0.6457	2.4736
TAF4B	0.007637	0.020701	0.772717	2.4703
HSPE1	0.0033377	0.0092727	0.65165	2.4695
PRR5L	0.0026445	0.0073956	0.632043	2.4664
STRN3	0.0076628	0.020773	0.773378	2.4654
XRCC5	0.0026616	0.0074464	0.632043	2.4652
CORO1C	0.0020442	0.0057743	0.586368	2.4634
PDZRN3	0.0009754	0.0027984	0.51538	2.4633
STK24	0.001146	0.0032812	0.524551	2.4613
STX6	2.35E-05	7.68E-05	0.160891	2.4572
AKT1	0.0034524	0.0095721	0.654627	2.457
SENP7	0.0027174	0.007588	0.634799	2.4529
C2orf71	0.003484	0.0096538	0.655905	2.452
LTB	0.0019371	0.0054886	0.582684	2.4517
CCDC130	8.91E-05	0.0002697	0.36669	2.4473
RELB	0.0003222	0.0009616	0.412998	2.4416
ARFGAP1	0.0036047	0.0099815	0.661307	2.4381
RABEP1	0.001535	0.00435	0.539071	2.4338
TEAD1	0.0026216	0.0073322	0.6295	2.4311
C10orf55	0.0087882	0.02365	0.777567	2.4307
TIMD4	0.0013948	0.003949	0.535455	2.4305
PIKFYVE	0.0054505	0.014991	0.739604	2.4295
CLDN24	0.0086674	0.023359	0.777567	2.4292
KHDC3L	0.0038594	0.010663	0.670554	2.4264
ANKRD9	0.013261	0.03494	0.807511	2.425
GCK	0.0063548	0.017357	0.749684	2.4237
DDIAS	0.0032182	0.0089493	0.649463	2.4234
WNT10A	0.0036694	0.01016	0.663716	2.4222
TNKS2	0.0016869	0.0047977	0.549205	2.4203
ZNF792	0.0013924	0.0039433	0.535455	2.4202
CES5A	0.0077767	0.021069	0.773873	2.4149
ETV5	0.0023881	0.0067094	0.6126	2.4143
ZNF600	0.0033068	0.009191	0.65165	2.4064

EPB41L1	0.0072807	0.019783	0.767286	2.406
RAD1	0.0059649	0.011523	0.675896	2.4048
FAM118B	0.015655	0.040897	0.82361	2.404
DSG4	0.0093815	0.025202	0.777567	2.4038
CTDSP1	0.00866	0.023339	0.777567	2.403
HSDL2	0.0027801	0.0077636	0.634799	2.3948
NMNAT2	0.021858	0.056125	0.863212	2.3914
GALNT3	0.003904	0.010791	0.670598	2.3897
C7orf77	0.0062562	0.017103	0.747765	2.3875
FGFR4	0.0011327	0.0032414	0.524551	2.3824
MYBL2	0.0009556	0.0027465	0.51538	2.3817
EIF1AX	0.012067	0.031978	0.79022	2.3742
WDR27	0.021722	0.055805	0.861852	2.3692
AXDND1	0.0041609	0.011469	0.675896	2.3689
RPA1	0.0083206	0.022482	0.777567	2.3658
ASIC1	0.0034587	0.0095878	0.654627	2.3649
ARHGAP33	0.0009777	0.0028021	0.51538	2.3609
OSBPL3	0.010952	0.029234	0.785276	2.3607
GLCCI1	0.0022354	0.0062922	0.608785	2.3598
MYL5	0.0043943	0.012128	0.690454	2.3598
SEMA4D	0.0005978	0.0017474	0.490453	2.3543
DPYSL2	0.0001489	0.0004579	0.385149	2.3542
FBXO34	0.0029496	0.0082396	0.643094	2.3506
INTS7	0.032591	0.032533	0.79022	2.3497
CDYL	0.0058966	0.016152	0.741385	2.3473
MORN1	0.002777	0.0077552	0.634799	2.3449
DGCR8	0.0075293	0.020429	0.771733	2.3437
RASGRP4	0.0002003	0.0005942	0.385149	2.3422
NUP210L	0.0034594	0.0095888	0.654627	2.3353
NPAS3	0.0080332	0.021746	0.777567	2.3348
ZKSCAN7	0.016277	0.042447	0.829966	2.3327
OR8I2	0.01572	0.041068	0.823933	2.3325
LHX1	0.0002655	0.0007928	0.395405	2.3278
BRD4	0.0056491	0.0155	0.739604	2.3247
GPATCH4	0.0009141	0.0026301	0.51538	2.322
NEUROG1	0.010714	0.028602	0.781445	2.3204
DSN1	0.0060061	0.016451	0.743368	2.3193
ATP5O	0.009662	0.02591	0.777567	2.3193
TMEM18	0.0080929	0.021906	0.777567	2.3173
IQGAP3	0.0015886	0.0045094	0.539071	2.3148

PPP3CB	0.011347	0.0302	0.79022	2.3126
MAGEB1	0.0025911	0.0072535	0.6295	2.3058
PFKP	0.0025728	0.0072016	0.6295	2.3015
PKNOX1	0.0071105	0.019339	0.765749	2.3003
NFKBIE	0.005587	0.015334	0.739604	2.2996
SEC31A	0.0051229	0.014137	0.725274	2.2975
TXN2	0.0005918	0.0017322	0.490453	2.2967
CNNM2	0.0016669	0.0047416	0.546094	2.2961
AXIN1	0.0001948	0.0005842	0.385149	2.2956
COPB2	0.0068053	0.018546	0.759768	2.2905
KIF26B	0.0063643	0.017385	0.749684	2.2883
TMEM79	0.0050042	0.013803	0.720188	2.2862
C14orf80	0.0066792	0.018195	0.755293	2.2859
UBE2E1	0.0097603	0.02617	0.777567	2.2813
TSPAN15	0.013646	0.035908	0.811054	2.281
LPL	0.0091386	0.024571	0.777567	2.2803
DDX55	0.0013433	0.0038148	0.53381	2.2799
LAPTM4B	0.006596	0.017974	0.754444	2.2755
ZC3H15	0.0065447	0.01784	0.754444	2.271
SAAL1	0.018572	0.048081	0.845235	2.2674
TSPAN18	0.0061863	0.016916	0.745671	2.2673
GIN54	0.0063596	0.017369	0.749684	2.2661
ADAMTS18	0.019222	0.049683	0.846385	2.266
TEX14	0.029509	0.074212	0.877552	2.265
YIPF2	0.00577	0.01583	0.739604	2.2617
NFYC	0.0087332	0.023515	0.777567	2.258
TMEM241	0.0080016	0.021666	0.777567	2.2576
ARL15	0.00957	0.025662	0.777567	2.2559
MAML2	0.0169	0.043986	0.83573	2.2548
FAM153A	0.016813	0.043774	0.83573	2.2538
OCRL	0.0003369	0.0010083	0.412998	2.2531
INTS11	0.0019465	0.0055232	0.582803	2.2525
TMC5	0.0079071	0.021421	0.776982	2.2525
CCDC173	0.0084391	0.02278	0.777567	2.2515
ZNF184	0.0082617	0.02233	0.777567	2.2511
TVP23B	0.0002238	0.0006712	0.385149	2.2504
MTBP	0.0068216	0.018585	0.759768	2.2493
RD3L	0.021587	0.055479	0.86087	2.249
KREMEN1	0.010684	0.028525	0.781445	2.2482
ITPKC	0.011793	0.031289	0.79022	2.2472

NDST3	0.000273	0.0008149	0.395405	2.2446
FGFR1OP	0.0041761	0.01151	0.675896	2.2446
SNRK	0.0028308	0.0079009	0.637083	2.2398
SLC3A2	0.0040013	0.011079	0.673127	2.2391
ZNF592	0.046981	0.11346	0.928334	2.2385
USP17L3	0.0015753	0.0044737	0.539071	2.2384
PROK1	0.0040836	0.011276	0.673127	2.2371
ENDOG	0.012776	0.033743	0.796665	2.2364
AADAC	0.037471	0.0923	0.900037	2.236
GRSF1	0.0055826	0.01532	0.739604	2.2348
SLC3A1	0.0044496	0.012305	0.691699	2.2342
KIAA2013	0.0058512	0.016044	0.741385	2.2324
HORMAD2	0.016064	0.041914	0.826598	2.2322
EMC1	0.018194	0.033719	0.796665	2.2311
CDC42	0.0014762	0.0041723	0.539071	2.2287
HIST1H2BN	0.0076216	0.020666	0.772717	2.2279
FBXO3	0.011604	0.030821	0.79022	2.2213
MTA3	0.0040277	0.011146	0.673127	2.2191
CCDC107	0.0046257	0.0128	0.700037	2.2184
SYAP1	0.0001555	0.0004762	0.385149	2.218
CACFD1	0.0011758	0.0033672	0.524551	2.2107
MECP2	0.022619	0.057931	0.865981	2.2103
MUT	0.0037092	0.010266	0.663716	2.21
M6PR	0.015058	0.039441	0.819274	2.2092
GLTP	0.0059057	0.016172	0.741385	2.2075
EDIL3	0.025174	0.064084	0.870595	2.2053
ABHD13	0.0004666	0.001393	0.469855	2.2013
RPS21	0.010769	0.028754	0.781445	2.201
SELENOM	0.018057	0.046863	0.841908	2.199
FXN	0.031355	0.078427	0.877706	2.1962
ADGRB3	0.020372	0.0525	0.854866	2.1948
FBXW2	0.010964	0.029268	0.785276	2.1946
ZAR1L	0.006727	0.018314	0.756927	2.19
CLEC12A	0.020323	0.052371	0.854866	2.1896
ZNF75D	0.012357	0.032705	0.79022	2.189
TREML1	0.036531	0.090172	0.893821	2.1878
PPP1R8	0.0090378	0.024308	0.777567	2.1827
SUPT4H1	0.0016395	0.0046614	0.546094	2.1817
STARD3NL	0.0009809	0.0028105	0.51538	2.1816
VWCE	0.011415	0.030367	0.79022	2.1802

COL9A3	0.011221	0.029882	0.79022	2.1796
AKT2	0.0036406	0.010082	0.663487	2.1769
SLC35F5	0.0003335	0.0009968	0.412998	2.1749
MAGEA6	0.0074986	0.02035	0.771672	2.1714
RASSF3	0.000238	0.0007106	0.385149	2.1713
RRAD	0.013755	0.036188	0.811054	2.169
RILP	0.016086	0.041969	0.826598	2.1683
SYT2	0.0011941	0.0034159	0.524551	2.1669
FKBP3	0.0012869	0.0036633	0.529665	2.1669
GBP6	0.0091442	0.024588	0.777567	2.1661
CLDN7	0.0002394	0.0007137	0.385149	2.166
MLLT10	0.012934	0.034149	0.801261	2.1658
ANKRD20A3	0.017282	0.032091	0.79022	2.1646
SLC25A12	0.0091667	0.024647	0.777567	2.1625
ZNF283	0.0068426	0.018638	0.759768	2.1619
SLX4	0.027959	0.070572	0.877552	2.1619
TOR3A	0.017571	0.045659	0.836807	2.1605
LRRC27	0.0069719	0.018982	0.763459	2.1596
ZBTB40	0.014029	0.03688	0.812672	2.1595
STRADA	0.0087662	0.023589	0.777567	2.1594
ZNF774	0.013998	0.036807	0.812153	2.1578
NDUFA7	0.0023676	0.0066581	0.6126	2.1566
DR1	0.017679	0.045939	0.838346	2.156
CER1	0.01008	0.02698	0.777567	2.1536
CBX3	0.0043707	0.012064	0.690454	2.1511
OR5B12	0.010751	0.028703	0.781445	2.1508
PYCR2	0.010927	0.029174	0.785276	2.1494
HSP90AA1	0.0079218	0.021465	0.776982	2.1481
PSMG4	0.015771	0.04119	0.823933	2.1465
HCN2	0.0099232	0.026584	0.777567	2.1451
IZUMO1	0.002485	0.0069679	0.623739	2.1446
HSD17B13	0.010087	0.026997	0.777567	2.1432
INF2	0.027542	0.069601	0.877552	2.1432
EWSR1	0.0027479	0.0076792	0.634799	2.1431
ORM1	0.0018665	0.0052904	0.574286	2.1422
WDR63	0.000517	0.0015152	0.474193	2.1414
PRPF6	0.0003848	0.0011456	0.425451	2.1411
MAVS	0.0085366	0.023026	0.777567	2.1399
SUV39H2	0.0097082	0.026027	0.777567	2.138
MERTK	0.0057805	0.015859	0.739604	2.1379

CCDC47	0.012048	0.031927	0.79022	2.1367
HOGA1	0.017281	0.044933	0.83573	2.1365
ZBTB11	0.0010812	0.0031072	0.524551	2.1339
FAM102B	0.010439	0.027905	0.781445	2.1321
SEC11A	0.0098241	0.026332	0.777567	2.132
GGTLC1	0.0066551	0.018139	0.755293	2.1308
C9orf66	0.0045975	0.012729	0.700037	2.1307
HTR1B	0.014043	0.036916	0.812672	2.1269
C11orf98	0.0067615	0.018418	0.757987	2.1266
SNPH	0.0084337	0.022764	0.777567	2.1262
OR8D1	0.020843	0.053677	0.85564	2.1256
DKKL1	0.0040607	0.011223	0.673127	2.1246
IQCB1	0.006713	0.018271	0.756807	2.1221
MFSD6L	0.0098009	0.026283	0.777567	2.1218
MARF1	0.011858	0.031458	0.79022	2.1203
ECH1	0.02561	0.065108	0.872768	2.1182
ABLIM1	0.016514	0.043062	0.834217	2.1175
SLC35G6	0.012074	0.031995	0.79022	2.1168
TMEM99	0.012468	0.032961	0.79022	2.1154
SCO2	0.0015786	0.0044842	0.539071	2.1153
ATP6V1B1	0.022593	0.057862	0.865981	2.1148
CASP8AP2	0.016843	0.043845	0.83573	2.1126
SASH3	0.0088288	0.02375	0.777567	2.111
RGPD8	0.0023303	0.0065543	0.6126	2.1076
ANKRD20A4	0.074919	0.074926	0.877552	2.1048
TRNAU1AP	0.016034	0.041835	0.826541	2.1043
CYB5R1	0.02741	0.069308	0.877552	2.1035
VPS39	0.015215	0.039832	0.821334	2.1017
ZNF44	0.022645	0.057989	0.865981	2.1014
TIMM23	0.01498	0.039247	0.819274	2.1011
RSPO2	0.016979	0.04419	0.83573	2.1006
SLC28A2	0.0088434	0.023788	0.777567	2.0959
GNAO1	0.0009654	0.0027712	0.51538	2.0958
SHC4	0.0005224	0.0015314	0.474193	2.0955
DDB2	0.047249	0.11402	0.928338	2.0949
ALDH3A1	0.0063041	0.017224	0.749589	2.0948
TCL1B	0.028614	0.072125	0.877552	2.0946
FAM178B	0.0012602	0.0035884	0.525405	2.0935
COQ2	0.0042496	0.011725	0.681447	2.0922
TSLP	0.017633	0.045825	0.837088	2.092

SNTG2	0.028898	0.072784	0.877552	2.0919
ME1	0.046166	0.11167	0.926364	2.0913
GDF5	0.0014001	0.0039595	0.535455	2.0908
UCHL5	0.015255	0.028528	0.781445	2.0901
RABGEF1	0.0019383	0.0054912	0.582684	2.0897
CHRNA	0.0062741	0.017144	0.747845	2.0888
MAP3K3	0.010384	0.02777	0.781445	2.0885
SLC18A2	0.0089189	0.023991	0.777567	2.0879
DDX51	0.012086	0.032028	0.79022	2.087
ASPSCR1	0.019334	0.049952	0.846385	2.0869
STARD9	0.019406	0.050114	0.846385	2.0849
ADAM17	0.001084	0.0031145	0.524551	2.0835
CNTN1	0.029305	0.073737	0.877552	2.0829
NAB2	0.031825	0.079491	0.879573	2.0824
POTED	0.038803	0.07013	0.877552	2.0816
TAX1BP3	0.08669	0.086671	0.891151	2.0815
TINF2	0.0055769	0.015307	0.739604	2.0812
INHBB	0.022559	0.057783	0.865981	2.0811
YBEY	0.010087	0.026997	0.777567	2.076
SDAD1	0.010336	0.027632	0.781445	2.0751
PCSK1N	0.034924	0.086537	0.891151	2.0747
XRCC2	0.013571	0.035699	0.811054	2.0746
SLC48A1	0.025455	0.064744	0.872768	2.0744
INTU	0.0016417	0.0046682	0.546094	2.0724
FN3KRP	0.01271	0.033574	0.795725	2.0724
OPN3	0.0077248	0.020941	0.773873	2.0722
DLK1	0.0047355	0.013098	0.706967	2.0718
ARHGAP32	0.0077923	0.02112	0.773873	2.0694
TEF	0.0017607	0.0049974	0.558212	2.0668
ASTE1	0.045535	0.11029	0.926364	2.0667
PPIAL4C	0.005534	0.015192	0.739604	2.0657
FZD5	0.017152	0.04461	0.83573	2.0654
IMPA2	0.015961	0.04167	0.825347	2.0649
ABCA6	0.0078079	0.021169	0.773873	2.0641
TNFAIP8	0.009962	0.02667	0.777567	2.0633
CRMP1	0.015822	0.041317	0.824067	2.0628
PTS	0.03168	0.079152	0.878903	2.0623
CNPY2	0.02594	0.065853	0.876559	2.0622
TARBP2	0.015786	0.041224	0.823933	2.0609
LRP11	0.0066199	0.018046	0.755293	2.0599

APOB	0.010702	0.028577	0.781445	2.0584
RBMXL3	0.074449	0.17092	0.958137	2.0581
MOCS1	0.03483	0.086309	0.891151	2.0566
ADAMTS10	0.035601	0.08809	0.892638	2.0563
ABHD17A	0.0081338	0.022005	0.777567	2.0516
CROT	0.010457	0.027947	0.781445	2.0512
ARID3B	0.0074426	0.020196	0.771672	2.0482
NPAS4	0.018817	0.048695	0.846385	2.0474
GINM1	0.0012356	0.003527	0.525405	2.0473
ARID5B	0.013201	0.034787	0.806214	2.0467
DRAXIN	0.015436	0.040365	0.82361	2.0466
TUBB3	0.010348	0.027669	0.781445	2.0451
MS4A6A	0.011542	0.030662	0.79022	2.0446
SGTA	0.0074935	0.020332	0.771672	2.0436
CAMKMT	0.010545	0.028165	0.781445	2.0419
ARMCX5	0.010324	0.027606	0.781445	2.0398
ZBP1	0.021663	0.055664	0.861759	2.0388
LCE1E	0.0061677	0.01687	0.745671	2.0382
INAFM2	0.0013019	0.0037016	0.529665	2.0379
USP22	0.010689	0.028542	0.781445	2.0363
SPDEF	0.013955	0.036708	0.812153	2.0356
TCF15	0.017289	0.044954	0.83573	2.0338
HIST1H3D	0.088823	0.0888	0.89281	2.0331
TMEM8A	0.0052574	0.014491	0.731839	2.0324
VDR	0.012318	0.032607	0.79022	2.032
SPINK1	0.032276	0.080552	0.883201	2.0315
RING1	0.047065	0.11362	0.928334	2.0314
MFSD8	0.0084121	0.022717	0.777567	2.0298
IFNA5	0.02043	0.052639	0.854866	2.0283
TM4SF5	0.019142	0.049489	0.846385	2.0279
COG5	0.023357	0.059719	0.866014	2.0269
ANKRD39	0.026708	0.067687	0.877552	2.025
HASPIN	0.021009	0.054084	0.856547	2.0242
SLC25A33	0.01033	0.02762	0.781445	2.0235
TRIM49D2	0.031118	0.077889	0.877552	2.0223
TCEAL6	0.015873	0.041447	0.825347	2.0214
OSBPL1A	0.0035631	0.0098824	0.661307	2.0212
ZNF786	0.0009176	0.0026375	0.51538	2.0163
CYP11B1	0.011179	0.029787	0.790181	2.0147
CLUL1	0.000759	0.0021982	0.51538	2.0132

OTUD7B	0.012151	0.032189	0.79022	2.0123
ADA	0.0077819	0.021087	0.773873	2.0118
ZBTB16	0.024195	0.061713	0.869622	2.0112
GPR149	0.0060327	0.016515	0.743388	2.0102
SBSPON	0.016477	0.042975	0.833833	2.0068
BLOC1S3	0.013274	0.034975	0.807511	2.0057
HIST1H2BL	0.065212	0.11429	0.928498	2.0053
BHMT2	0.014987	0.039261	0.819274	2.0025
HMX3	0.0026153	0.0073164	0.6295	2.0013
CRTC1	0.012093	0.032049	0.79022	2.0013
MUC5AC	0.014697	0.038567	0.819274	2.001
OPLAH	0.004112	0.011351	0.674217	2.0006
PIK3R4	0.042738	0.1041	0.915977	2.0004
EFCAB6	0.02287	0.058573	0.865981	2.0001

Table 15. AML samples

Specimen	Gender	Age at Diagnosis	Karyotype
AML-2017-114 (JM78)	M	4	46,XY,der(10)?add(10)(p13)ins(10;11)(p12;q?23q?21),?add(10)(p12),del(11)(q21q23)[14]/47,sl,+8[6] MLL/AF10, PTPN11

Table 16. Pharmacokinetic analysis of inhibitors

	Compound 14	Compound 15
Tier 1 Mic t1/2 (r, min)	>30	>30
Tier 2 Mic t1/2 (r / m / h, min)	N.D. / 25 / N.D.	68 / 29 / 102
Plasma Prot Bind (% free - ms, h)	38.6, 26.5	6.85, 2.46
Solubility (mg / mL)	>48	31
PAMPA (10⁻⁶ cm/s)	746	495

Compound 14 (PO dosing at 30 mg/kg)		
Time Point (h)	Mean Total Drug Concentration (nM)	Mean Free Drug Concentration (nM)
0.083	449	173
0.25	869	336
0.5	932	360
1	801	309
2	562	217
4	262	101
8	78	30
24	0	0

Compound 15 (PO dosing at 100 mg/kg)		
Time Point (h)	Mean Total Drug Concentration (nM)	Mean Free Drug Concentration (nM)
0.083	2672	183
0.25	3845	263
0.5	3764	258
1	3018	207
2	2034	139
4	1594	109
8	726	50
24	9	1

CLAIMS

1. A method of treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS) in a subject in need thereof, the method comprising administering to the subject a compound that inhibits IRAK1 and IRAK4.
2. The method of claim 1, wherein the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis.
3. The method of claim 1, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.
4. The method of claim 1, wherein the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2.
5. The method of claim 4, wherein the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2.
6. The method of any one of claims 1 to 5, wherein the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, FLT3 expression, NF- κ B signaling, TLR signaling, IL-1 signaling, or a combination thereof.
7. The method of claim 6, wherein the subject in need thereof has elevated IRAK1 expression, IRAK4 expression, or a combination thereof.

8. The method of claim 6 or 7, wherein the subject in need thereof has elevated FLT3 expression.
9. The method of any one of claims 1 to 8, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.
10. The method of any one of claims 1 to 9, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.
11. The method of any one of claims 1 to 10, wherein the compound has IRAK4:IRAK1 potency ratio of less than about 40.
12. The method of any one of claims 1 to 11, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes compared to a healthy control subject and/or decreased expression of one or more IRAK1/4-associated genes compared to a healthy control subject.
13. The method of claim 12, wherein the subject in need thereof has elevated expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.
14. The method of claim 12 or 13, wherein the subject in need thereof has decreased expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7,

ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 compared to the healthy control subject.

15. The method of any one of claims 12 to 14, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

16. The method of claim 15, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

17. The method of claim 15 or 16, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

18. The method of any one of claims 1 to 17, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

19. The method of any one of claims 1 to 18, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS in the subject in need thereof.

20. The method of claim 19, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.

21. The method of any one of claims 1 to 20, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof after the administration is stopped.

22. The method of claim 21, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.

23. The method of any one of claims 1 to 22, wherein the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010), (I_a-5010)-(I_d-5010), (II-5010), (II_a-5010), (II_b-5010), (III-5010), (III_a-5010), (III_b-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

24. A method of determining effectiveness of a compound in treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining the compound's IRAK1 IC₅₀ and IRAK4 IC₅₀;

calculating an IRAK4:IRAK1 potency ratio from the IRAK1 IC₅₀ and the IRAK4 IC₅₀ of the compound;

wherein a potency ratio of less than about 40 is indicative of effectiveness of the compound in treating the inflammatory disease/disorder, AML, or MDS.

25. The method of claim 24, further comprising administering the compound to a subject with an inflammatory disease/disorder, AML, or MDS, treating the inflammatory disease/disorder, AML, or MDS.

26. A method of determining effectiveness of a compound in treating an inflammatory disease/disorder, acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS), comprising:

determining that the compound is an IRAK1/4 inhibitor which modifies the expression of one of more IRAK1/4-associated genes found to be differentially expressed in a subject with an inflammatory disease/disorder, AML, or MDS compared to a healthy control subject.

27. The method of claim 26, further comprising administering the compound to the subject, treating the inflammatory disease/disorder, AML, or MDS.

28. The method of claim 26 or 27, wherein the compound decreases the expression of one of more IRAK1/4-associated genes found to be elevated in the subject compared to the healthy control subject and/or increases the expression of one of more IRAK1/4-associated genes found to be decreased in the subject compared to the healthy control subject.

29. The method of any one of claims 26 to 28, wherein the compound decreases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2, AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

30. The method of any one of claims 26 to 29, wherein the compound increases the expression of one or more IRAK1/4-associated genes selected from: KRAS, SOX5, HMX2, TACC2,

AIFM2, ZNF438, FGD4, GRK5, ANK3, ZNF622, PWWP2B, SFXN3, SLC29A3, COL27A1, ARHGAP21, PDLIM1, CAMK1D, SCAF11, DNAJB12, TUBGCP2, DNMBP, JMJD1C, ELK1, SFMBT2, NRARP, DDIT4, DUSP5, INPP5A, BRD9, ZFYVE27, LRMP, SLC38A1, SLC12A7, ZMIZ1, ANO6, PRICKLE1, CALHM2, LINC00477, NIM1K, COMTD, ECHDC3, PAOX, LPCAT1, ARSG, PSTPIP2, VENTX, AMIGO2, PCED1B, PCED1B-AS1, and BAG3 in the subject.

31. The method of any one of claims 24 to 30, wherein the inflammatory disease/disorder is selected from chronic inflammation, sepsis, rheumatoid arthritis, hidradenitis suppurativa, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, psoriasis, Sjögren's syndrome, Ankylosing spondylitis, systemic sclerosis, Type 1 diabetes mellitus, Crohn's disease, and colitis.

32. The method of any one of claims 24 to 30, wherein the AML is relapsed AML, refractory AML, relapsed/refractory AML, AML with resistance to hypomethylating agents, AML with resistance to venetoclax, AML with resistance to hypomethylating agents and venetoclax, monocytic AML, or monocytic-like AML.

33. The method of any one of claims 24 to 30, wherein the MDS is MDS with a splicing factor mutation, MDS with a mutation in isocitrate dehydrogenase 1, or MDS with a mutation in isocitrate dehydrogenase 2.

34. The method of claim 33, wherein the MDS with a splicing factor mutation comprises MDS with a splicing factor mutation in U2AF1, SRSF2, SF3B1, or ZRSR2.

35. The method of any one of claims 24 to 34, wherein the compound has an IRAK1 IC₅₀ of less than about 75 nM.

36. The method of any one of claims 24 to 35, wherein the compound has an IRAK4 IC₅₀ of less than about 10 nM.

37. The method of any one of claims 24 to 36, wherein the compound is more effective at inhibiting cancer cell colony formation and/or cancer progenitor cell function when compared to a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.
38. The method of any one of claims 24 to 37, wherein the compound provides sustained treatment of the inflammatory disease/disorder, AML, or MDS when administered to a subject in need thereof.
39. The method of claim 38, wherein the sustained treatment is greater than the treatment provided from a compound which inhibits IRAK1 without inhibiting IRAK4 or inhibits IRAK4 without inhibiting IRAK1.
40. The method of any one of claims 24 to 39, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in a subject in need thereof after administration of the compound to the subject is stopped.
41. The method of claim 40, wherein the compound continues to treat the inflammatory disease/disorder, AML, or MDS in the subject in need thereof for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about one week, about two weeks, about three weeks, or about a month after the administration is stopped.
42. The method of any one of claims 24 to 41, wherein the compound is a compound of any one of Formulas (I-5007), (II_f-5007)-(II_k-5007), (II_m-5007)-(II_t-5007), (III_q-5007)-(III_s-5007), (IV-5007), (VI-5003), (VII-5008), (II_f-5008)-(II_k-5008), (II_m-5008), (II_n-5008), (II_p-5008)-(II_u-5008), (III_q-5008)-(III_s-5008), (I-5009), (II_f-5009)-(II_j-5009), (I-5010), (I_a-5010)-(I_d-5010), (II-5010), (II_a-5010), (II_b-5010), (III-5010), (III_a-5010), (III_b-5010), or a salt, ester, solvate, optical isomer, geometric isomer, or salt of an isomer of any one thereof.

NFkB v Kinase

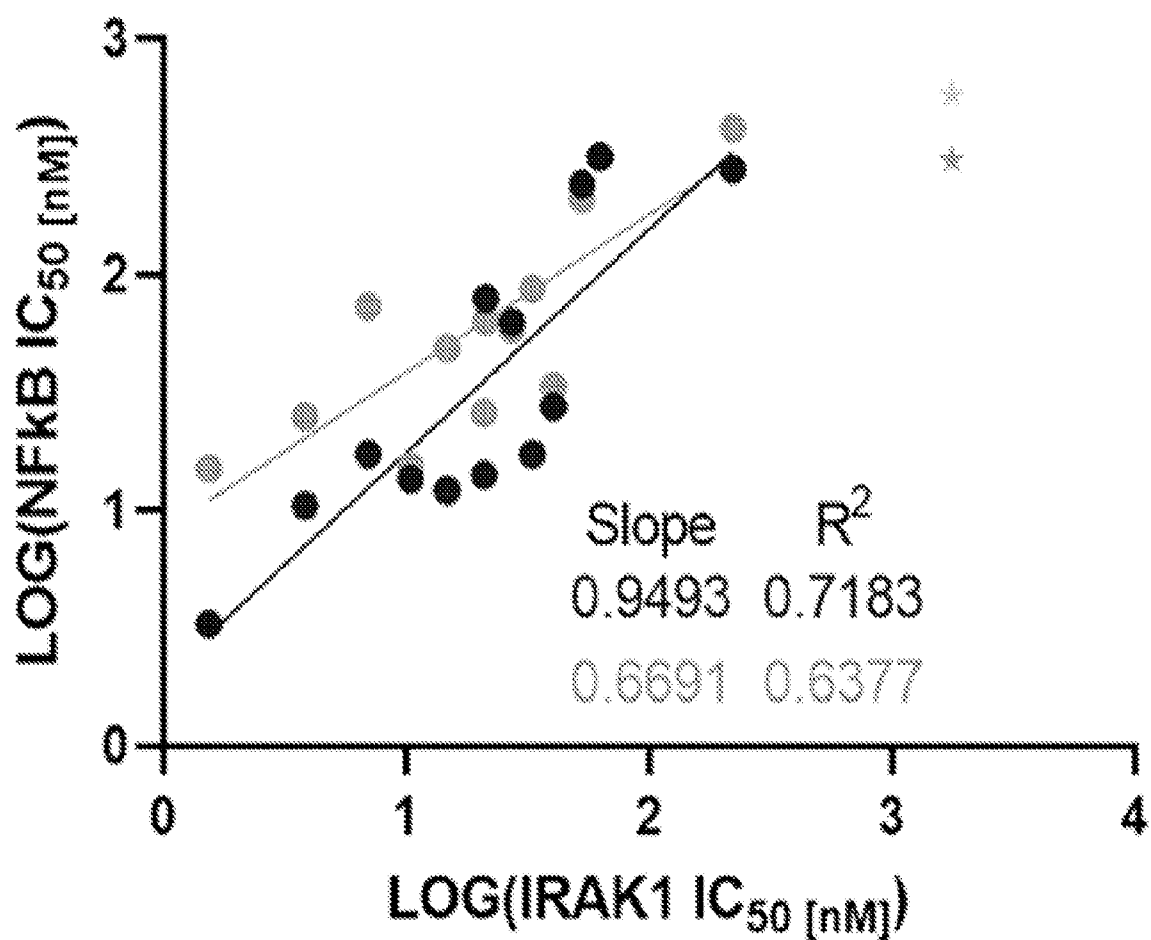
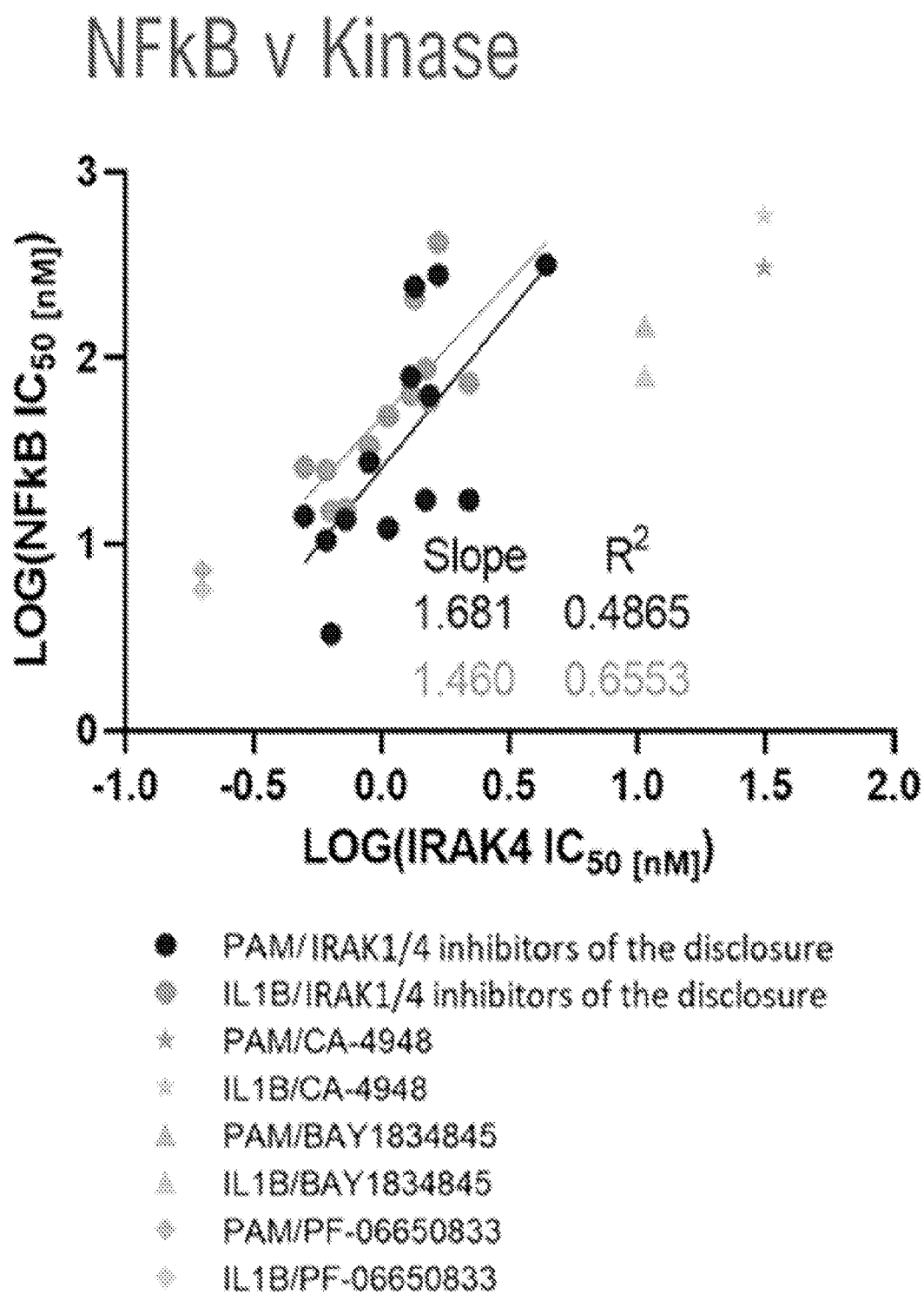


FIG. 1

**FIG. 2**

MDSL v NFkB

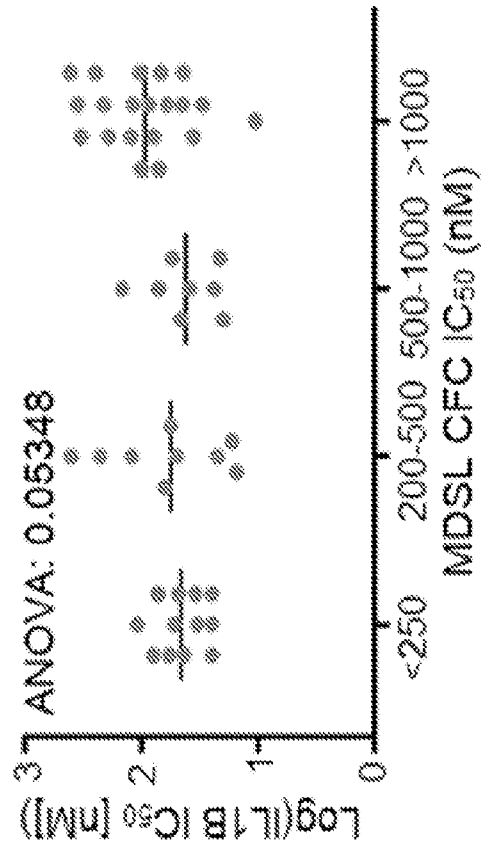
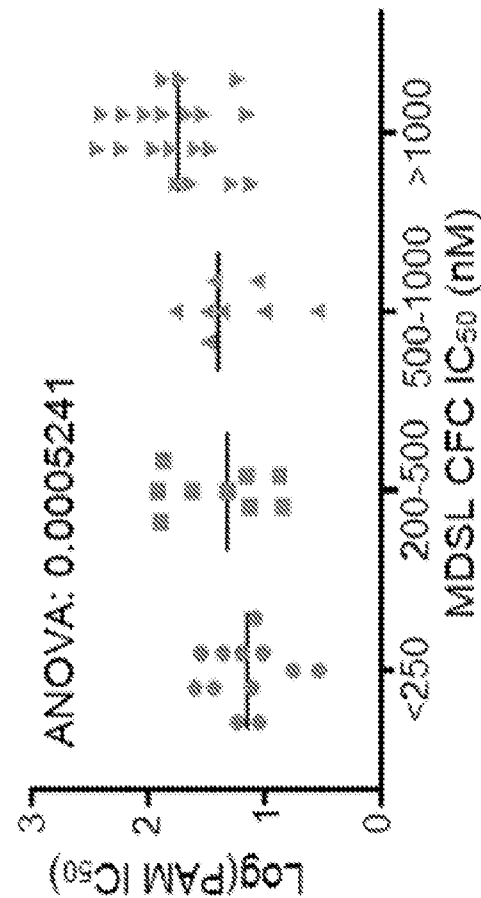


FIG. 3

THP-1 v NFkB

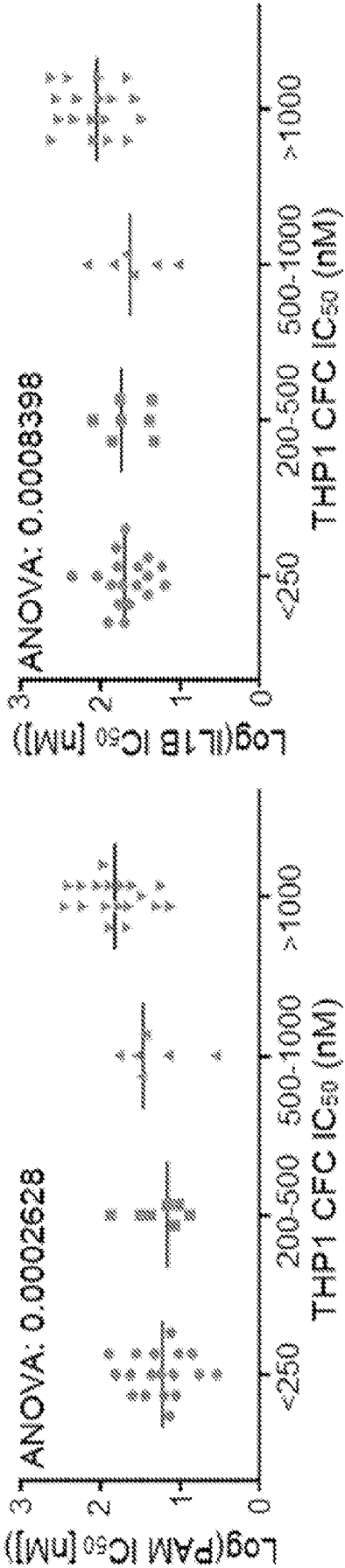
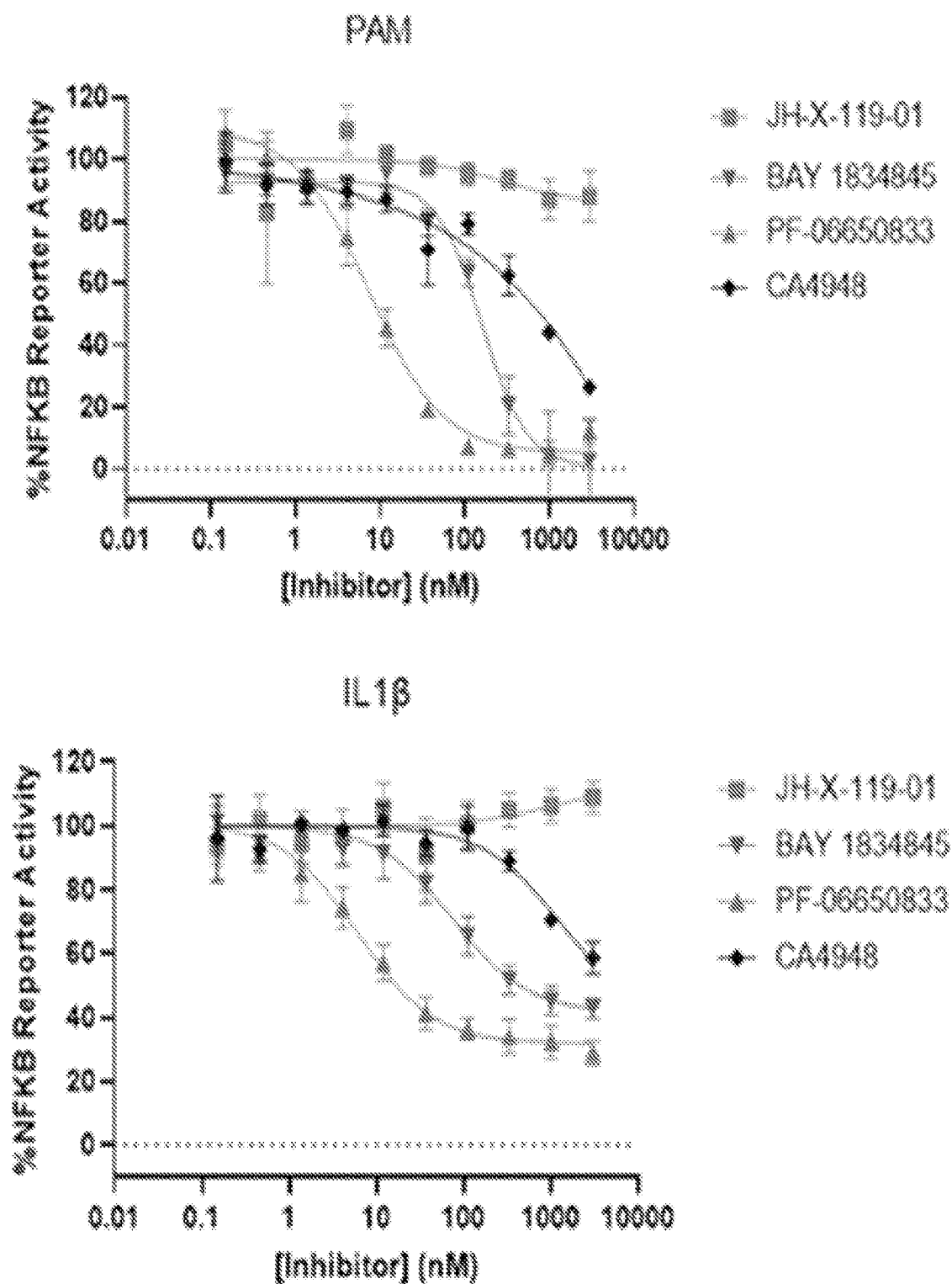
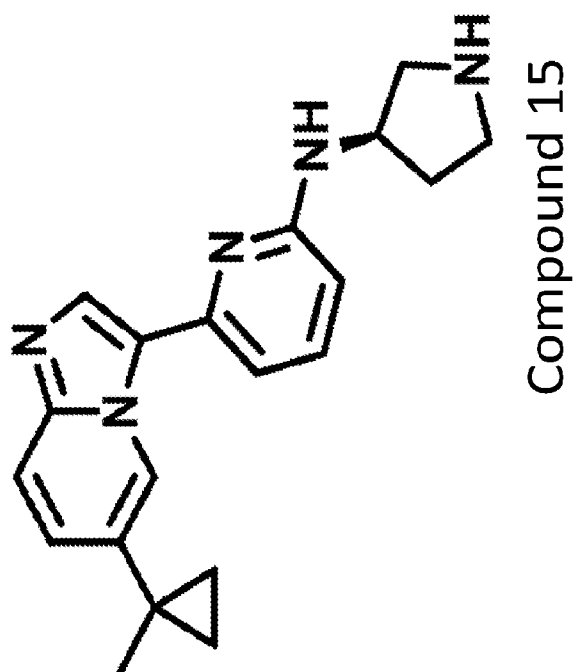


FIG. 4

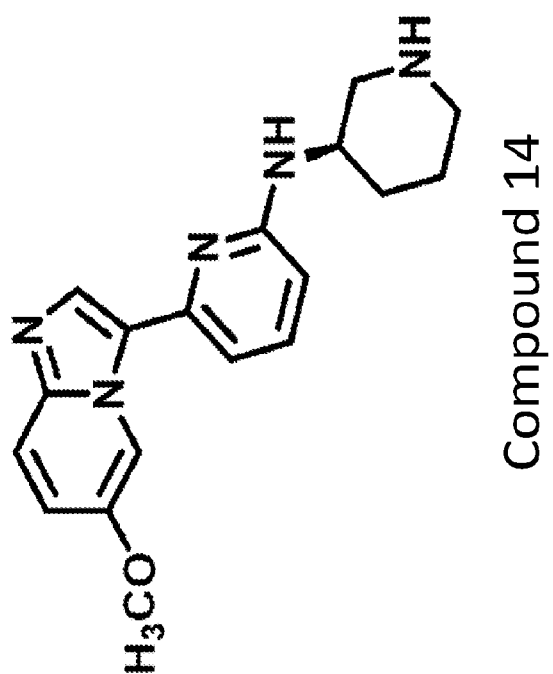
**FIG. 5**

			Kinase Profile			Average	
			IRAK1	IRAK4	FLT3 (nM)	PAM	IL1B
Compound	Target					IC50 (nM)	IC50 (nM)
PF-06650833	IRAK 4		Between 1-5 uM	0.2 nM	nM	6.85	7.18
BAY 1834845	IRAK 4			10.7 nM		139	94.1
JH-X-119-01	IRAK 1		9 nM	>10 uM No inhibition		21.3	75.5
CA 4948	IRAK 4 and FLT3		2.36 E3 nM	10.4 nM	1.76	501	650

FIG. 5 (Continued)

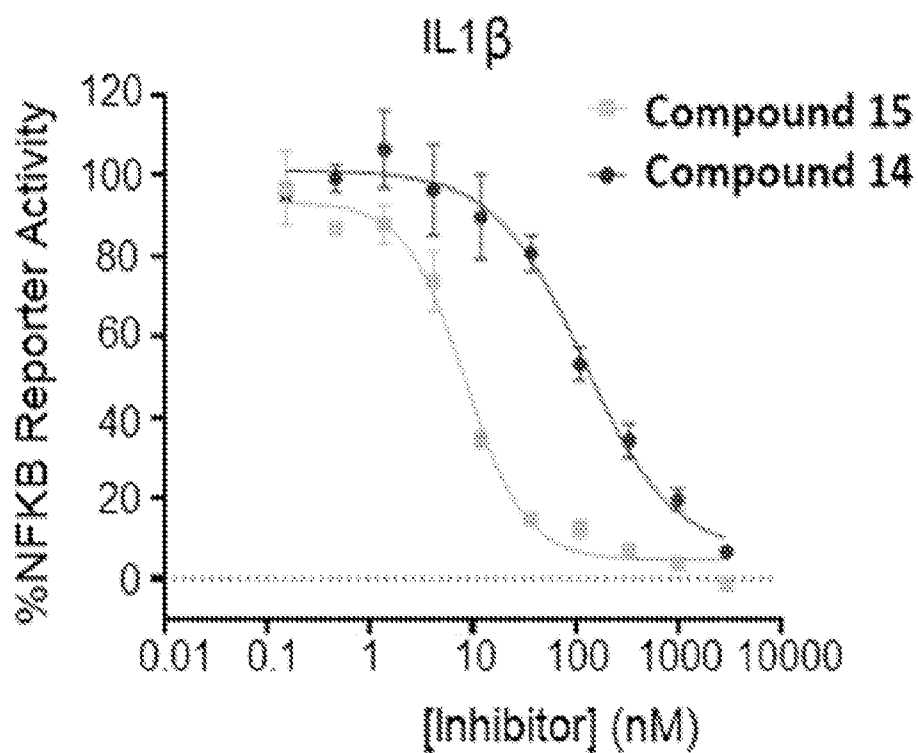
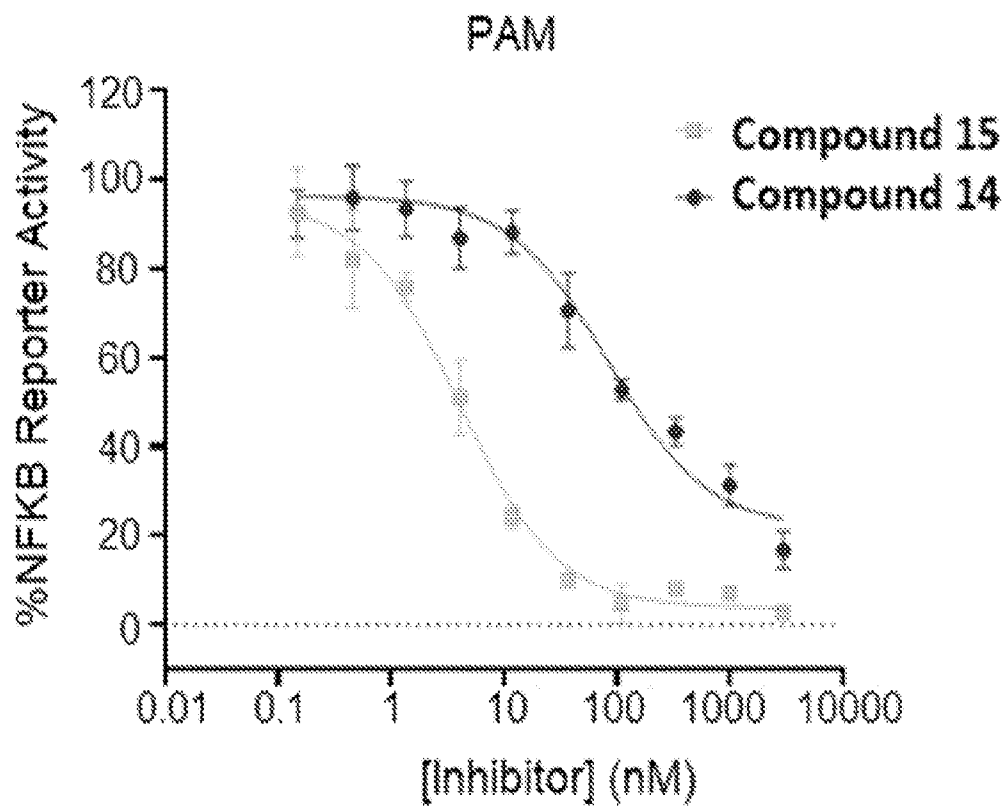


Compound 15



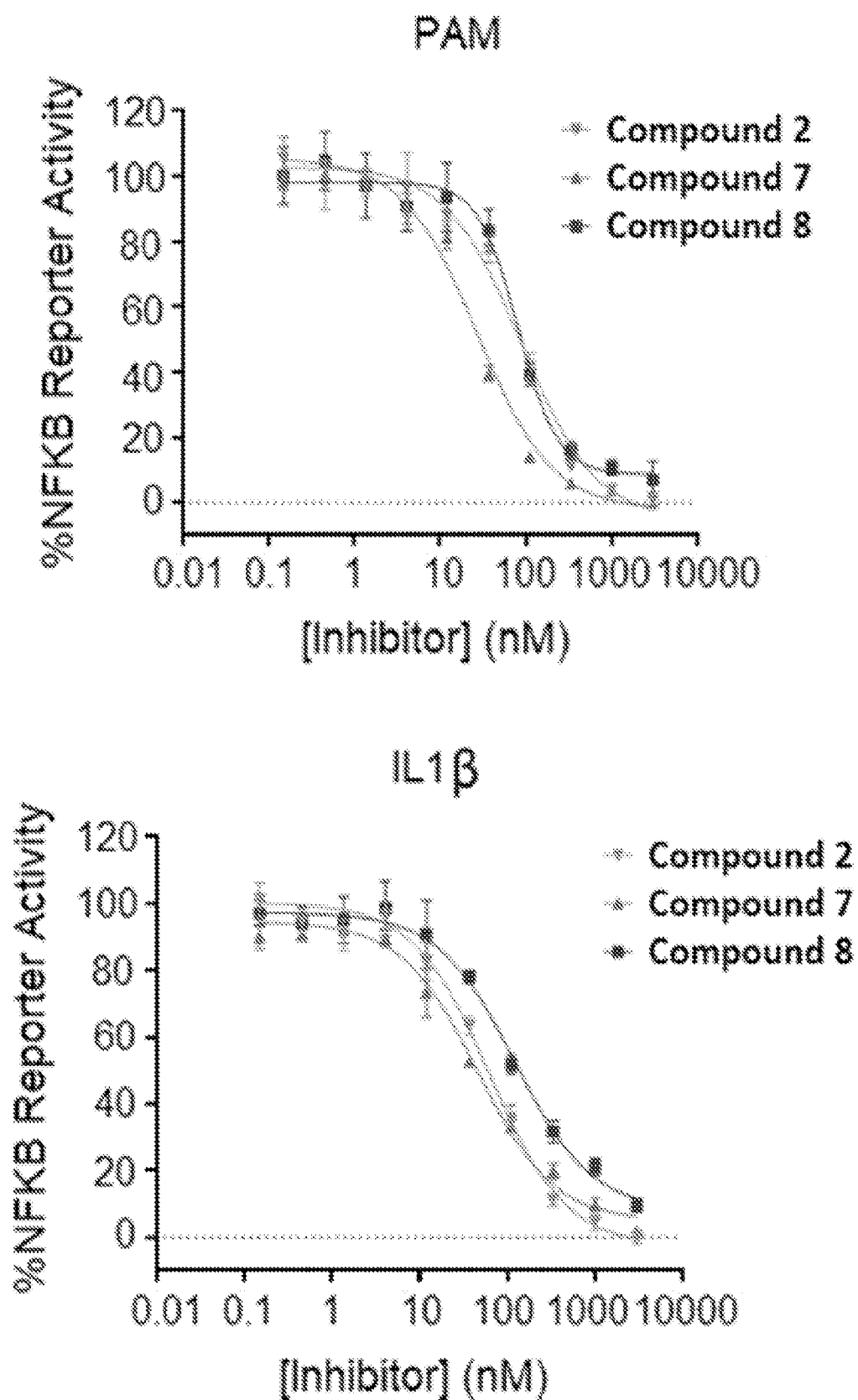
Compound 14

FIG. 6A

**FIG. 6B**

							Average	
			Kinase Profile				PAM	IL1B
Compound	Target	IRAK 1	IRAK 4	FLT3 (nM)	IC50 (nM)		IC50 (nM)	
Compound 14	IRAK 4	520 nM	5.19 nM	<0.988	73.8		227	
Compound 15	IRAK 1/4	32 nM	0.884 nM	<0.508	6.3		9.26	

FIG. 6B (Continued)

**FIG. 7**

			Kinase Profile					Average	
Compound	Target	IRAK 1	IRAK 4	FLT3 (nM)	PAM	IL1B			
Compound 8	IRAK 1/4	27.2 nM	1.54 nM	<0.508	IC50 (nM)	IC50 (nM)			
Compound 7	IRAK 1/4	1.54 nM	<0.694 nM	<0.508	14.6	86.7			103
Compound 2	IRAK 1/4	21.3 nM	1.3 nM	<0.508	95.3	65.2			29.6

FIG. 7 (Continued)

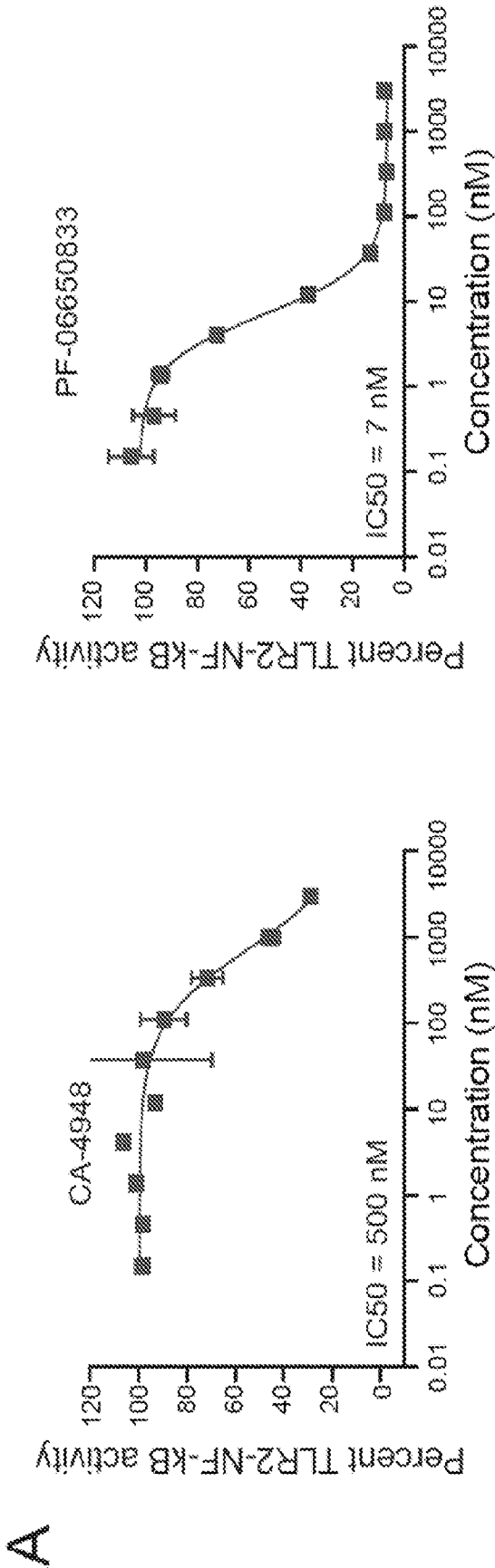


FIG. 8A

B

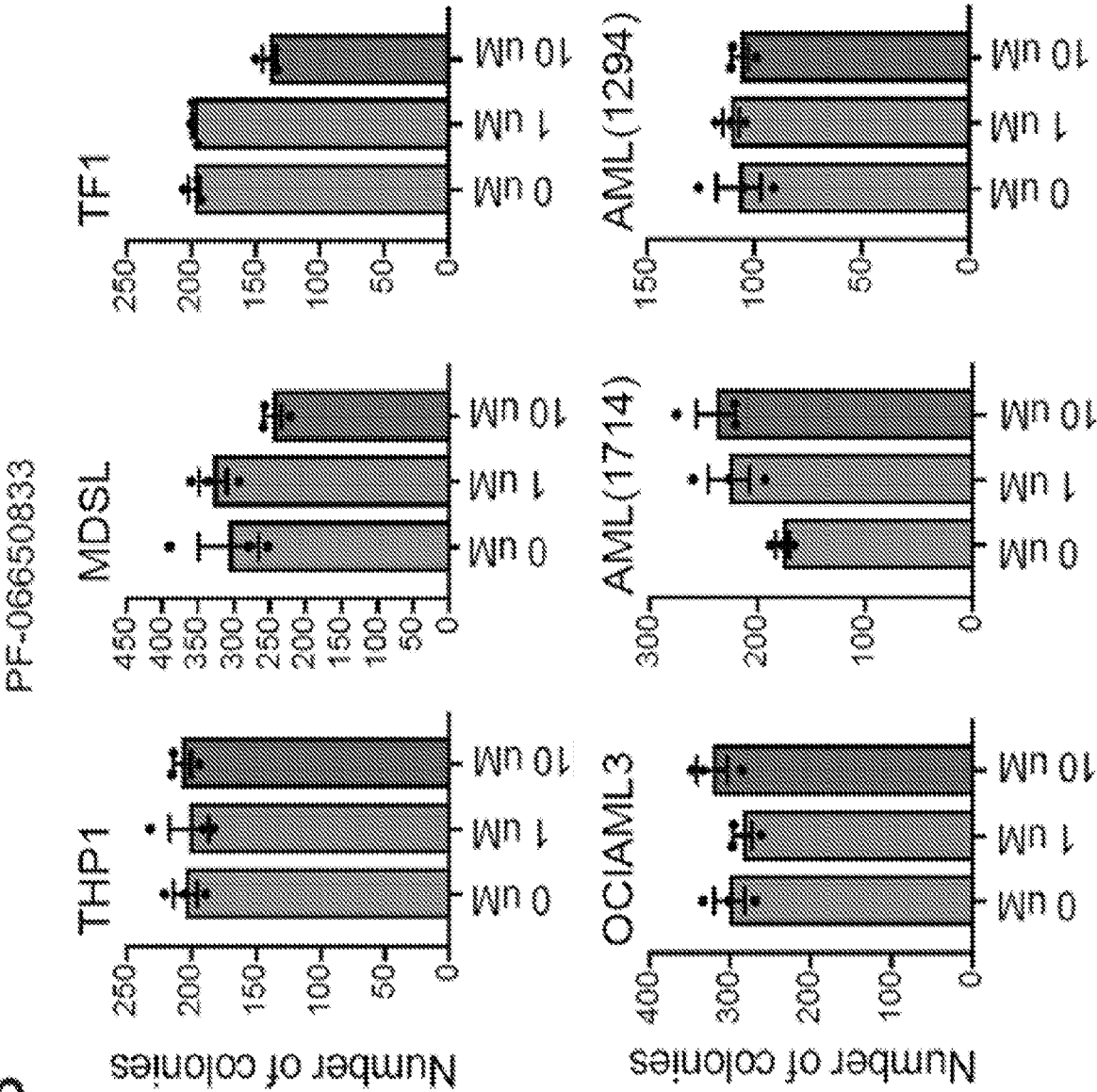


FIG. 8B

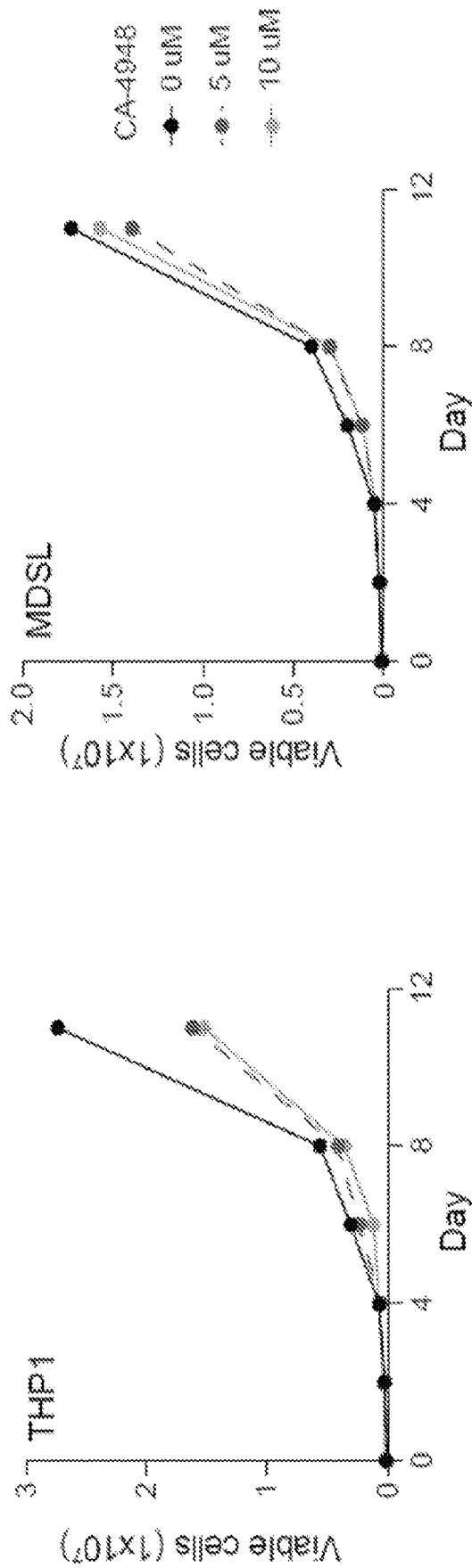


FIG. 8C

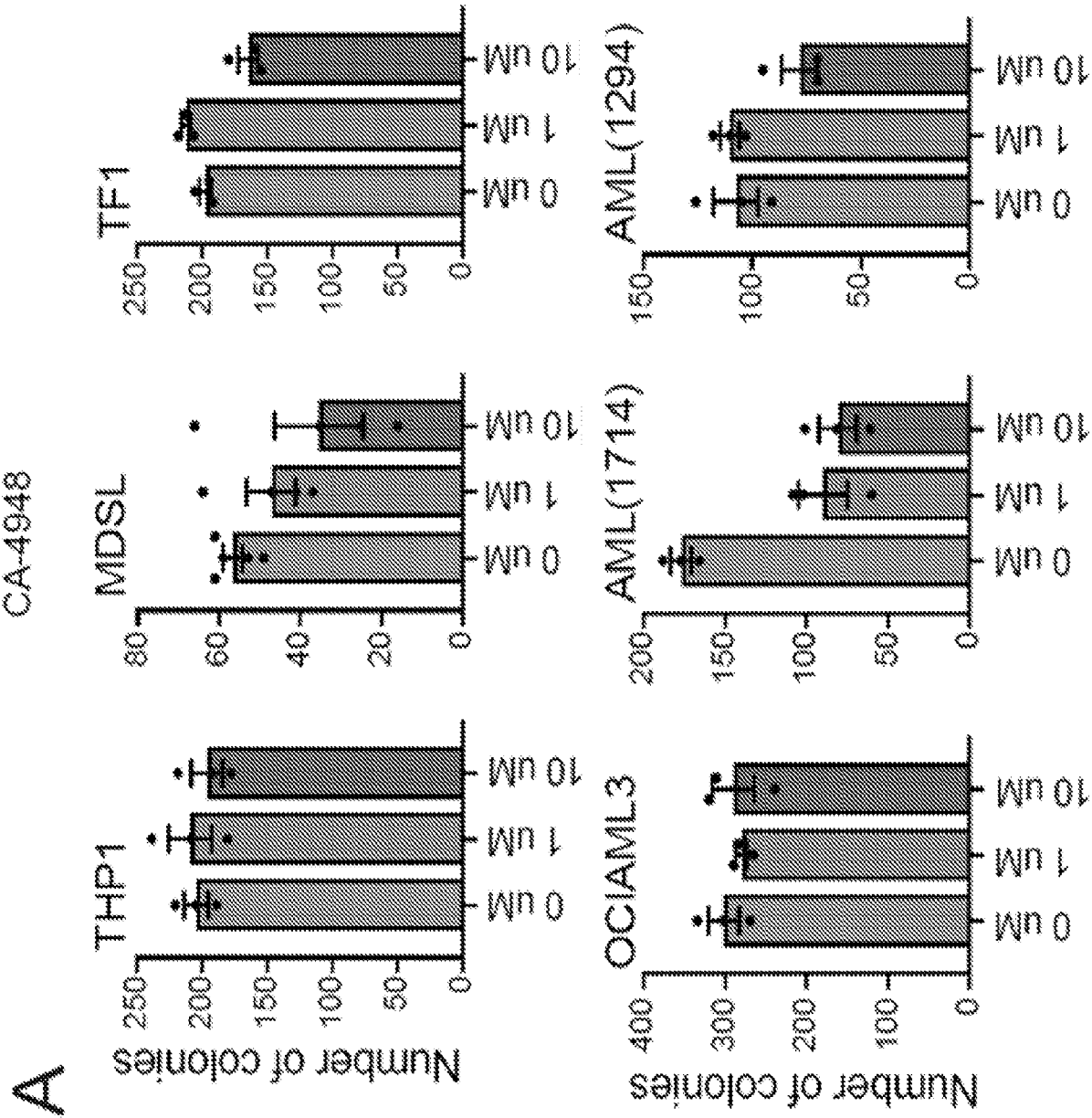


FIG. 9A

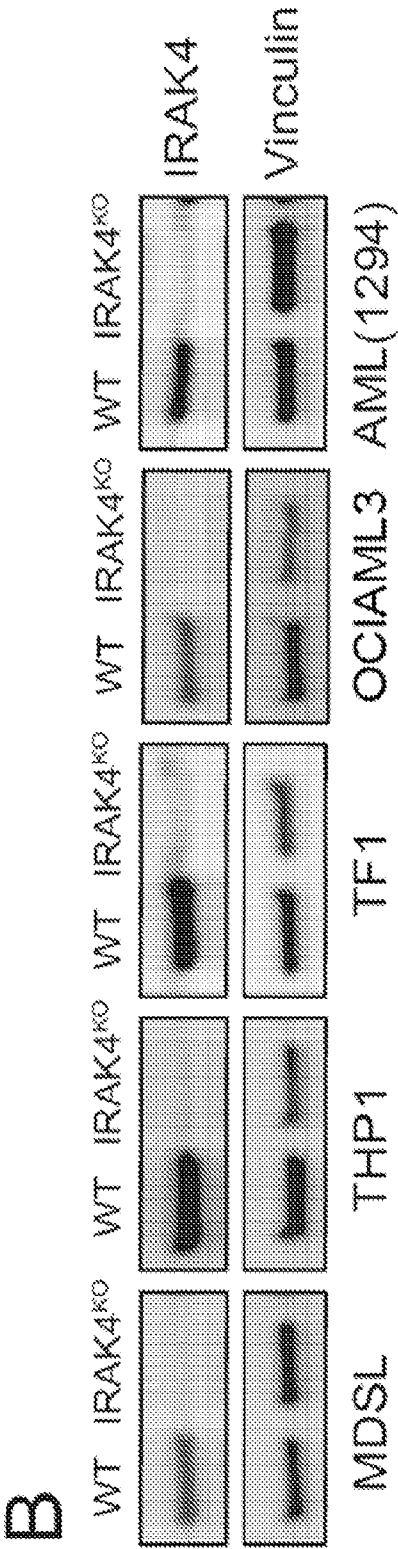


FIG. 9B

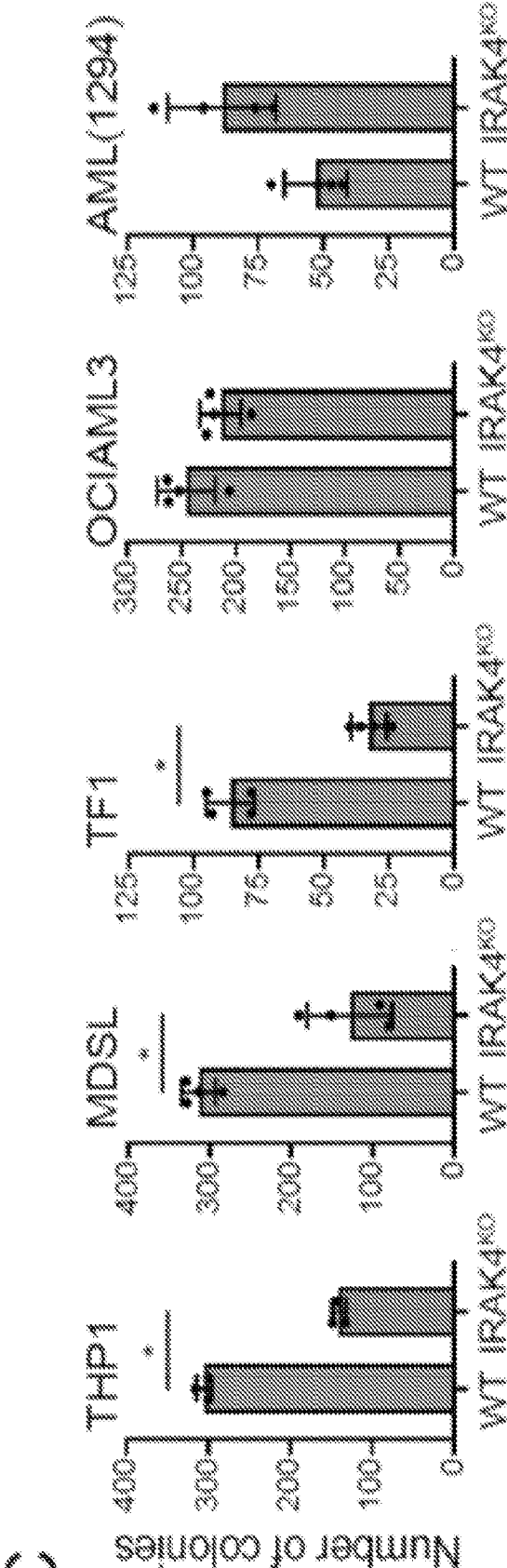
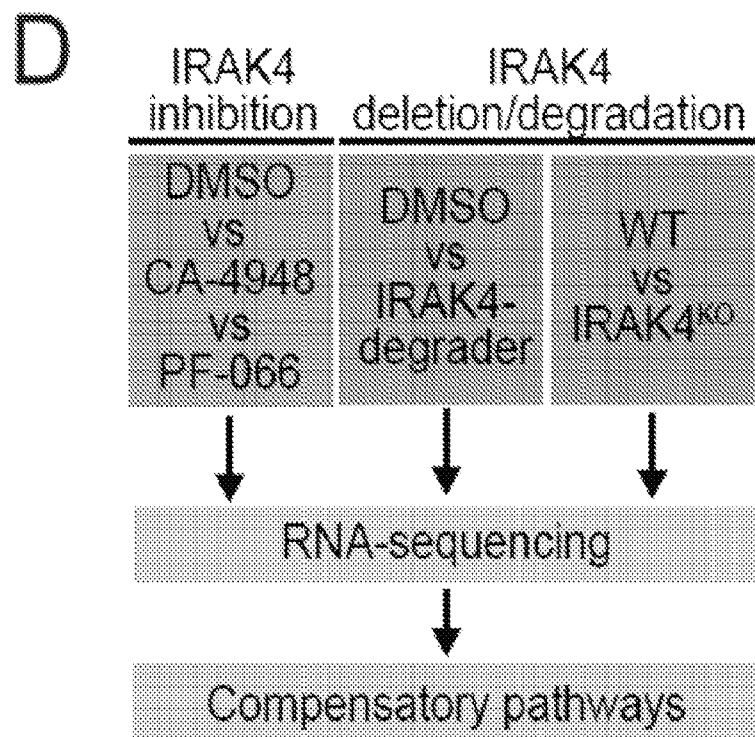
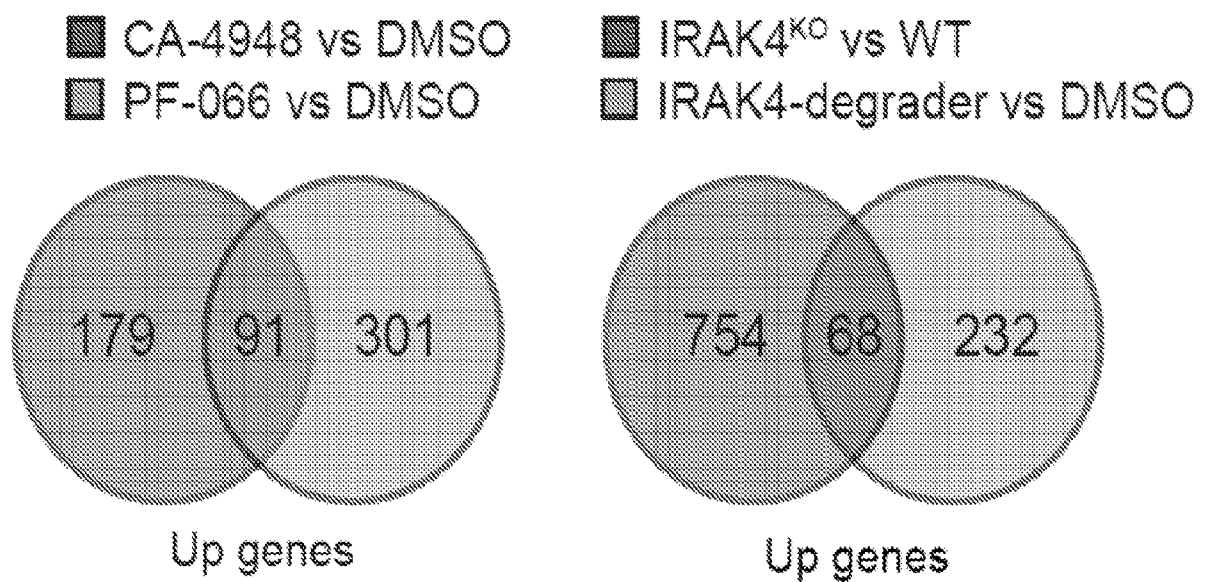


FIG. 9C

**FIG. 9D****E****FIG. 9E**

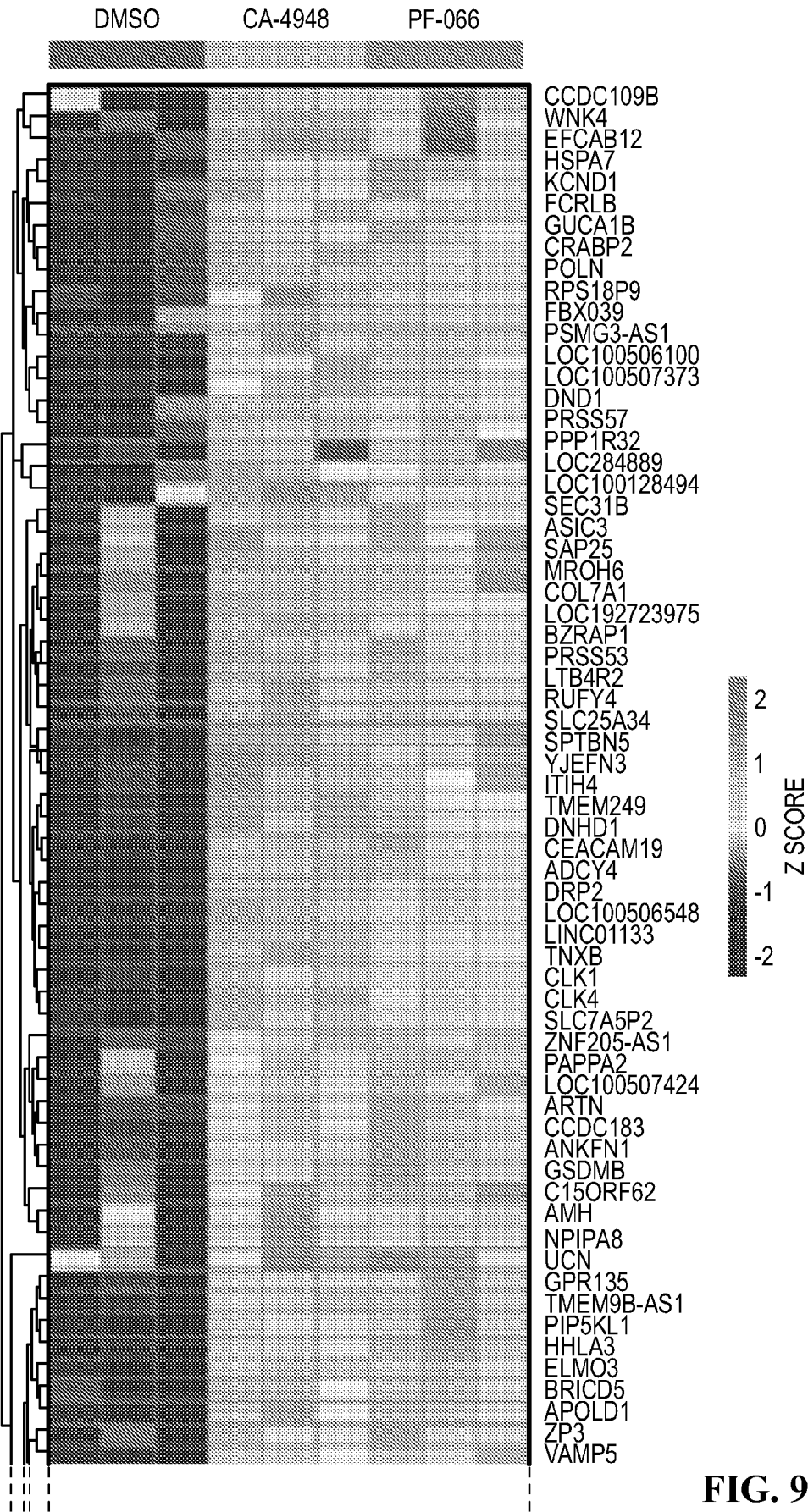
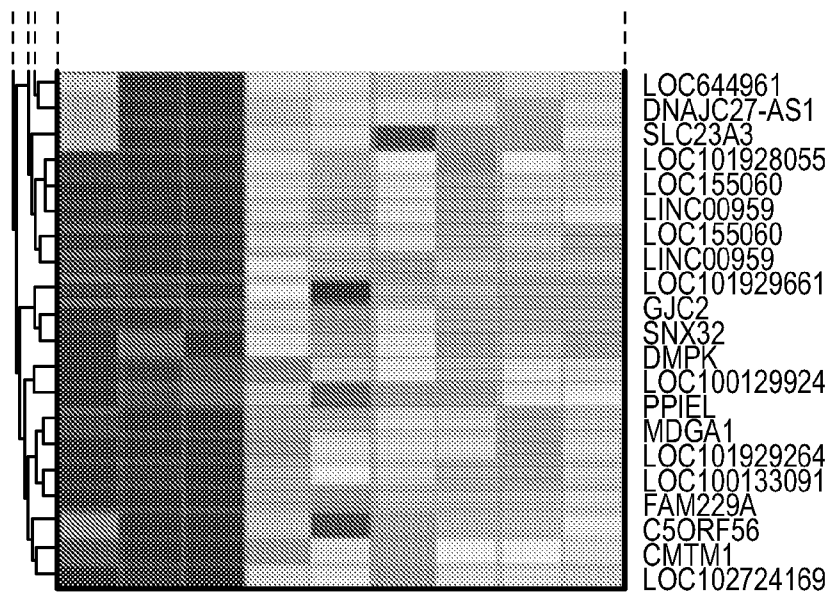


FIG. 9F

**FIG. 9F (Continued)**

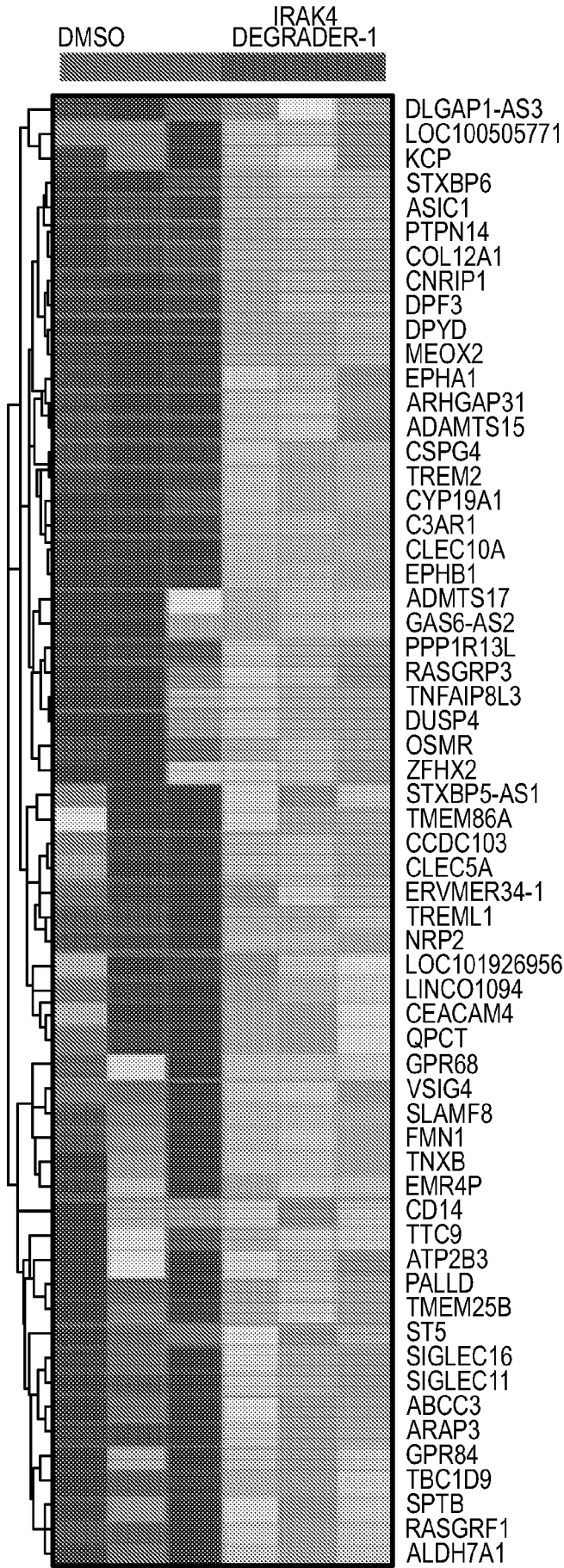


FIG. 9G

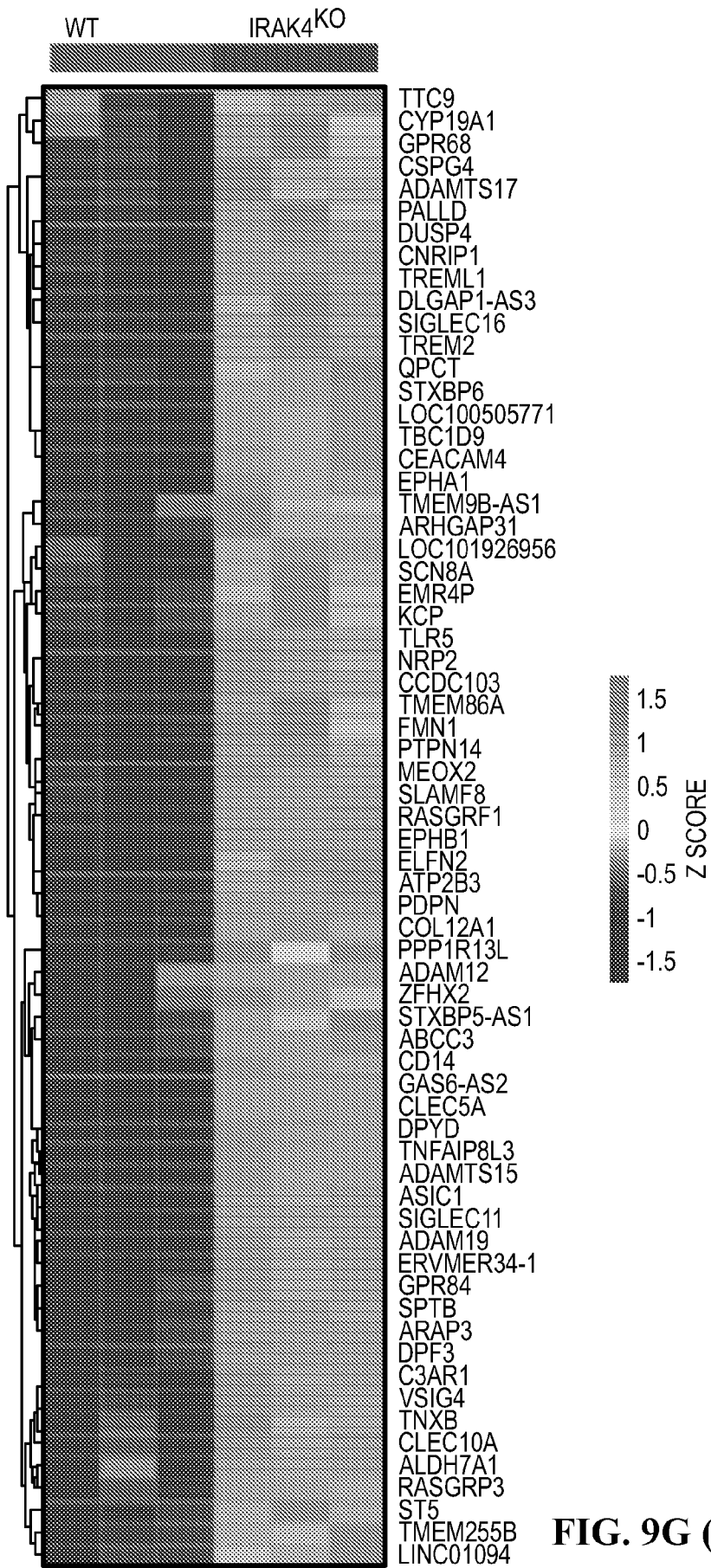


FIG. 9G (Continued)

H

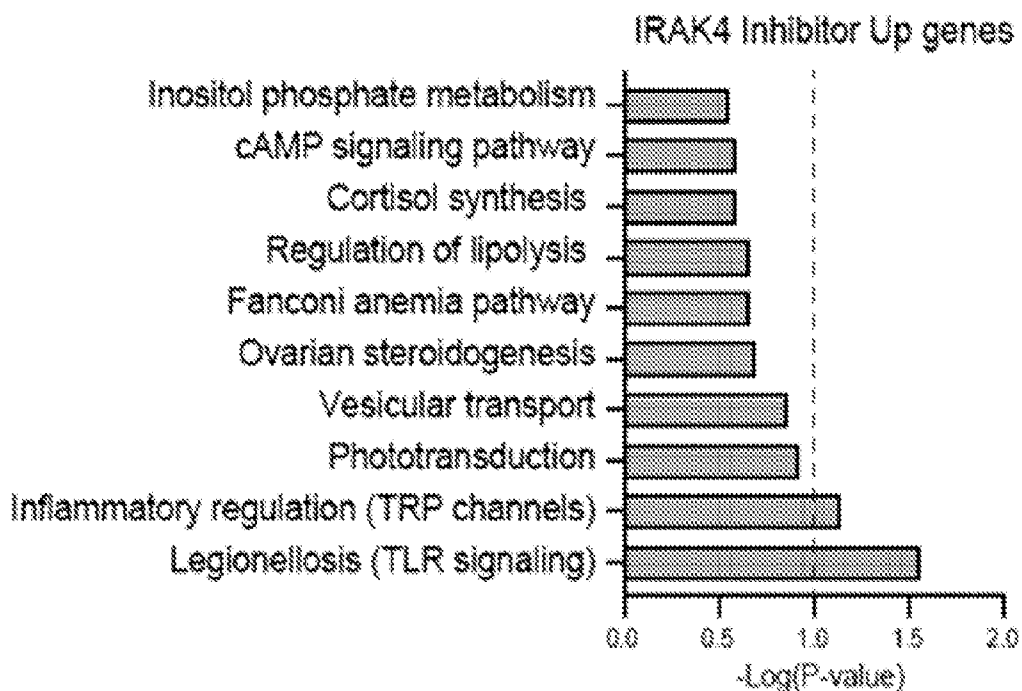


FIG. 9H

I

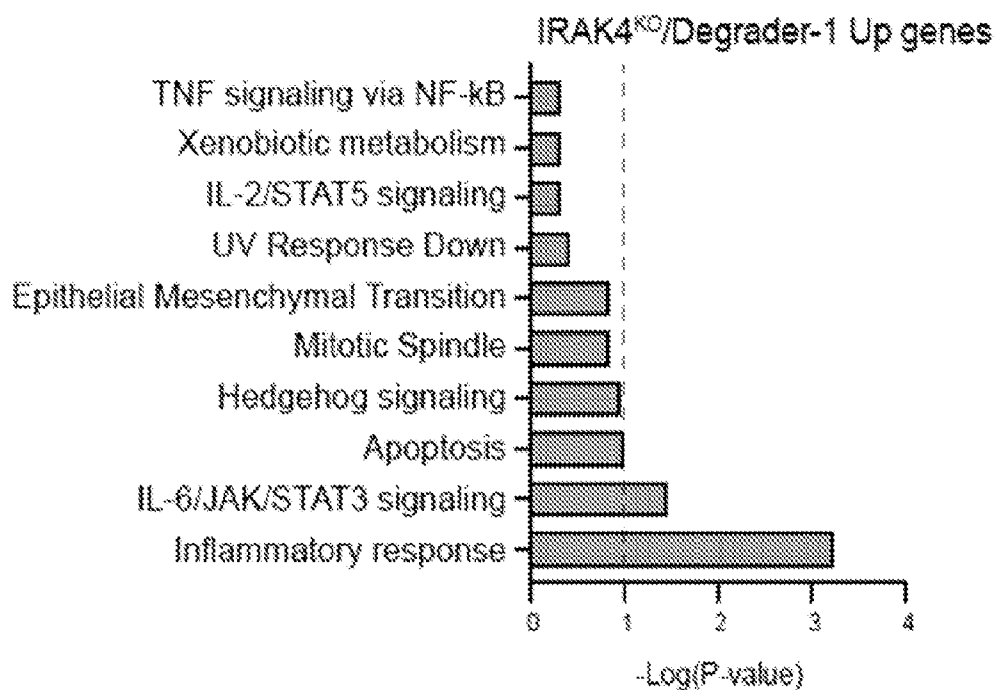


FIG. 9I

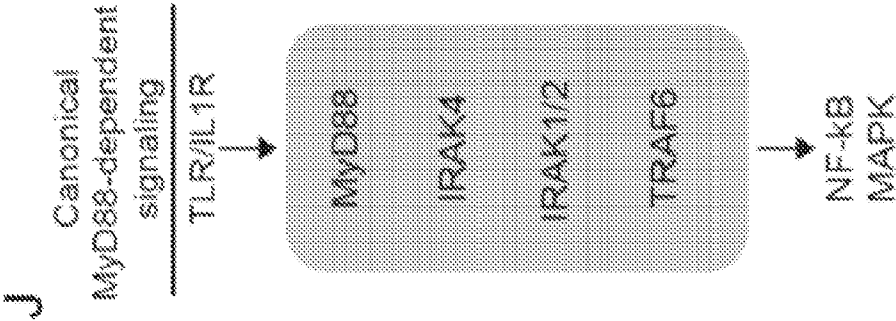


FIG. 9J

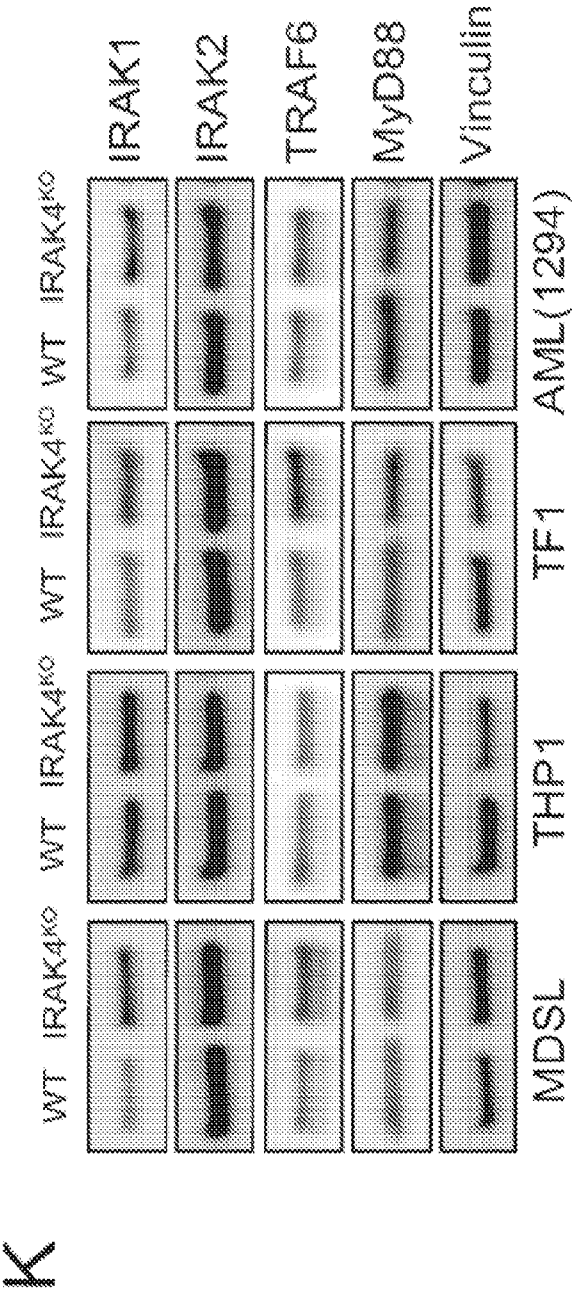
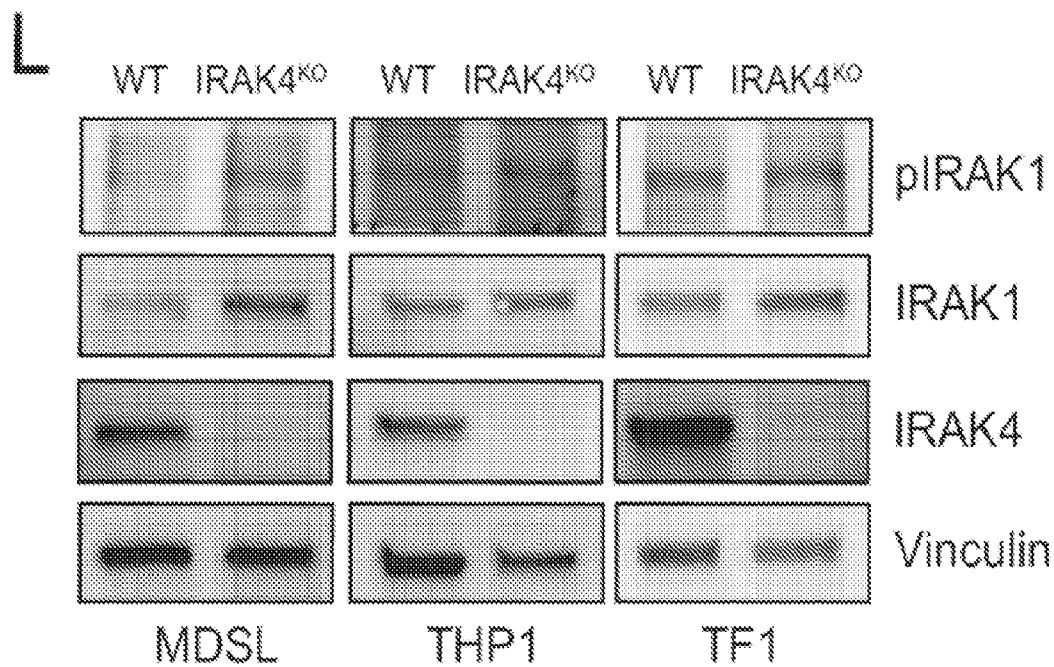
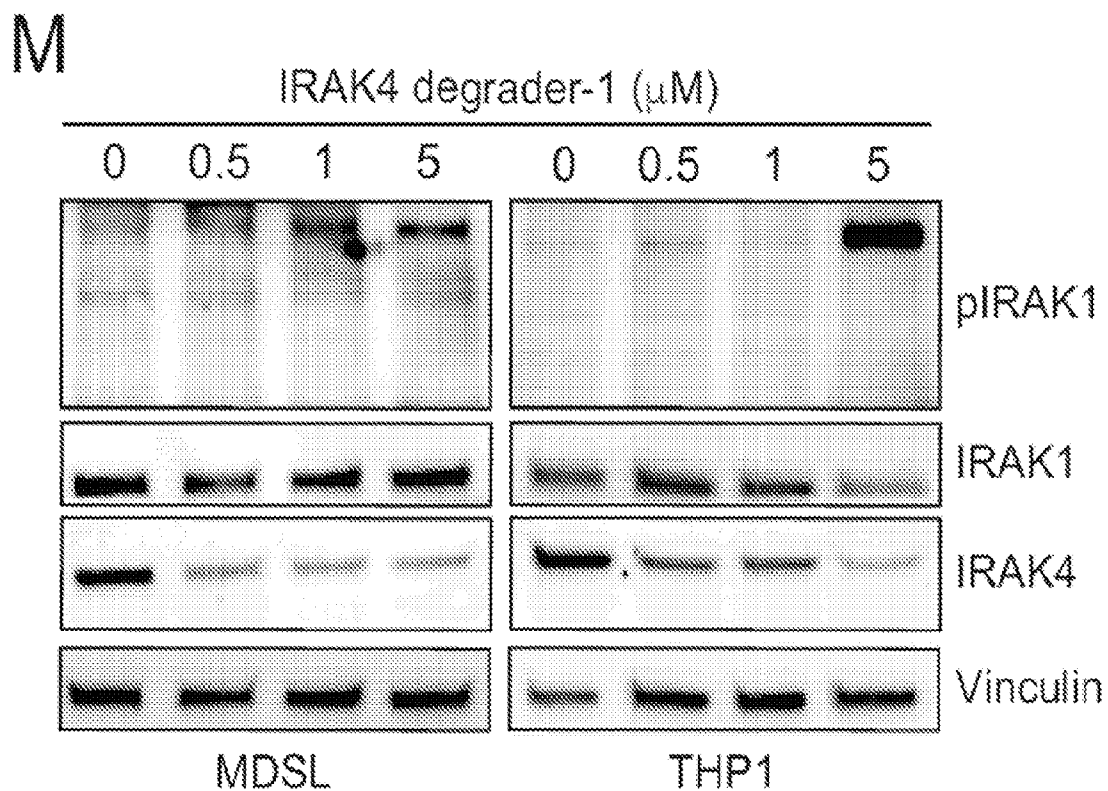


FIG. 9K

**FIG. 9L****FIG. 9M**

N

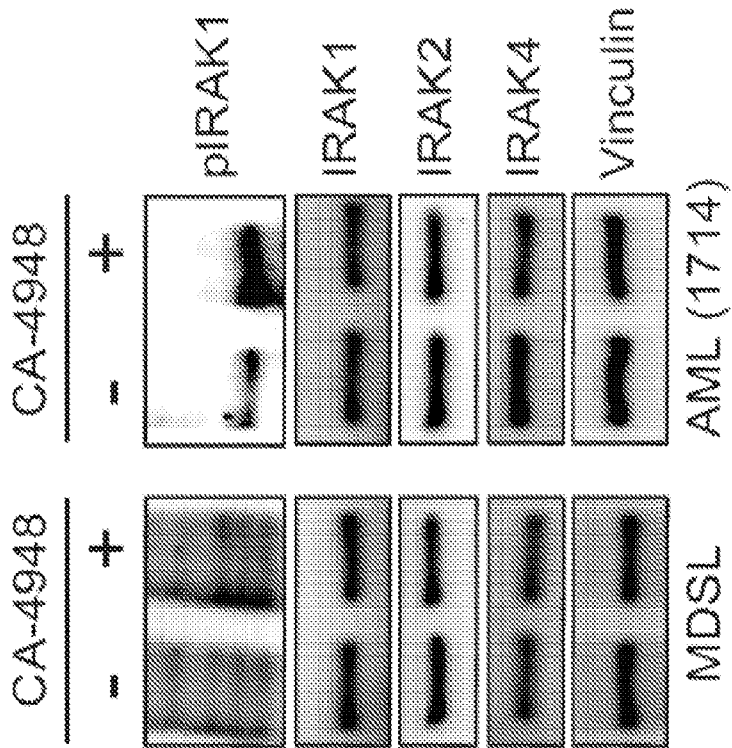


FIG. 9N

A

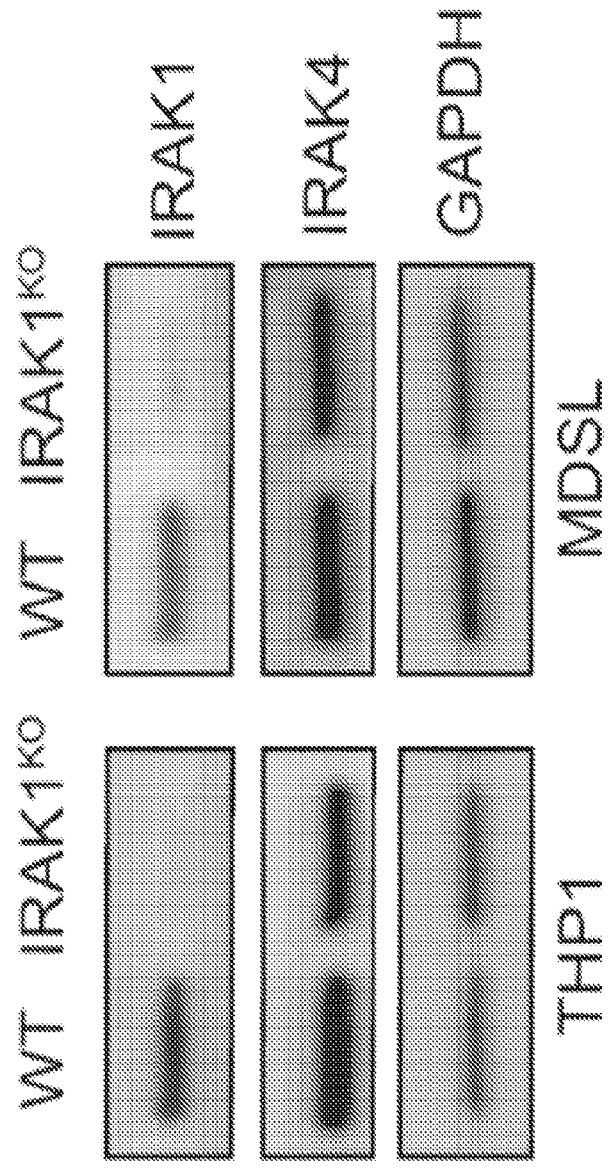


FIG. 10A

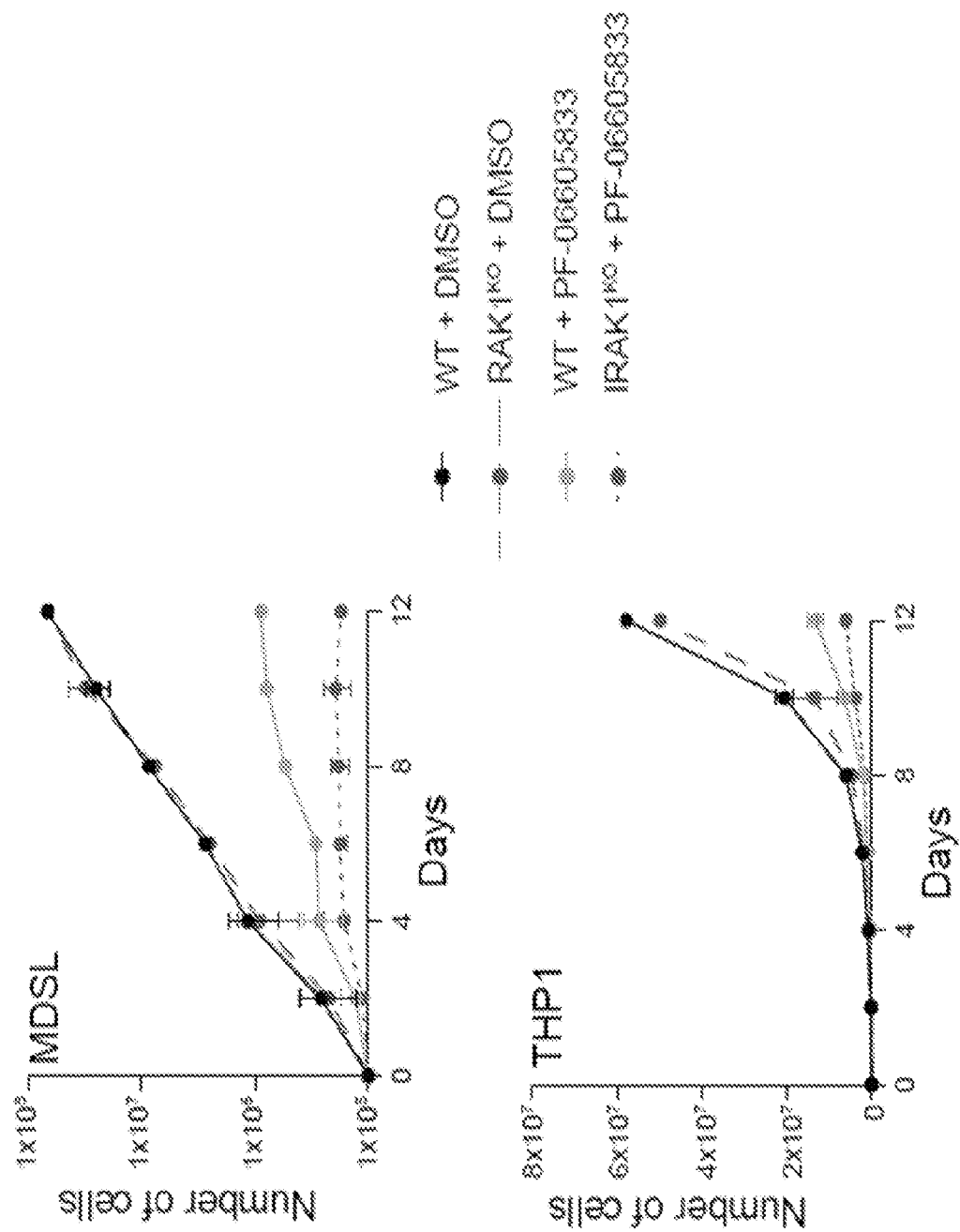


FIG. 10B

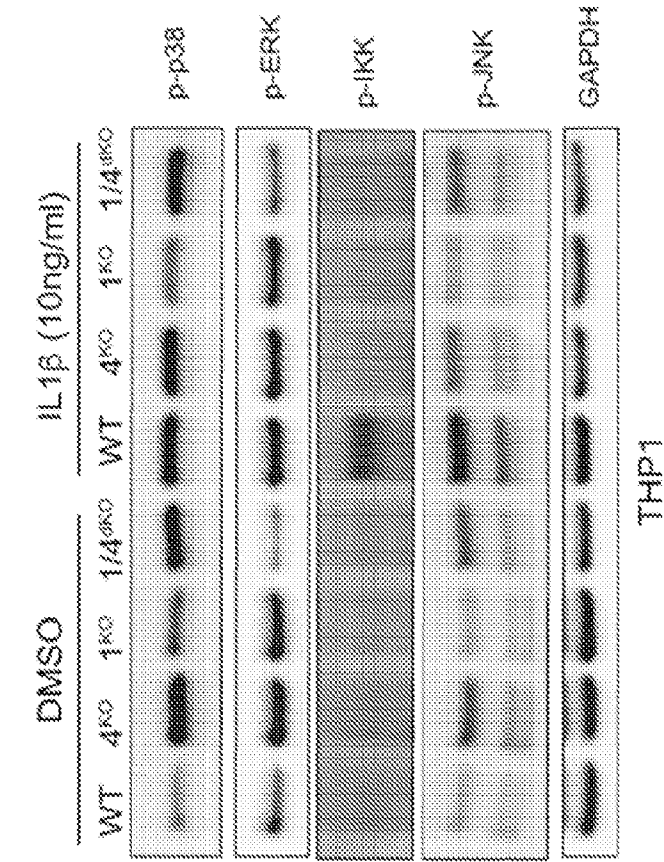


FIG. 10D

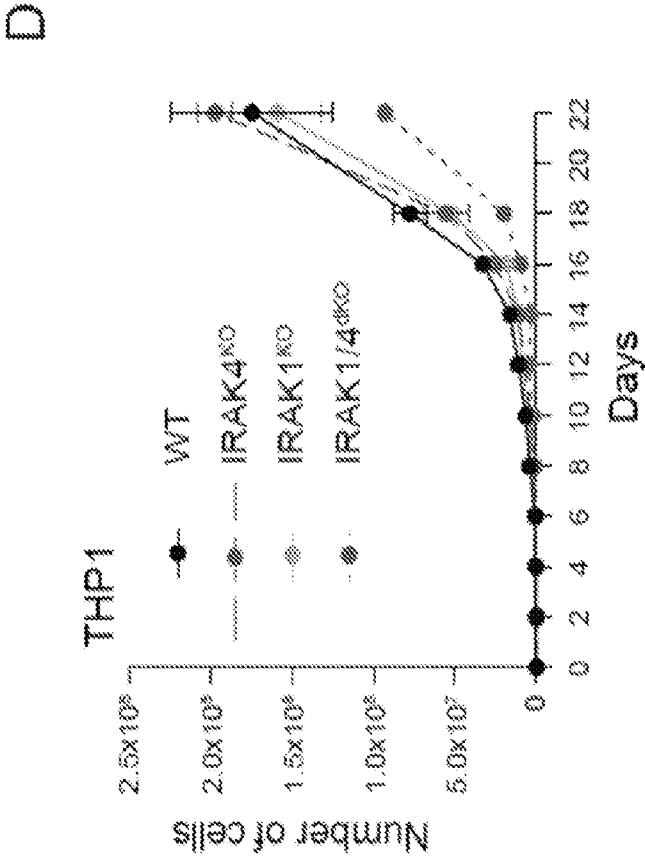


FIG. 10C

E

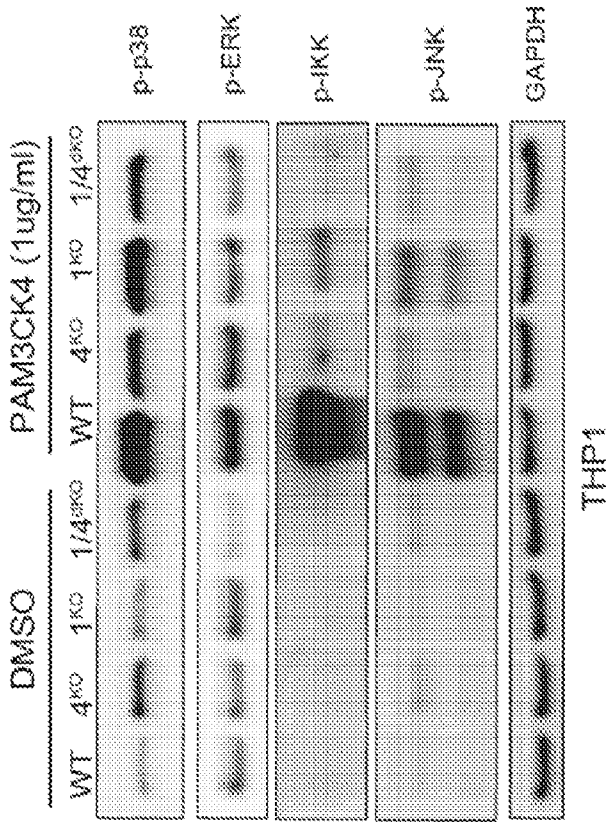


FIG. 10E

F

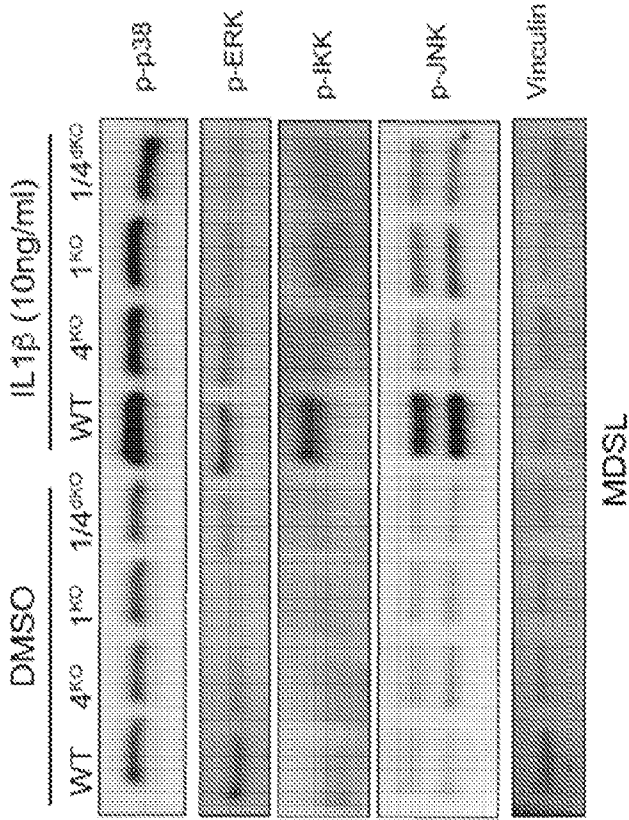


FIG. 10F

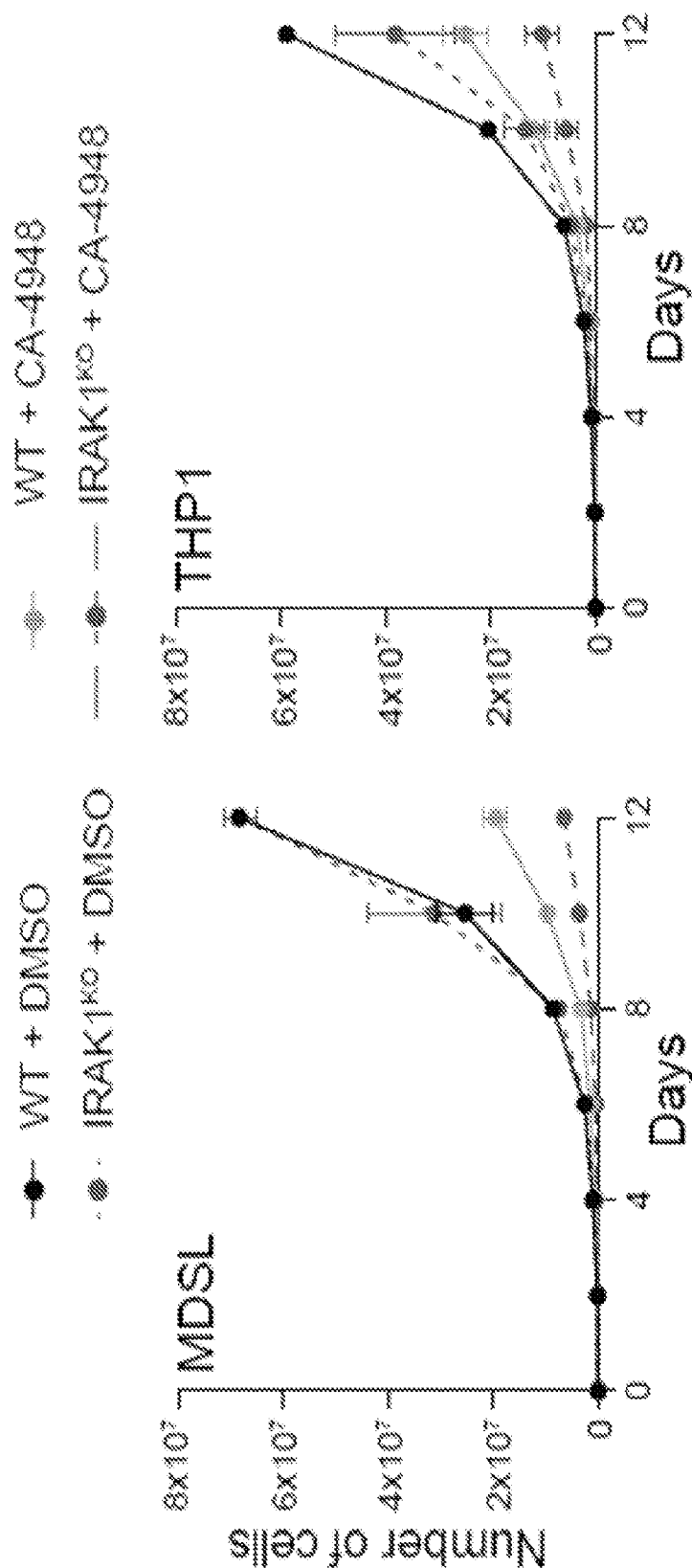
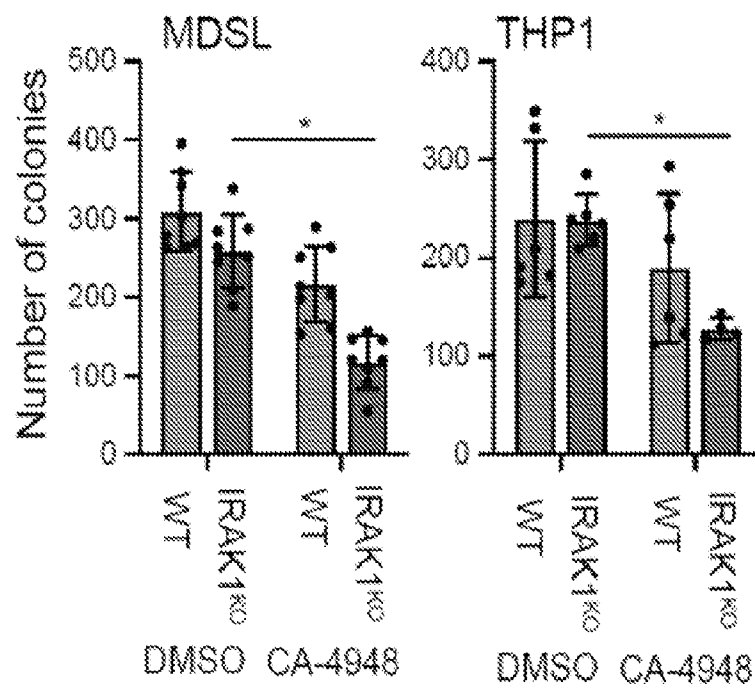
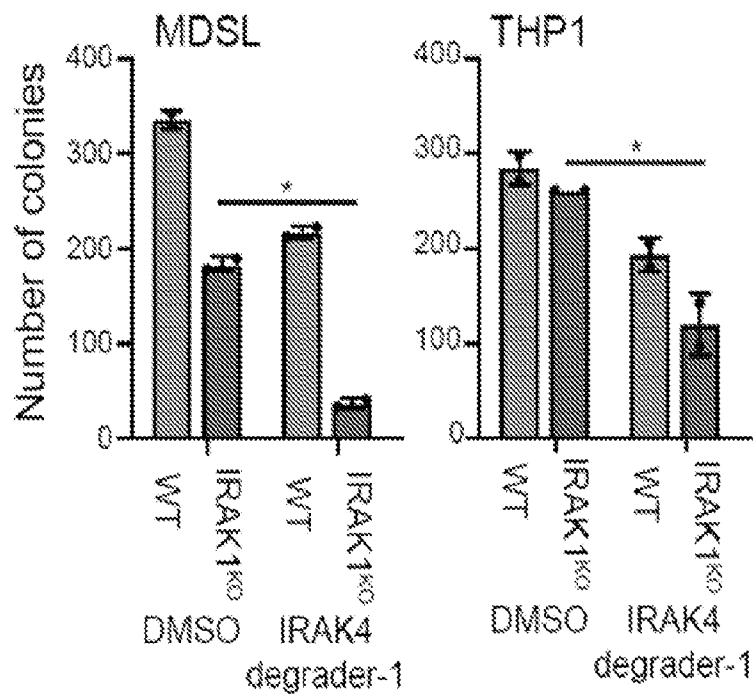


FIG. 11A

B**FIG. 11B****C****FIG. 11C**

D

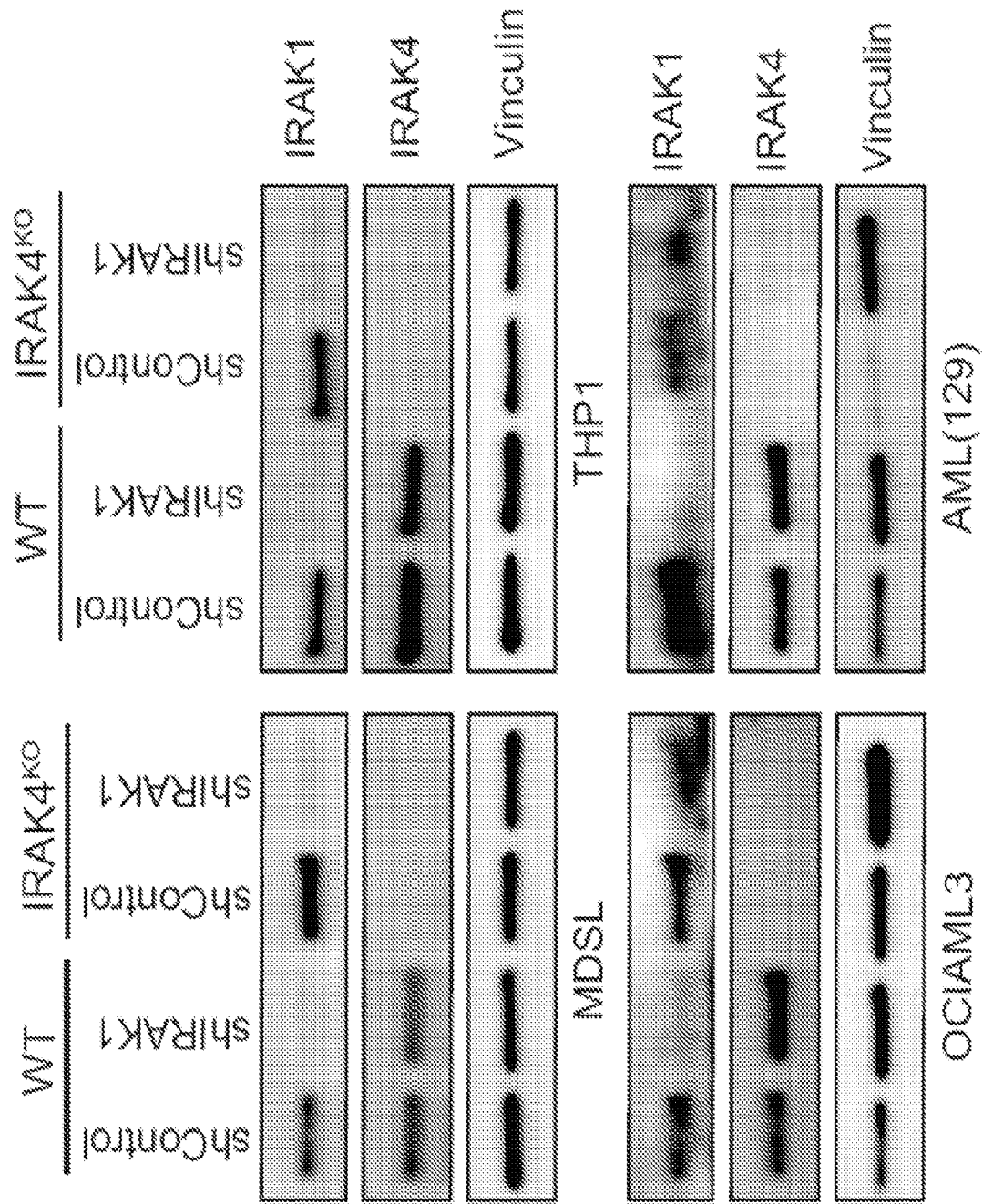
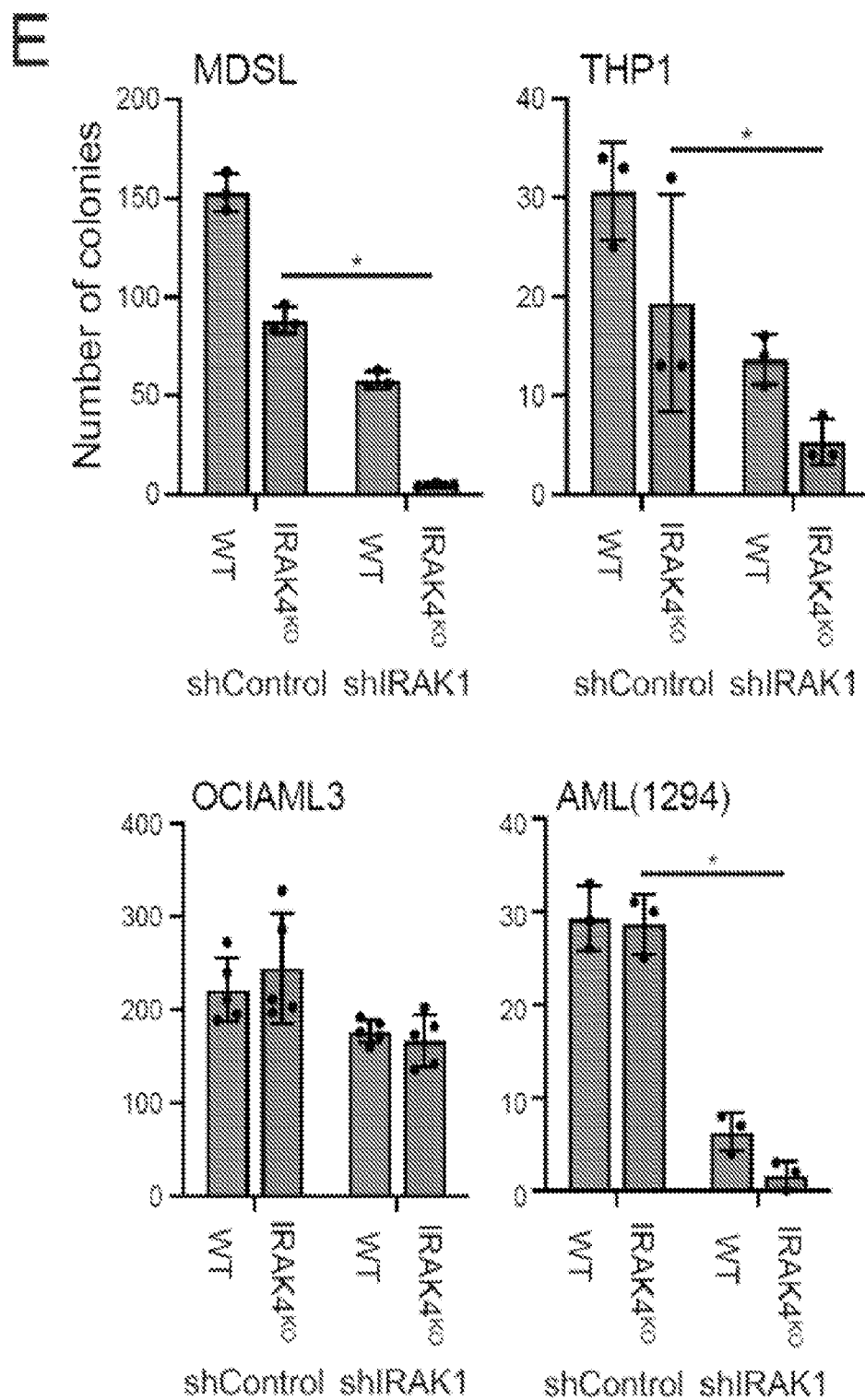


FIG. 11D

**FIG. 11E**

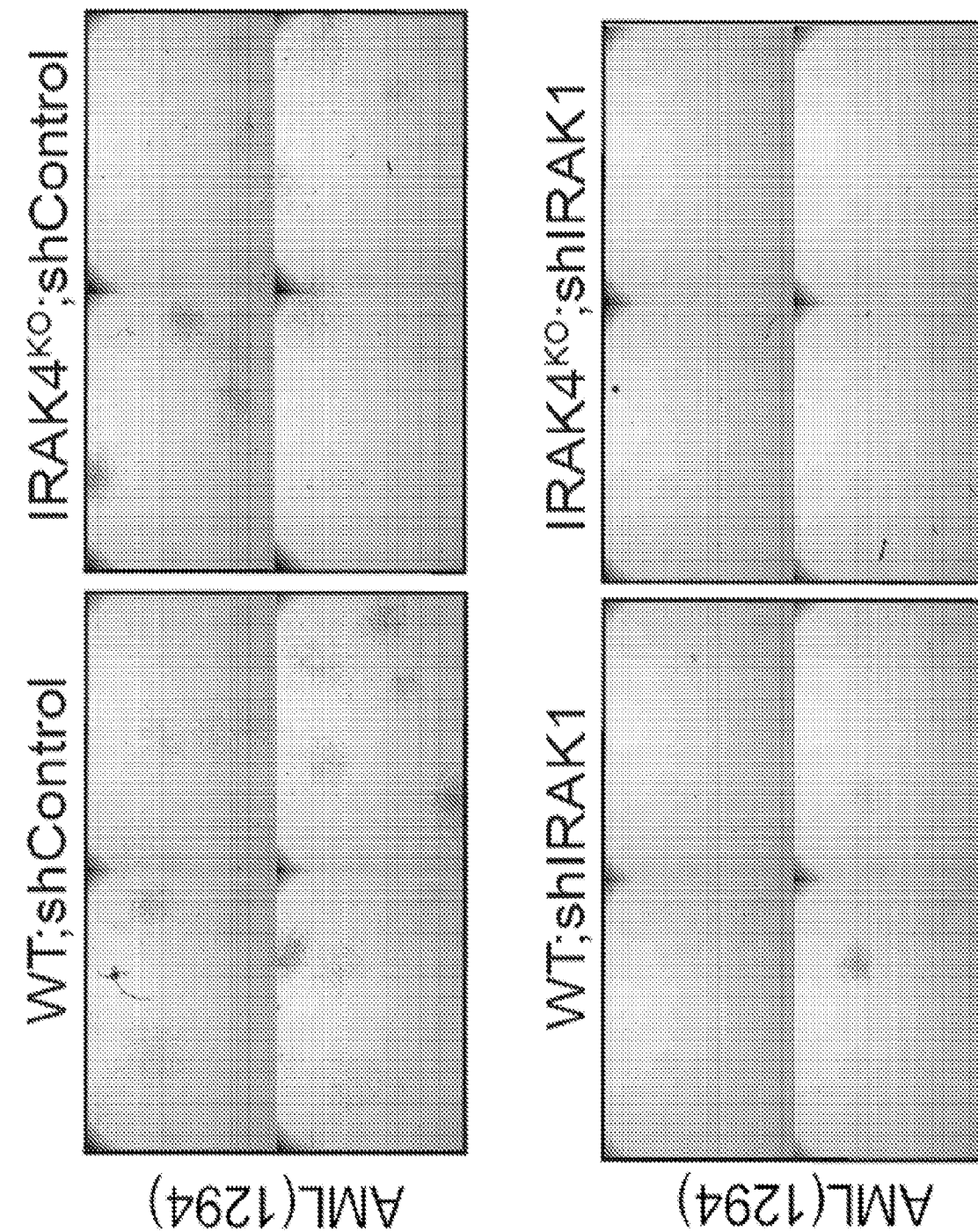


FIG. 11F

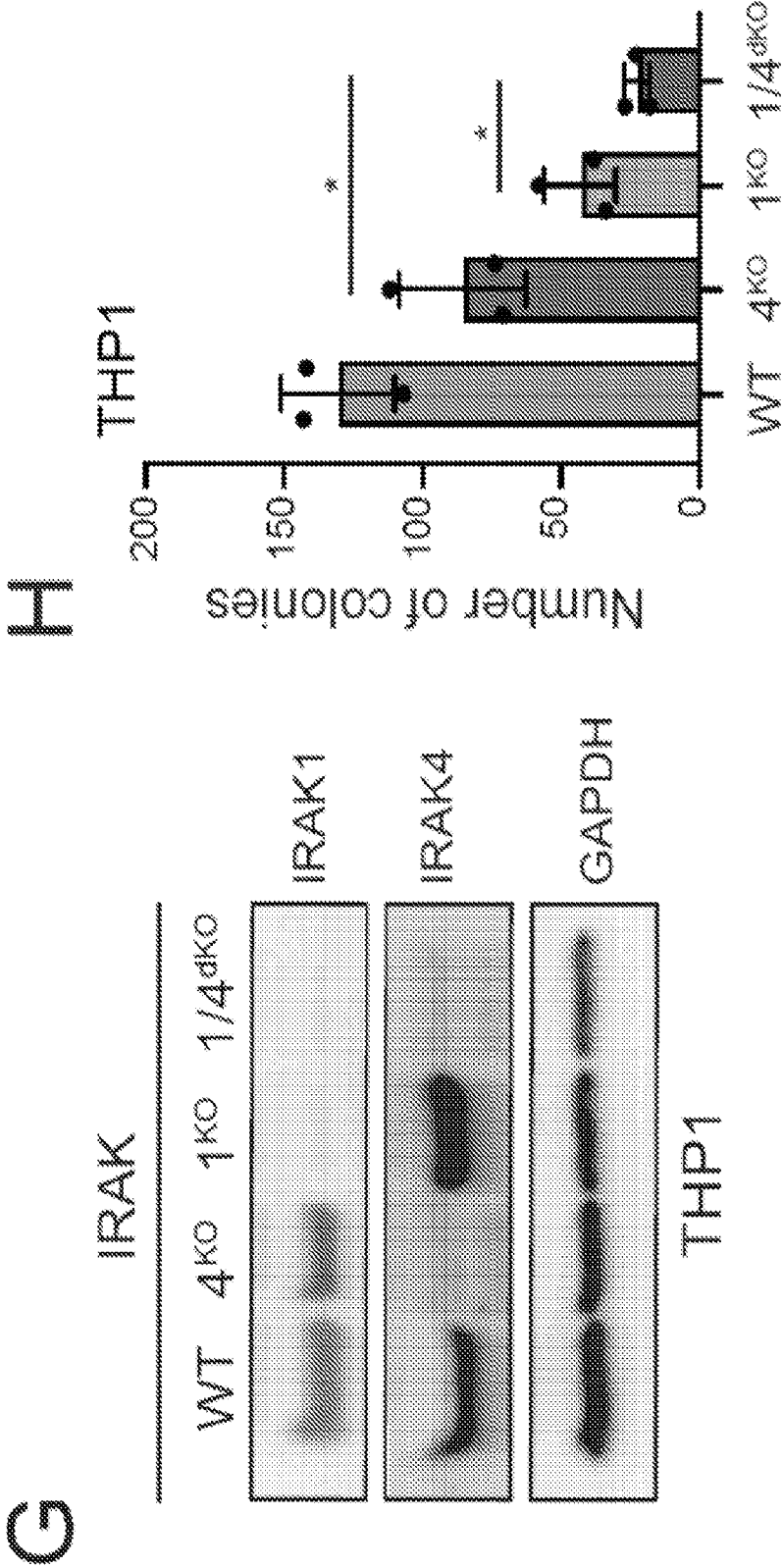


FIG. 11H

FIG. 11G

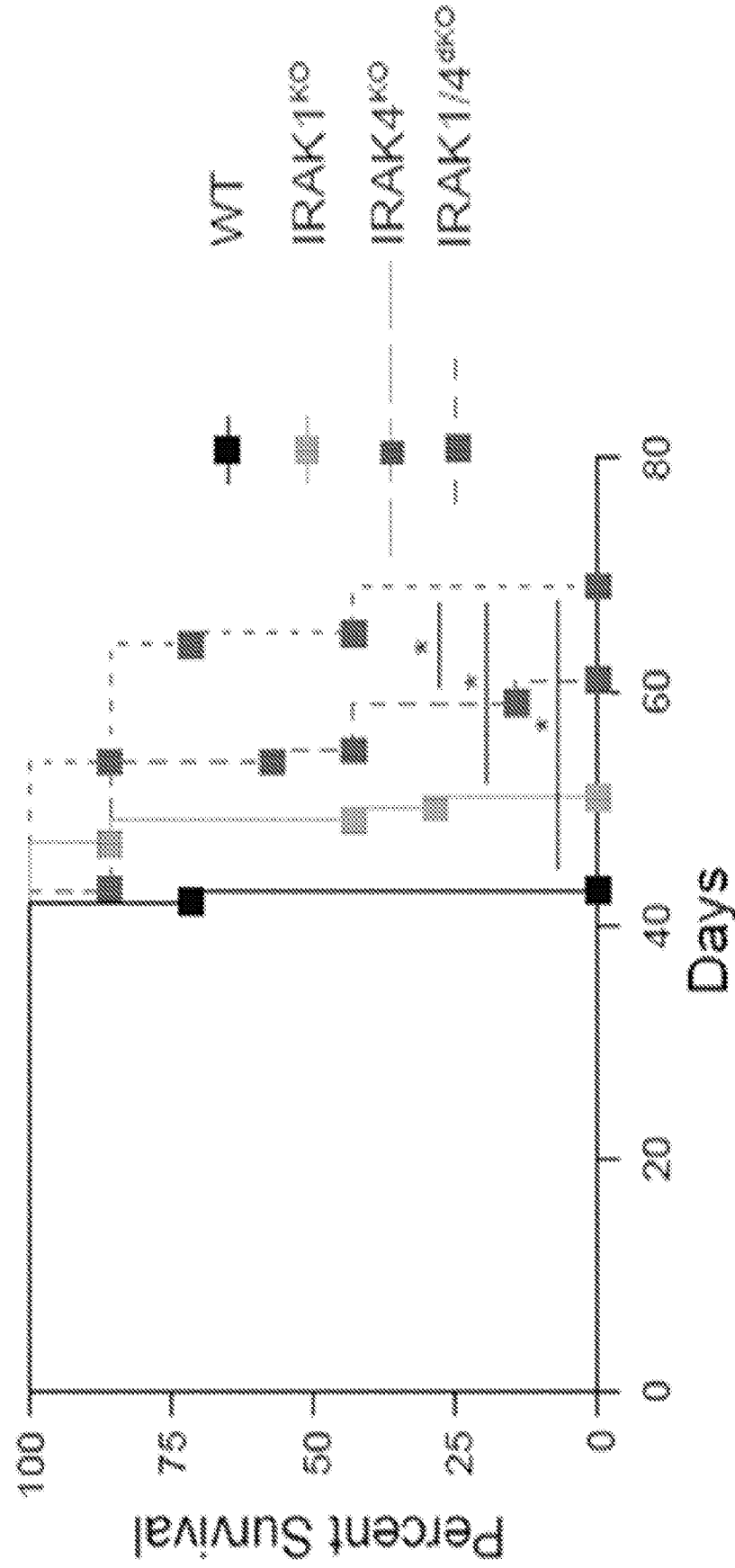


FIG. 11I

K

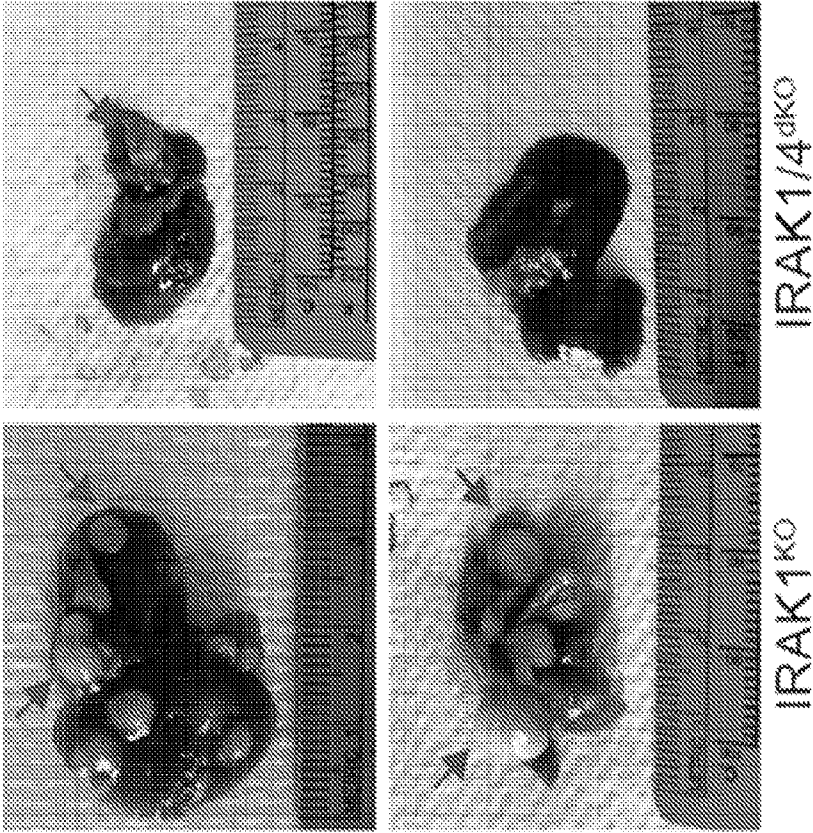


FIG. 11K

J

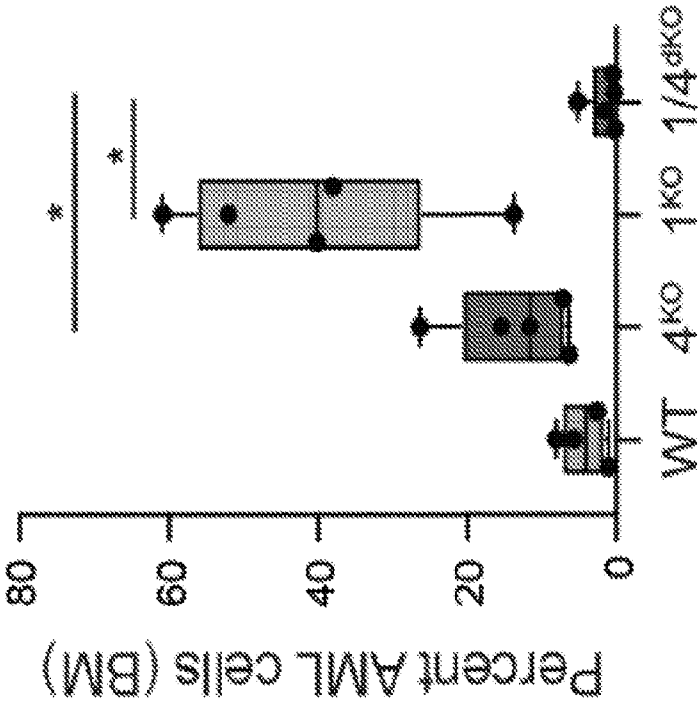


FIG. 11J

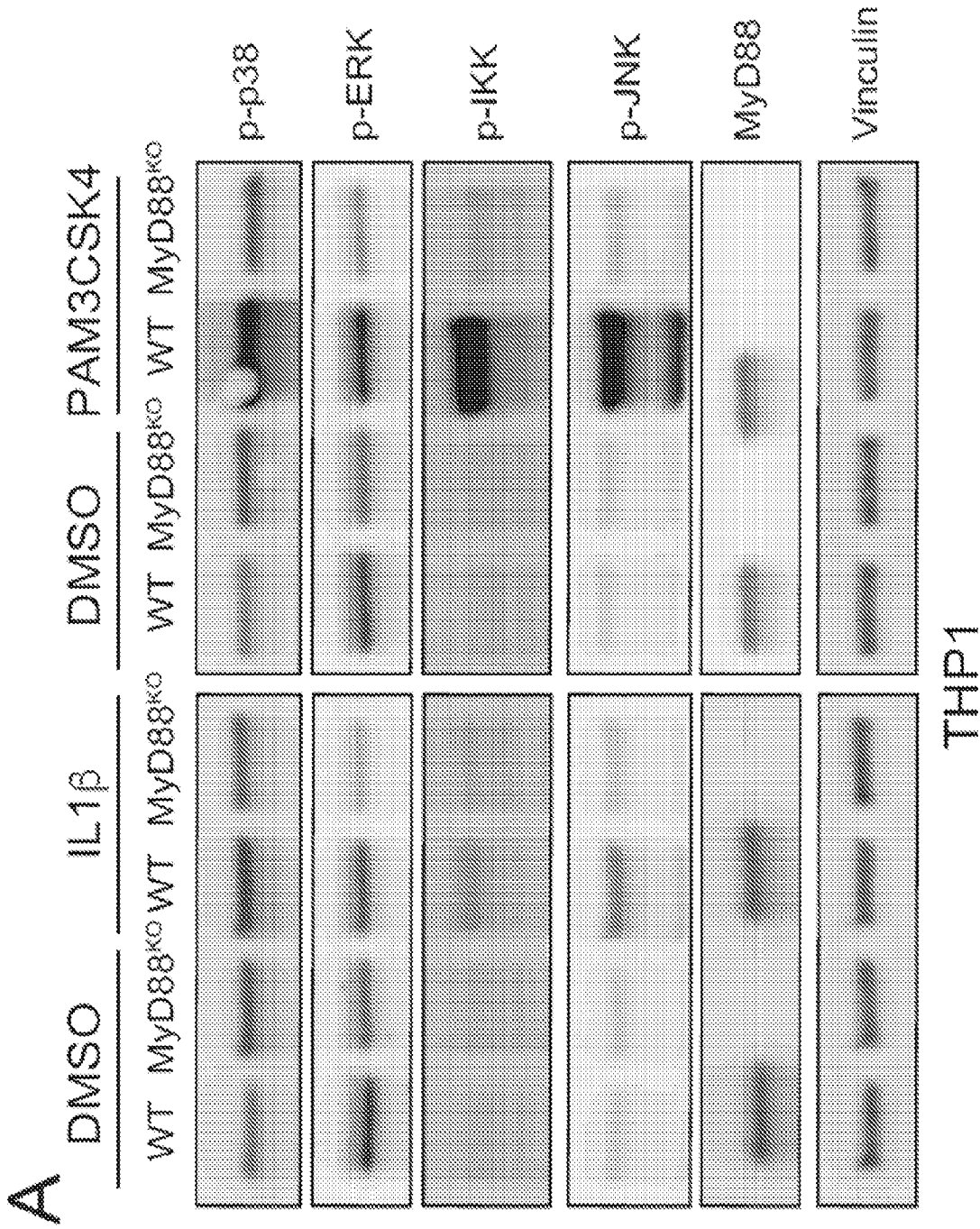


FIG. 12A

B

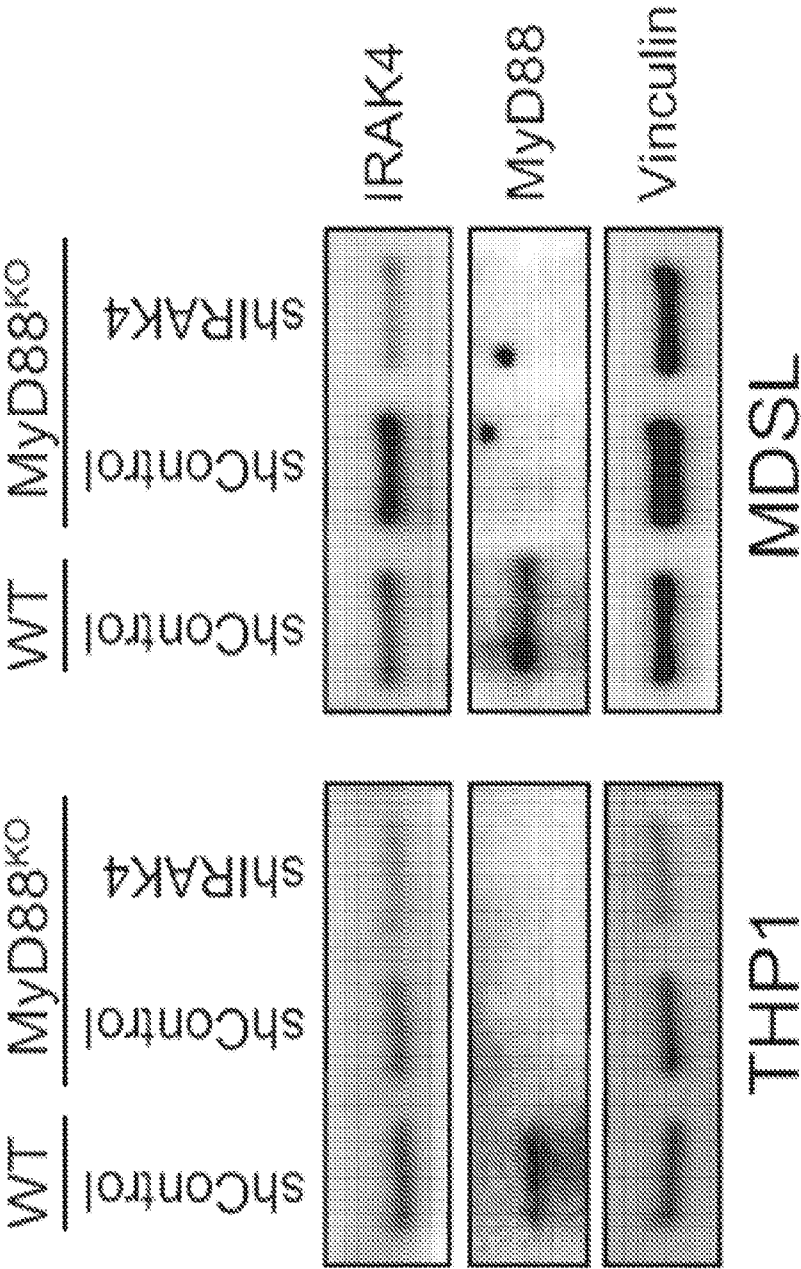


FIG. 12B

C

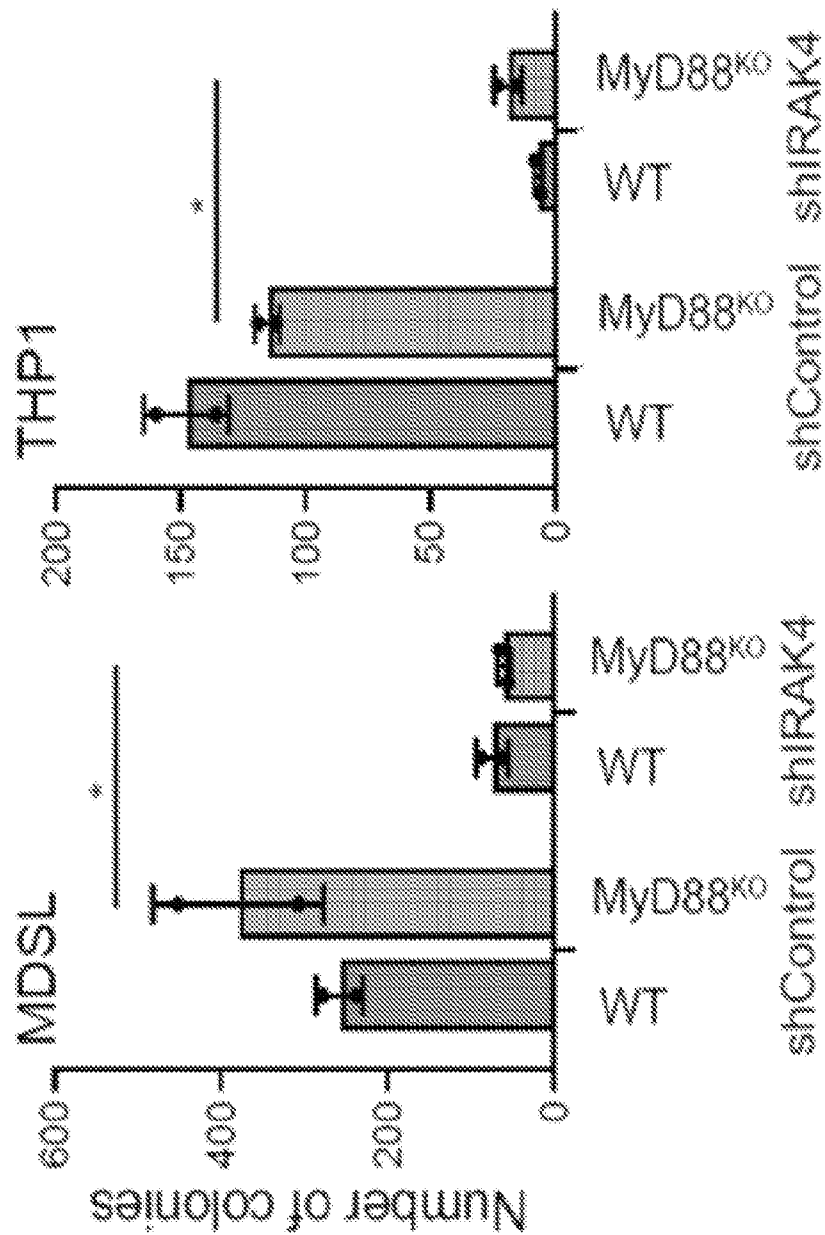
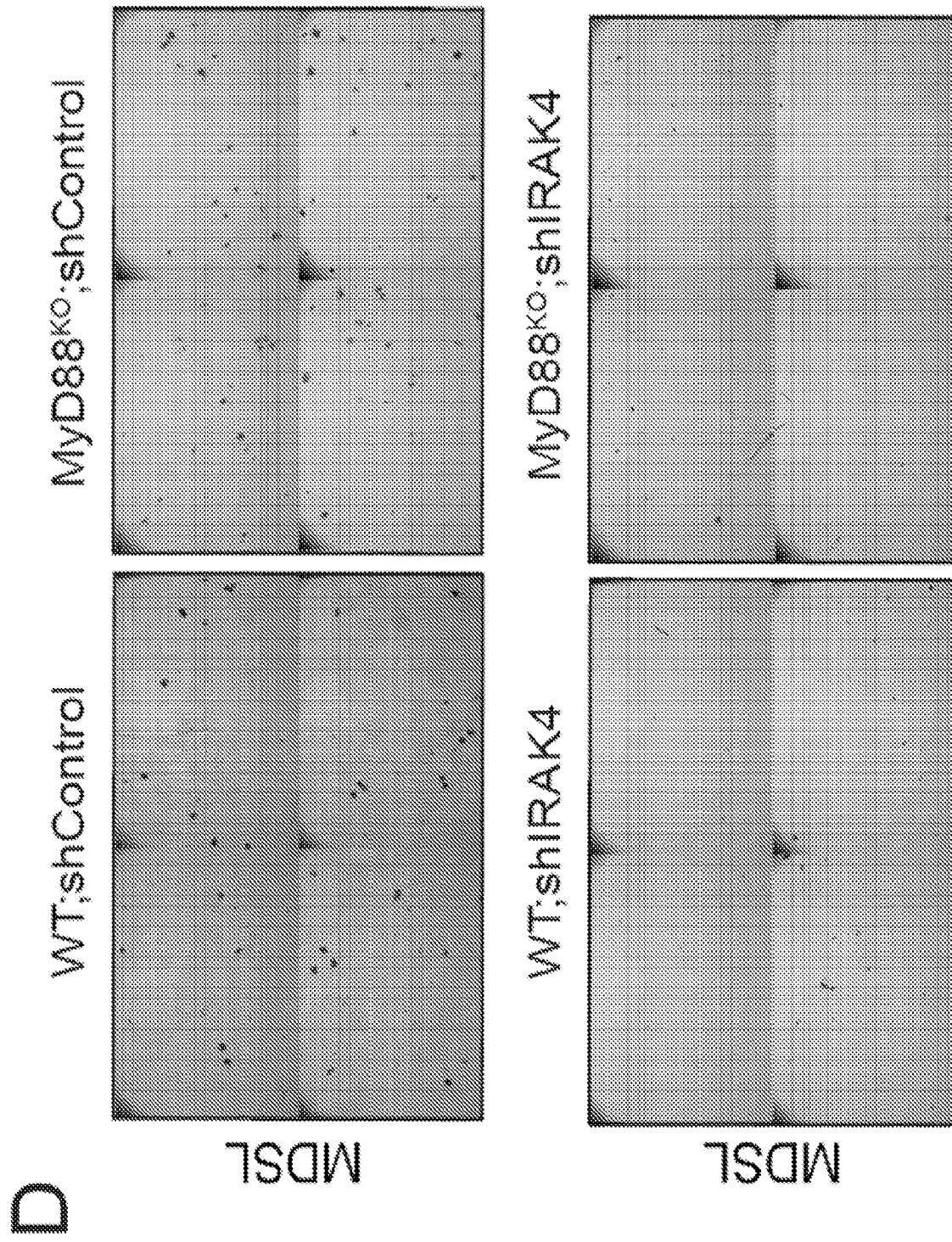


FIG. 12C

**FIG. 12D**

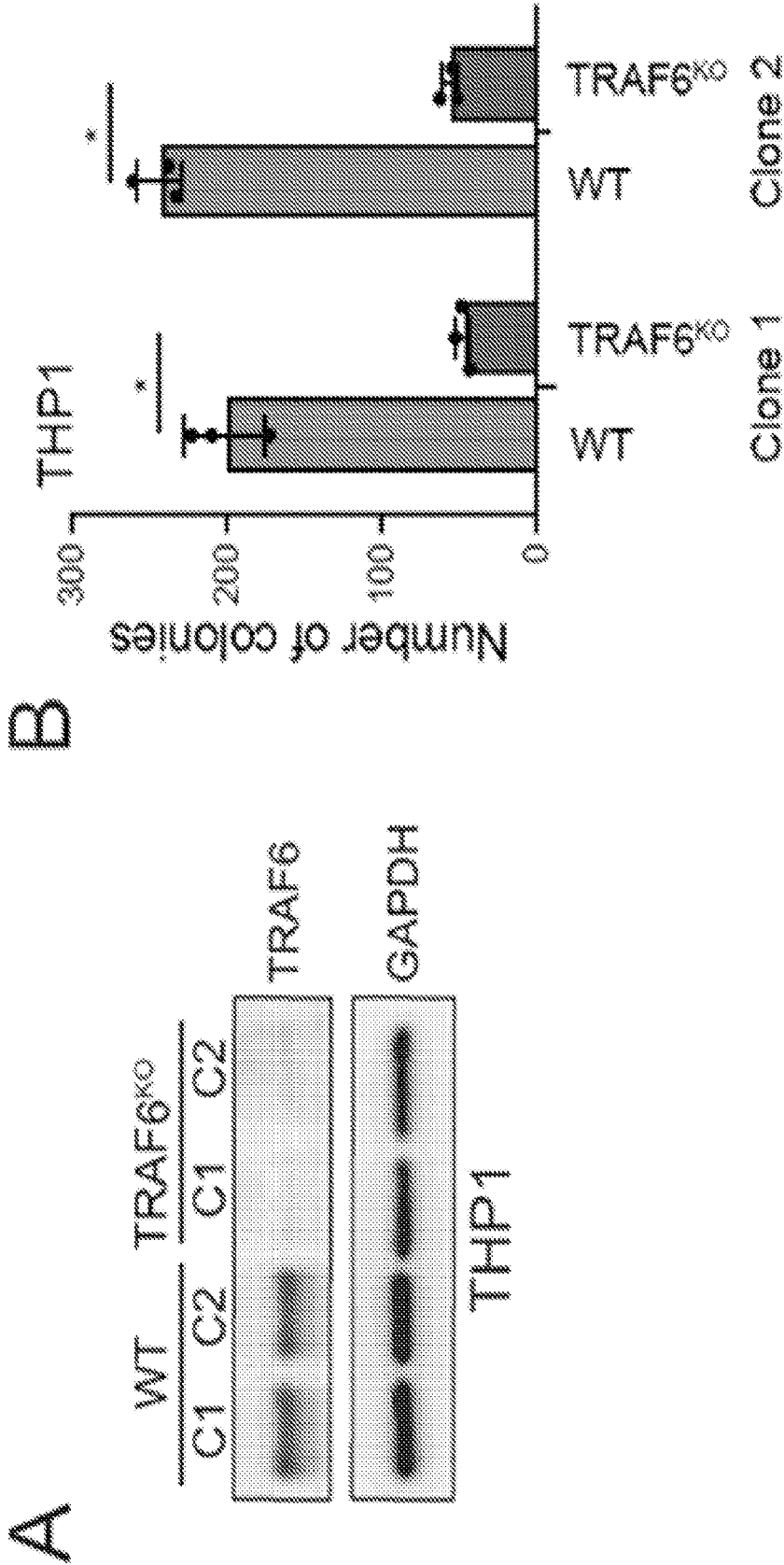


FIG. 13A

FIG. 13B

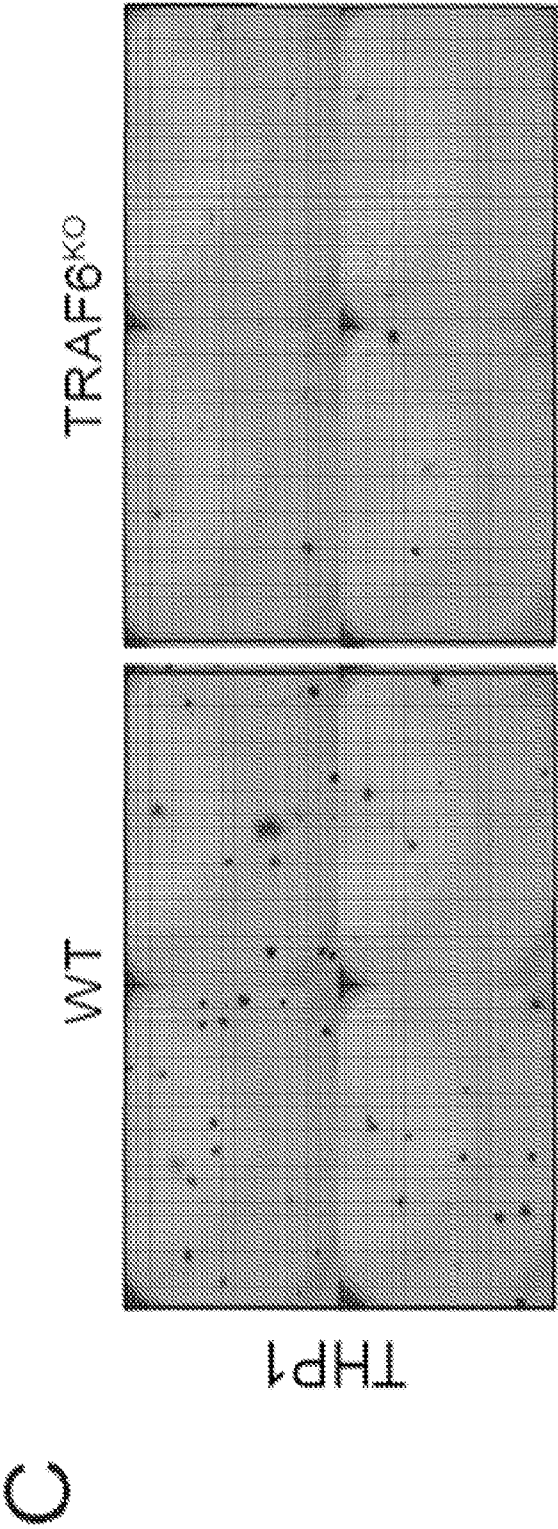


FIG. 13C

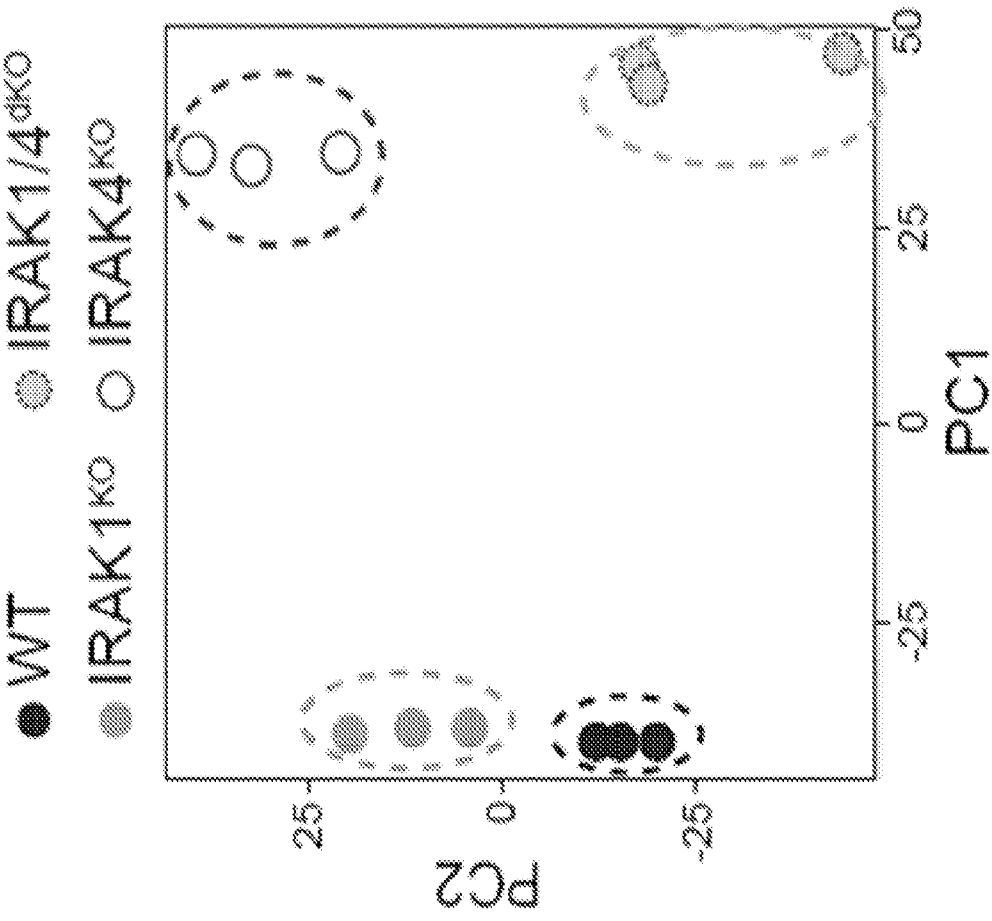
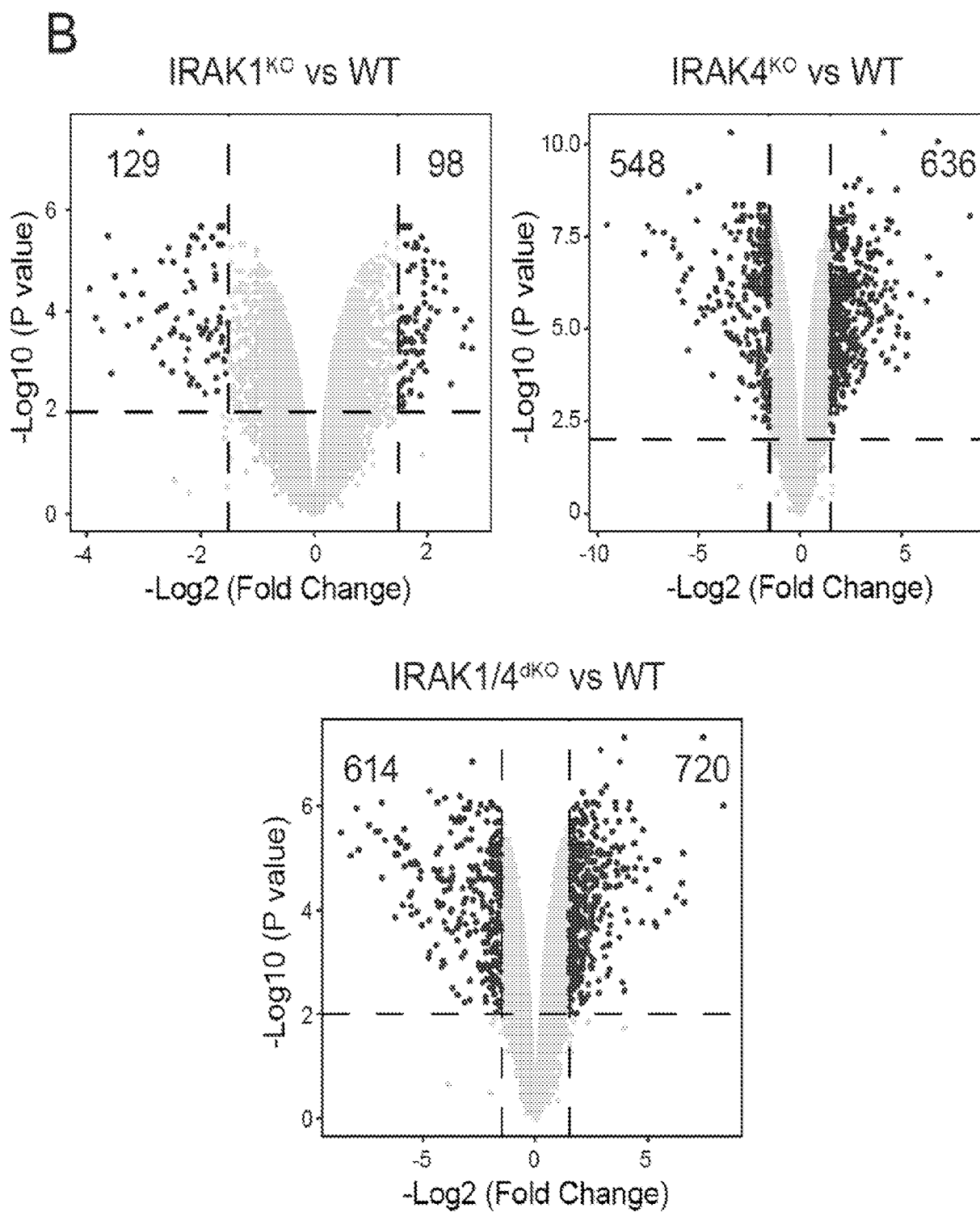
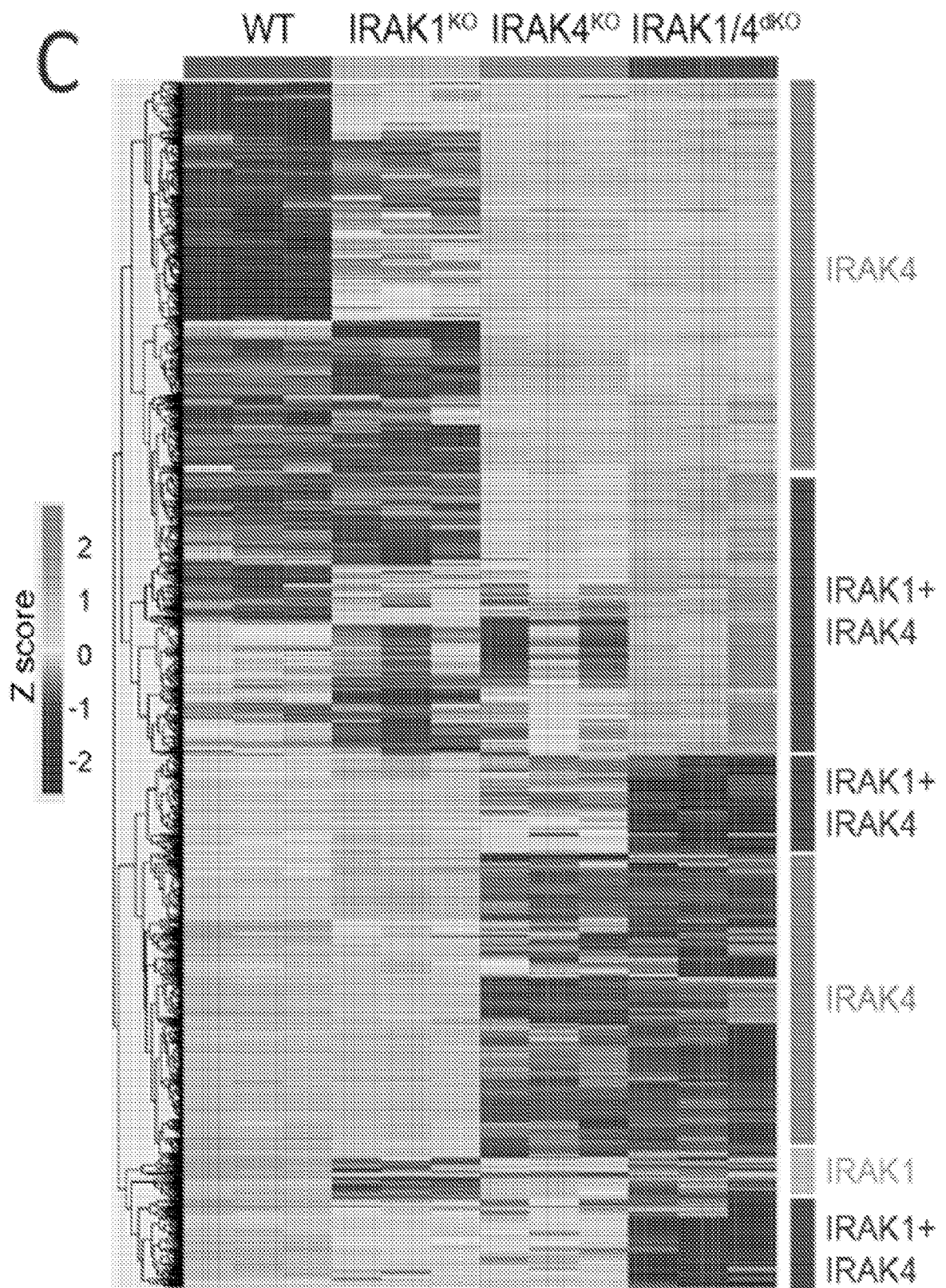


FIG. 14A

**FIG. 14B**

**FIG. 14C**

D

MyD88-independent genes

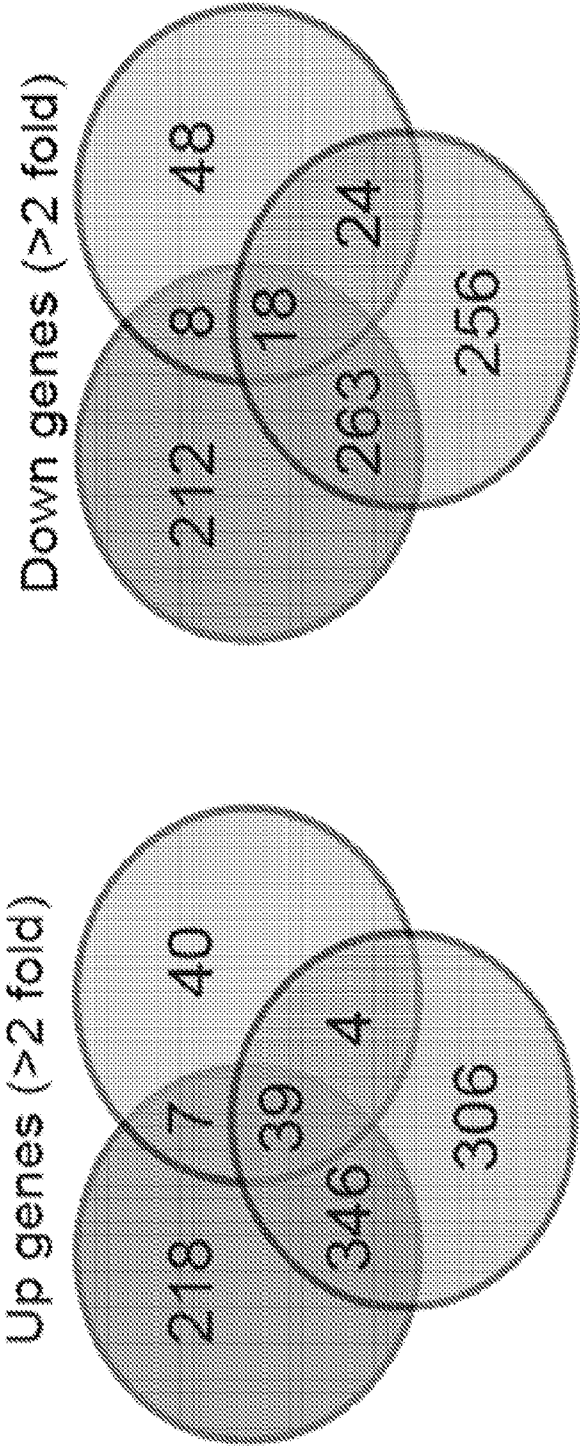
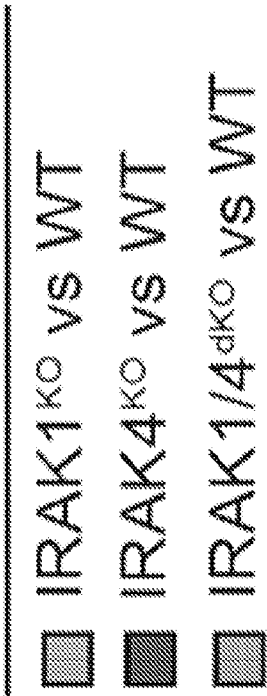


FIG. 14D

E

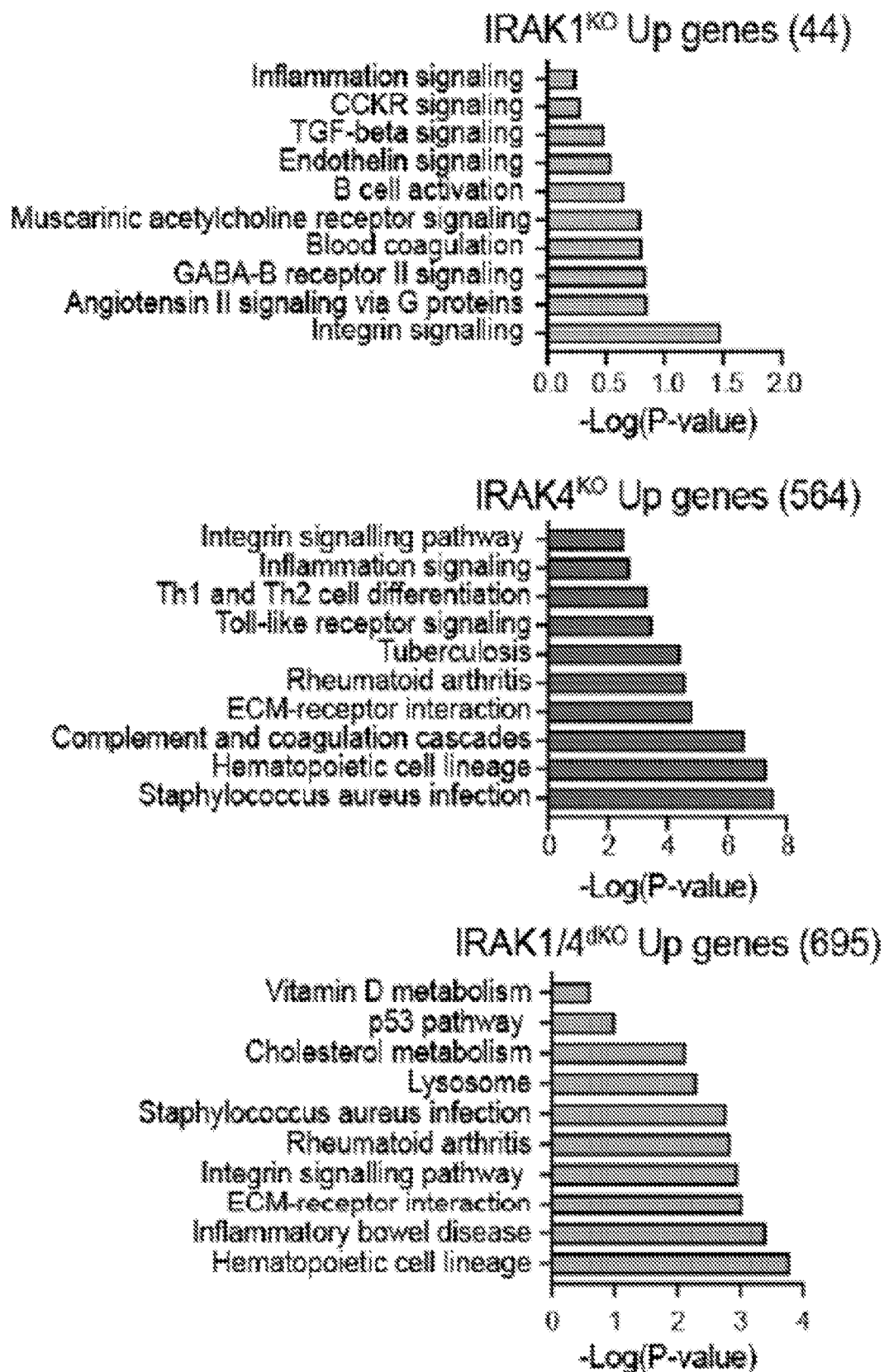
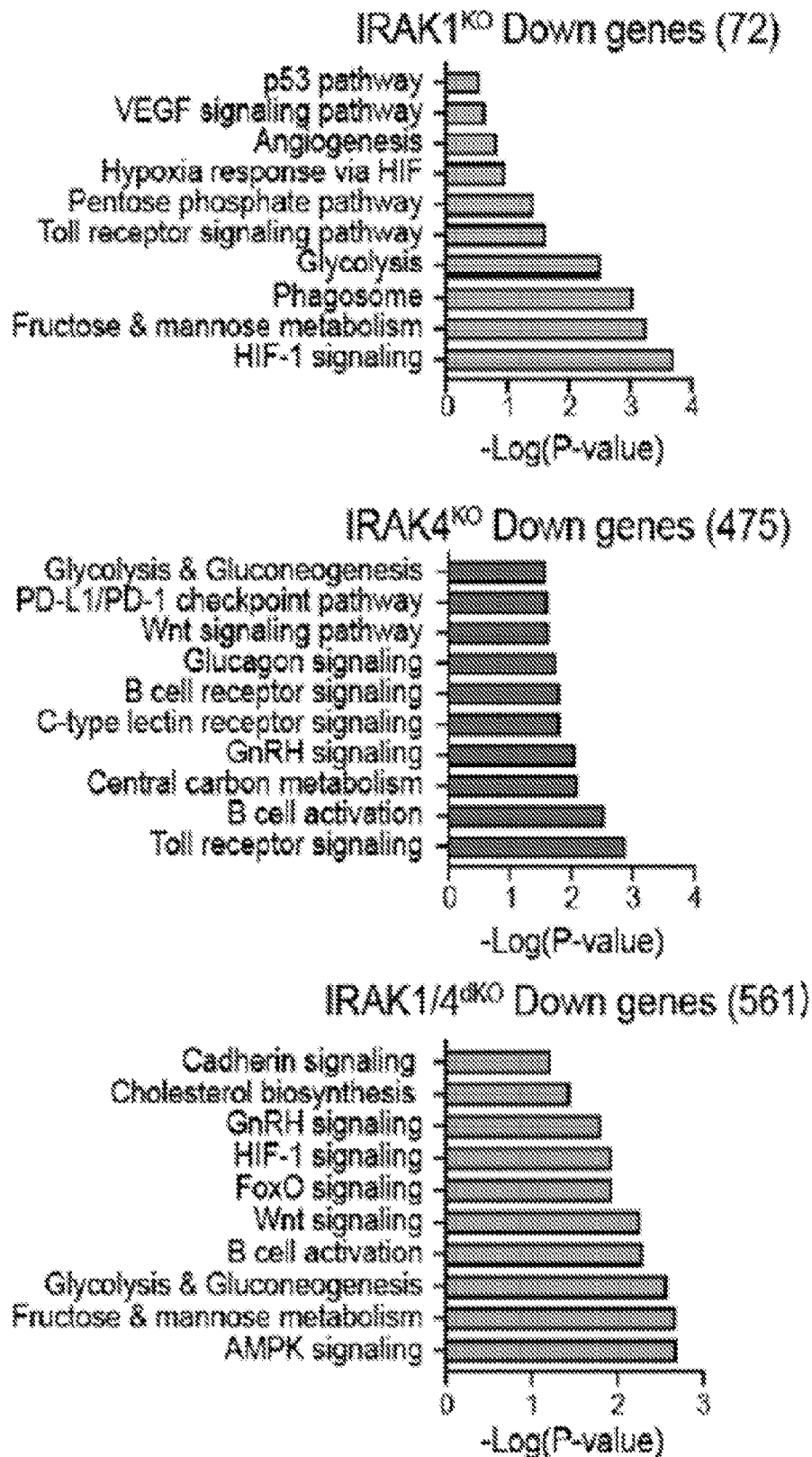


FIG. 14E

E

**FIG. 14E (Continued)**

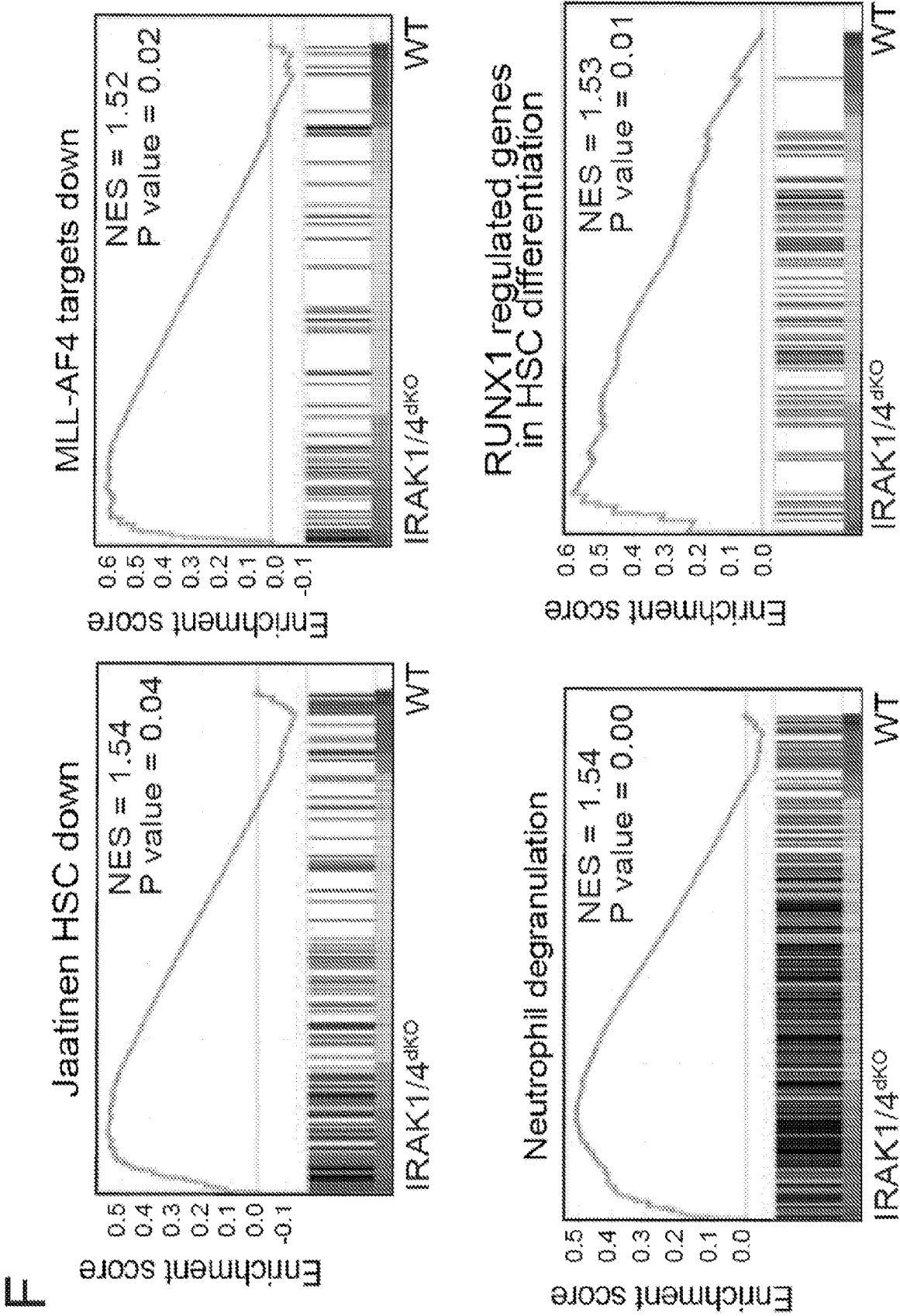


FIG. 14F

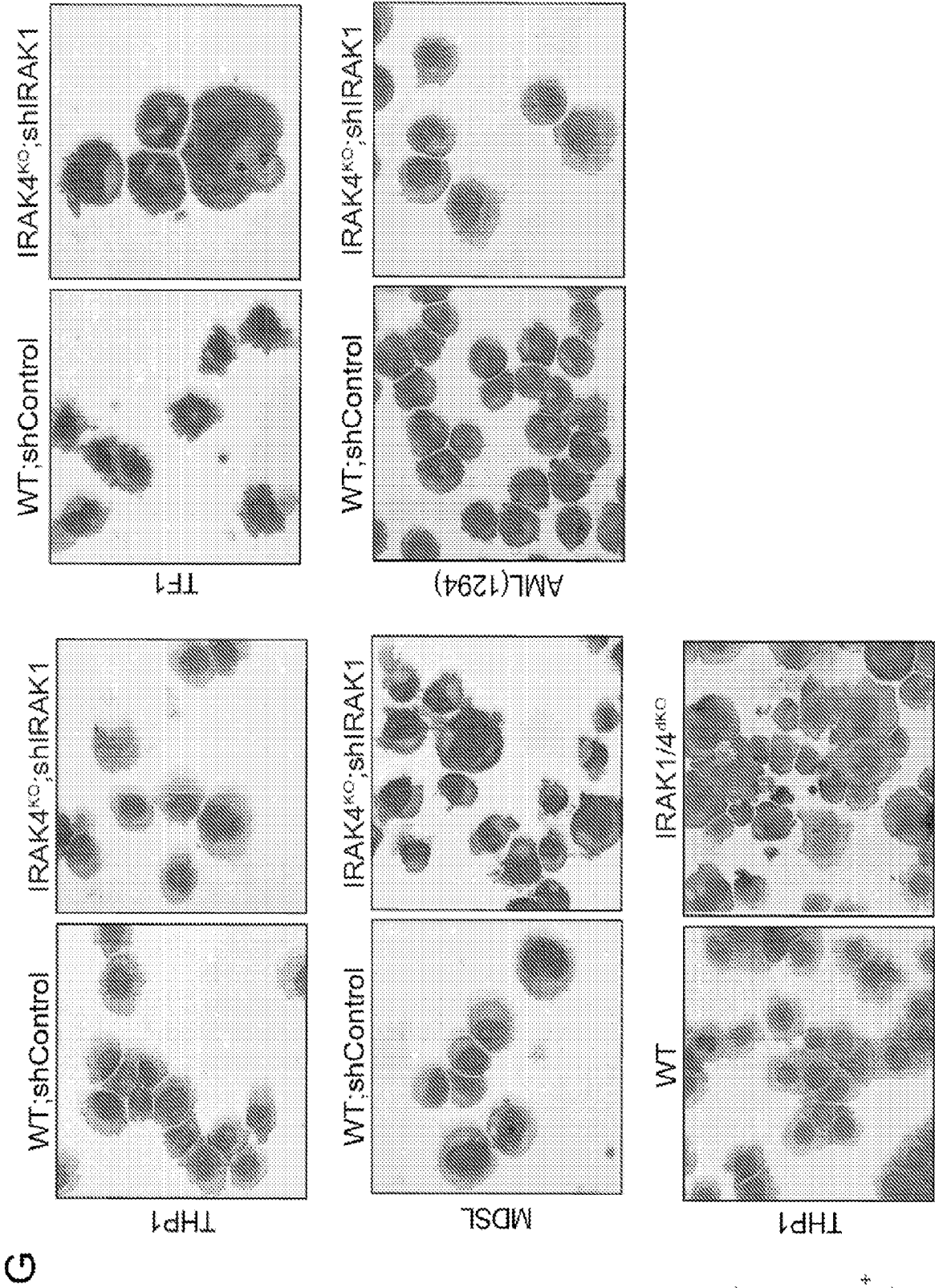


FIG. 14G

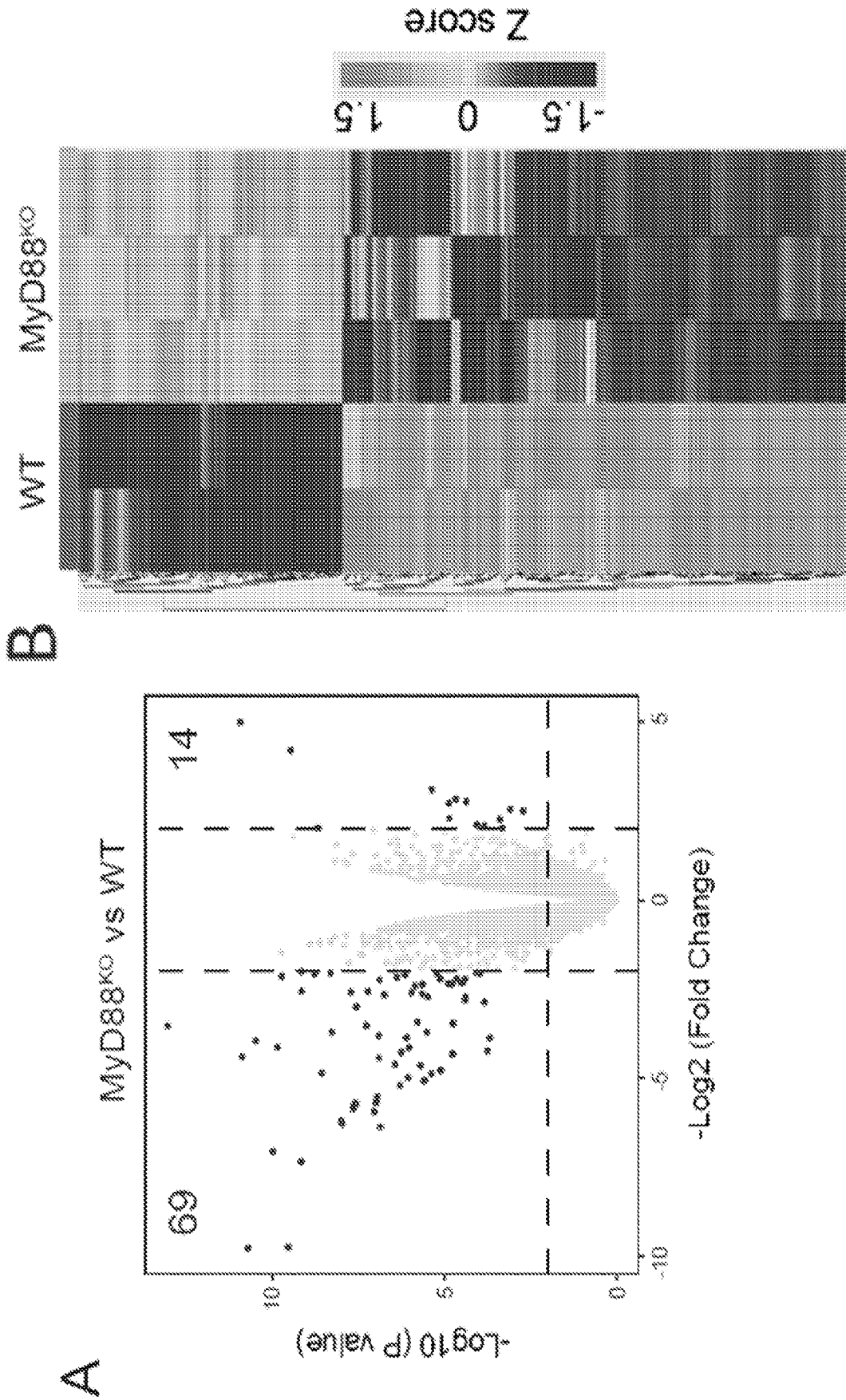


FIG. 15A

FIG. 15B

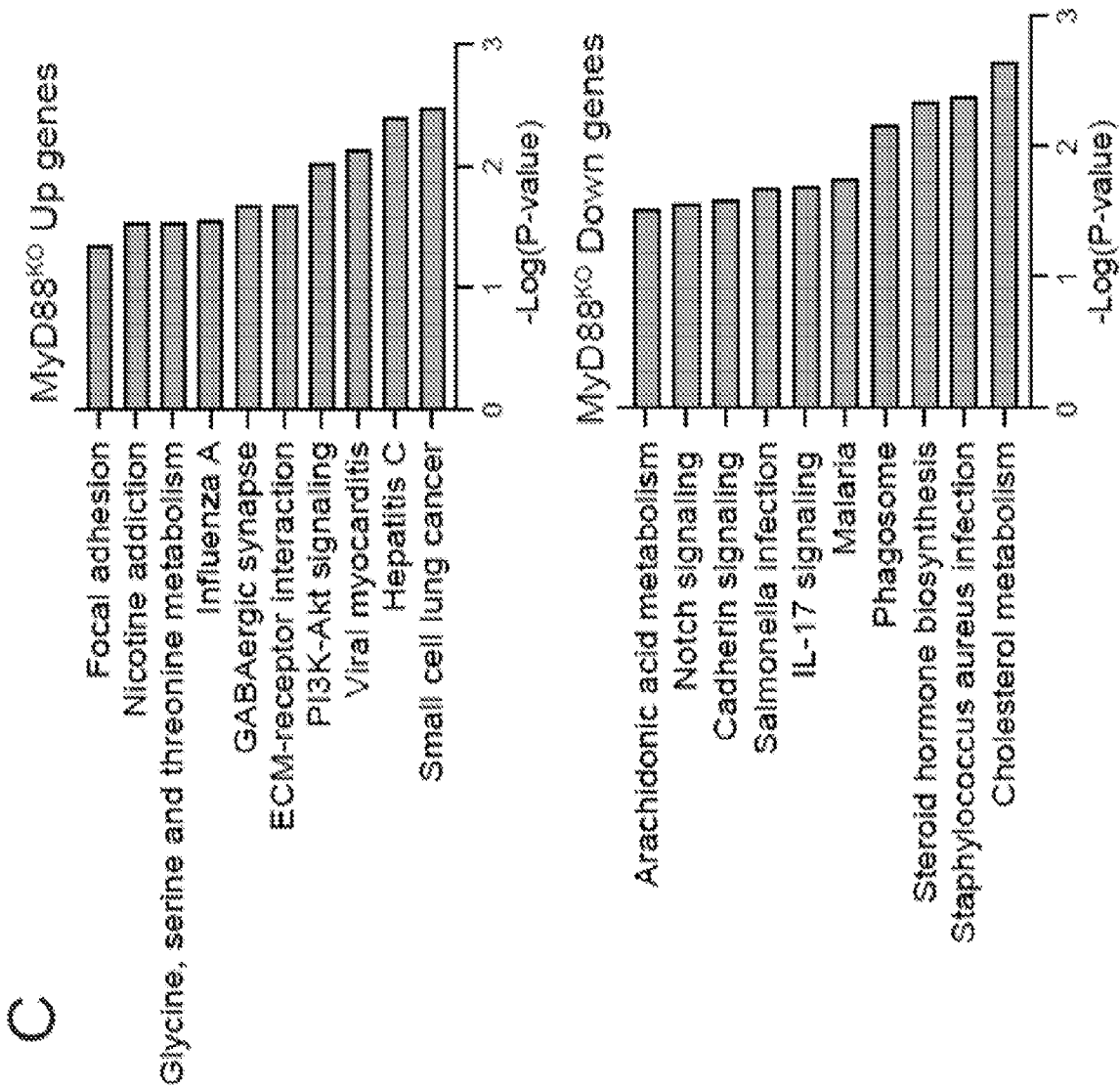


FIG. 15C

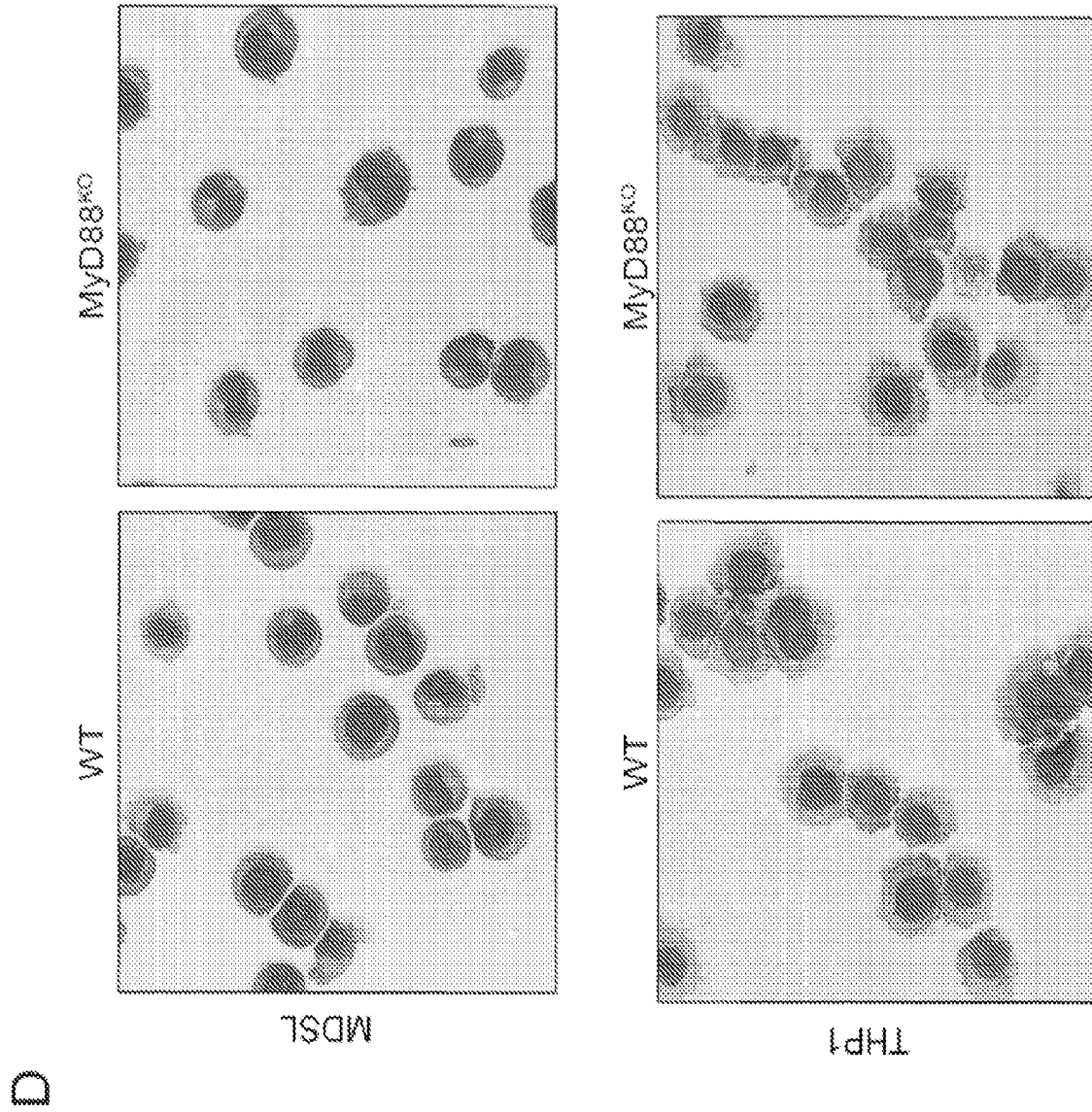
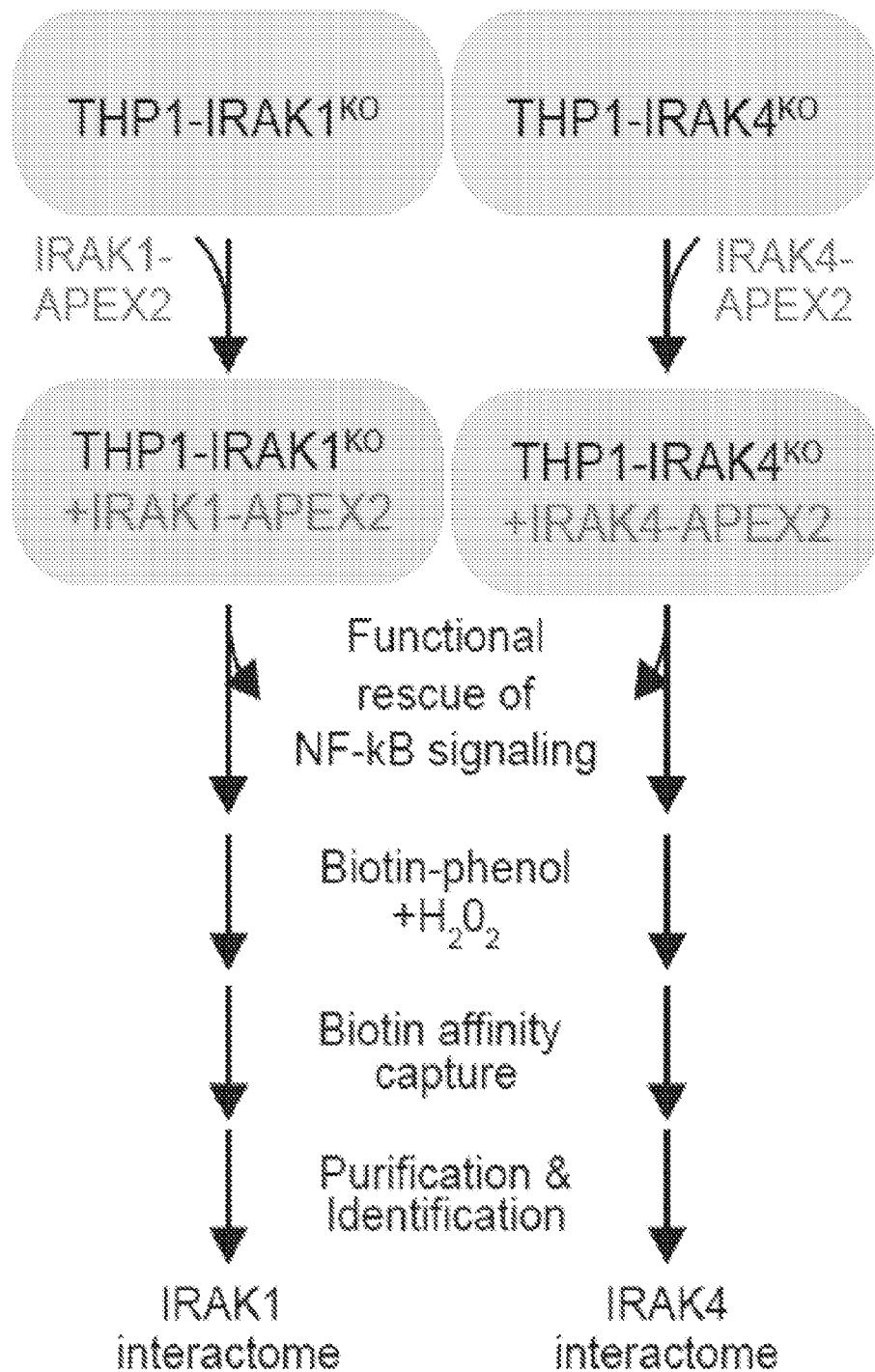


FIG. 15D

A**FIG. 16A**

B

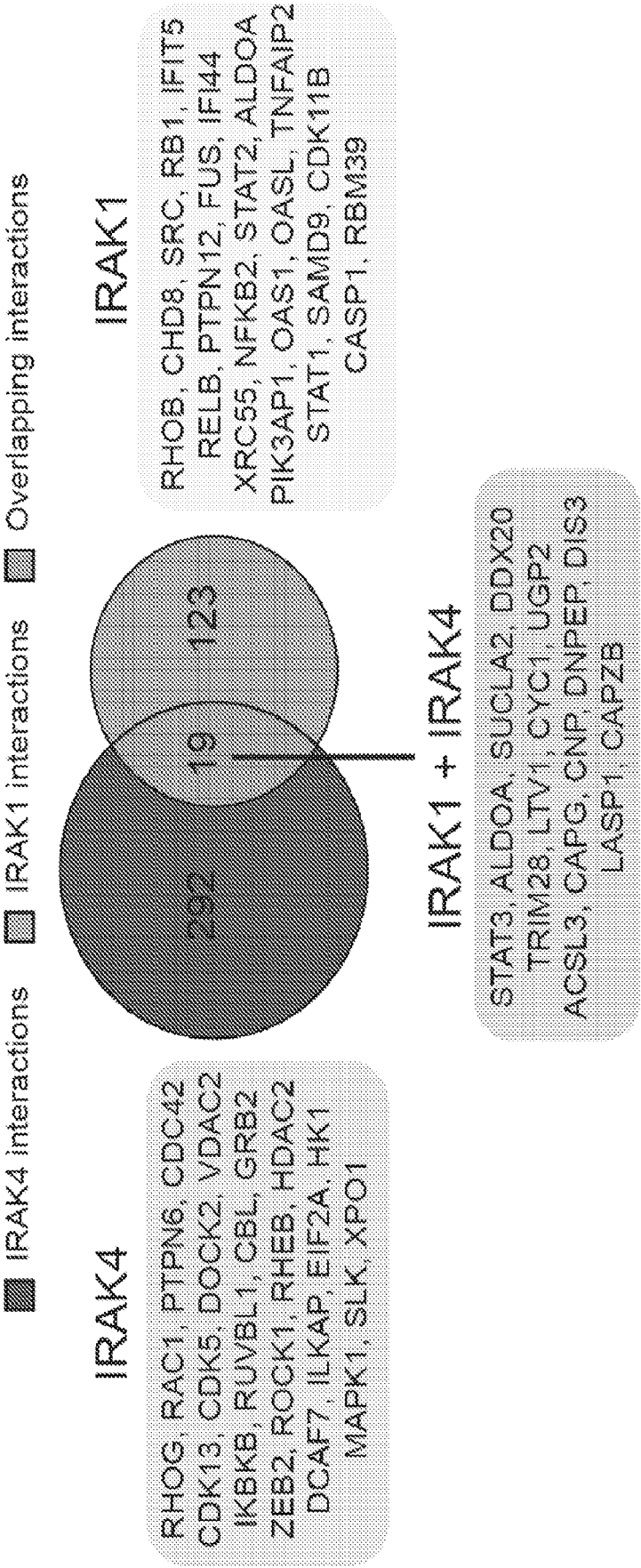


FIG. 16B

C

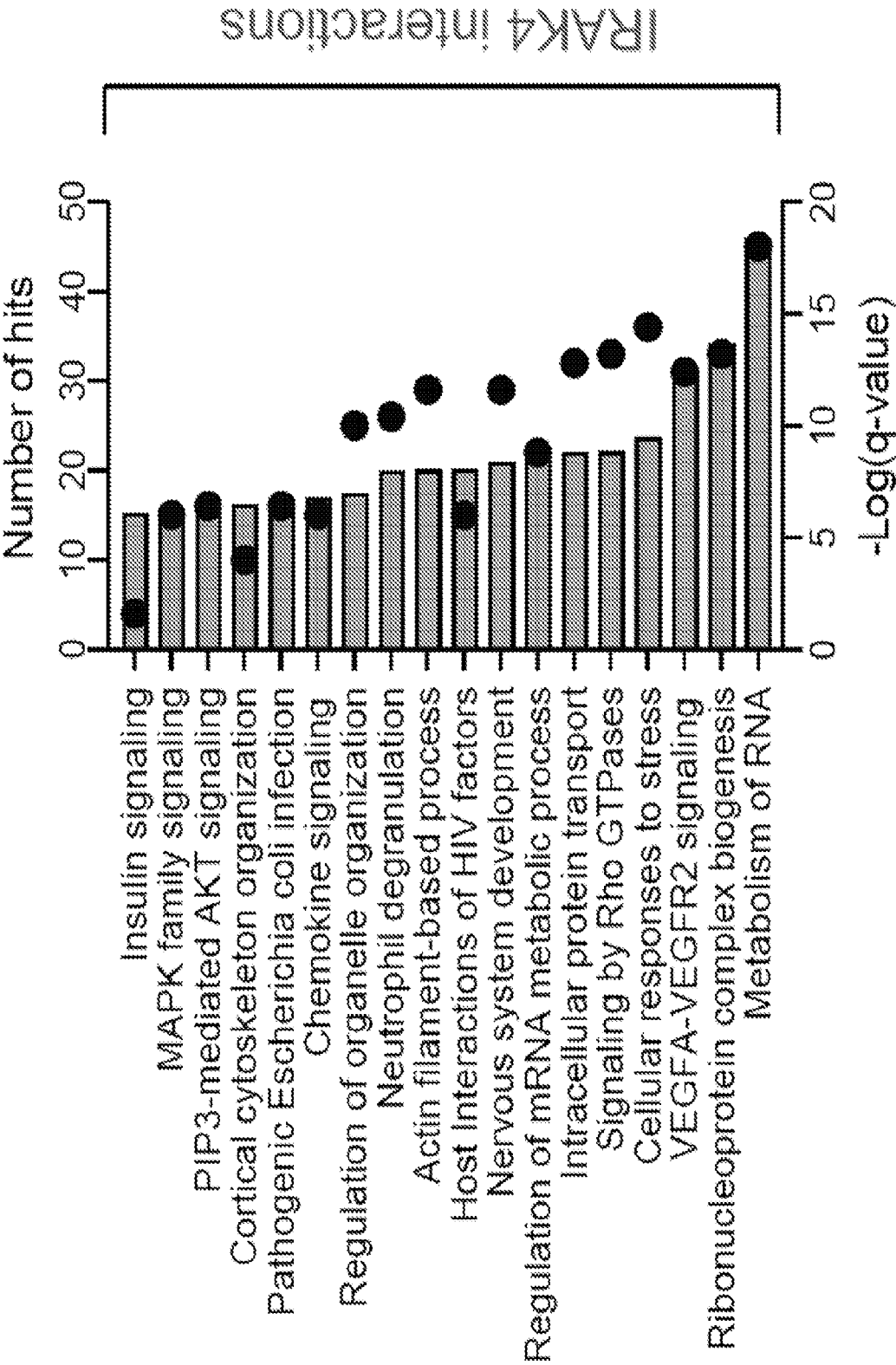


FIG. 16C

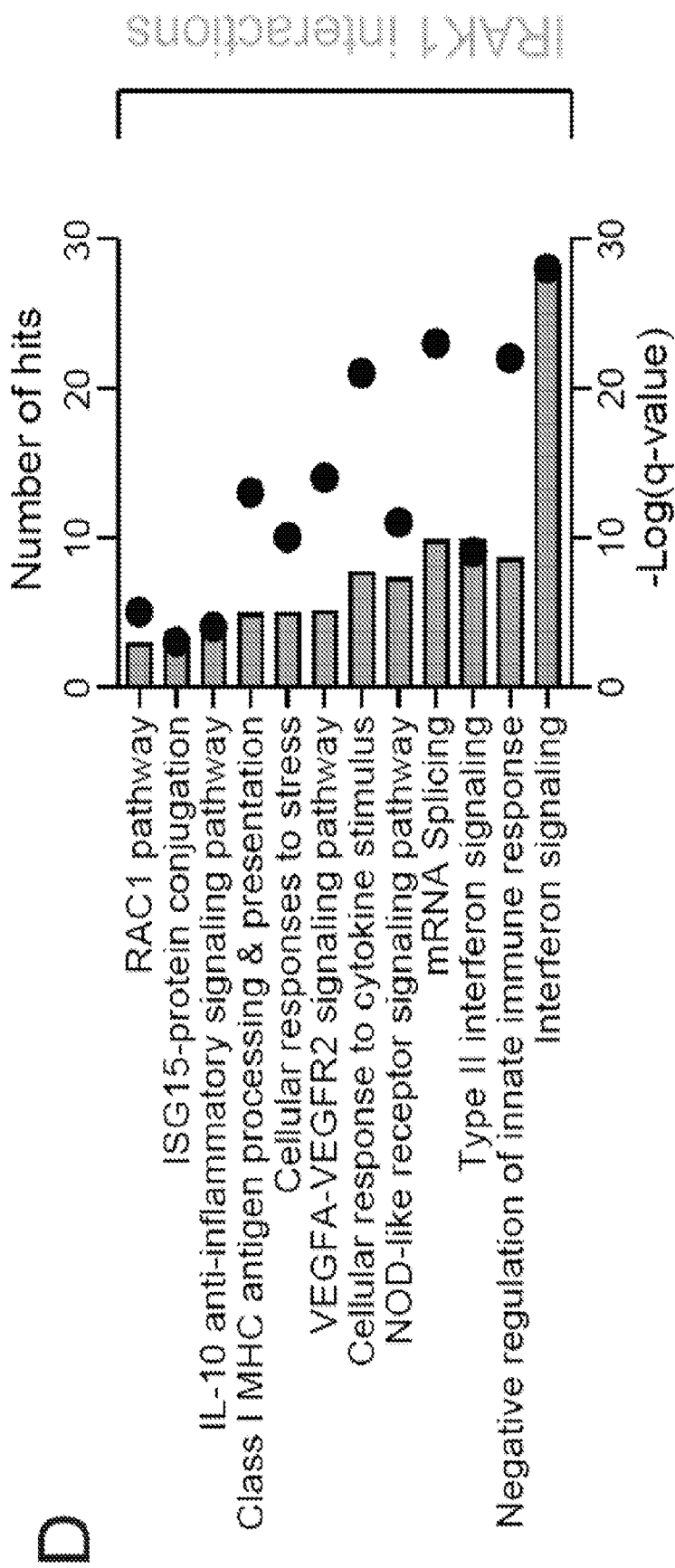


FIG. 16D

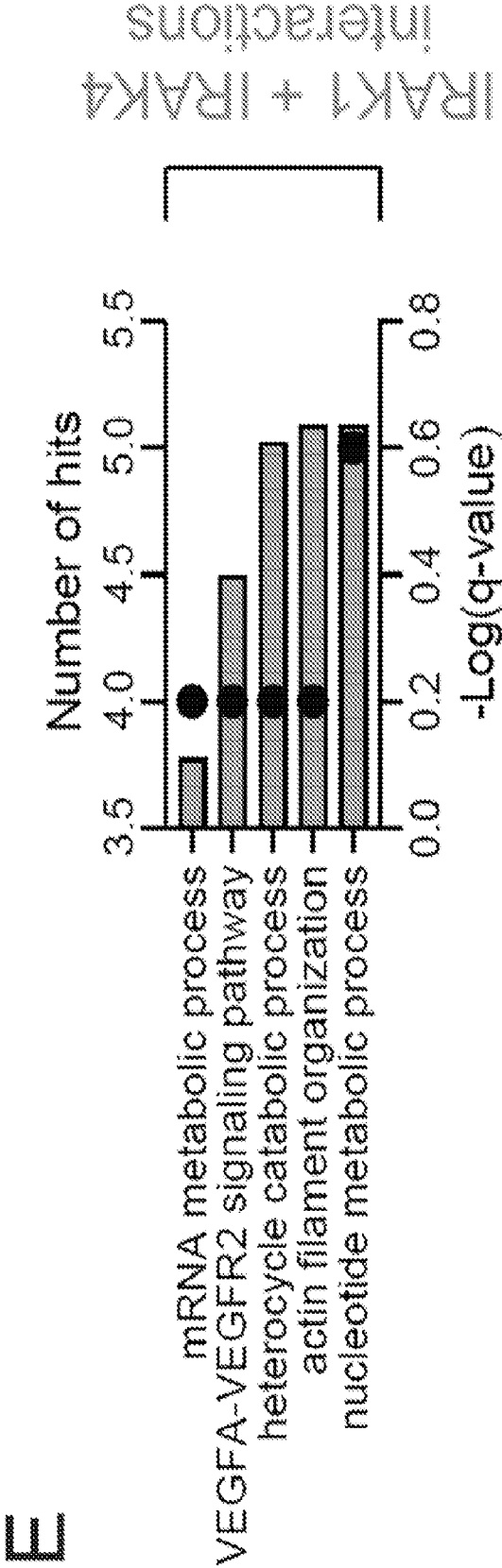


FIG. 16E

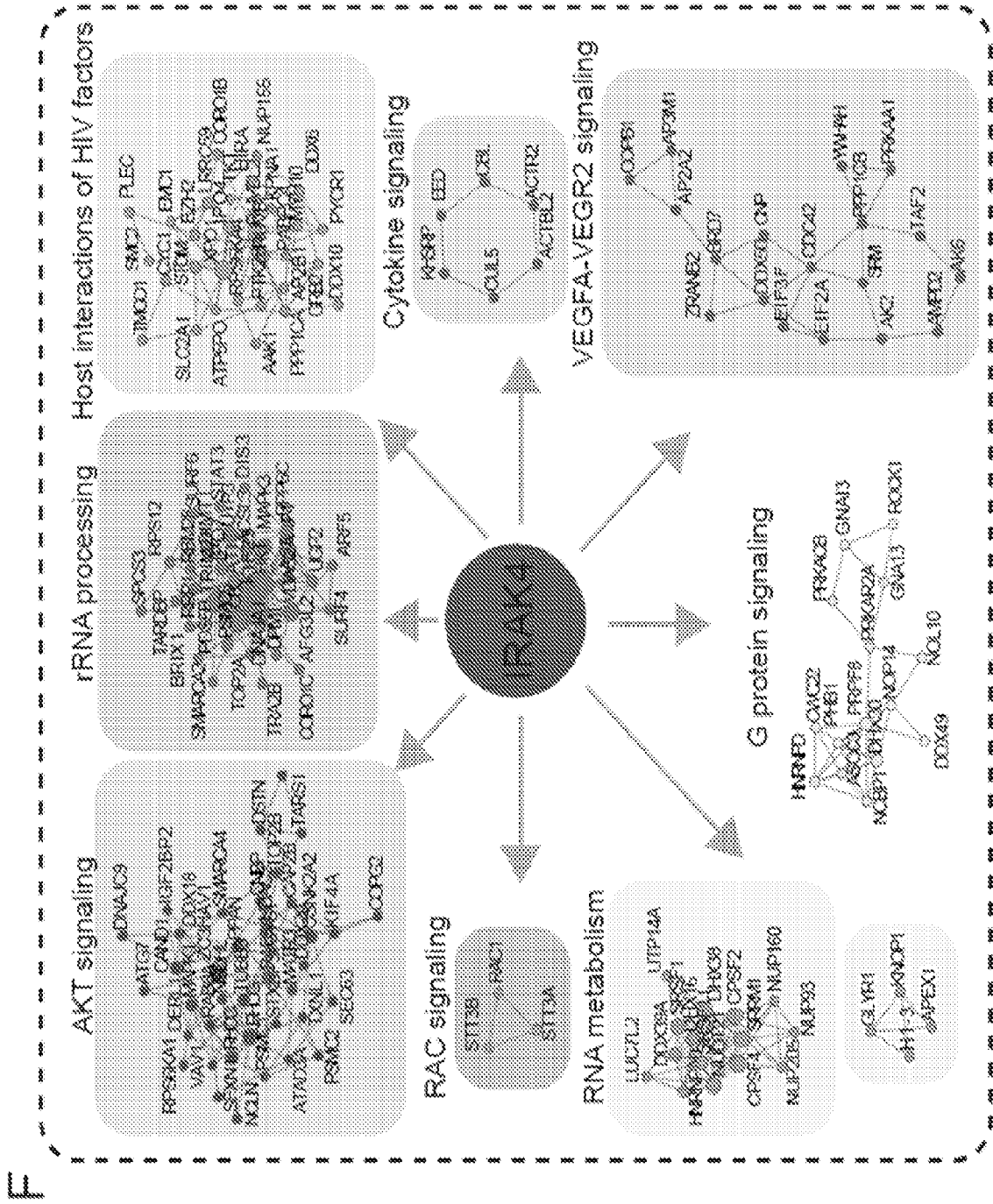


FIG. 16F

G

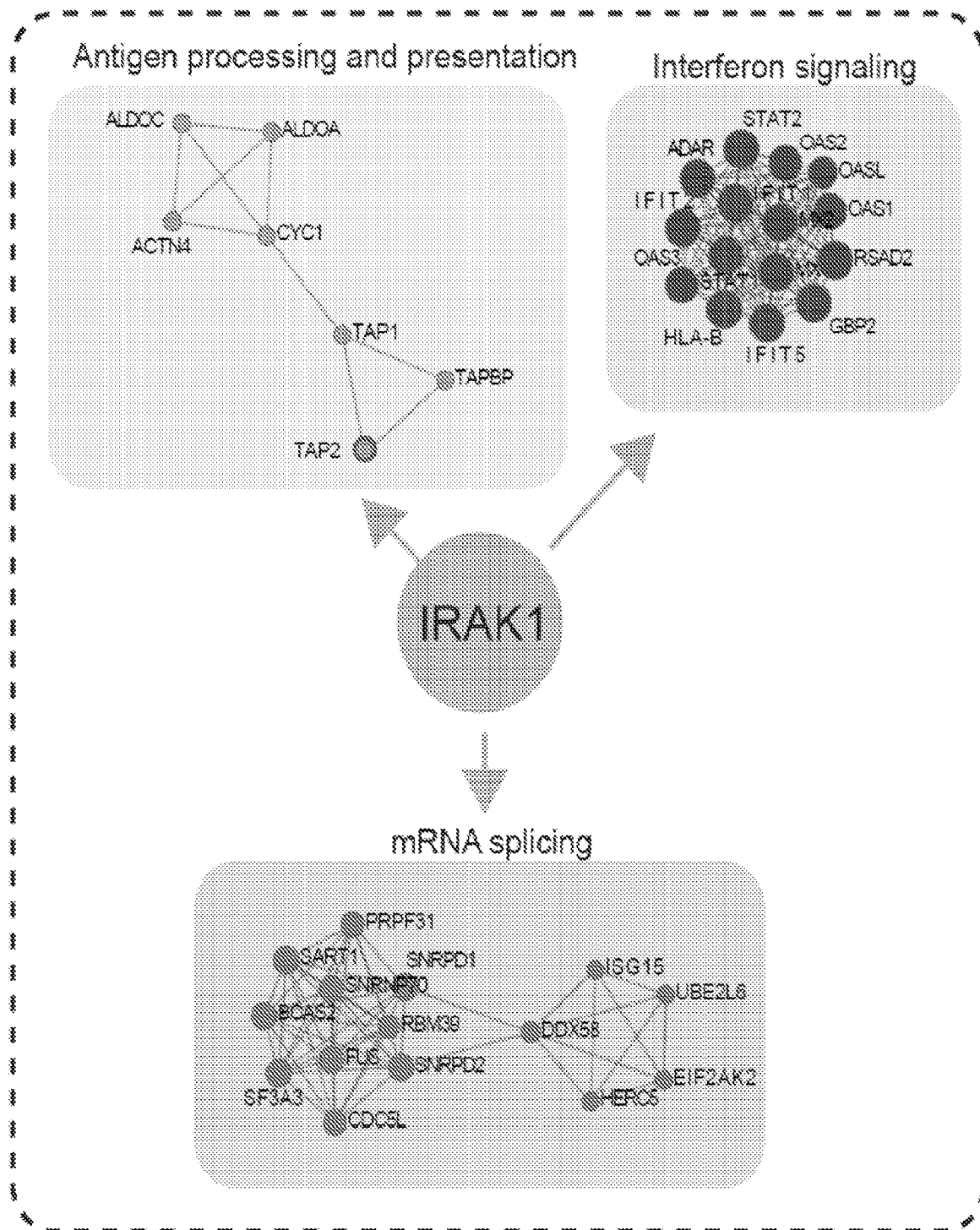


FIG. 16G

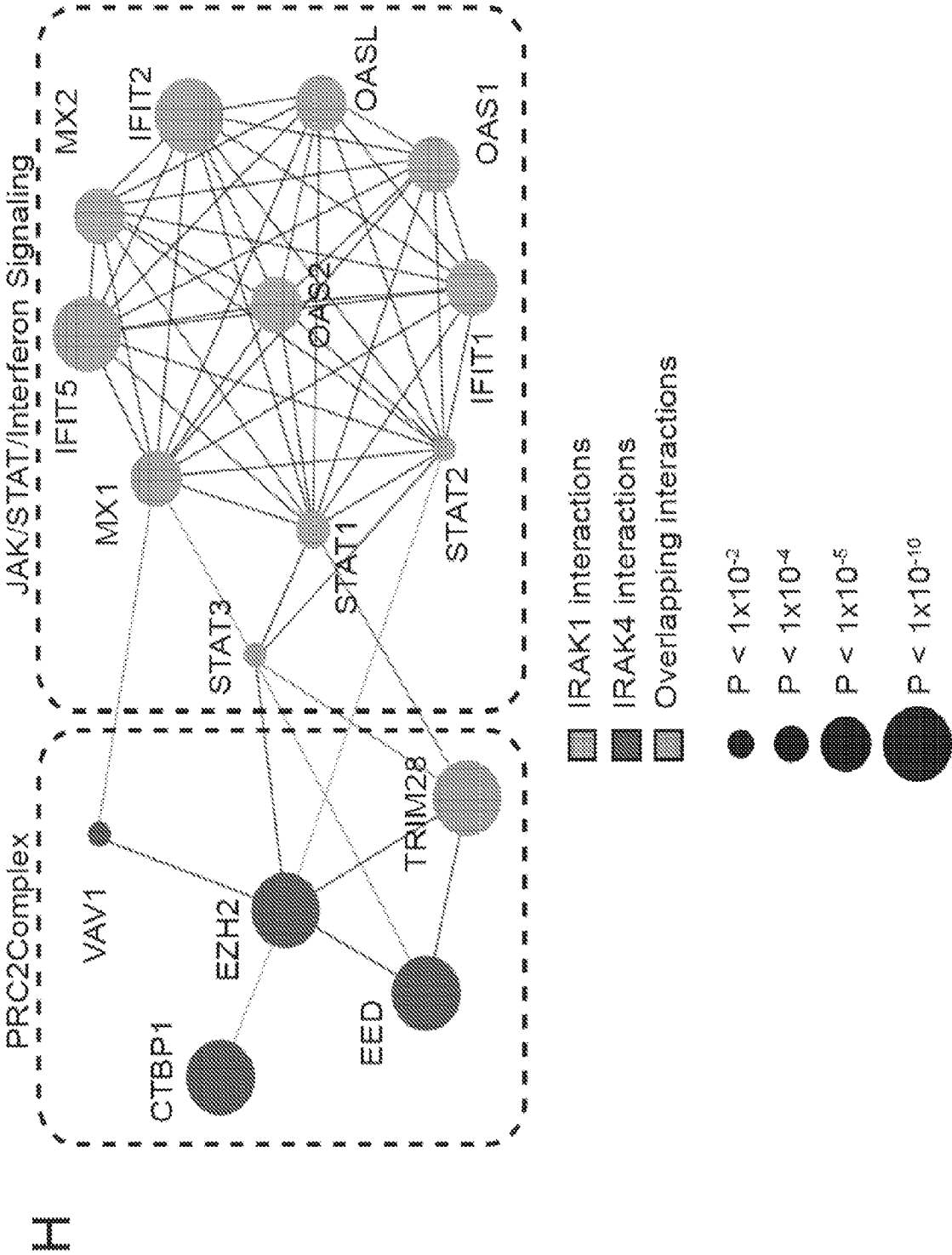


FIG. 16H

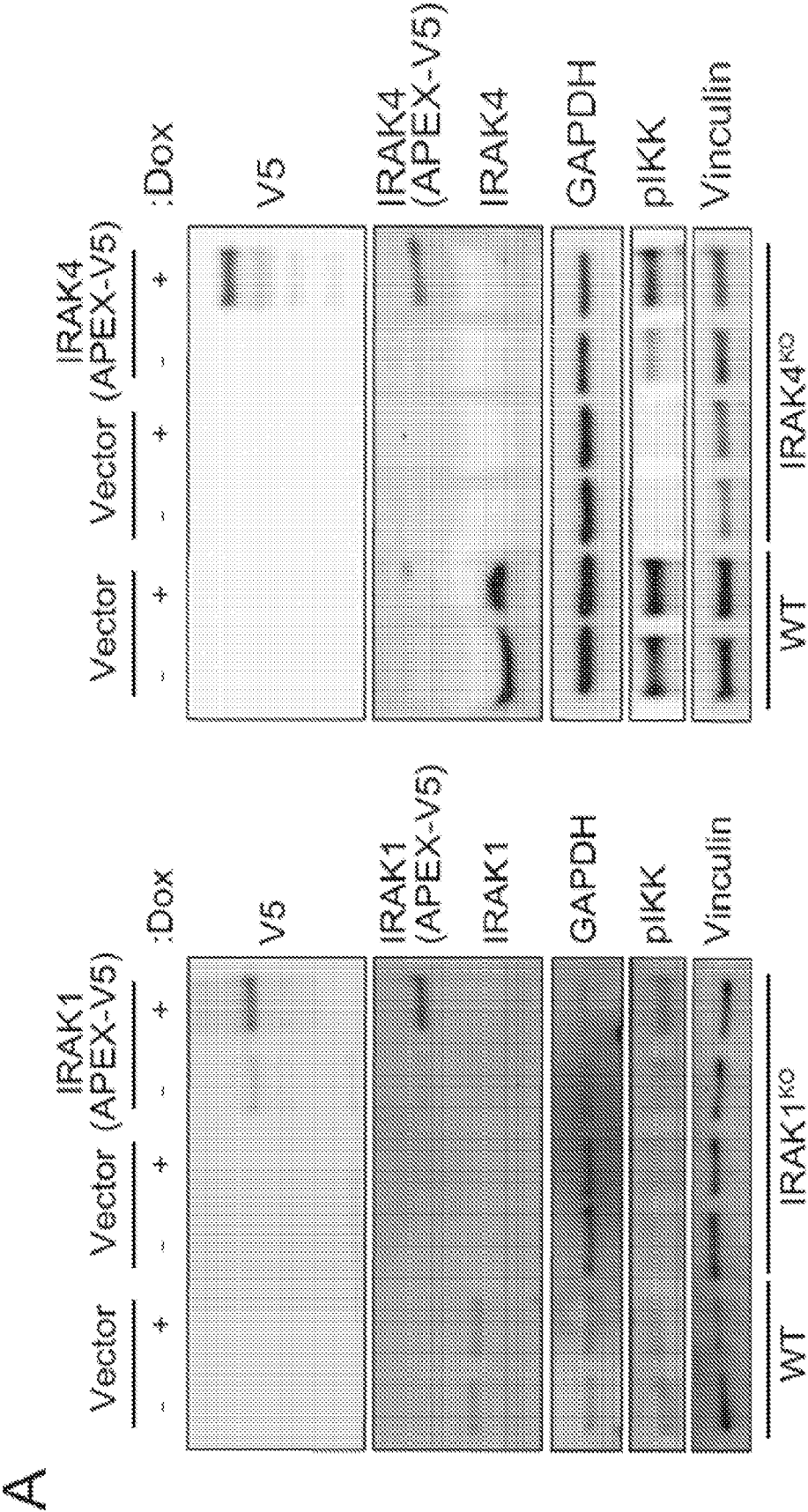


FIG. 17A

B

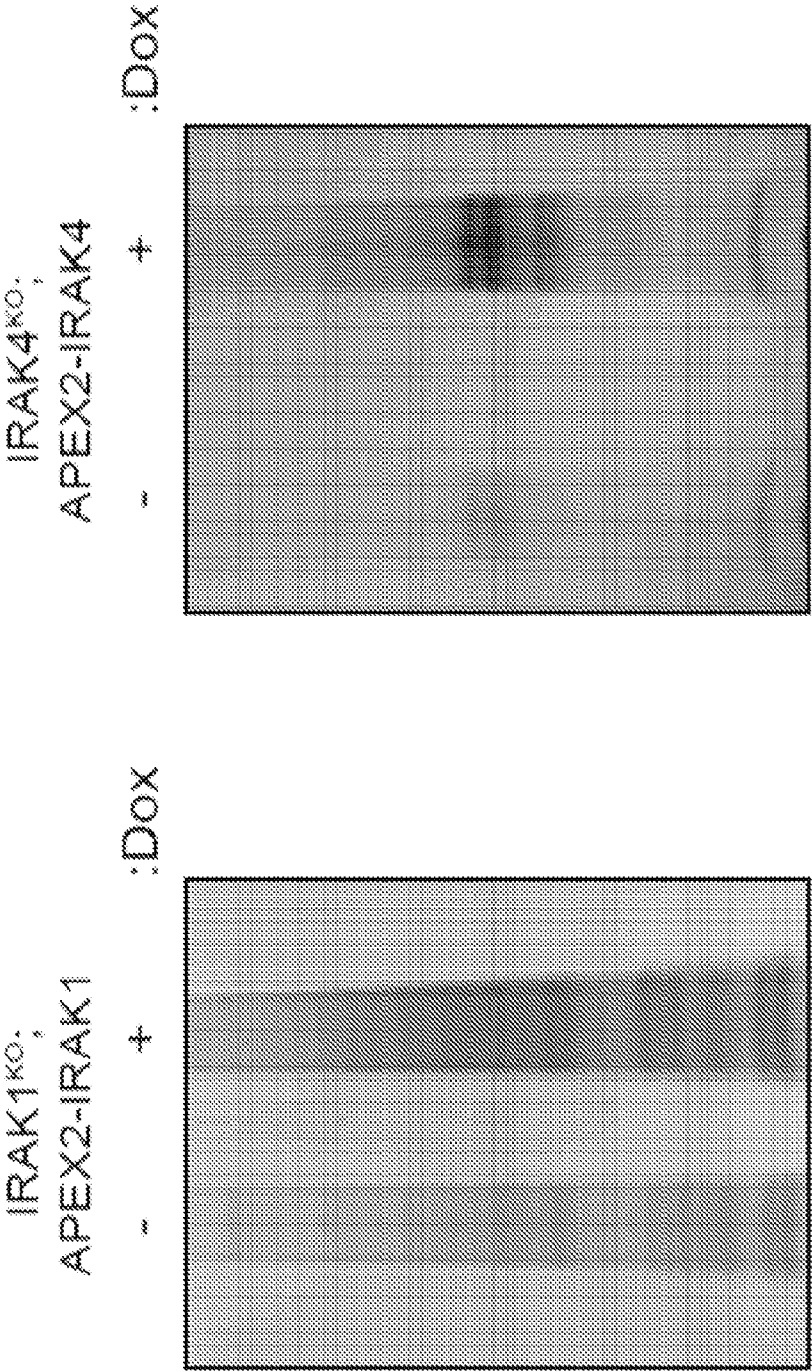


FIG. 17B

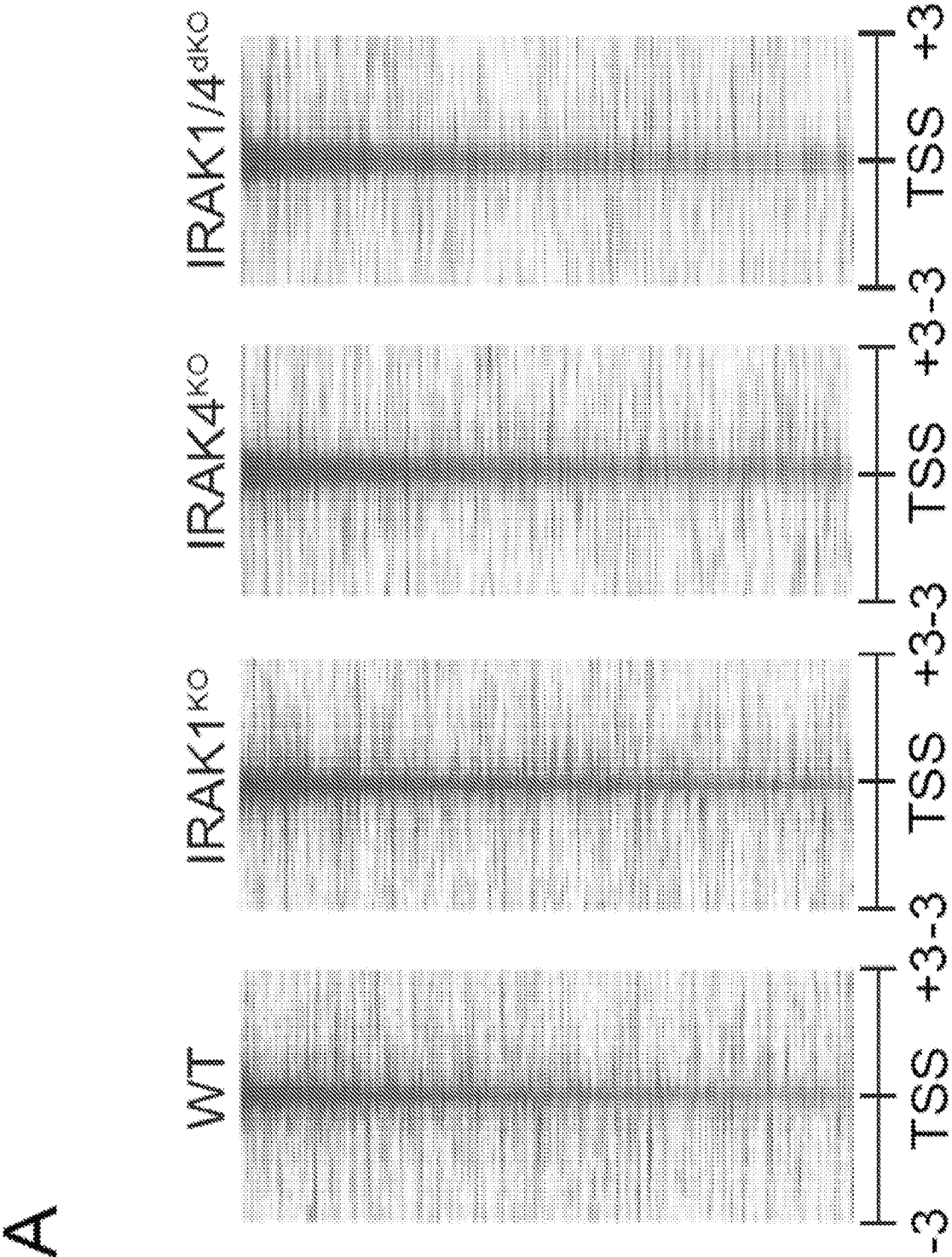
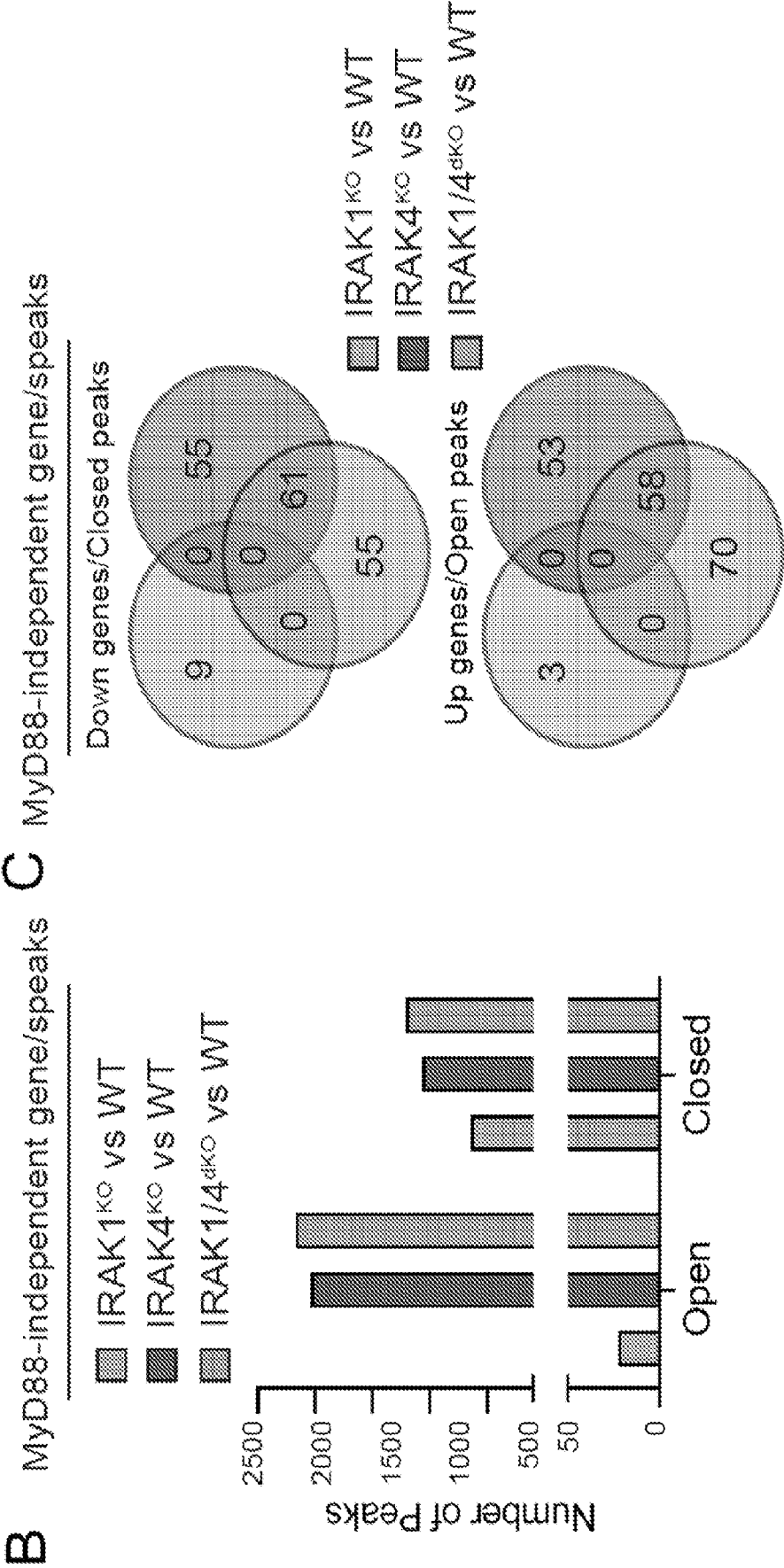


FIG. 18A



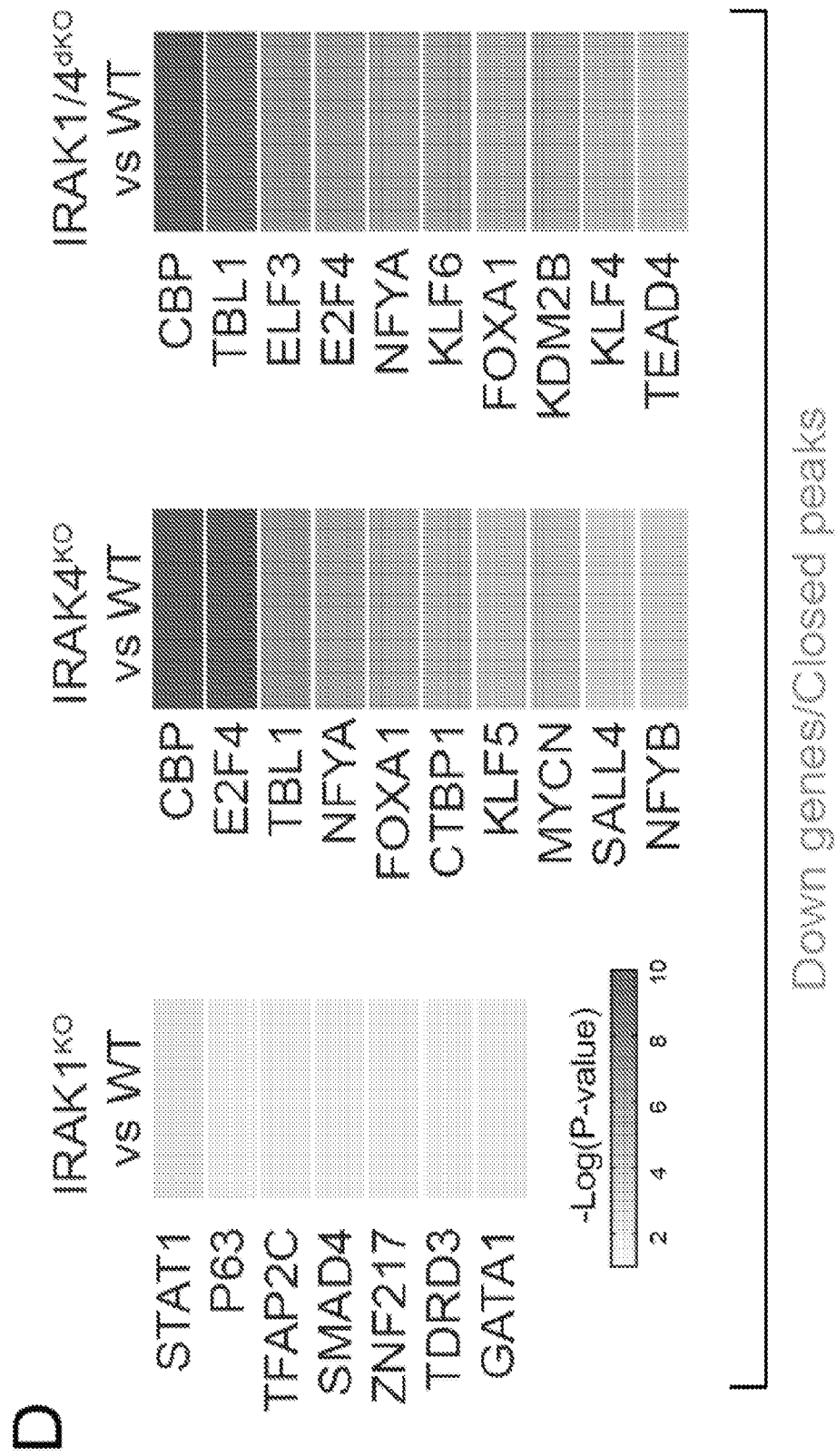


FIG. 18D

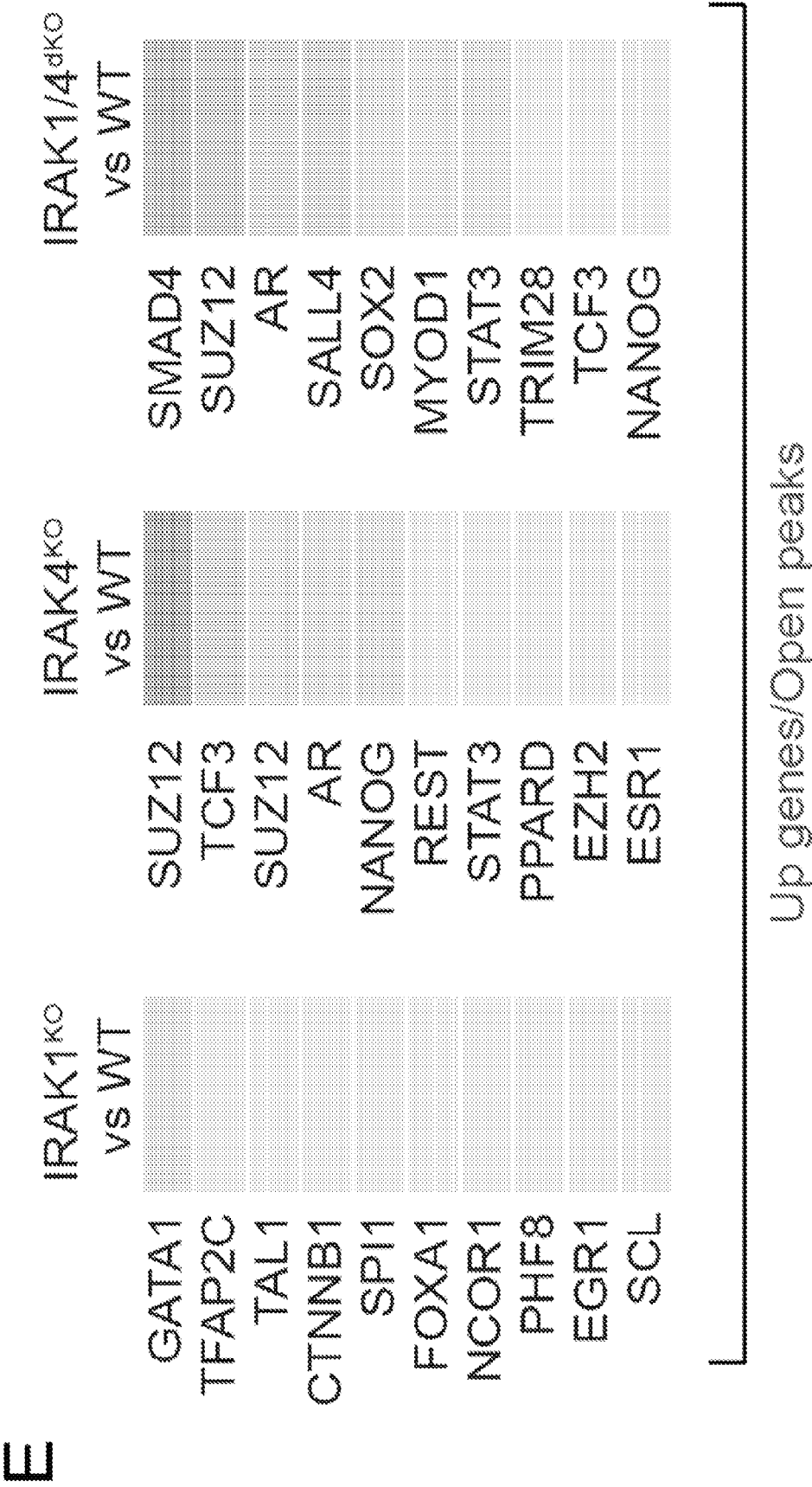
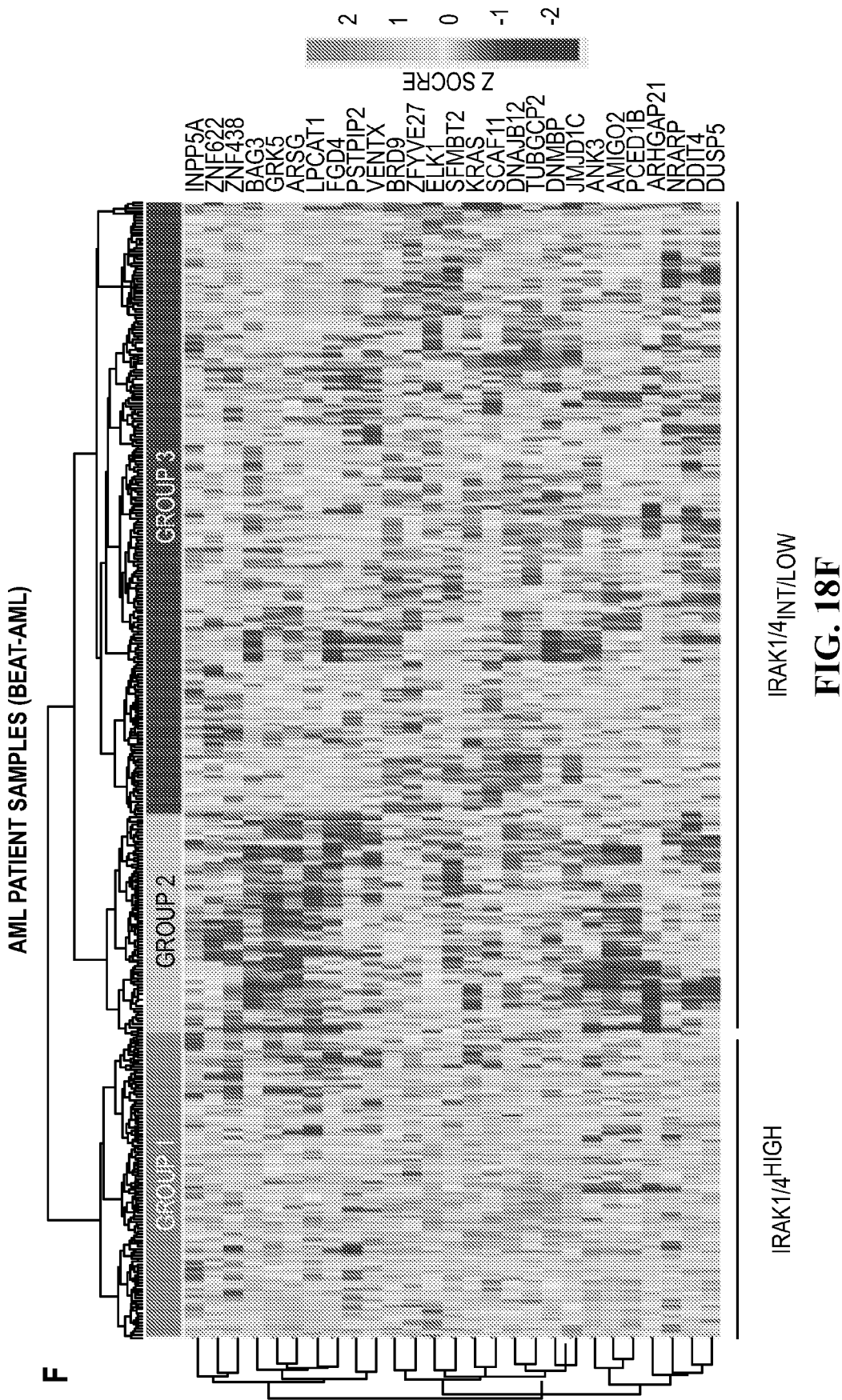


FIG. 18E



G

AML patient samples (BEAT-AML)

IRAK1/4 ^{High} (n = 123)		IRAK1/4 ^{Int/Low} (n = 337)	
Gene mutation	P value	Gene mutation	P value
BCOR	0.007	CEBPA	0.006
SRSF2	0.019	NPM1	0.019
JAK2	0.029	FLT3	0.034
TET2	0.03	GATA2	0.048
RUNX1	0.07	PTPN11	0.22
EZH2	0.26	KRAS	0.31
TP53	0.27	IDH1	0.36

FIG. 18G

H

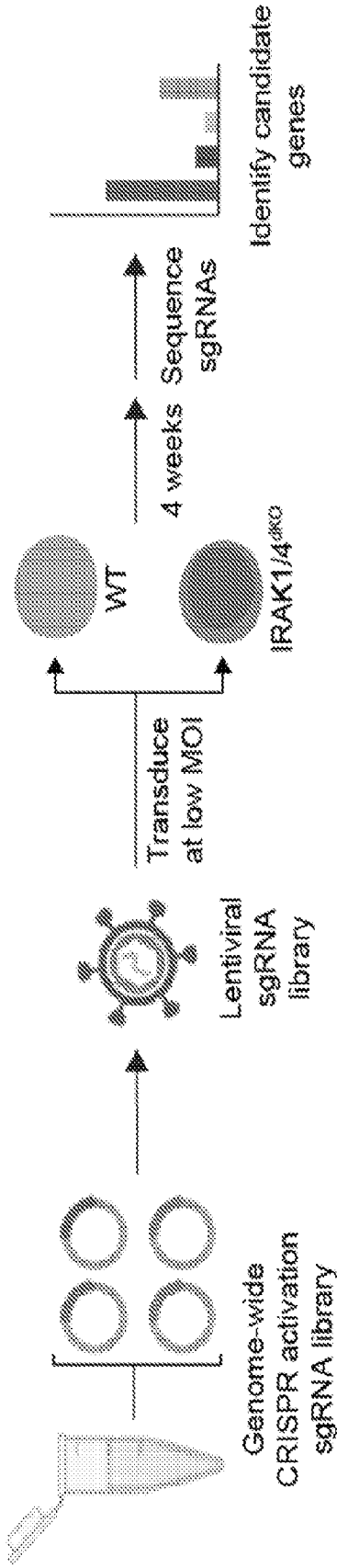


FIG. 18H

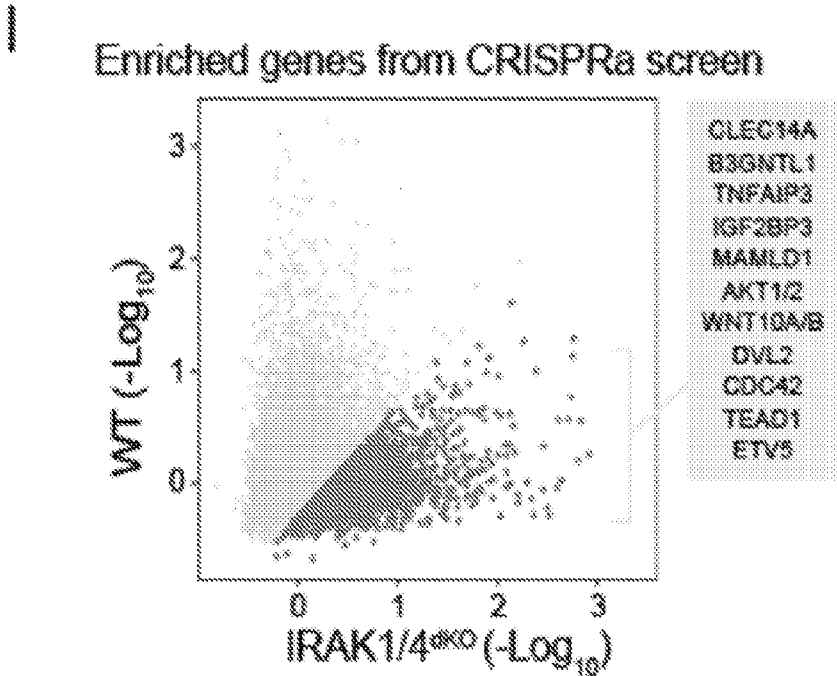


FIG. 18I

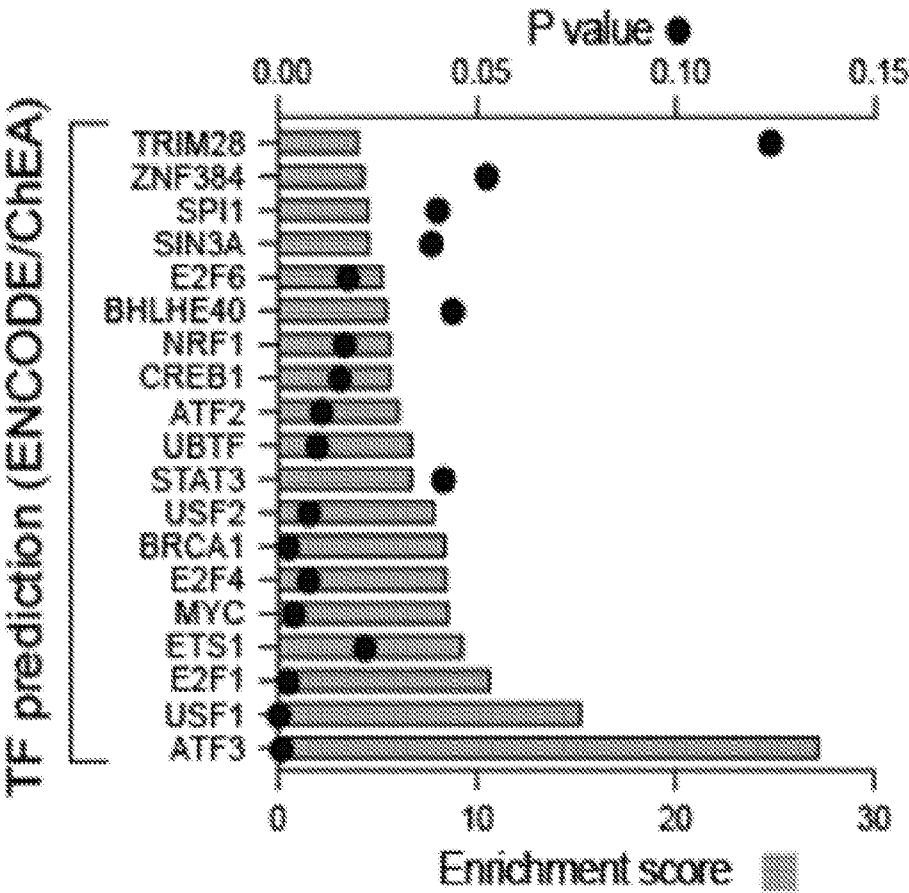


FIG. 18J

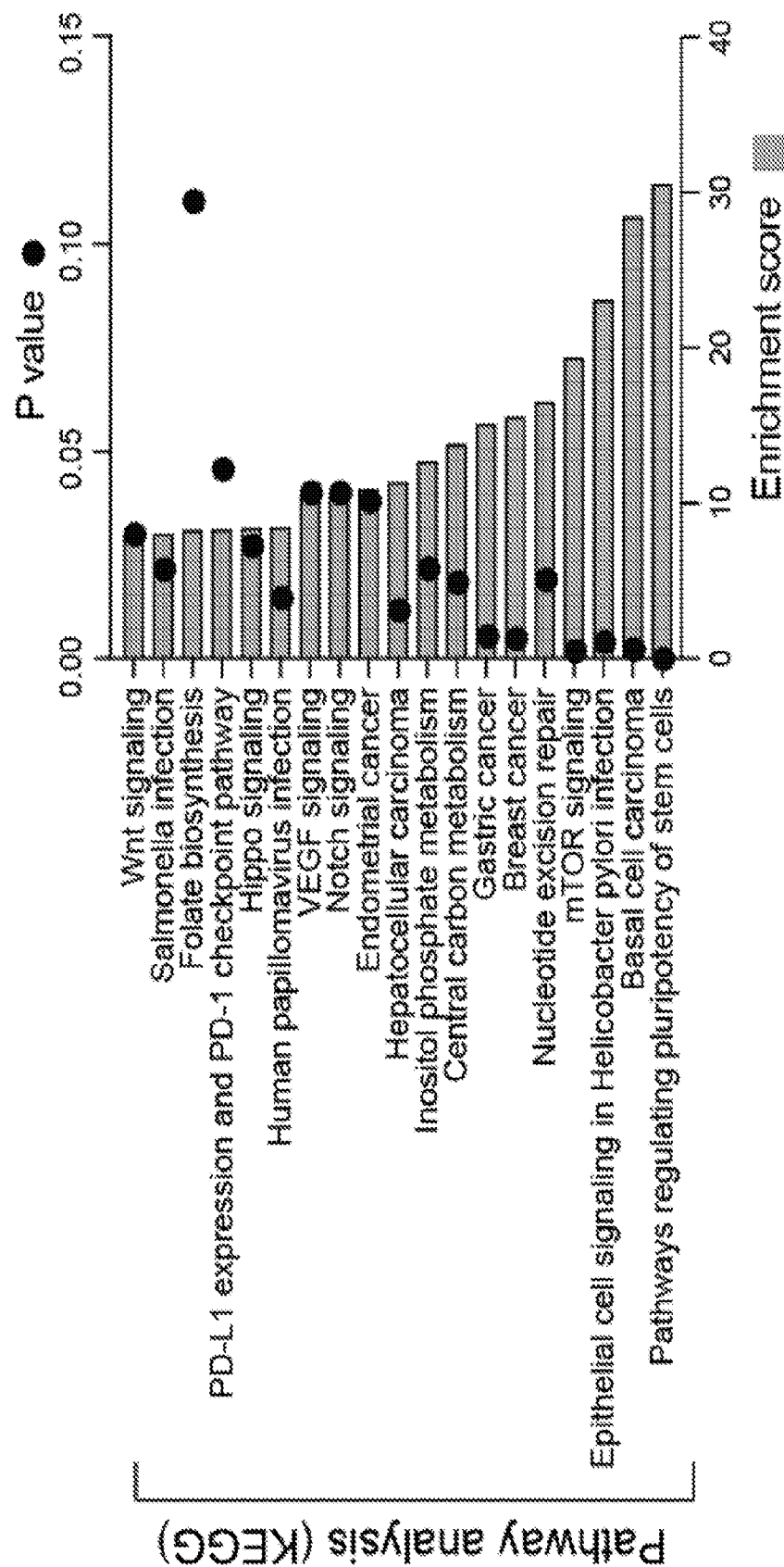


FIG. 18K

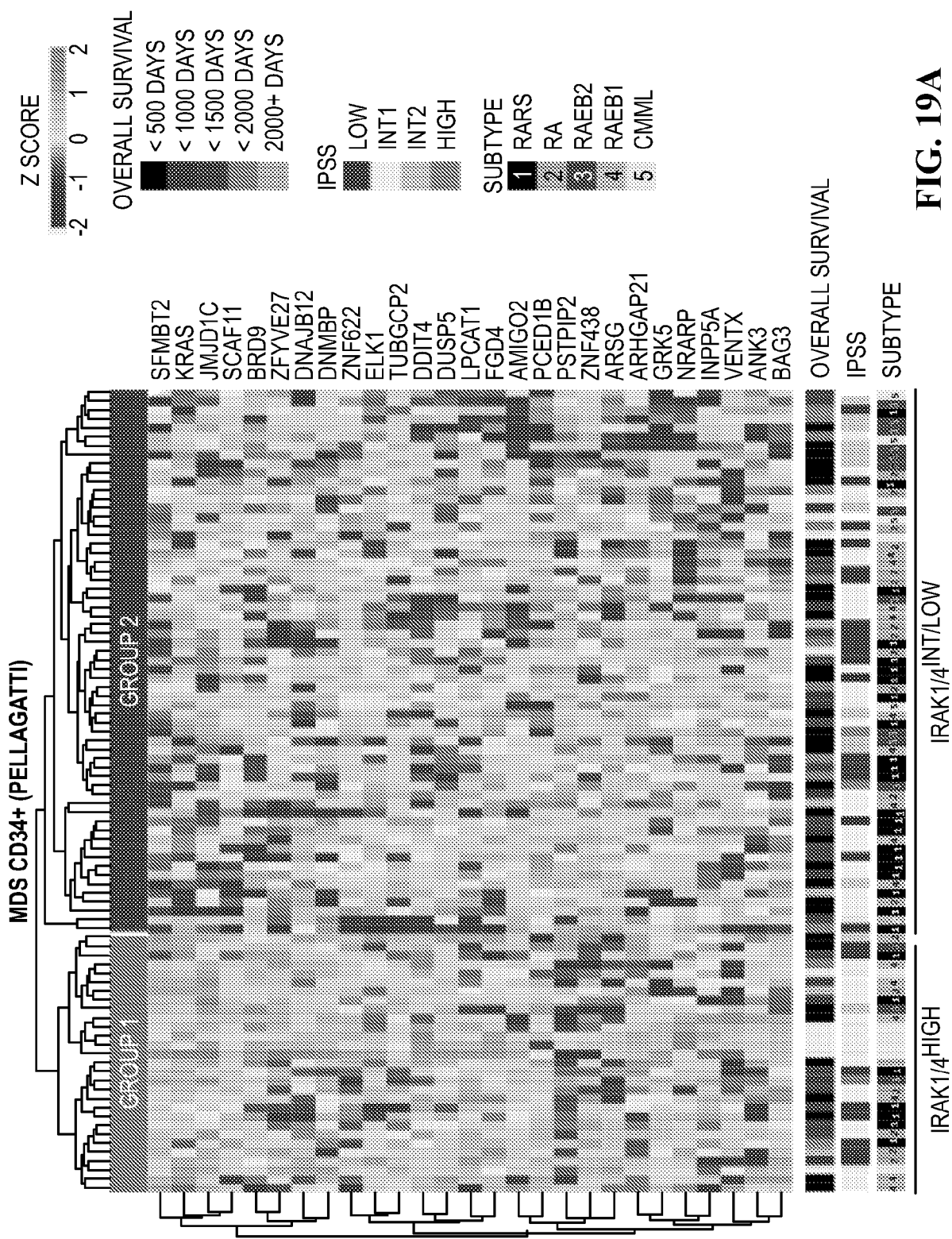


FIG. 19A

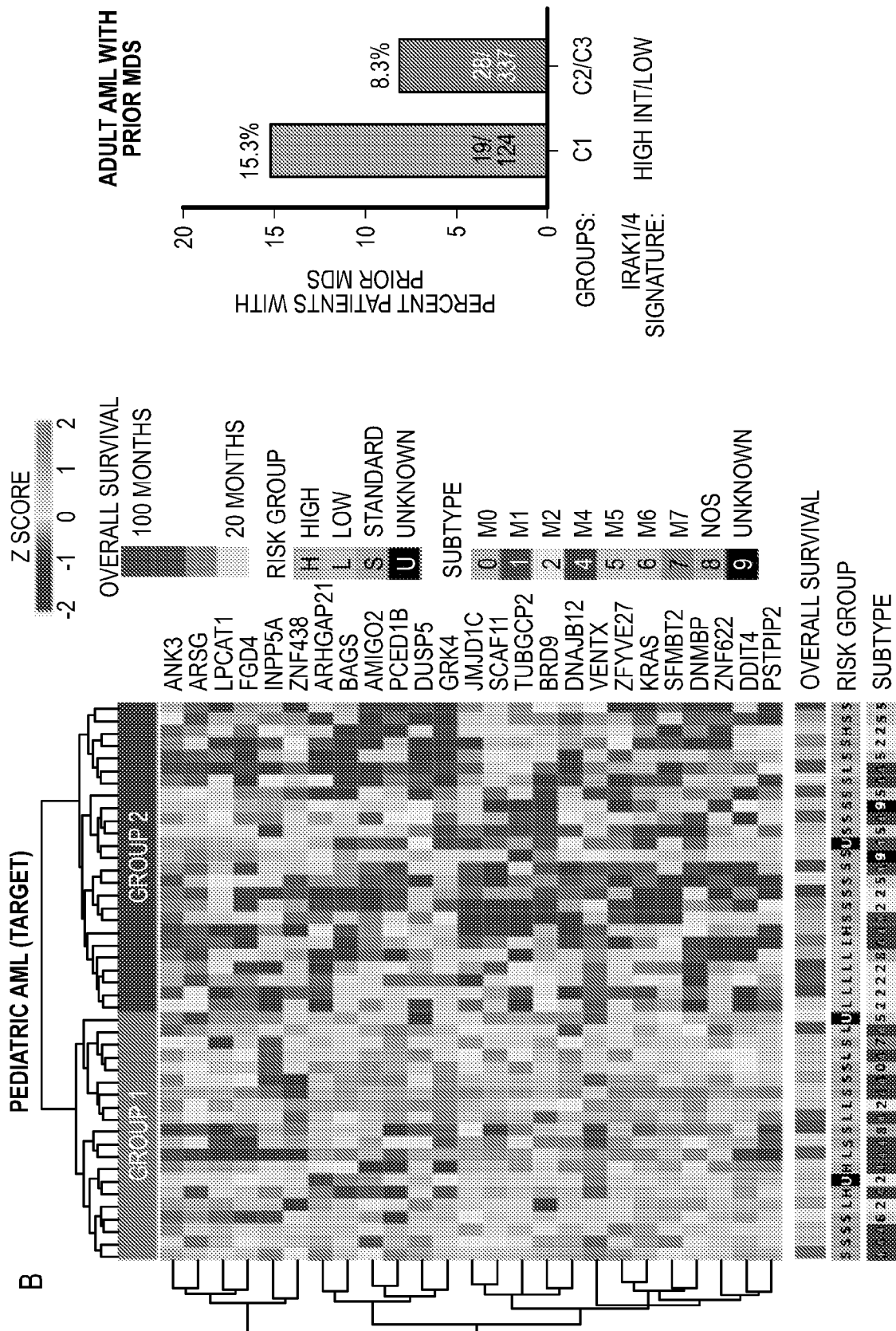


FIG. 19C

FIG. 19B

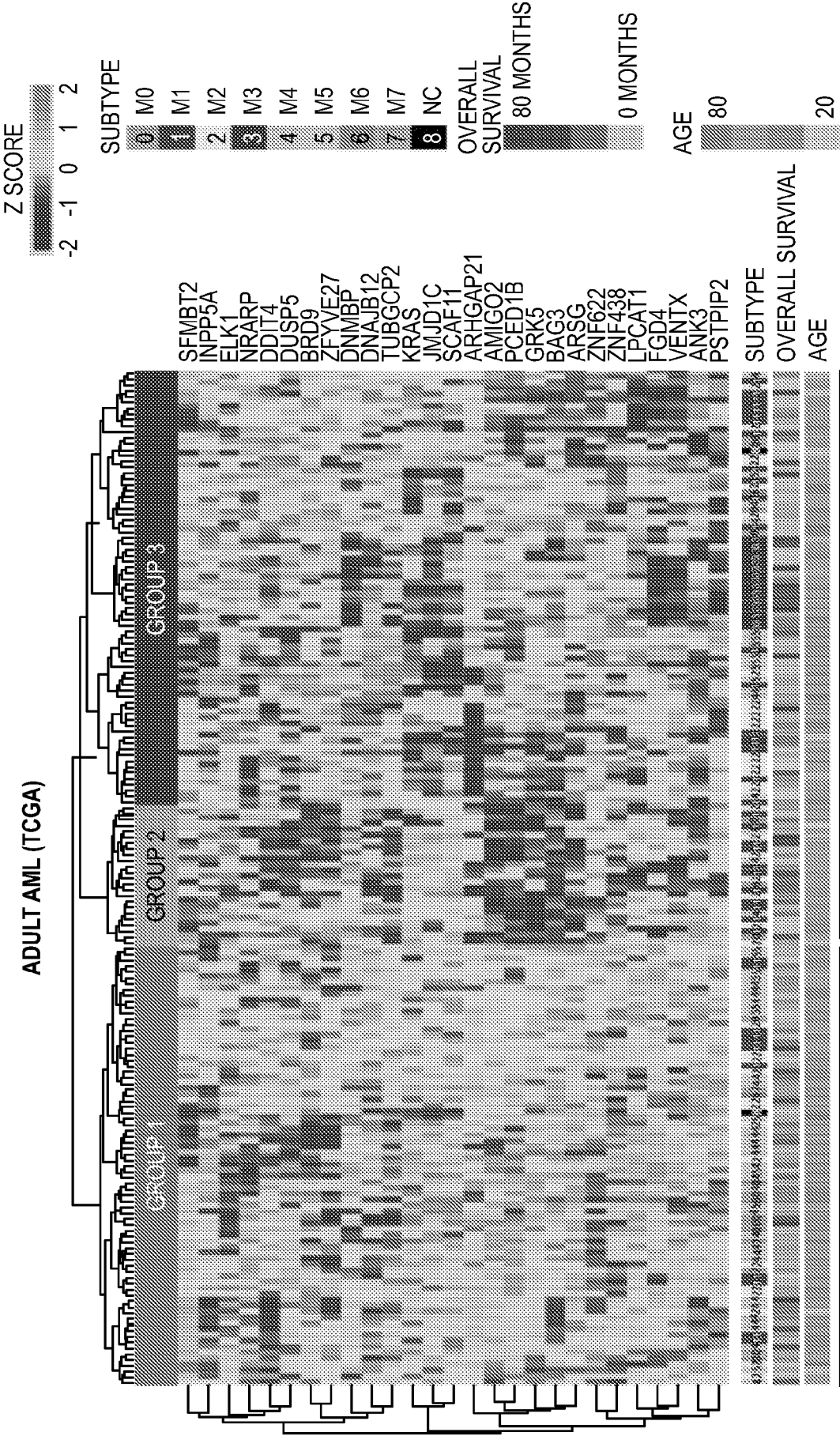


FIG. 19D

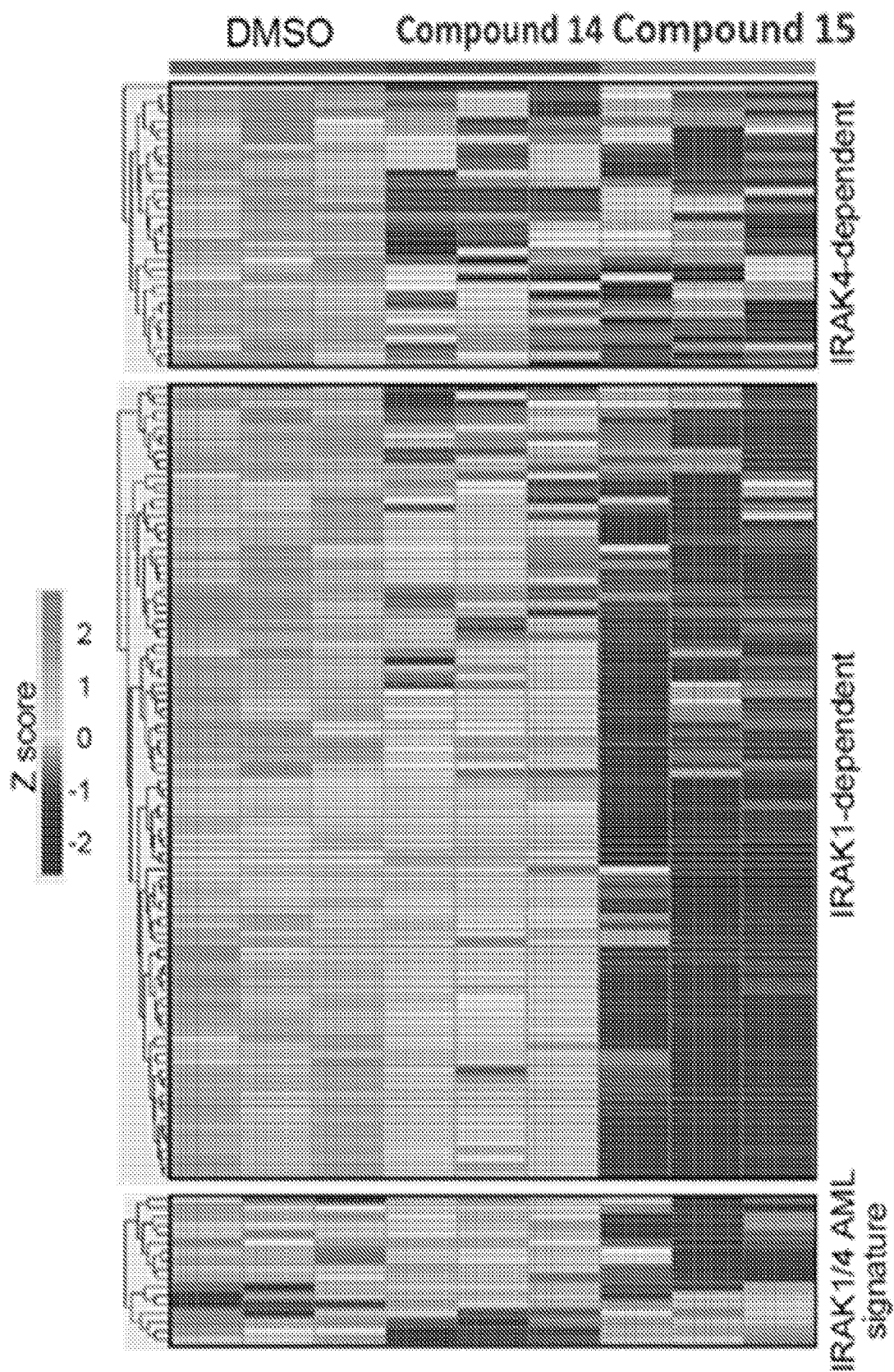
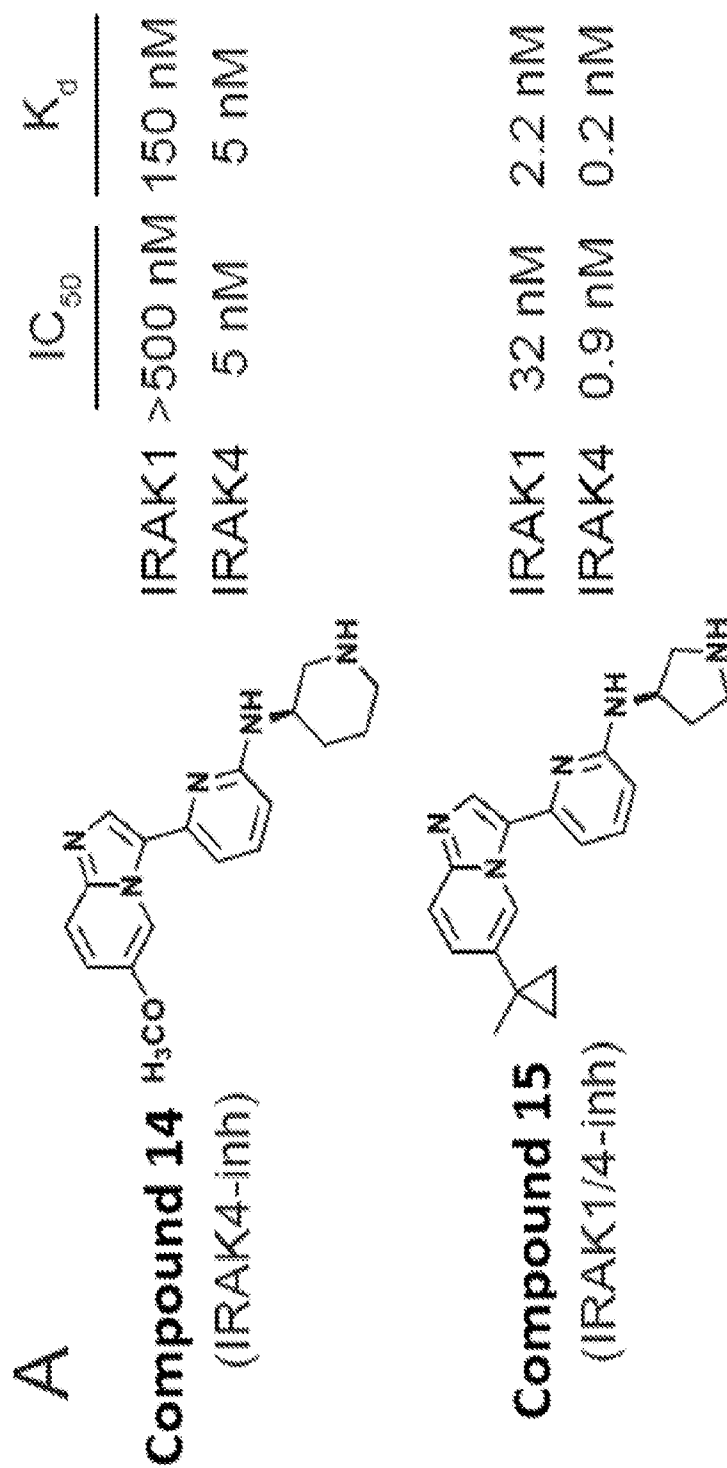
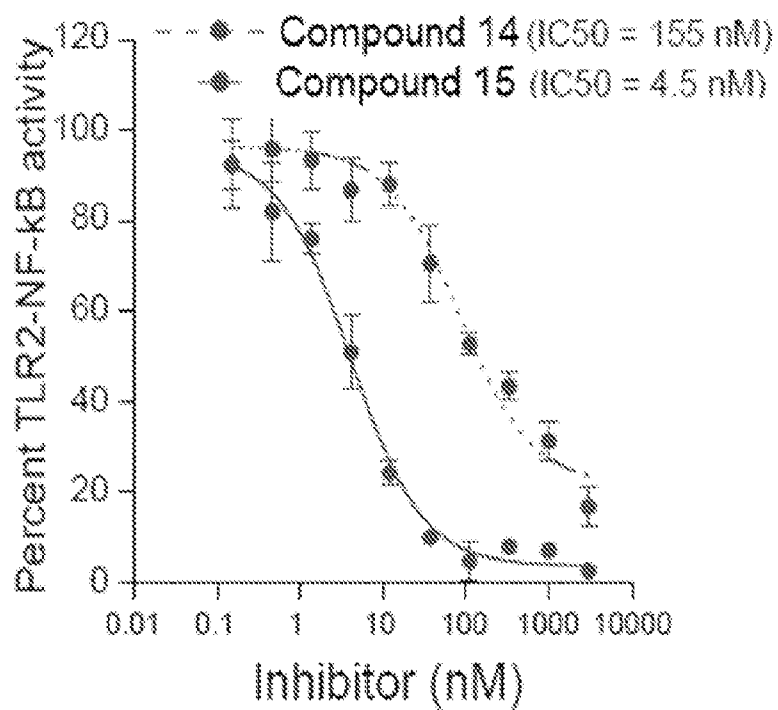
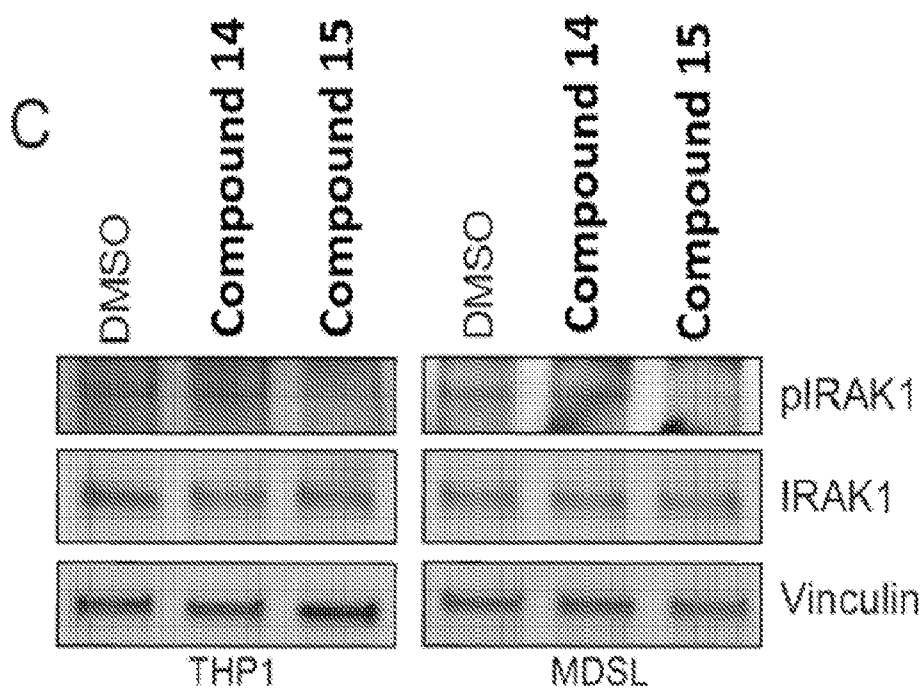


FIG. 20D

**FIG. 20A**

**FIG. 20B****FIG. 20C**

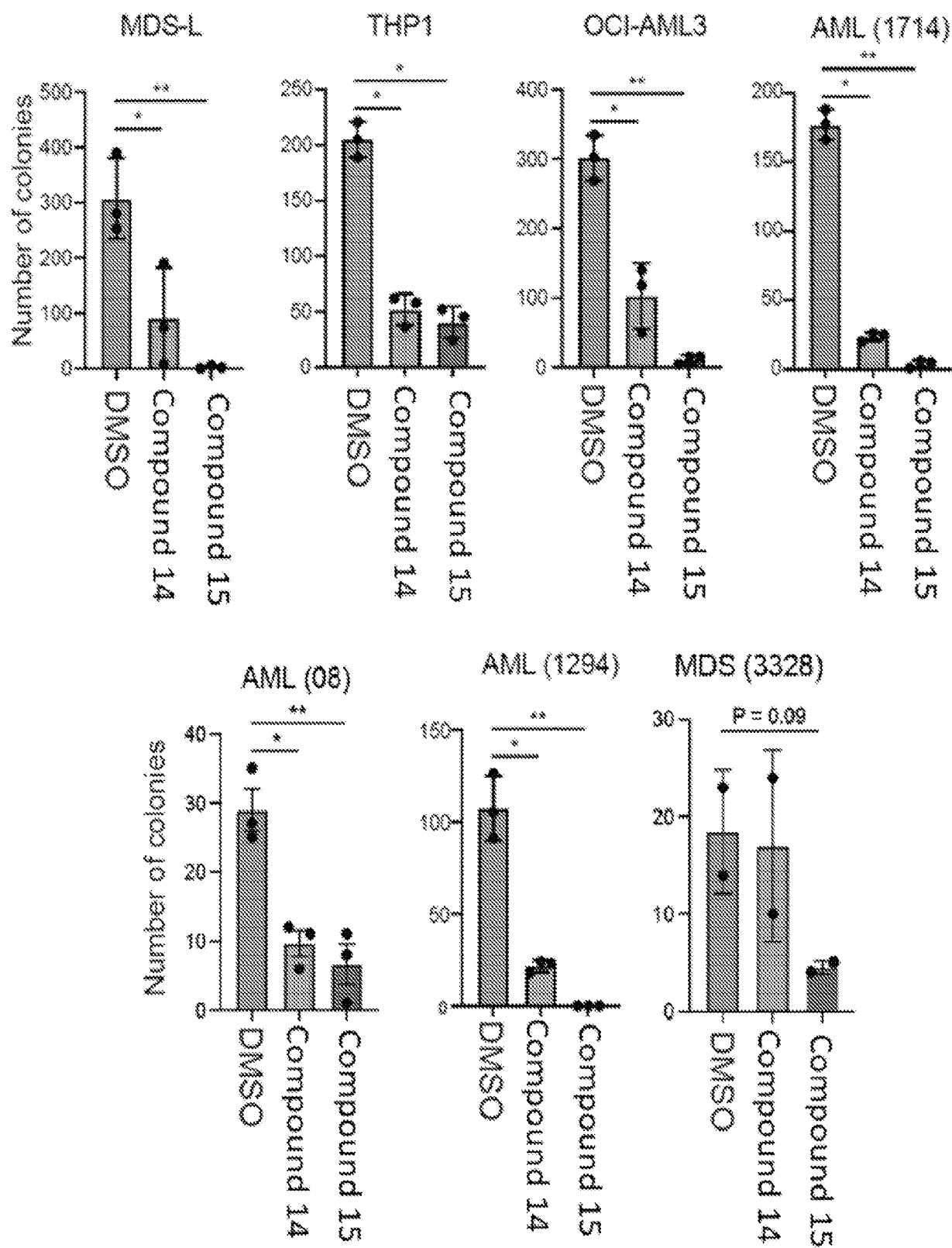


FIG. 20E

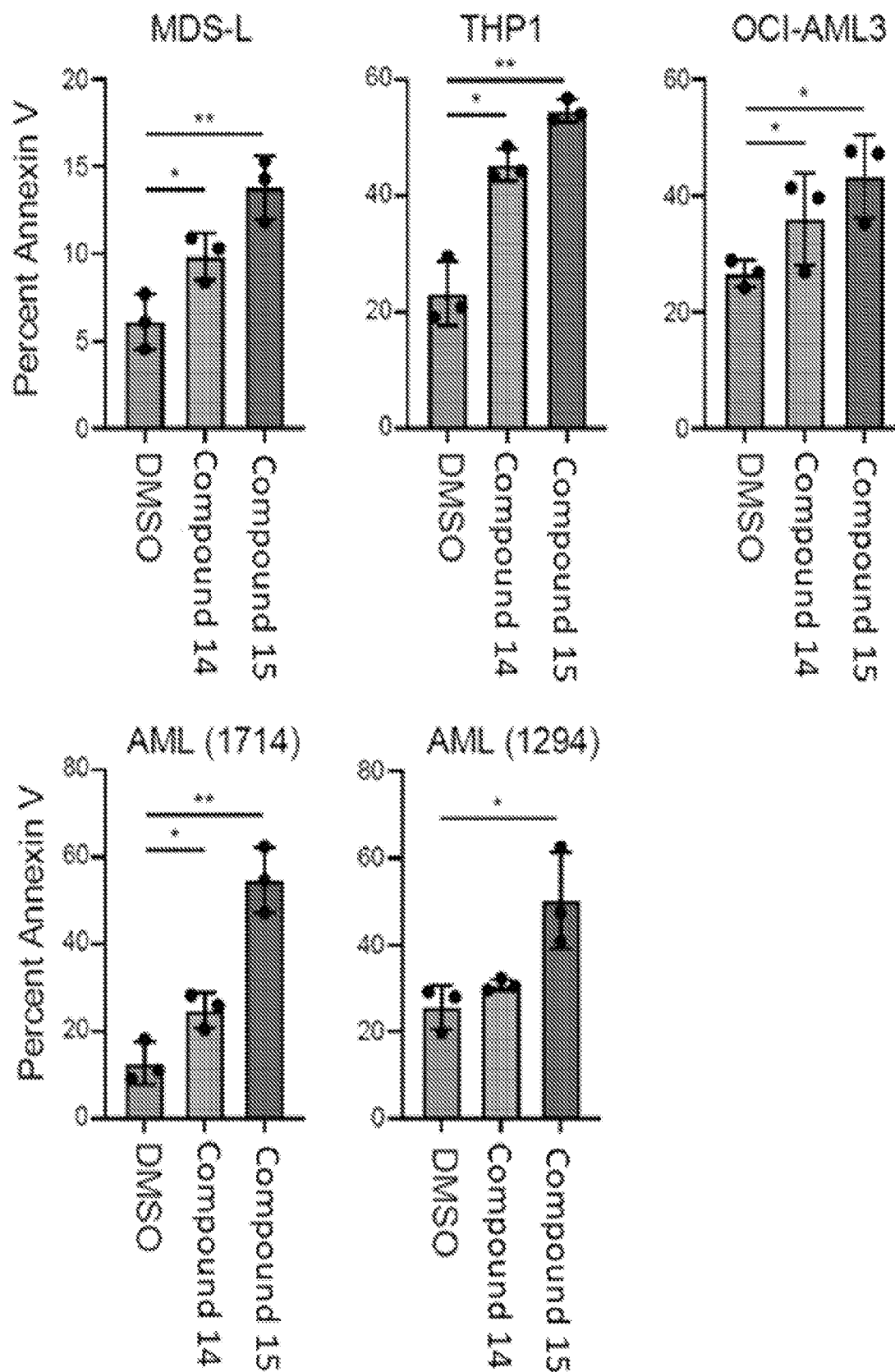
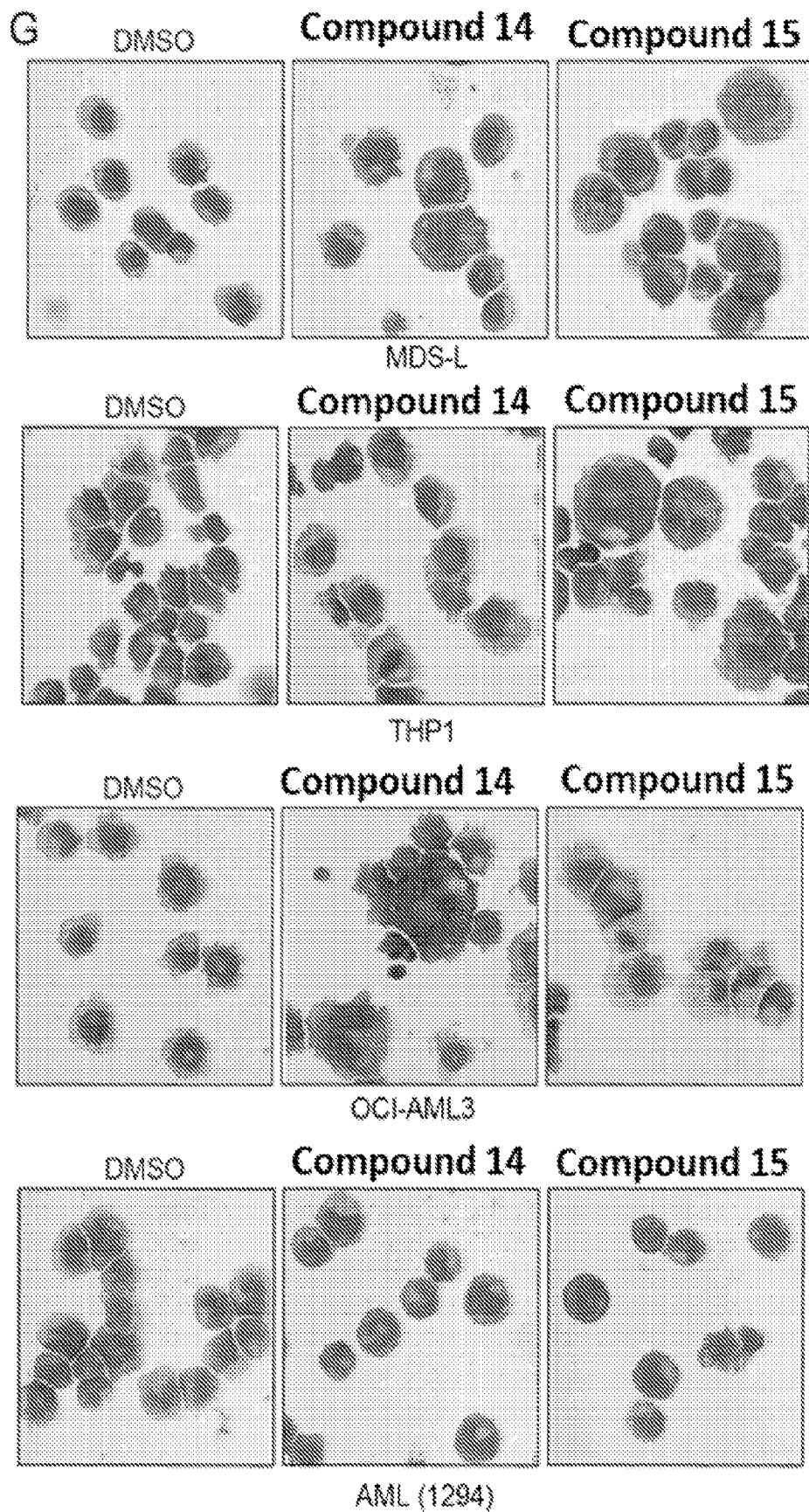


FIG. 20F

**FIG. 20G**

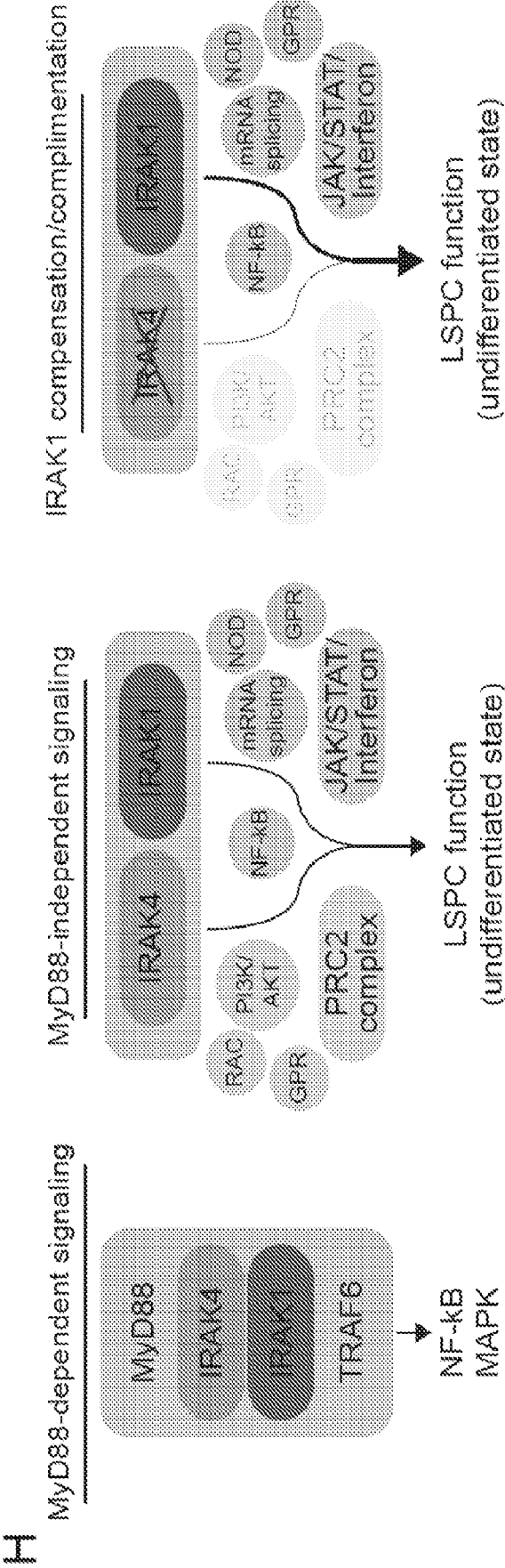


FIG. 20H

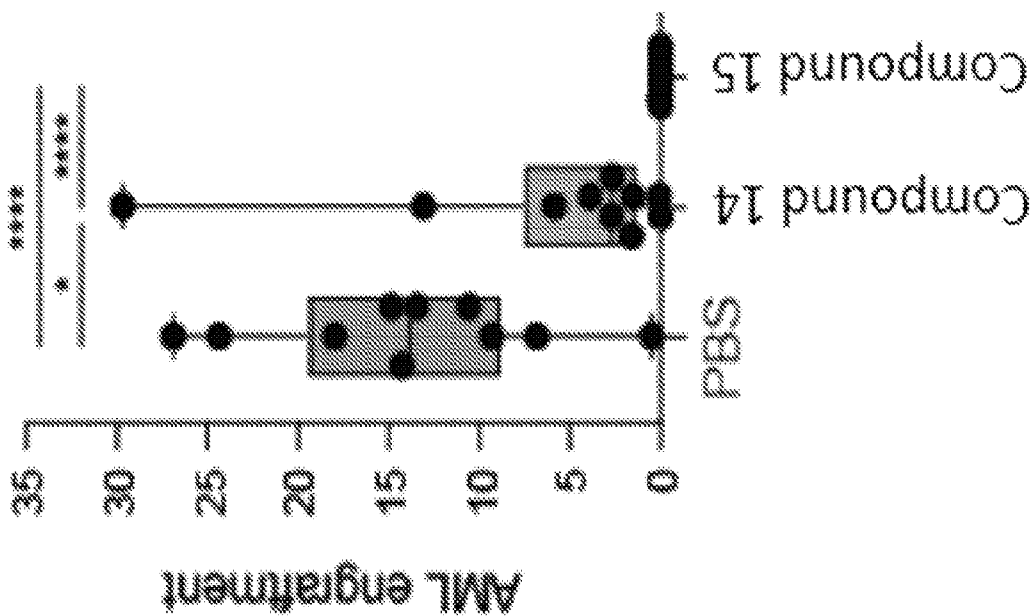


FIG. 20J

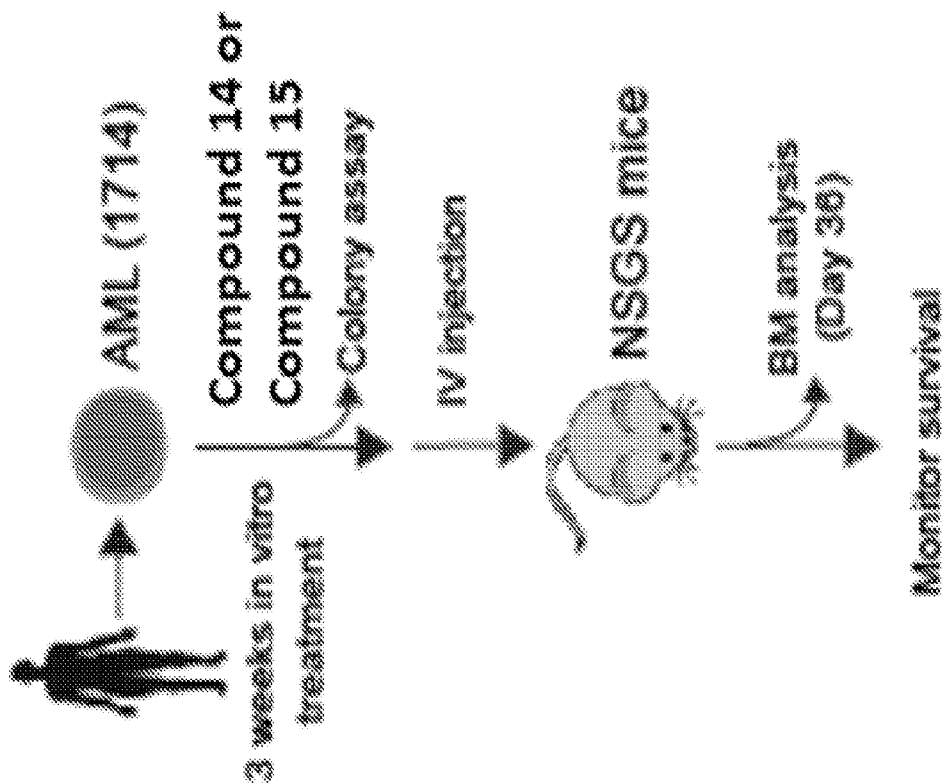


FIG. 20I

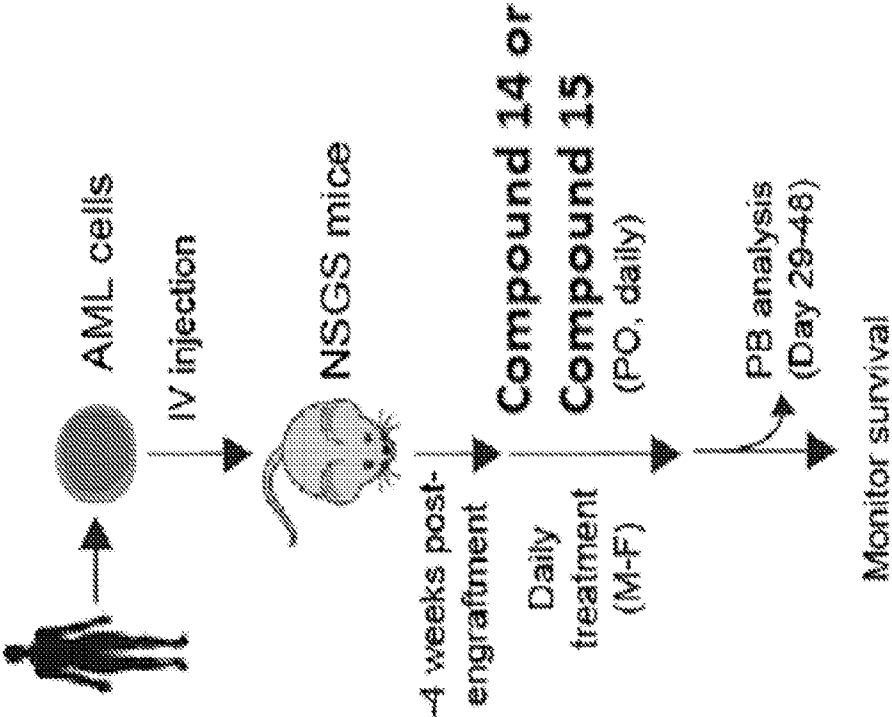


FIG. 20L

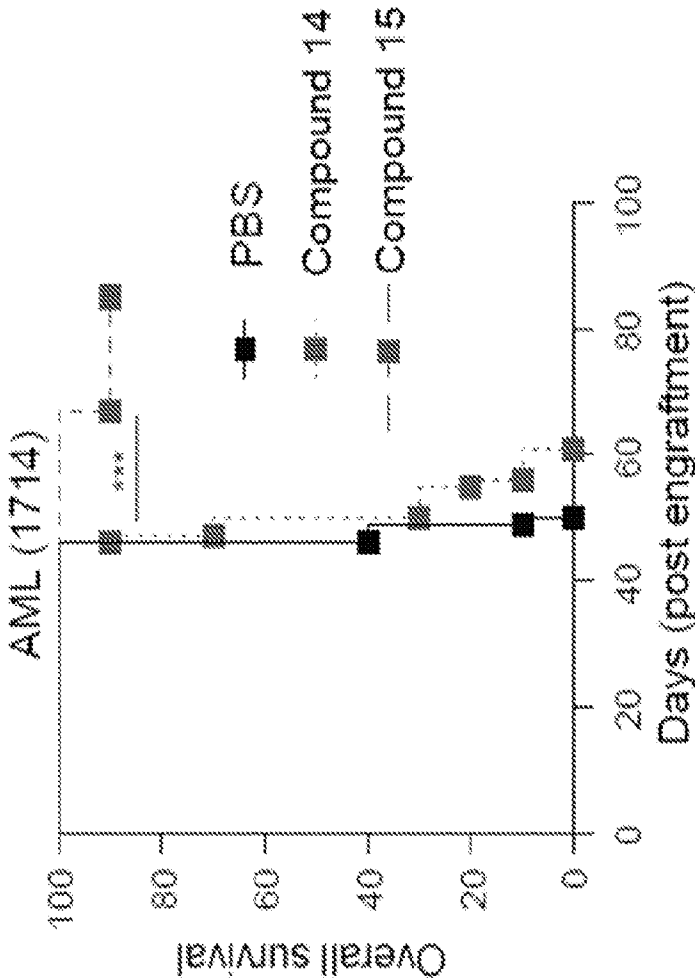


FIG. 20K

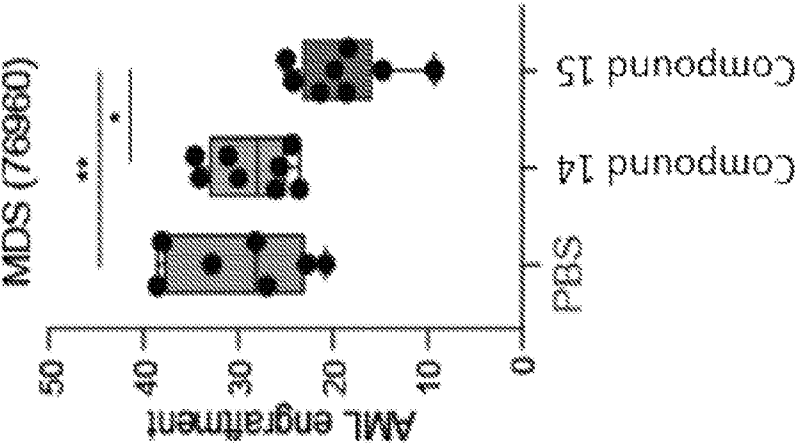


FIG. 200

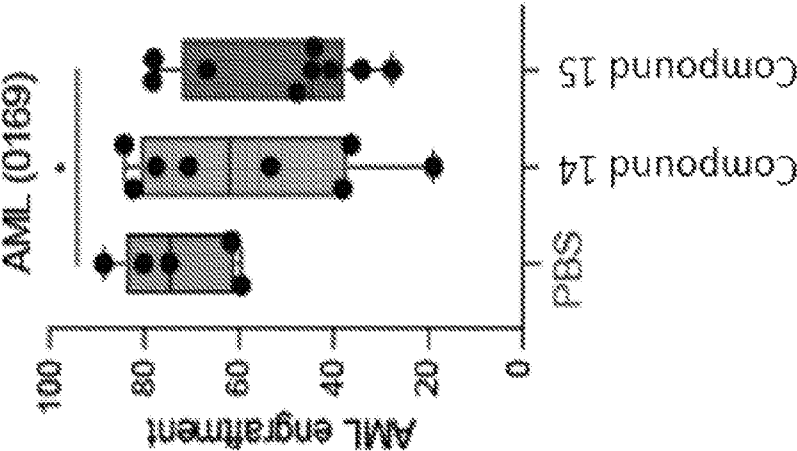


FIG. 20N

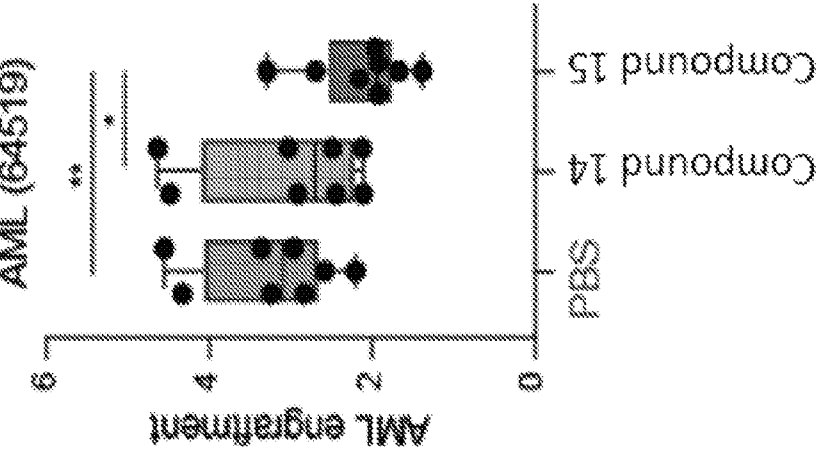


FIG. 20M

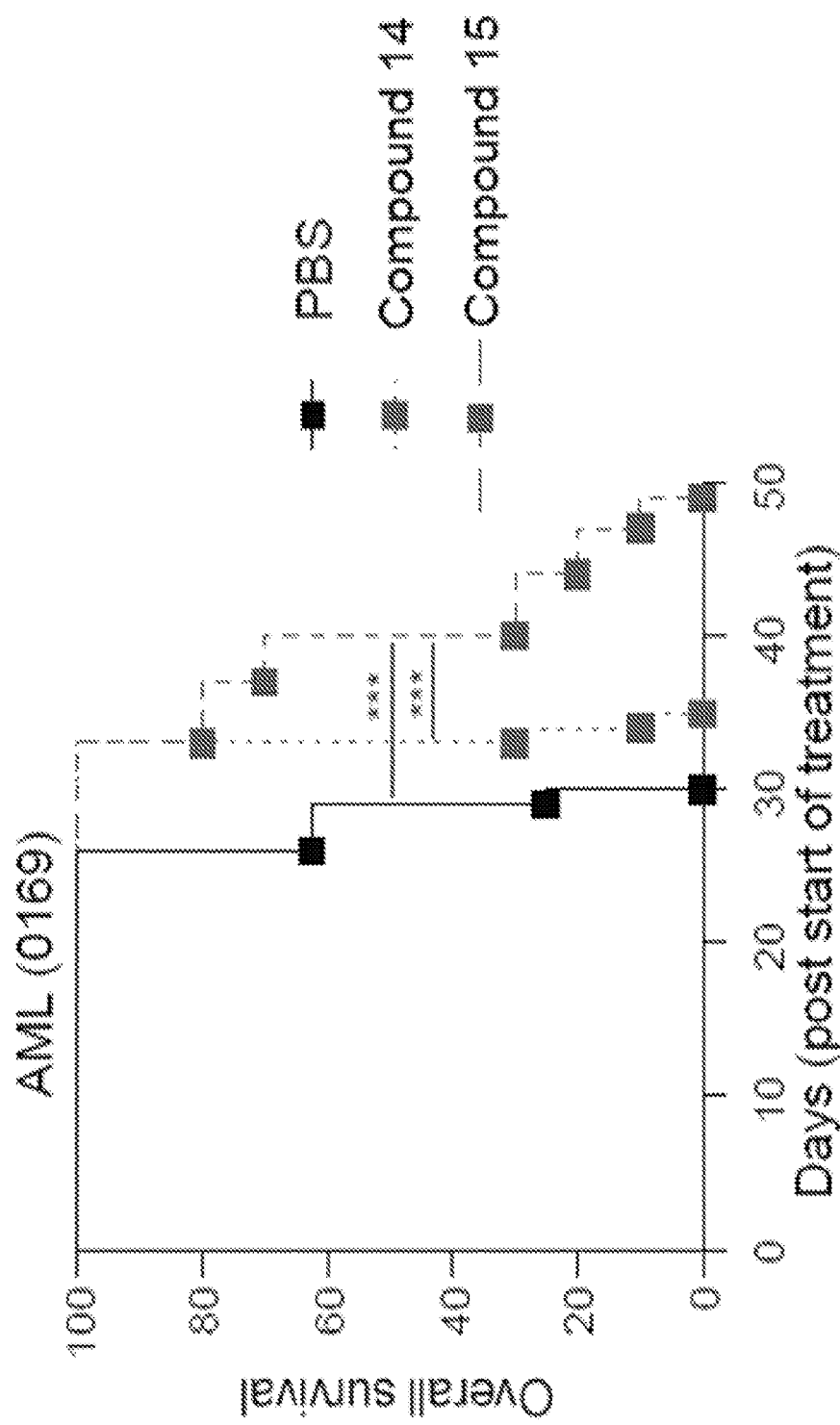
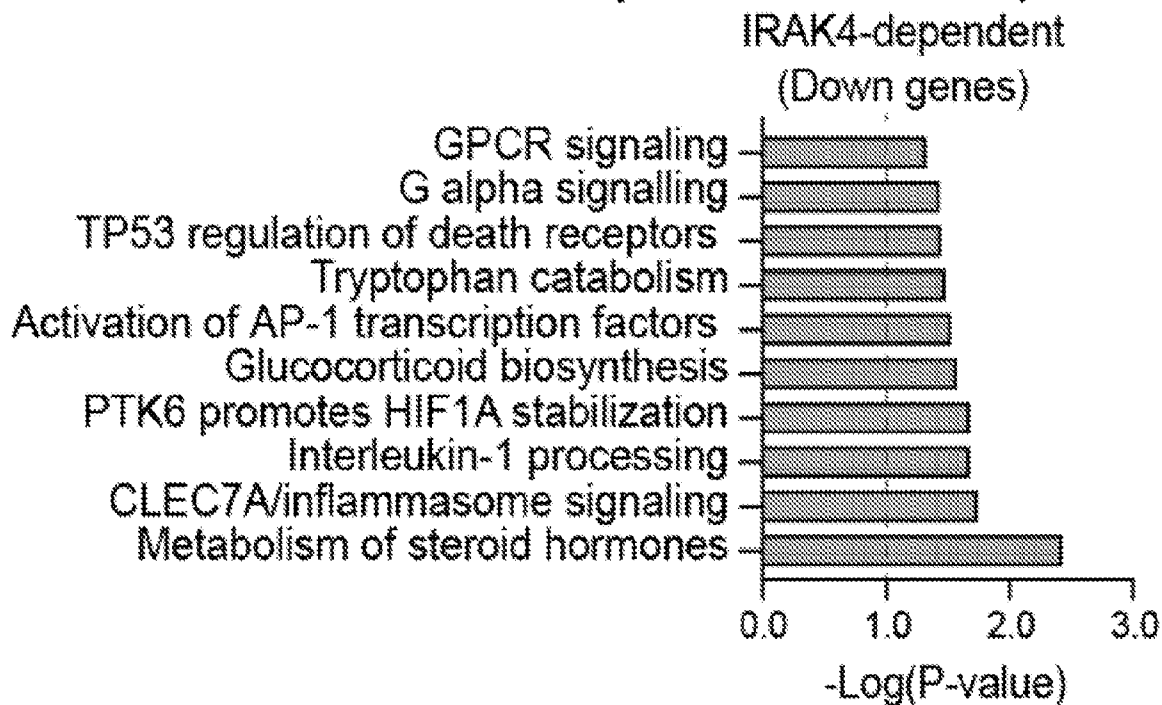
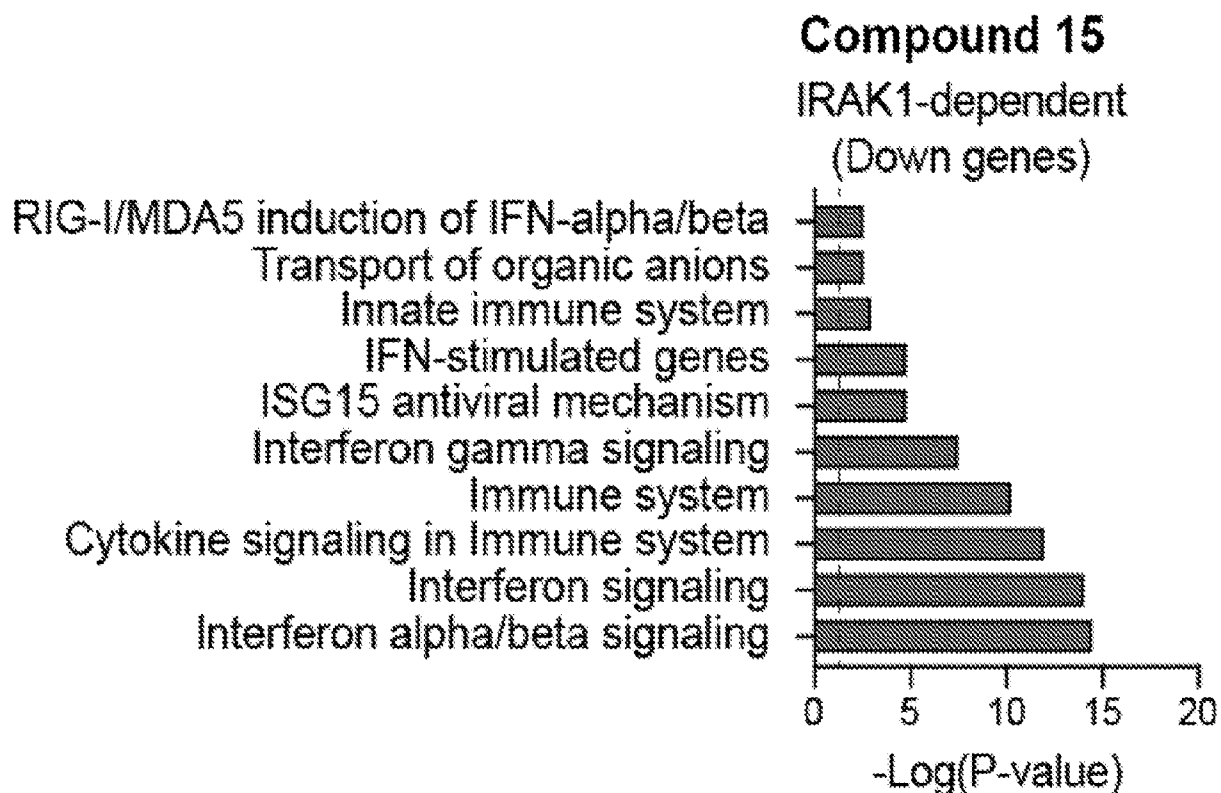


FIG. 20P

Compound 14 and Compound 15**FIG. 21A****FIG. 21B**

C

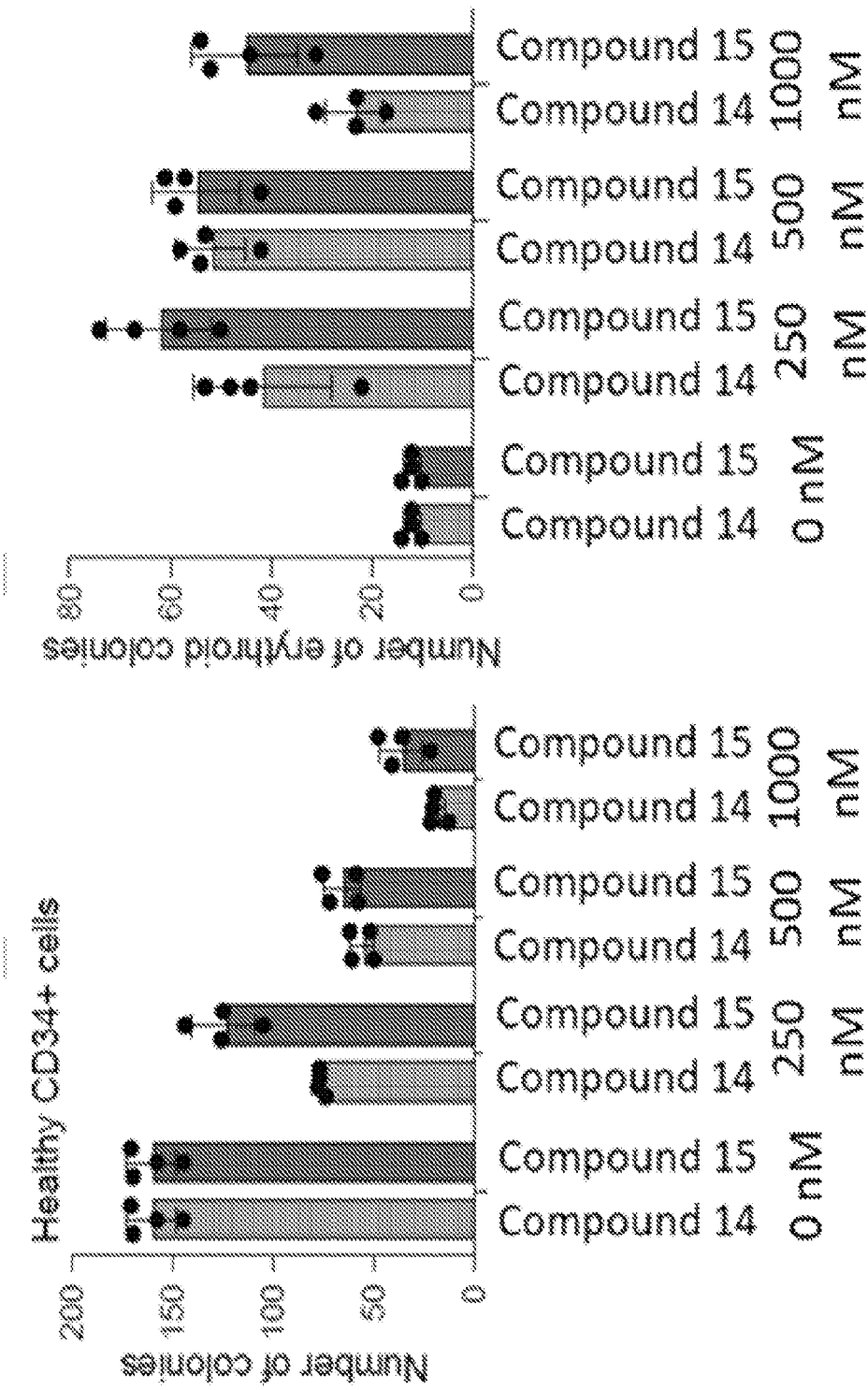


FIG. 21C

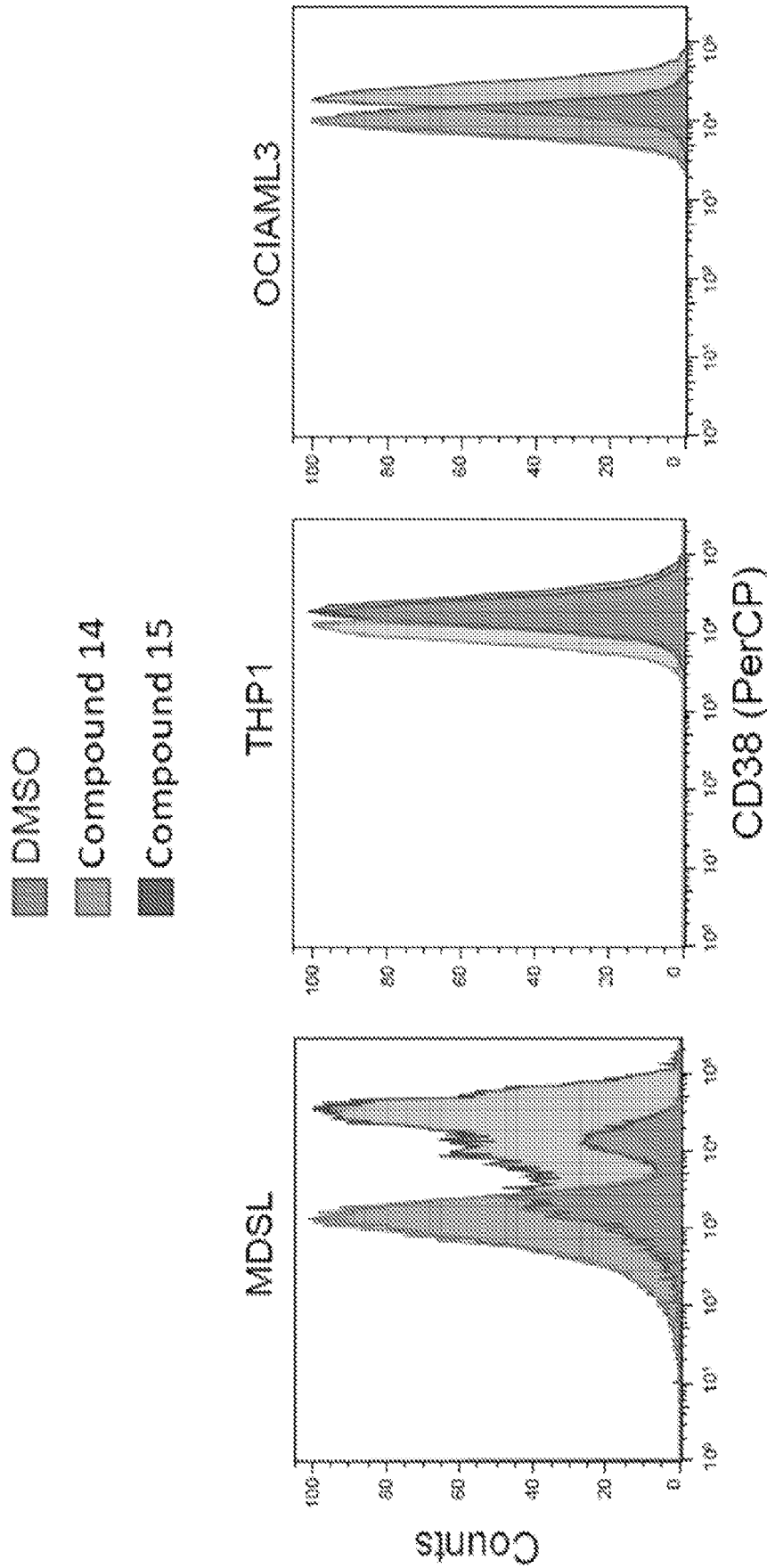


FIG. 21D

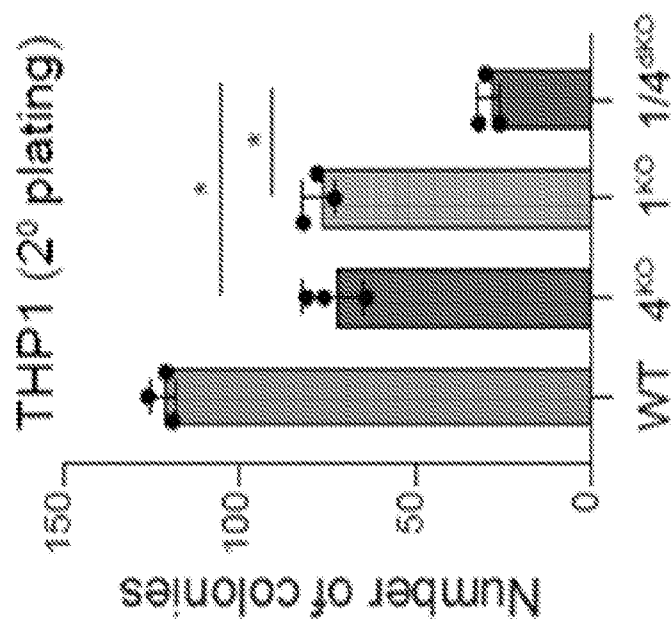


FIG. 22A

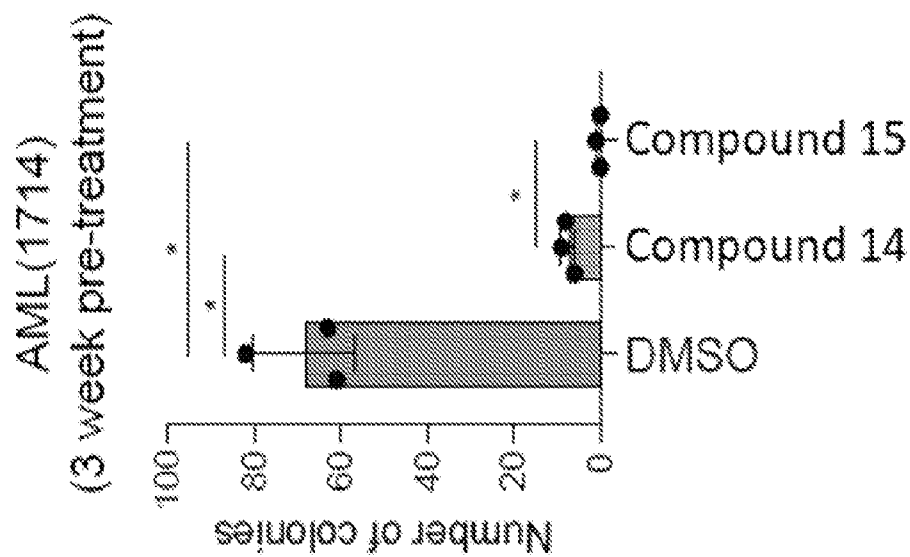


FIG. 21E

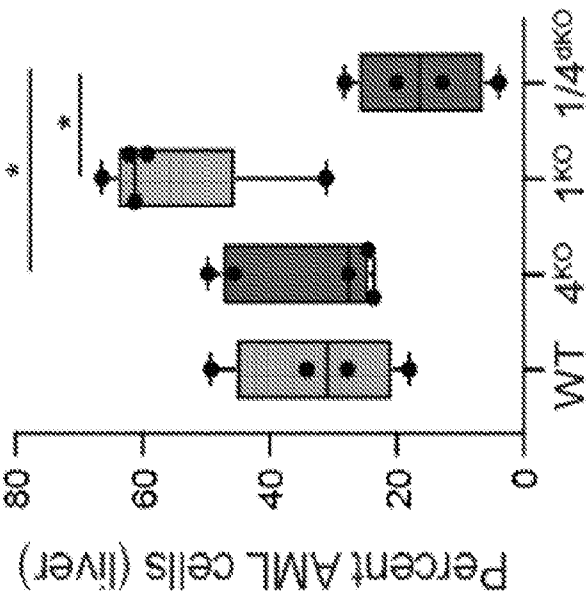


FIG. 23

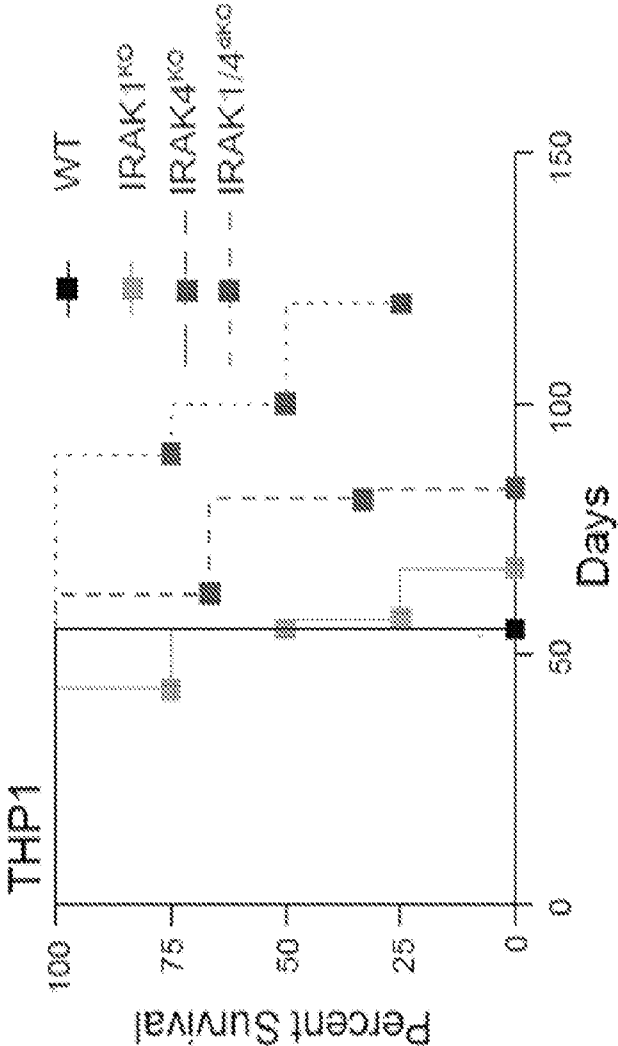


FIG. 22B

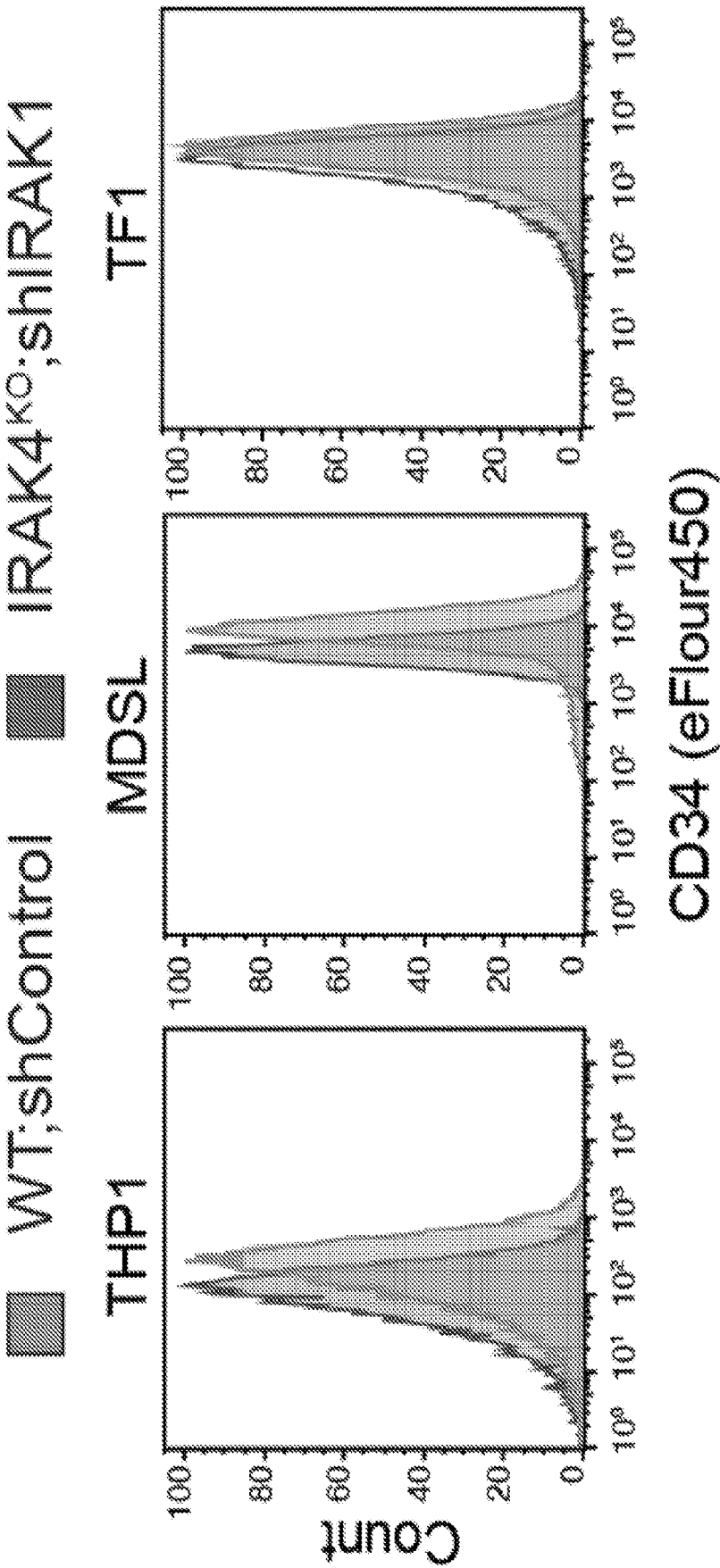
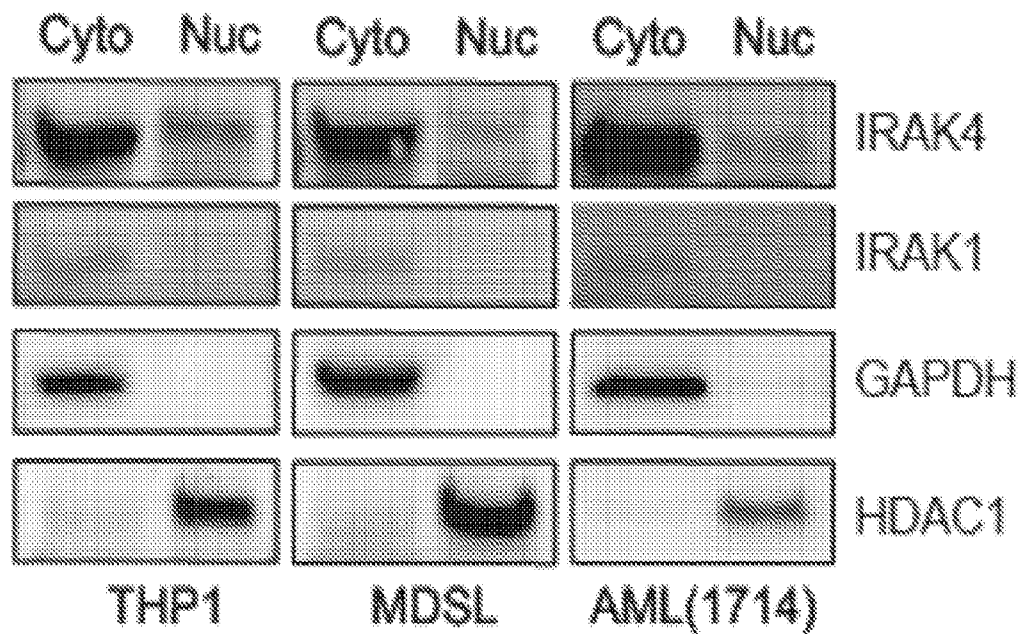
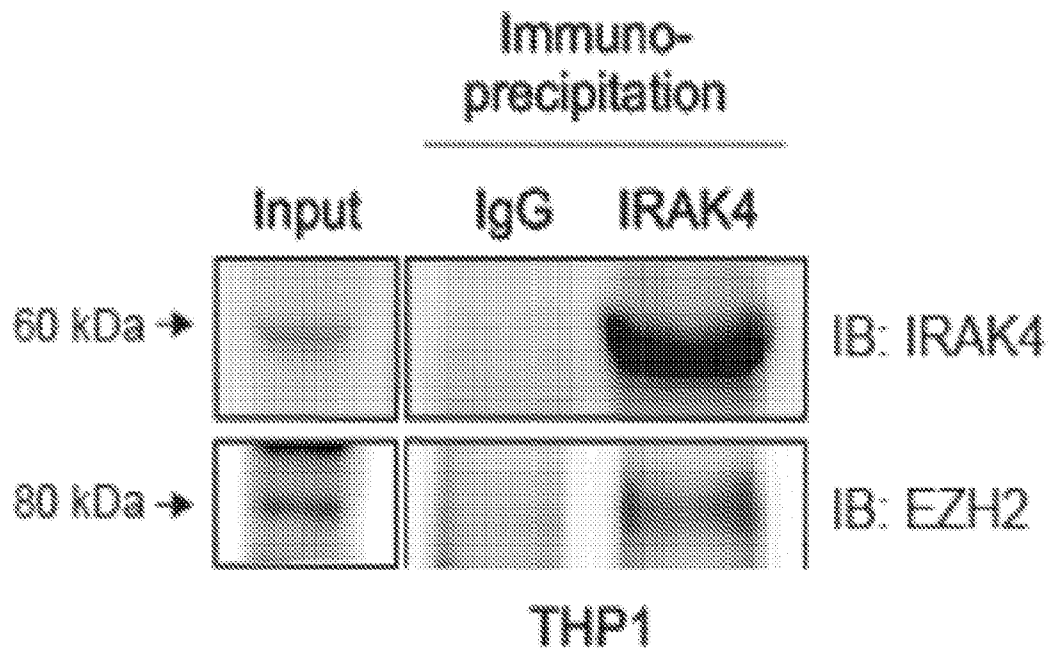


FIG. 24

**FIG. 25A****FIG. 25B**

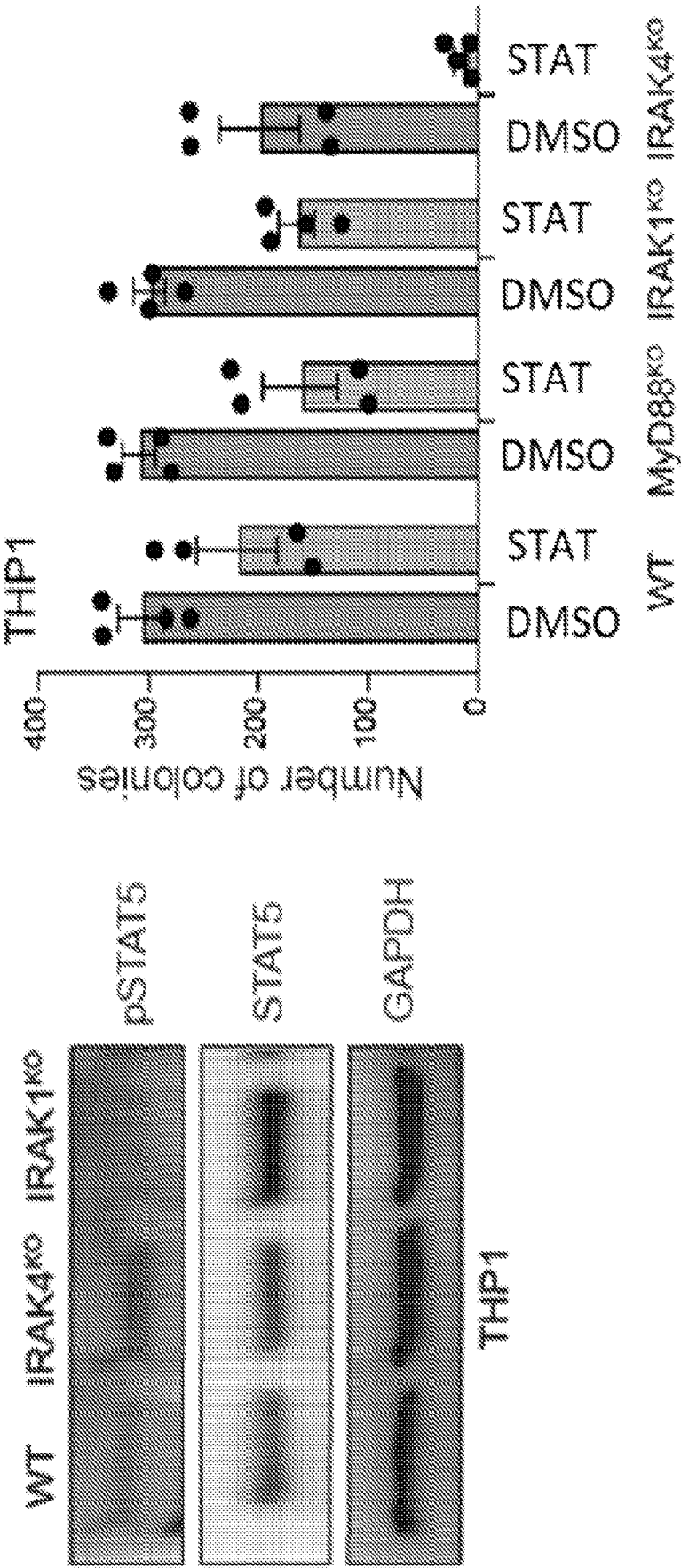


FIG. 25C

FIG. 25D

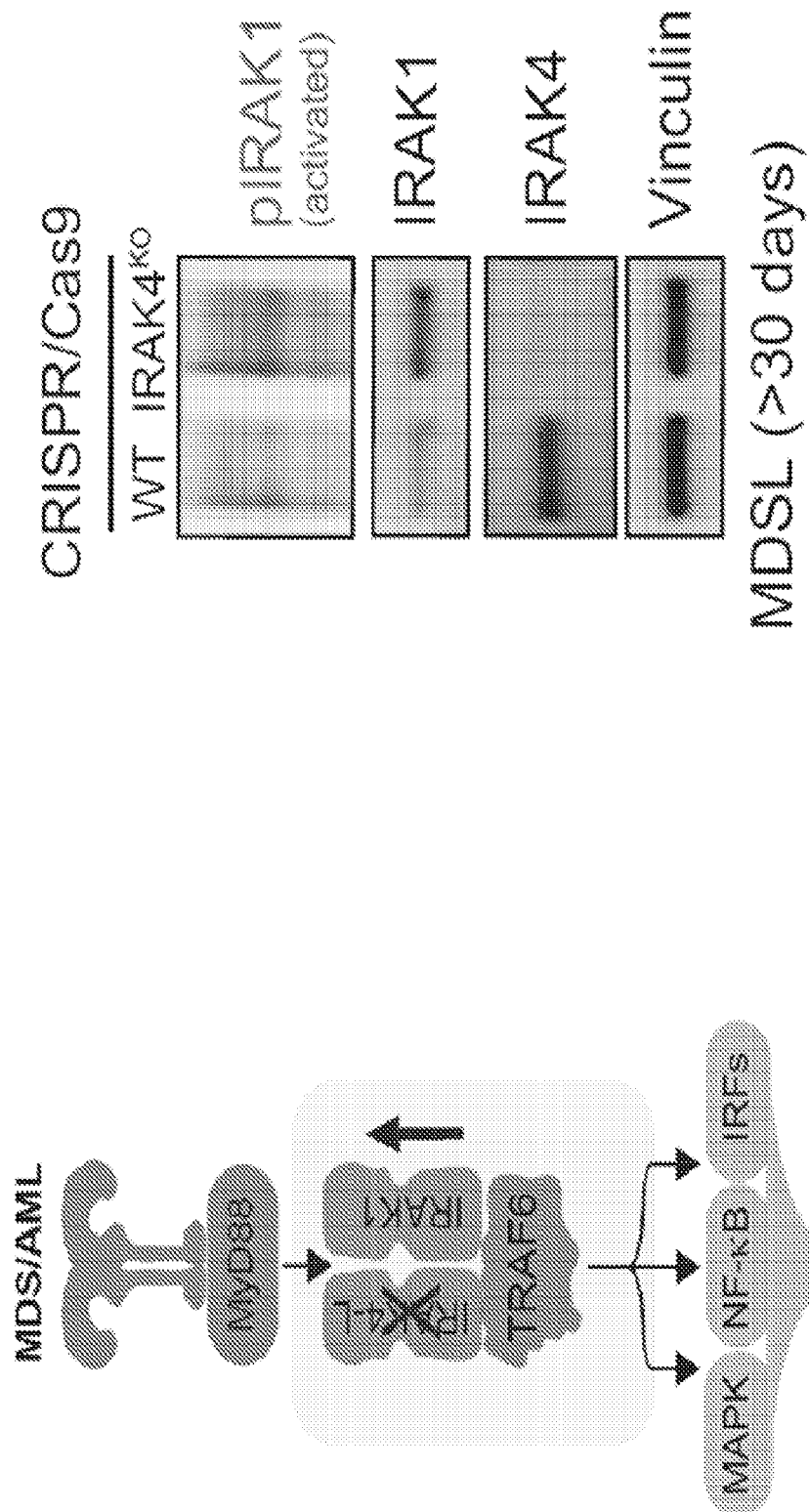


FIG. 26

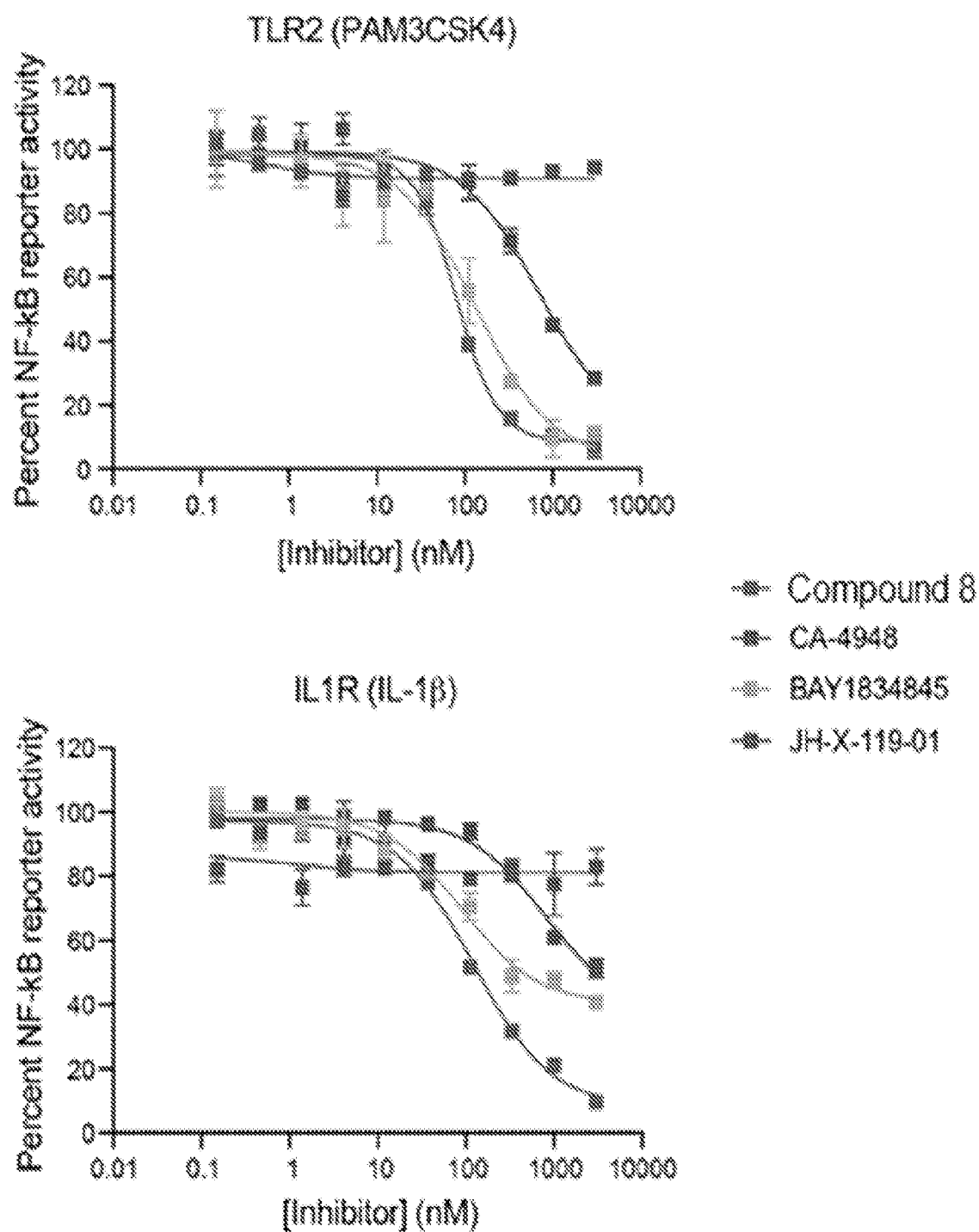
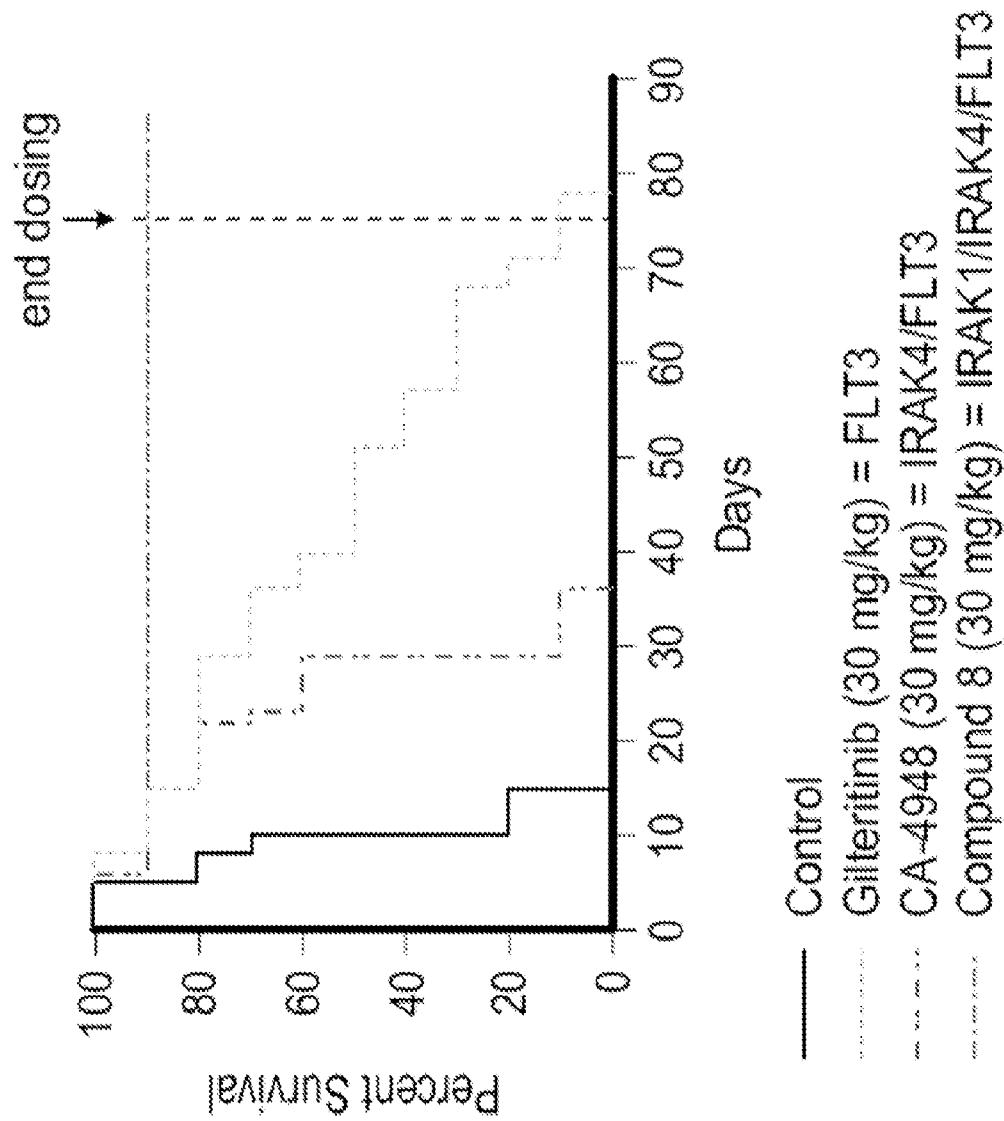


FIG. 27



Survival of NSGS xenografted with MOLM14 FLT3-ITD(D835Y); QD, PO

FIG. 28

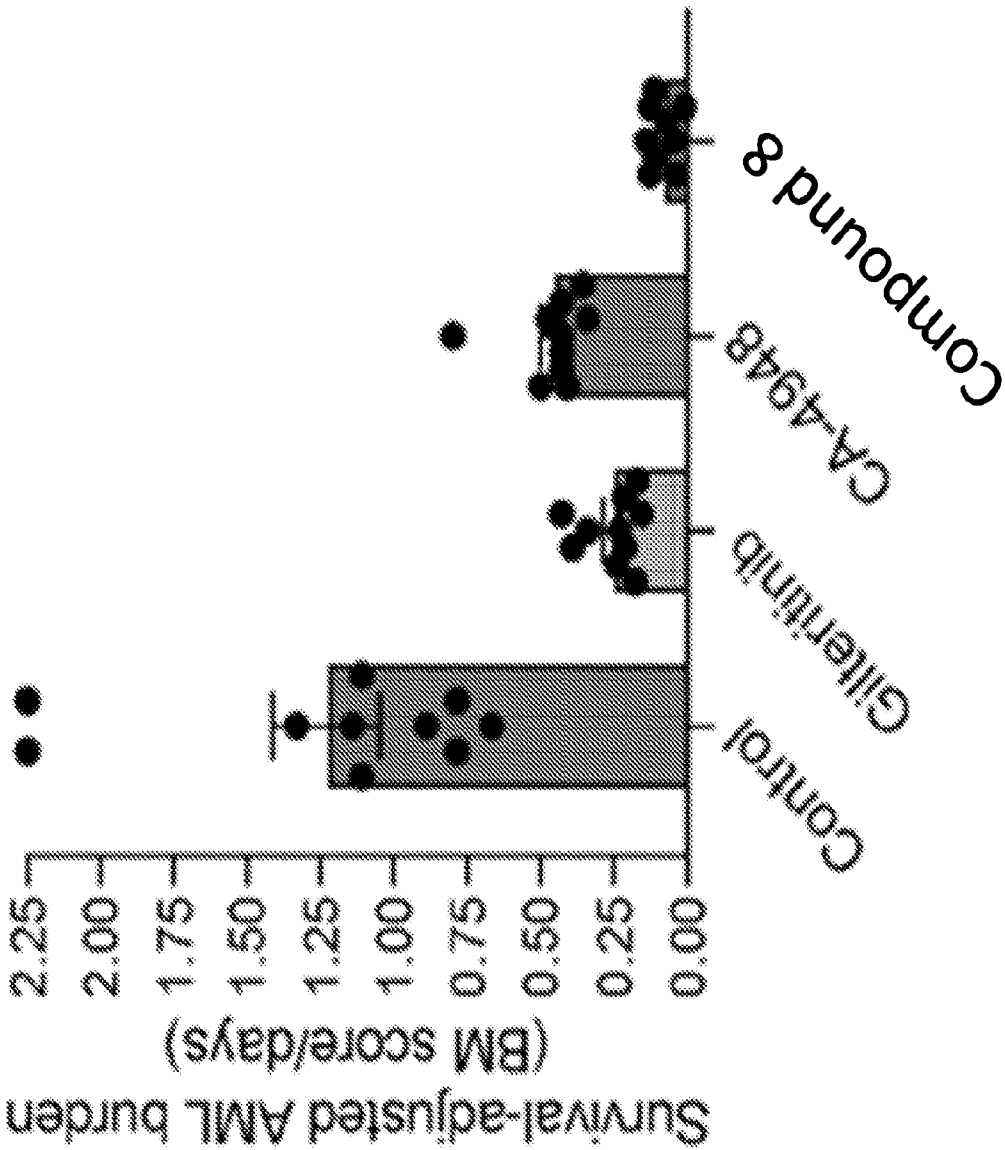


FIG. 28 (Continued)

RNA-seq performed on isogenic THP1 AML Cells
(WT, IRAK1 KO, IRAK4 KO, IRAK1/4 dKO)



Defined the IRAK1/4 signature based on IRAK1/4 dKO
(50 genes that were down-regulated and associated with
closed chromatin marks in dKO; overexpressed in AML)

FIG. 29A

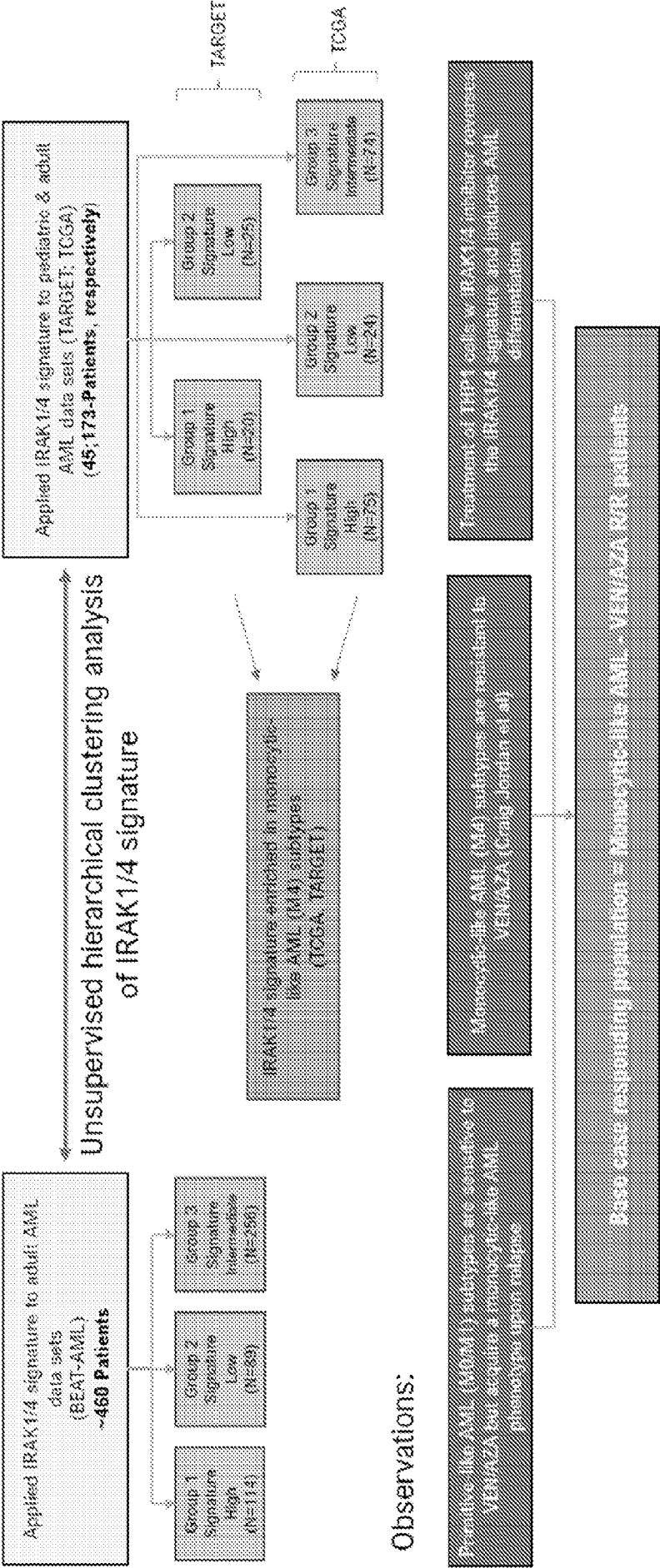


FIG. 29B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/71435

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.: 8-23, 29-42
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:

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 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.:

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US23/71435

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07D 471/02; A61P 29/00; A61P 35/00; C07D 513/22 (2023.01)

ADD.

CPC - INV. C07D 471/02; A61P 29/00; A61P 35/00; C07D 513/22

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2022/026935 A1 (CHILDREN'S HOSPITAL MEDICAL CENTER, et al.) 3 February 2022; paragraphs [0016], [0018], [0072], [00232], [00258], [00472], [00480], [00485]; table 32	1-7, 26-28 --- 24-25
Y	US 2015/0118229 A1 (ABBVIE INC.) 30 April 2015; abstract; paragraph [0105]	24-25
A	US 2017/0275284 A1 (MERCK PATENT GMBH) 28 September 2017; entire document	1-7, 24-28
P,X	(ROSENBAUM, JS et al.) Inhibition of Both IRAK1 and IRAK4 Is Required for Complete Suppression of NF-Kb Signaling across Multiple Receptor-Mediated Pathways in MDS and AML. Blood. 15 November 2022; pages 1-3; entire document; DOI: 10.1182/blood-2022-167783.	1, 3-7, 24-25

☐ Further documents are listed in the continuation of Box C.☐ 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

"D" document cited by the applicant in the international application

"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

14 November 2023 (14.11.2023)

Date of mailing of the international search report

DEC 19 2023

Name and mailing address of the ISA/

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Shane Thomas

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