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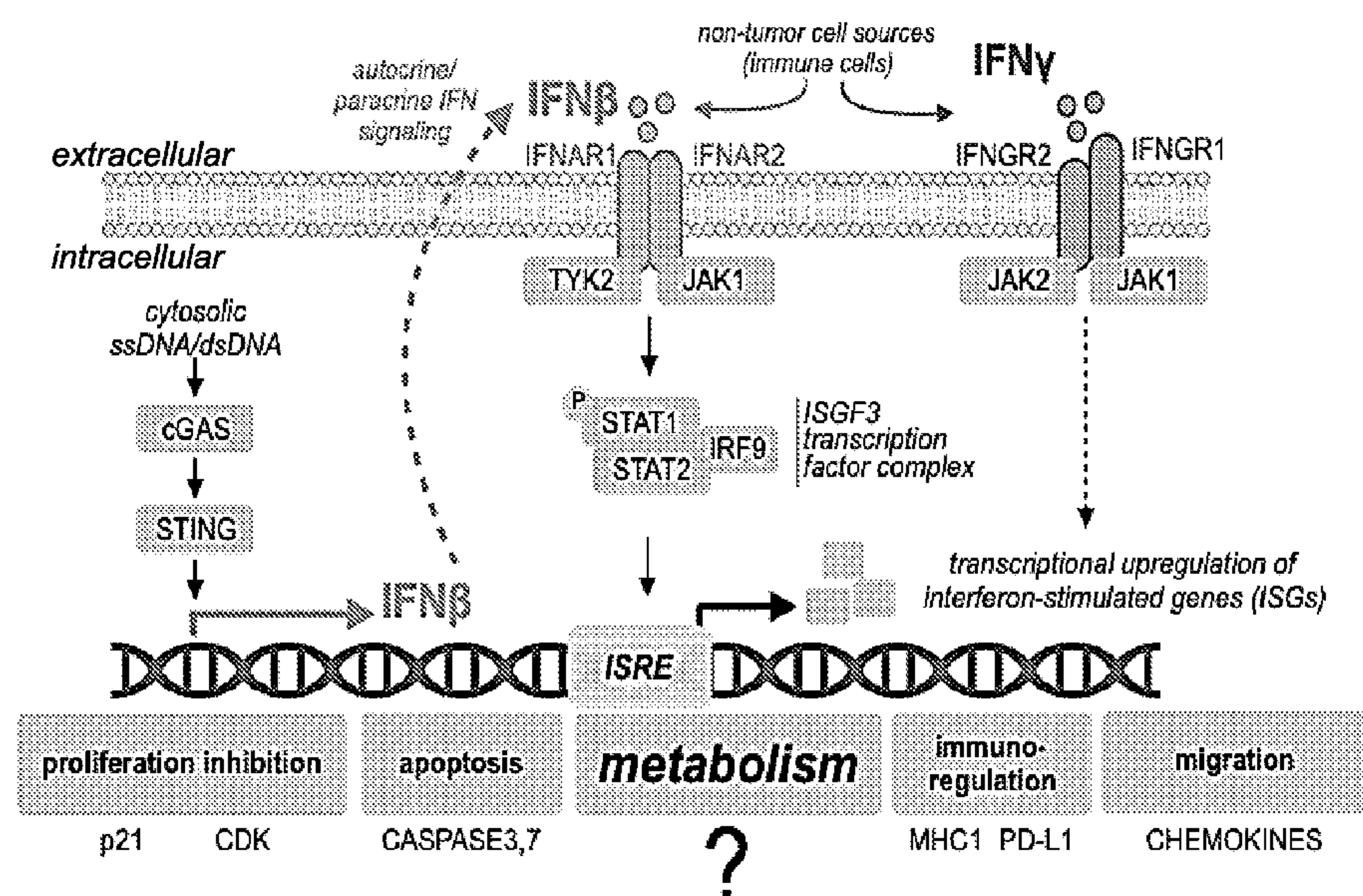


FIG. 1

(57) Abstract: The disclosure provides, inter alia, methods of treating cancer with ATR kinase inhibitors and/or NAMPT inhibitors, including, for example, methods of treating cancers that have an increased level of interferon or interferon signaling pathway activity. Provided herein are methods of treating cancer in a patient in need thereof comprising determining the level of IFN or IFN signaling pathway activity in a sample obtained from a patient; and administering to the patient an effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor.

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INTERFERON SIGNALING AS A CANCER BIOMARKER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Application No. 62/939,337 filed November 22, 2019, the disclosure of which is incorporated by reference herein in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with government support under Grant Number CA187678, awarded by the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED AS AN ASCII FILE

[0003] An Informal Sequence Listing forms part of the disclosure.

BACKGROUND

[0004] Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease for which new, rationally designed therapies are urgently needed. In addition to activating KRAS mutations, a dense stromal compartment and an inflammatory, cytokine rich microenvironment are defining characteristics of PDAC tumors. Among cytokines in the PDAC tumor environment, interferons are particularly important as they regulate the expression of hundreds of genes, many of which have established pro- or anti-tumor functions.

[0005] The median overall survival of patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) is less than one year and PDAC is expected to become the second most common cause of cancer related death in the United States by 2020. Contributing to this poor prognosis is the near universal resistance of PDAC tumors to current pharmacological and immunotherapy treatment regimens and it is clear that a better understanding of fundamental biology is required for the development of new therapies for this disease. Accordingly, substantial efforts have been dedicated towards defining genomic and transcriptional PDAC subtypes to ultimately guide precision medicine treatment approaches. In mutations are detected in 4-7% of patients and are associated with response to PARP inhibitors. Additionally, two transcriptional subtypes have been recurrently identified in PDAC patient samples and include the basal-like/mesenchymal/squamous and classical/epithelial/progenitor. However, the distinct biological behavior and targetable vulnerabilities of these subtypes are not well defined.

[0006] In addition to a near universal penetrance of KRAS mutations and a dense stromal

component, PDAC is defined by a pro-inflammatory, cytokine-rich tumor microenvironment. Among cytokines present in PDAC tumors interferons (IFNs), are particularly important and influence cancer development, progression, and response to DNA damaging therapy. Type I IFNs (IFN α , IFN β and IFN λ) are constitutively produced in the PDAC tumor microenvironment by stromal, immune, and potentially tumor cells (**FIG. 1**). One signaling network regulating the production of type I IFNs is the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)/stimulator of IFN genes (STING) pathway which is induced by cytoplasmic single-stranded and double-stranded DNA (ssDNA, dsDNA). Type I IFNs function by binding to specialized receptors, IFNAR1 and IFNAR2, and inducing a JAK1/TYK2-mediated signaling cascade which results in transcriptional activation of hundreds of IFN-stimulated genes including STAT1 and MX1, canonical surrogate markers of type I IFN signaling. Paradoxically, IFNs exert both pro- and anti-tumor effects: IFNs impair cancer cell proliferation in vitro but chronic exposure has been linked with resistance to radiation, chemotherapy and immune checkpoint blockade. Additionally, it remains to be determined if IFN signaling in tumors can be leveraged therapeutically.

[0007] The roles of type I IFNs in modulating immunity and eliciting anti-pathogen responses are well-characterized, but only recently has emphasis been placed on their metabolic effects. PDAC tumors undergo extensive metabolic reprogramming that enables them to adapt to chronic nutrient deprivation and also functions as a form of immunosuppressive microenvironmental conditioning. Drivers of metabolic reprogramming in PDAC include oncogenes (KRAS), physiologic factors (hypoxia), and heterotypic cellular interactions with stromal cells and immune cells. Type I IFNs have been linked to the regulation of lipid and energy metabolism in immune and epithelial cells, however, whether and how type I IFN signaling reprograms PDAC metabolism remains to be determined. (Refs.1-18).

[0008] In view of the foregoing, there is a need for defining crosstalk between cytokine signaling, stress response networks and metabolism in PDAC to enable improved treatment regimens. The present disclosure addresses this need, and provides additional benefits.

SUMMARY

[0009] Provided herein are methods of treating cancer in a patient in need thereof comprising administering to the patient an effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor; wherein the cancer has increased levels of IFN or IFN signaling pathway activity.

[0010] Provided herein are methods of treating cancer in a patient in need thereof comprising determining the level of IFN or IFN signaling pathway activity in a sample obtained from a

patient; and administering to the patient an effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor.

[0011] Provided herein are methods of classifying a cancer in a subject comprising measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient; comparing expression levels of the plurality of target genes to a control; and classifying the cancer as responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor.

[0012] Provided herein are methods of method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, thereby identifying that the cancer patient is responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor.

[0013] These and other embodiments are described in detail herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIG. 1** depicts interferon pathways. Interferons (IFNs) are pleiotropic cytokines that modulate multiple aspects of cancer cell biology. Measured intracellular dNTPs vs. estimated dNTPs required for DNA replication in mammalian cells. cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; ISRE: interferon-sensitive response element; IFNAR: interferon-alpha/beta receptor; IFNGR: interferon-gamma receptor; STAT1: signal transducer and activator of transcription 1.

[0015] **FIG. 2** demonstrates that IFN signaling biomarkers are enriched in PDAC tumors. Provided are representative immunohistochemistry (IHC) images of primary PDAC samples probed for the interferon regulated gene MX1 obtained at 20x magnification.

[0016] **FIGS. 3A-3K** demonstrate IFN signaling biomarkers are enriched in PDAC and IFN activates the replication stress response pathway. **FIG. 3A** presents analysis of IFN response metagene signature in the TCGA PDAC dataset. **FIG. 3B** are representative immunohistochemistry (IHC) images of primary PDAC samples probed for total STAT1 and plot histoscores from 26 PDAC tumors. Histoscores were calculated as a sum of the intensity of staining (0, negative; 1, weak; 2, median; or 3, strong) multiplied by the percentage of tumor cells at that intensity (0-300 range). **FIG. 3C** presents immunoblot analysis of DANG cells

treated $\pm$ 100 U/mL IFN β for the indicated timepoints *in vitro* and lysates prepared from SUIT2 cells grown as subcutaneous tumors in NSG mice. Immunoblot analysis of DANG PDAC cells. **FIG. 3D** is nLC-MS/MS proteomics/phosphoproteomics analysis of SUIT2 cells treated $\pm$ 100 U/mL IFN β for 24 hours. An FDR of 1% was used to identify significantly altered proteins. An FDR of 0.1% was used to identify significantly altered phosphopeptides. KSEA analysis was used to identify significantly-altered phosphoproteins. **FIG. 3E** is a graph showing ATR substrates identified by KSEA as being significantly altered by IFN β from experiment in **FIG. 3D**. **FIG. 3F** is an immunoblot analysis of SUIT2 cells treated with 100 U/mL IFN β for indicated time-points. **FIG. 3G** is a graph showing IncuCyte live-cell imaging analysis of SUIT2 cells treated 100 U/mL IFN β (mean $\pm$ SD, n=6, student's t-test, **** P<0.0001). **FIG. 3H** present EdU-pulse flow cytometry analysis of SUIT2 cells. Cells were treated for 24 hours $\pm$ 100 U/mL IFN β and subsequently pulsed with 10 μ M EdU for 2 h (mean $\pm$ SD; n=2). **FIG. 3I** is immunoblot analysis of a panel of PDAC cell lines treated $\pm$ 100 U/mL IFN β for 24 hours. **FIG. 3J** is a graph demonstrating fFold change in the percentages of S-phase cells following treatment $\pm$ 100 U/mL IFN β for 24 hours in a panel of 13 PDAC cell lines (mean $\pm$ SD, n=2, one-way ANOVA: P< 0.0001). **FIG. 3K** are representative images for STAT1 and phospho-CHEK1_{S345} IHC analysis of serial sections of PDAC patient tumor samples.

[0017] **FIGS. 4A-4F** demonstrate Type I IFN signaling restricts dNTP pools. **FIG. 4A** illustrates the experimental approach to investigate the effects of IFN signaling on nucleotide metabolism in PDAC cells. **FIGS. 4B-C** are graphs showing LC-MS/MS analysis of dNTP pools in SUIT2 (**B**) and YAPC (**C**) cells treated for 24 hours $\pm$ 100 U/mL IFN β in media containing 1 g/L [¹³C₆]glucose (mean $\pm$ SD; n=3). **FIG. 4D** is a graph summary of nucleotide metabolism genes significantly altered by IFN β treatment as determined by nLC-MS/MS in **FIG. 1D**. **FIG. 4E** is an immunoblot analysis of SUIT2 and YAPC cells treated $\pm$ 100 U/mL IFN β or $\pm$ 10 ng/mL IFN γ for 24 hours. **FIG. 4F** depicts a working model summarizing the interactions between IFN and nucleotide metabolism.

[0018] **FIGS. 5A-5K** demonstrate that STING controls IFN signaling and nucleotide metabolism in xenograft tumors. **FIG. 5A** is a schematic of the regulation of autocrine/paracrine IFN β production by the cGAS/STING signaling pathway. **FIG. 5B** is a graph of IncuCyte live-cell imaging analysis of SUIT2 TetR; STING^{R248M} cells treated + 50 ng/mL DOX in anchorage-independent culture (mean $\pm$ SD; n=6; student's t-test, **** P<0.0001). **FIG. 5C** is an immunoblot analysis of SUIT2 TetR; STING^{R248M} cells treated $\pm$ 50 ng/mL doxycycline (DOX) $\pm$ 1 μ M ruxolintinib (JAKi) $\pm$ 100 U/mL IFN β for the indicated timepoints (mean $\pm$ SD, n=6, student's t-test, **** P<0.0001). **FIG. 5D** presents growth curves of SUIT2 TetR; STING^{R248M}

subcutaneous tumors in NSG mice treated $\pm$ DOX measured using CT imaging (mean $\pm$ SEM, n=6, student's t-test, *** P<0.001). **FIG. 5E** is immunoblot analysis of STING^{R248M} subcutaneous tumors at the endpoint of experiment in FIG. 5D. **FIG. 5F** presents growth curves of DANG STING WT and STING KO subcutaneous tumors in NCG mice measured using caliper measurements (mean $\pm$ SEM, n=6, student's t-test, *** P<0.001). **FIG. 5G** is an immunoblot analysis of DANG STING WT and STING KO tumors at the endpoint of experiment in FIG. 5F. **FIG. 5H** presents growth curves of SUIT2 TetR; STING^{R248M}; LUC orthotopic tumors in NCG mice treated $\pm$ DOX measured using bioluminescence (BLI) imaging (mean $\pm$ SD, n=6, student's t-test, * P<0.05). **FIG. 5I** presents immunoblot analysis of SUIT2 TetR; STING^{R248M}; LUC orthotopic tumors at the endpoint of experiment in FIG. 5H. **FIG. 5J** is data presenting [¹⁸F]FLT PET analysis of SUIT2 TetR; STING^{R248M} subcutaneous tumors. **FIG. 5K** is data presenting [¹⁸F]FDG PET analysis of SUIT2 TetR; STING^{R248M} subcutaneous tumors.

[0019] FIGS. 6A-6G demonstrate ATR inhibitors synergize with IFN. **FIG. 6A** represents the high-throughput phenotypic screen evaluating the anti-proliferative effects of 430 protein kinase inhibitors, tested at 7-point dose response, against SUIT2 cells treated $\pm$ 100 U/mL IFN β for 72 hours (DDR: DNA damage response; RSR: replication stress response). **FIG. 6B** is a graph of the Cell Titer Glo analysis of SUIT2 cells treated $\pm$ 100 U/mL IFN β $\pm$ 500 nM ATR inhibitor (ATRi) in anchorage-independent culture conditions (mean $\pm$ SD; n=4; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 6C** is a graph of the immunofluorescence microscopy analysis of ssDNA in SUIT2 cells treated $\pm$ 100 U/mL IFN β $\pm$ 500 nM ATRi for 24 h (mean $\pm$ SD; n=10; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 6D** is a graph of the flow cytometry analysis of pH2A.X_{S139} levels in SUIT2 cells treated $\pm$ 100 U/mL $\pm$ 500 nM ATRi for 48 h (mean $\pm$ SD; n=2; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 6E** is a graph of AnnexinV/PI flow cytometry analysis of SUIT2 cells treated for 72 hours $\pm$ 100 U/mL IFN β $\pm$ 500 nM ATRi (mean $\pm$ SD; n=2; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 6F** present Incucyte live cell imaging analysis of a panel of PDAC cell lines in 2D culture treated $\pm$ 100 U/mL $\pm$ 250 nM ATRi (mean $\pm$ SD, n=6). **FIG. 6G** demonstrates propidium iodide (PI) cell cycle analysis of a panel of PDAC cell lines treated $\pm$ 100 U/mL $\pm$ 250 nM ATRi for 48 hours.

[0020] FIGS. 7A-7C demonstrate ATR inhibitors and IFN synergistically impair de novo nucleotide biosynthesis by down-regulating E2F target genes. **FIG. 7A** presents immunoblot

analysis of PDAC cell lines characterized as sensitive (red) or insensitive (black) to the combination of IFN β and berzosertib (ATRi). Cells were treated for 48 hours $\pm$ 100 U/mL IFN β $\pm$ 250 nM ATRi. **FIG. 7B** is a graph of LC-MS/MS analysis of dCTP pools in SUIT2 cells treated for 24 h $\pm$ 100 U/mL IFN β $\pm$ 500 nM ATRi (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, *** P<0.001; **** P<0.0001). **FIG. 7C** presents LC-MS/MS analysis of the contribution of [$^{13}\text{C}_6$]glucose to newly replicated DNA in SUIT2 cells treated for 24 hours $\pm$ 100 U/mL IFN β $\pm$ 500 nM ATRi (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001).

[0021] FIGS. 8A-8E demonstrate ATR inhibition impairs the growth of PDAC cells with high interferon signaling. **FIG. 8A** is a graph of IncuCyte live-cell imaging analysis of SUIT2 TetR STING^{R248M} cells treated + 50 ng/mL DOX $\pm$ 500 nM ATRi in anchorage-independent culture (mean $\pm$ SD; n=6; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 8B** are representative images from the endpoint of experiment in FIG. 8A. **FIG. 8C** is a pictorial of the approach to test the interaction between STING activation and ATR inhibition in vivo. SUIT2 TetR fLuc cells were engineered with a STING^{R248M} or shATR transgene and implanted into the pancreas of NCG mice. **FIG. 8D** are representative BLI images of tumor bearing mice 21 days following initiation of doxycycline treatment. **FIG. 8E** is a graph of the fold change in BLI signal on day 21 compared to baseline signal.

[0022] FIGS. 9A-9C demonstrate analysis of the IFN signature in TCGA, GTEX and CCLE datasets. **FIG. 9A** is an analysis of the IFN response metagene signature across TCGA and GTEX datasets ordered by fold change in median tissue-matched TCGA/GTEX values (PAAD: pancreatic adenocarcinoma). **FIG. 9B** presents extended analysis of data in FIG. 9A. **FIG. 9C** presents heatmap analysis of the IFN response metagene signature in the CCLE pancreatic cancer cell line dataset. Columns represent individual pancreas cancer cell lines.

[0023] FIGS. 10A-10C represent immunohistochemistry analysis of IFN signaling biomarkers in primary patient specimens. **FIG. 10A** represents a summary of STAT1 and MX1 immunohistochemistry (IHC) analysis of PDAC patient derived (n=33) and cell line (n=17) xenograft tumors. Histoscores were calculated as a sum of the intensity of staining (0, negative; 1, weak; 2, median; or 3, strong) multiplied by the percentage of tumor cells at that intensity (0-300 range). **FIG. 10B** are representative images of STAT1 and MX1 IHC analysis of PDAC cell line xenograft tumors. **FIG. 10C** are representative images of STAT1 and MX1 IHC analysis of PDAC patient derived xenograft tumors.

[0024] FIGS. 11A-11D demonstrate extended analysis of IFN signaling in PDAC cells and patient samples. **FIG. 11A** presents immunoblot analysis of a panel of PDAC cell lines treated $\pm$ 100 U/mL IFN β for 24 hours. **FIG. 11B** graphically depicts reactome gene ontology analysis of significantly altered proteins following treatment with IFN for 24 hours from FIG. 3D. **FIG. 11C** are images of representative pCHEK1_{S345} IHC analysis of primary PDAC samples. Histoscores are indicated. **FIG. 11D** is a graph showing the correlation between STAT1 and pCHEK1_{S345} IHC histoscores across panel of PDAC patient samples (n=23).

[0025] FIGS. 12A-12G demonstrate Type I IFN signaling up-regulates SAMHD1 mediated nucleotide pool phosphohydrolysis and restricts DNA synthesis. **FIG. 12A** is a chart providing a summary of genes related to nucleotide catabolism significantly altered by IFN β in SUIT2 cells. **FIG. 12B** presents immunoblot validation of SUIT2 SAMHD1 CRISPR/Cas9 knockout (KO) and dCK KO isogenic cells. **FIG. 12C** provides the experimental design. **FIG. 12D** are graphs showing total [¹³C₆] glucose labeled intracellular metabolite and extracellular media metabolite levels of SUIT2 WT, SAMHD1 KO and dCK KO cells using LC-MS/MS (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, ** P<0.01; **** P<0.0001). **FIG. 12E** demonstrate contribution of [¹³C₆] glucose to newly replicated DNA in SUIT2 WT, SAMHD1 KO and dCK KO cells treated for 24 hours $\pm$ 100 U/mL IFN β for 24 h hours using LC-MS/MS (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 12F** presents time-course immunoblot analysis of IFN β treated SUIT2 cells. For extended treatment studies cells were passaged and media was refreshed every 72 hours. **FIG. 12G** are graphs showing LC-MS/MS analysis of dNTP pools in SUIT2 cells treated for 24 hours or 21 days (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, * P<0.05; ** P<0.01; *** P<0.001).

[0026] FIGS. 13A-13F demonstrate nucleoside phosphorylases and kinases mediate nucleoside efflux. **FIG. 13A** is a schematic overview of dGTP biosynthesis, catabolism and recycling. **FIG. 13B** demonstrates LC-MS/MS analysis of glucose labeled media dG and dC in SUIT2 cells treated for 24 hours $\pm$ 100 U/mL IFN β $\pm$ 1 μ M BCX-1777 (PNPi) in media containing 1 g/L [¹³C₆]glucose (mean $\pm$ SD; n=3). For calculation of normalized MS response glucose labeled (n+5) dG or dC counts were normalized to internal standard counts. **FIG. 13C** is a schematic representation of the roles of SAMHD1 and nucleoside kinases deoxycytidine kinase (dCK) and thymidine kinase 1 (TK1) in regulating dN efflux in IFN-treated cells. **FIG. 13D** presents immunoblot validation of TK1 KO SUIT2 cells treated with 100 U/mL IFN β for 24 hours. **FIG. 13E** provides LC-MS/MS analysis of dT and dC efflux following 24 hours treatment of SUIT2 parental and TK1 KO cells with 100 U/mL IFN β in media containing 1 g/L

[$^{13}\text{C}_6$] glucose. TK1 cells were maintained in the presence of 1 μM DI-82 (dCKi) (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, * $P<0.05$; ** $P<0.01$). **FIG. 13F** is a table showing the calculation of normalized dC and dT efflux rates from experiment in FIG. 13E (mean $\pm$ SD; n=3). dR1P: deoxyribose-1-phosphate; PNP: purine nucleoside phosphorylase.

[0027] FIGS. 14A-14H demonstrate the cGAS/STING pathway is active in a subset of PDAC cell lines. **FIG. 14A** shows analysis of STING (TMEM173) transcript levels across TCGA tumor datasets relative to normal tissue (PAAD: pancreatic adenocarcinoma). **FIG. 14B** presents IHC analysis of STING expression in PDAC tumors (n=145). **FIG. 14C** demonstrates RT-PCR analysis of IFN β transcript levels in a panel of PDAC cell lines 6 h subsequent to transfection with 25 $\mu\text{g}/\text{mL}$ interferon stimulatory DNA (ISD); n.d.: not detected, mean $\pm$ SD, n=2, student's t-test, n.s.: not significant; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$). **FIG. 14D** provides immunoblot analysis of cGAS and STING expression in a panel of PDAC cell lines. **FIG. 14E** presents RT-PCR analysis of IFN β transcript levels in a panel of PDAC cell lines 6 hours subsequent to transfection with 10 $\mu\text{g}/\text{mL}$ of a non-hydrolyzable bisphosphorothioate 2'-3'-cGAMP analog (cGAMP; mean $\pm$ SD, n=2, student's t-test, ** $P<0.01$; **** $P<0.0001$). **FIG. 14F** presents immunoblot analysis of DANG cells following transfection with 10 $\mu\text{g}/\text{mL}$ 2'-3'-cGAMP $\pm$ 1 μM ruxolitinib (JAKi). **FIG. 14G** presents immunoblot analysis of DANG cells following transfection with 10 $\mu\text{g}/\text{mL}$ cGAMP $\pm$ 1 μM JAKi. **FIG. 14H** presents ELISA analysis of IFN β levels in DANG cell supernatant 6 hours or 24 hours following transfection with 10 $\mu\text{g}/\text{mL}$ cGAMP for (veh: vehicle, 24 h lipofectamine alone, mean $\pm$ SD, n=3).

[0028] FIGS. 15A-15G demonstrate tumor cell STING mediates constitutive IFN signaling in PDAC tumors. **FIG. 15A**: Immunoblot analysis of SUI2 cells treated $\pm$ 100 U/mL IFN β for the indicated timepoints *in vitro* and lysates prepared from SUI2 cells grown as subcutaneous tumors in NSG mice. **FIG. 15B** is an immunoblot analysis of SUI2 TetR-GFP or TetR-STING^{R248M} cells treated $\pm$ 50 ng/mL DOX for 72 hours. **FIG. 15C** is immunoblot validation of DANG parental and STING CRISPR/Cas9 knockout (KO) cells. **FIG. 15D** are images presenting IHC analysis of subcutaneous DANG WT and STING KO xenograft tumors from FIG. 5F. **FIG. 15E** is a chart demonstrating analysis of ISRE-luciferase reporter activity in HS766T WT ISRE-fLUC and STING KO ISRE-fLUC cells *in vitro* following 6 hours transfection with cGAMP or treatment with 100 U/mL IFN β (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** $P<0.0001$). **FIG. 15F** are images showing analysis of ISRE-fLUC reporter activity in HS766T WT and STING KO ISRE-fLUC subcutaneous xenograft tumors *in vivo* using bioluminescence imaging (mean $\pm$ SEM, n=4,

student's t-test). **FIG. 15G** is immunoblot analysis of protein lysates prepared from HS766T WT and STING KO subcutaneous xenograft tumors.

[0029] FIGS. 16A-16I demonstrates IFN signaling increases tumor cell [^{18}F]FLT accumulation *in vitro* and *in vivo*. **FIG. 16A** is a schematic of the regulation of FLT accumulation by competition with the endogenous substrate for TK1, thymidine (dT). **FIG. 16B** is a graph showing results of [^{18}F]FLT uptake assay in SUIT2 cells treated $\pm$ 100 U/mL IFN β for 24 hours and subsequently pulsed with 18.5 kBq [^{18}F]FLT $\pm$ indicated amount of dT for 2 hours (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). Insert indicated dT concentration required to inhibit [^{18}F]FLT accumulation by 50% (IC-50). **FIG. 16C** presents immunoblot analysis of SUIT2 shC and shTYMP cells treated $\pm$ 100 U/mL IFN β for 24 hours. **FIG. 16D** is a graph showing results of [^{18}F]FLT uptake assay in SUIT2 cells treated with 100 U/mL IFN β $\pm$ 1 μM ruxolitinib (JAKi) for 24 h and subsequently pulsed with X μCi ^{18}F -FLT + 1 μM dT for 2 h (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 16E** presents immunoblot analysis of SUIT2 and YAPC cells treated with either 100 U/mL IFN β or 10 ng/mL IFN γ for 24 hours. **FIG. 16F** is a graph showing results of [^{18}F]FLT uptake assay in SUIT2 shC and shTYMP cells treated $\pm$ 100 U/mL IFN β or $\pm$ 10 ng/mL IFN γ for 24 hours and subsequently pulsed with X μCi ^{18}F -FLT $\pm$ 1 μM dT for 2 hours (mean $\pm$ SD; n=3; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 16G** is a graph showing results of [^{18}F]FLT uptake assay in YAPC cells treated with 100 U/mL IFN β for 24 hours and subsequently pulsed with 18.5 mBq ^{18}F -FLT + 1 μM dT for 2 hours (mean $\pm$ SD, n=3, student's t-test, n.s.: non significant). **FIG. 16H** pictorially represents results of [^{18}F]FLT and [^{18}F]FDT analysis bilateral SUIT2 TetR; STING^{R248M} and SUIT2 TetR; STING^{R248M} tumor-bearing mice treated with DOX. **FIG. 16I** is a graph showing results of LC-MS/MS analysis of plasma dT levels in SUIT2 TetR-STING^{R248M} tumor bearing mice treated $\pm$ DOX from FIGS. 5J and 5K (mean $\pm$ SD, n=3, student's t-test, n.s.: non significant).

[0030] FIGS. 17A-17C illustrate replication stress response inhibitors and IFN β exhibit synergy in PDAC cells. **FIG. 17A** is a schematic of the replication stress response pathway and related small molecule inhibitors. **FIG. 17B** are graphs showing Cell Titer Glo analysis of replication stress response inhibitor IC-50 in SUIT2 cells treated $\pm$ 100 U/mL IFN β for 72 h (mean $\pm$ SD, n=4). **FIG. 17C** is an immunoblot analysis of SUIT2 cells treated with 100 U/mL IFN $\pm$ 500 nM berzosertib or 1 μM AZD-6738.

[0031] FIGS. 18A-18H show IFN and ATR inhibitors synergistically induce DNA damage

and apoptosis. **FIG. 18A** are representative ssDNA immuno-fluorescence microscopy images from experiment in FIG. 6C. **FIG. 18B** provides representative inflow cytometry plots from experiment in FIG. 6D. **FIG. 18C** provides representative inflow cytometry plots from experiment in FIG. 6E. **FIG. 18D** provides cell cycle and immunoblot analysis of SUI2 cells treated with 100 U/mL IFN β + 500 nM berzosertib (ATRi) $\pm$ 5 μ M palbociclib (CDK4/6i) as indicated. **FIG. 18E** are graphs showing cell cycle analysis of A13A primary PDAC cells treated $\pm$ 100 U/mL IFN β + 500 nM ATRi for 24 hours. **FIG. 18F** is a graph showing Cell Titer Glo analysis of A13A cells treated $\pm$ 100 U/mL IFN β + 500 nM ATRi for 72 hours (mean $\pm$ SD; n=4; one-way ANOVA, * P<0.05; ** P<0.01; **** P<0.0001). **FIG. 18G** are graphs showing flow cytometry cell cycle analysis of human pancreatic ductal epithelial (HPDE) cell treated $\pm$ 100 U/mL IFN β + 500 nM ATRi for 24 hours. **FIG. 18H** is a graph showing Cell Titer Glo analysis of HPDE cells treated $\pm$ 100 U/mL IFN β + 500 nM ATRi for 72 hours (mean $\pm$ SD; n=4).

[0032] FIGS. 19A-19C show ATR inhibition down-regulates nucleotide metabolism related protein expression in IFN-exposed PDAC cells. **FIG. 19A** presents immunoblot analysis of SUI2 cells treated for 48 hours with a titration of berzosertib (ATRi) in the presence of 100 U/mL IFN β . **FIG. 19B** are graphs showing RT-PCR analysis of SUI2 cells treated for 24 hours with 100 U/mL IFN β $\pm$ 250 nM ATRi (mean $\pm$ SD; n=6; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, * P<0.05; ** P<0.01; **** P<0.0001). **FIG. 19C** presents immunoblot analysis of SUI2 cells treated as indicated in the presence of the proteasome inhibitor MG132.

[0033] FIGS. 20A-20C demonstrate STING activation sensitizes PDAC cells to ATR inhibition. **FIG. 20A** presents immunoblot analysis of YAPC STING^{R248M} cells treated $\pm$ 50 ng/mL doxycycline (DOX) $\pm$ 1 μ M ruxolintinib (JAKi) $\pm$ 100 U/mL IFN β for the indicated timepoints. **FIG. 20B** is a graph showing IncuCyte live-cell imaging analysis of YAPC TetR STING^{R248M} cells treated $\pm$ 50 ng/mL DOX $\pm$ 500 nM ATRi in anchorage-dependent culture (mean $\pm$ SD; n=6; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, *** P<0.001; **** P<0.0001). **FIG. 20C** is a graph showing IncuCyte live-cell imaging analysis of SUI2 TetR STING^{R248M} cells treated + 50 ng/mL DOX $\pm$ 500 nM ATRi $\pm$ 1 μ M JAKi in anchorage-independent culture (mean $\pm$ SD; n=6; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001).

[0034] FIGS. 21A-21F demonstrate IFN β and ATR inhibitors synergistically enhance sensitivity to olaparib in PDAC cells. **FIG. 21A** presents an immunoblot analysis of SUI2 and DANG PDAC cell lines treated for 24 hours $\pm$ 100 U/mL IFN β $\pm$ 250 nM ATRi. **FIG. 21B** is an

image of crystal violet proliferation analysis of SUIT2 cells treated with 100 U/mL IFN β $\pm$ 100 nM ATRi $\pm$ 4 μ M olaparib for 7 days. **FIG. 21C** provides flow cytometry analysis of pH2A.X_{S139} levels in SUIT2 cells treated with 100 U/mL $\pm$ 200 nM ATRi $\pm$ 4 μ M olaparib for 48 hours (mean $\pm$ SD; n=2; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, **** P<0.0001). **FIG. 21D** provides Annexin V/PI flow cytometry analysis of SUIT2 cells treated for 72 hours with 100 U/mL IFN β $\pm$ 200 nM ATRi $\pm$ 4 μ M olaparib (mean $\pm$ SD; n=2; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, ** P<0.01). **FIG. 21E** shows Cell Titer-Glo analysis of SUIT2, DANG and A13A cells treated for 72 hours with olaparib $\pm$ ATRi in the presence of 100 U/mL IFN β (mean, n=4). **FIG. 21F** shows AnnexinV/PI flow cytometry analysis of A13A primary culture treated for 72 hours with 100 U/mL IFN β $\pm$ 200 nM ATRi $\pm$ 4 μ M olaparib (mean $\pm$ SD; n=2; one-way ANOVA corrected for multiple comparisons by Bonferroni adjustment, *** P<0.001).

[0035] FIGS. 22A-22C demonstrate SAMHD1 is induced by IFN β in cancer-associated fibroblasts. **FIG. 22A** is a schematic representation of potential metabolic crosstalk between PDAC cancer cells and PDAC cancer associated fibroblasts (CAFs). **FIG. 22B** presents an immunoblot of human pancreatic CAFs treated with 100 U/mL IFN β for 24 hours. **FIG. 22C** is a graph showing [¹³C₆] glucose-labeled deoxycytidine efflux measured in the culture media levels of CAFs cultured in [¹³C₆] glucose and treated $\pm$ 100 U/mL IFN β for 24 hours measured using LC-MS/MS. MS counts were normalized to extracted protein (mean $\pm$ SD, n=3, student's t-test, *** P<0.001).

[0036] FIG. 23 provides the resources used as described in Example 3.

[0037] FIGS. 24A-24F show that type I IFN in the tumor microenvironment reduces NAD(H) levels in PDAC cells. **FIG. 24A**: Identification of IFN β as the key cytokine implicated in the reduction of NAD levels. NAD levels in Panc 03.27 cells cultured with indicated cytokines were measured (n=4). IFN β 100 U/mL. TNFa 10 ng/mL. IL-6 10 ng/mL. EGF 50 ng/mL. TGFI3 10 ng/mL. IL-10 250 pg/mL. LIF 500 pg/mL. FGF 100 ng/ mL. PDGF 50 ng/mL. MCSF 5 ng/mL. GMCSF 100 ng/mL. **FIGS. 24B-24C**: Effects of IFN β on NAD(H) levels across a panel of PDAC cell lines. NAD and NADH levels in indicated PDAC cells were measured after 24 h culture with and without 100 U/mL IFN β . **FIGS. 24D-24E**: Supporting evidence that the *in vivo* tumor microenvironment in a subset of PDAC tumors decreases cancer cell NAD levels. NAD levels from indicated PDAC cells collected from cell culture and from xenograft tumors were compared (n=4). **FIG. 24F**: Type I IFN signaling is present in a subset of PDAC tumors. IHC staining of type I IFN signaling markers MX1 and STAT1 were performed in xenograft tumors collected in the experiment described in panel C.***, P<0.001. ****, P<0.0001. ns, not significant.

[0038] FIGS. 25A-25B show that IFN β elevates the expression of NAD(H) consuming enzymes PARP9, PARP10, and PARP14. **FIG. 25A:** PARP9, PARP10, and PARP14 transcription levels were significantly upregulated after exposure to IFN β . Panc 03.27 cells (upper panel) and SUI2 cells (lower panel) were cultured with 100 U/ mL IFN β prior to quantification of PARP9, PARP10, and PARP14 mRNA levels (n=3). ND, not detected. **FIG. 25B:** PARP9, PARP10, and PARP14 protein levels were measured after exposure to IFN β . Indicated PDAC cells were cultured with 100 U/mL IFN β prior to immunoblot analysis of PARP9, PARP10, and PARP14 protein levels in whole cell lysates. *, P<0.05. ** P<0.01. ***, P<0.001. ****, P<0.0001.

[0039] FIGS. 26A-26H show PARP9, PARP10, and PARP14 induction by IFN β reduces NAD(H) levels. **FIGS. 26A-26B:** PARP9, PARP10, and PARP14 were knocked down by three shRNAs per gene in Panc 03.27 and SUI2 cells. MX1, PARP9, PARP10, and PARP14 protein levels were measured with and without exposure to IFN β 100 U/mL. **FIGS. 26C-26F:** Knockdown of PARP9, PARP10, or PARP14 significantly rescued NAD, and NADH levels decreased by IFN β (n=4). NAD and NAD levels were measured in Panc 03.27 and SUI2 cells following 24 hour exposure to 100 U/mL IFN β . **FIG. 26G:** subsets of PDAC tumors within the TCGA pancreatic cancer dataset with high and low expression levels of type 1 IFN signaling (STAT1 and MX1) and PARP9, PARP10, and PARP14. **FIG. 26H:** PDAC PDX models with high or low levels of PARP9, PARP10, and PARP14 in tumor sections from PDAC PDX models XWR6, XWR60, XWR8, and XWR200. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001.

[0040] FIGS. 27A-27J show type 1 IFN signaling results in NAD(H) consumption through upregulation of PARP9/10/14, increasing PDAC cell dependency on NAMPT and sensitizing them to NAMPT inhibitors (NAMPTi) in vitro. **FIGS. 27A-27B:** IFN β enhanced the NAD(H)-depleting effect of NAMPTi, Panc 03.27 and SUI2 cells were cultured with 100 U/mL IFN β and 8 nM NAMPTi FK866 for 24 hours prior to NAD and NADH measurements. **FIGS. 27C-27D:** IFN β and NAMPTi inhibited mitochondrial respiration and decreased glycolytic reserve in Panc 03.27 cells. Cells were incubated with 100 U/mL IFN β and 8 nM NAMPTi FK866 for 24 hours prior to measuring oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). **FIG. 27E:** Western blot demonstrated increased pAMPK expression in combination-treated PDAC cells compared to either treatment alone which is rescued by NR supplementation. SUI2 cells were incubated +/- 100 U/mL IFN β +/- 8 nM FK866 +/- 500 uM NR for 48 hours. **FIG. 27F:** NAD(H) reduction by IFN β /NAMPTi suppressed PARP activity in DNA repair. Panc 03.27 cells were exposed to indicated treatments for 48 hours prior to

immunoblot analysis of MX1 and PARP. IFN β , 100 U/mL. NAMPTi FK866, 4 nM. NR, 500 μ M. **FIG. 27G:** IFN β enhanced the effect of NAMPTi on inducing DNA damage. Panc 03.27 cells were incubated +/- 100 U/mL IFN β +/- 8 nM FK866 +/- 500 μ M NR for 48 hours prior to pH2A.X quantification by flow cytometry. **FIG. 27H-27I:** IFN β enhanced the effect of NAMPTi on inducing apoptosis. Panc 03.27 cells were incubated +/- 100 U/mL IFN β +/- 8 nM FK866 +/- 500 μ M NR for 48 hours prior to Annexin V/propidium iodide (PI) quantification by flow cytometry. Apoptosis was quantified by the amount of Annexin V positive cells. **FIG. 27J:** proposed model of NAD depletion induced by inhibition of NAMPT in combination with IFN β signaling, thus blocking salvage of the NAM product of PARP9/10/14. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001; ns, not significant.

[0041] **FIGS. 28A-28F** show that Type I IFN signaling sensitizes PDAC cells to NAMPT inhibitors (NAMPTi) *in vitro*. **FIGS. 28A-28B:** IFN β enhances the potency of NAMPTi in both 2D and 3D cultures. PDAC cell lines and primary PDAC cultures (A2.4 and AM1283) were treated with NAMPTi FK866 or LSN3154567 for 72 h with and without 100 U/mL IFN β supplementation. Cell viability was measured by CellTiter-Glo assay and IC50 values were determined using GraphPad Prism 7. **FIGS. 28C-28D:** Cytotoxicity of the combination of IFN β and NAMPTi in PDAC cells was rescued by nicotinamide riboside (NR) supplementation. PDAC cells were incubated $\pm$ 8 nM FK866 $\pm$ 100 U/mL IFN β $\pm$ 500 μ M NR in 2D or 3D cultures. Cell viability was determined by CellTiter-Glo assay. **FIGS. 28E:** IFN β sensitizes cells to NAMPTi in both PDAC mono-culture and co-culture with PDAC cancer associated fibroblasts (CAFs). SUI2/GFP cell spheroids with and without CAF/mCherry were treated $\pm$ 8 nM FK866 $\pm$ 100 U/mL IFN β . Green and red fluorescence was monitored by IncuCyte every 3 h for a 7-day period. **FIGS. 28F:** Representative fluorescence images of spheroids at the experiment endpoint in panel C. *, P<0.05. **, P<0.01. ***, P<0.001. ****, P<0.0001. ns, not significant.

[0042] **FIGS. 29A-29G** show inactivation of type 1 IFN signaling promotes resistance to NAMPT inhibitors. **FIGS. 29A-29B:** profiling of broad panel of PDAC xenograft models for *in vivo* type 1 IFN signaling based on IHC analyses of type 1 IFN signaling marker MX1. **FIG. 29C:** a loss-of-function PDAC model of autocrine type 1 IFN signaling. PATU8988T cells underwent knock-out of the type 1 IFN receptor. 2 of these KO models were chosen and were exposed to 100 U/mL IFN β supplementation in cell culture for 48 hours, prior to immunoblot analyses of type 1 IFN signaling marker MX1 and PARP9/10/14. **FIG. 29D:** schematic of *in vivo* experimental design. **FIG. 29E:** curves of bioluminescence intensity of orthotopic PATU8988T WT or IFNAR1 KO-*fluc* tumors in mice treated with vehicle control or 10

mg/kg FK866 (daily ip). After confirmation of tumor establishment by bioluminescence imaging (BLI), treatments started on day 5 post-surgical implantation. Data are shown as mean $\pm$ SEM. N=8 per group. **FIG. 29F:** endpoint tumor weights after harvest of orthotopic PATU8988T WT and IFNAR1 KO tumors in mice treated with either vehicle or 10 mg/kg FK866 (daily ip). Data are shown as mean $\pm$ SEM. N=8 per group. **FIG. 29G:** treatments with vehicle control or 10 mg/kg FK866 were well tolerated by mice bearing PATU8988T WT or IFNAR1 KO-*fluc* orthotopic tumors. *, $P < 0.05$. **, $P < 0.01$. ***, $P < 0.001$. ****, $P < 0.0001$. ns, not significant.

[0043] **FIGS. 30A-30H** show increased Type I IFN signaling downstream of STING activation sensitizes tumors to NAMPT inhibitors. **FIG. 30A:** A gain-of-function PDAC model of doxycycline (DOX)-inducible autocrine type I IFN signaling. SUIT2 cells with a DOX-inducible active STING^{R284M} mutant were exposed to 50 ng/mL DOX in cell culture for 4 days, prior to immunoblot analyses of type I IFN signaling markers. **FIG. 30B:** DOX-induced type I IFN signaling significantly lowered NAD and NADH levels in SUIT2-STING^{R284M} cells. Cells were exposed to 50 ng/mL DOX for 5 days prior to NAD and NADH measurements (n=3). **FIG. 30C:** Schematic of *in vivo* experimental design. **FIG. 30D:** Curves of bioluminescence intensity of orthotopic SUIT2-STING^{R284M}-*fluc* tumors in mice with DOX diet and/or 10 mg/kg FK866 (daily i.p.). After confirmation of tumor establishment by bioluminescence imaging (BLI), treatments started on day 6 post-surgical implantation. Data are shown as mean $\pm$ SEM. N = 7 per group. **FIG. 30E:** BLI images of disease progression in indicated experimental groups. BLI measurement in photons per second per cm² per steradian (p/s/cm²/sr) was translated to color to indicate disease activity. A mouse died on day 30 due to tumor invasion into the gastrointestinal tract. **FIGS. 30F-30G:** BLI measurement of liver metastasis of SUIT2-STING^{R284M}-*fluc* tumor cells. 5 minutes after luciferin injection, mice were sacrificed and livers were harvested for BLI measurement. Left, BLI images of liver metastasis. Right, quantification of BLI intensity in livers. **FIG. 30H:** Immunoblot analysis of indicated proteins in tumor homogenates. Three representative tumors from each group were included for comparison.

[0044] **FIG. 31** shows the IC₅₀ values of the NAMPT inhibitors FK866 and LSN3154567 in a panel of PDAC cell lines and primary PDAC cells in 2D and 3D culture. The IC₅₀ values are shown as mean $\pm$ SD.

DETAILED DESCRIPTION

[0045] The practice of the technology described herein will employ, unless indicated specifically to the contrary, conventional methods of chemistry, biochemistry, organic chemistry, molecular biology, microbiology, recombinant DNA techniques, genetics, immunology, and cell biology that are within the skill of the art, many of which are described

below for the purpose of illustration. Examples of such techniques are available in the literature.

[0046] The terms “IFN” and “interferon” are used in accordance with their plain and ordinary meaning and refer to a group of signaling proteins made and released by host cells in response to the presence of a virus. IFNs belong to the class of proteins known as cytokines, molecules used for communication between cells to trigger the protective defenses of the immune system that help eradicate pathogens. Interferons are named for their ability to "interfere" with viral replication by protecting cells from virus infections. IFNs also have various other functions: they activate immune cells, such as natural killer cells and macrophages; they increase host defenses by up-regulating antigen presentation by virtue of increasing the expression of major histocompatibility complex (MHC) antigens. Many distinct IFN genes, proteins, and RNA have been identified in animals, including humans. They are typically divided among three classes: Type I IFN (e.g., IFN-alpha, IFN-beta, IFN-kappa, IFN-delta, IFN-epsilon, IFN-omega, IFN-zeta), Type II IFN (i.e., IFN-gamma), and Type III IFN (e.g., IFN-lambda1, IFN-lambda2, IFN-lambda3).

[0047] For the specific proteins described herein (e.g., interferon, STAT1, MX1, PARP9, PARP10, PARP14, and the like), the named protein includes any of the protein's naturally occurring forms, variants or homologs that maintain the protein transcription factor activity (e.g., within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the native protein). In embodiments, variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring form.

[0048] For the specific RNA described herein (e.g., interferon, STAT1, MX1, PARP9, PARP10, PARP14, and the like), the named RNA includes any of the RNA's naturally occurring forms, variants or homologs that maintain the RNA activity (e.g., within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the native RNA). In embodiments, variants or homologs have at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous nucleic acid portion) compared to a naturally occurring form.

[0049] “Pathway” refers to a set of system components involved in two or more sequential molecular interactions that result in the production of a product or activity. A pathway can produce a variety of products or activities that can include, for example, intermolecular interactions, changes in expression of a nucleic acid or polypeptide, the formation or

dissociation of a complex between two or more molecules, accumulation or destruction of a metabolic product, activation or deactivation of an enzyme or binding activity. Thus, the term "pathway" includes a variety of pathway types, such as, for example, a biochemical pathway, a gene expression pathway, a regulatory pathway, or a combination thereof.

[0050] The term "IFN pathway" or "IFN signaling pathway" refer to the intracellular signaling pathway activated when interferon levels are elevated in vivo and/or when interferon binds to its receptor (e.g., Type 1 IFN binds to IFNAR1 and/or IFNAR2) and induces, for example, the JAK1/TYK2-mediated signaling cascade which results in transcriptional activation of hundreds of IFN-stimulated genes including STAT1 and MX1, canonical surrogate markers of type I IFN signaling. See **FIG. 1**. The IFN signaling pathway substantially lowers NAD(H) levels through upregulating the expression of PARP9, PARP10, and PARP14, which are NAD-consuming enzymes. The IFN pathway is known in the art and described, for example, by Ivashkiv et al, Nat Rev Immunol, 14(1):36-49 (2014); Schreiber, J Biol Chem, 292(18):7285-7294 (2017). The IFN signaling pathway includes, but is not limited to, genes, RNA, and proteins.

[0051] The term "IFN pathway gene" refers to a gene in the IFN pathway. Such genes include, for example, PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS2, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, PSME1, and SOCS1. In embodiments, the IFN pathway gene comprises STAT1 and/or MX1. In embodiments, the IFN pathway gene comprises PARP9, PARP10, PARP14, STAT1, MX1, or a combination of two or more thereof. In embodiments, the IFN pathway gene comprises PARP9, PARP10, PARP14, or a combination of two or more thereof.

[0052] The term "IFN pathway RNA" or "IFN pathway RNA expression sequence" refer to an RNA expression sequence (e.g., mRNA) in the IFN pathway. The IFN pathway RNA is an RNA expression sequence transcribed by an interferon pathway gene. Such RNA includes, for example, PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the IFN pathway RNA comprises STAT1 and/or MX1. In embodiments, the IFN pathway RNA comprises PARP9, PARP10, PARP14, STAT1, MX1, or a combination of two or more thereof. In embodiments, the IFN pathway RNA comprises PARP9, PARP10, PARP14, or a combination of two or more thereof.

[0053] The term "IFN pathway protein" refers to a protein in the interferon pathway. The IFN pathway protein can be any protein encoded by an IFN pathway gene. In embodiments, the IFN pathway protein is PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44,

IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1. In embodiments, the IFN pathway protein comprises STAT1 and/or MX1. In embodiments, the IFN pathway protein comprises PARP9, PARP10, PARP14, STAT1, MX1, or a combination of two or more thereof. In embodiments, the IFN pathway protein comprises PARP9, PARP10, PARP14, or a combination of two or more thereof.

[0054] The term “and/or” refers to either or both of two stated possibilities. For example, the phrase “STAT1 and/or MX1” refers to: (i) STAT1, (ii) MX1, or (iii) STAT1 and MX1.

[0055] The term “activity” or “activity level” as used herein (e.g., IFN pathway activity or IFN signaling pathway activity) refers to a value representing the level of expression of all or a subset of genes in a particular pathway. In embodiments, activity level is determined by measuring gene expression in the IFN signaling pathway. A variety of suitable algorithms are available for calculating an activity level based on gene expression data from a plurality of genes. In embodiments, gene expression levels are analyzed using the Adaptive Signature Selection and InteGratioN toolkit (ASSIGN; e.g., Shen et al, 31(11):1745-53 (2015); available from BioConductor) to calculate an activity level. In embodiments, gene expression levels are analyzed using Gene Set Variation Analysis (GSVA; e.g., Hänzelmann et al, BMC Bioinformatics, 14:7 (2013)) to calculate an activity level. In embodiments, gene expression levels are analyzed using gene set enrichment analysis (GSEA; e.g., Barbie et al, Nature, 462(7269):108–112 (2009)) to calculate an activity level. In embodiments, expression levels for all genes of a particular signature are collectively expressed as a single activity level value (e.g., a score) for that signature. In embodiments, comparing gene expression values for genes of a signature to a reference is performed by comparing a score for that signature to a reference score.

[0056] The term “type 1 ISG signature” or “type 1 interferon-stimulated gene signature” is used in accordance with its plain and ordinary meaning and refers to the set of genes expressed upon interferon type I signaling. Upon increased interferon levels and/or IFN binding to cell surface receptors, a signal is transmitted through the membrane and into the cell, leading to changes in cellular properties. Interferon-stimulated genes (ISGs) take on a wide range of activities. PRRs, IRFs, and several signal transducing proteins described above such as JAK2, STAT1/2, and IRF9 are present at baseline but are also ISGs and reinforce the IFN response. Many ISGs control viral, bacterial, and parasite infection by directly targeting pathways and functions required during pathogen life cycles. Upregulation of chemokines and chemokine receptors enables cell-to-cell communication, whereas negative regulators of signaling help

resolve the IFN-induced state and facilitate the return to cellular homeostasis. Additional ISGs encode for proapoptotic proteins, leading to cell death under certain conditions.

[0057] The term “pCHEK_{S345}” is used in accordance with its plain and ordinary meaning and refers to CHEK1 protein that is phosphorylated at the serine in position 345. Checkpoint kinase 1, or Chk1 also known as CHEK1, is a serine/threonine-specific protein kinase that, in humans, is encoded by the *CHEK1* gene. Chk1 coordinates the DNA damage response (DDR) and cell cycle checkpoint response. Activation of Chk1 results in the initiation of cell cycle checkpoints, cell cycle arrest, DNA repair and cell death to prevent damaged cells from progressing through the cell cycle. Chk1 is regulated by ATR through phosphorylation, forming the ATR-Chk1 pathway. This pathway recognizes single strand DNA (ssDNA) which can be a result of UV-induced damage, replication stress and inter-strand cross linking. Chk 1 activation occurs primarily through the phosphorylation of the conserved sites, Ser-317, Ser-345 and less often at Ser-366.

[0058] The terms “ATR” and “ATR kinase” and “serine/threonine-protein kinase ATR” and “ataxia telangiectasia and Rad3-related protein” used in accordance with their plain and ordinary meaning and refer to a serine/threonine-specific protein kinase that plays a role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription and cell migration.

[0059] The term “ATR kinase inhibitor” is used in accordance with their plain and ordinary meaning and refers to a protein or small molecule that inhibits the activity of ATR. In embodiments, the inhibitor reduces the activity of ATR from an indirect or direct interaction.

[0060] The terms “PARP” and “Poly(ADP-ribose) polymerase” are used in accordance with their plain and ordinary meaning and refer to a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death.

[0061] The term “PARP9” refers to poly(ADP-ribose) polymerase family member 9, which is an enzyme that is encoded by the PARP9 gene, identified by UniProtKB number Q81XQ6.

[0062] The term “PARP10” refers to poly(ADP-ribose) polymerase family member 10, which is an enzyme that is encoded by the PARP10 gene, identified by UniProtKB number UniProtKB number Q53GL7.

[0063] The term “PARP14” refers to poly(ADP-ribose) polymerase family member 14, which is an enzyme that is encoded by the PARP14 gene, identified by UniProtKB number Q460N5.

[0064] The term “PARP inhibitor” is used in accordance with their plain and ordinary meaning and refers to a protein or small molecule that inhibits the activity of poly(ADP-ribose)

polymerase (PARP). In embodiments, the inhibitor reduces the activity of poly(ADP-ribose) polymerase from an indirect or direct interaction.

[0065] The term “nicotinamide adenine dinucleotide” or “NAD” refer to the essential pyridine nucleotide that serves as an essential cofactor in critical cellular bioenergetic and metabolic functions. NAD is synthesized via three major pathways: the de novo biosynthesis kynurenine pathway, the Preiss-Handler pathway, and the salvage pathway (Chiarugi et al. Nat Rev Cancer 2012;12(11):741-52). The kynurenine pathway starts with the catabolism of the amino acid tryptophan that is then converted via two steps to the intermediate kynurenine, which can generate NAD, kynurenic acid, or xanthurenic acid. The Preiss-Handler pathway and the salvage pathway synthesize NAD from pyridine bases. The Preiss-Handler pathway synthesizes NAD from nicotinic acid (NA) in three steps via the intermediate nicotinic acid adenine dinucleotide (NAAD). The NAD salvage pathway starts from the recycling of nicotinamide (NAM) to nicotinamide mono nucleotide (NMN) by intracellular nicotinamide phosphoribosyltransferase (NAMPT), followed by the conversion of NMN into NAD via the nicotinamide mononucleotide adenylyltransferases (NMNATs) (Chiarugi et al. Nat Rev Cancer 2012;12(11):741-52). A recent quantitative analysis revealed that liver cells actively synthesize NAD de novo from tryptophan, releasing NAM into the blood, thereby supporting NAD biosynthesis in the rest of the body, whereas both tumor cells and most other tissues use NAM as the main NAD source (Liu L, et al Cell Metab 2018;27(5):1067-80). NAMPT is the rate-limiting step by which tumor cells utilize NAM in the synthesis of NAD. It is also important to note that while there are many metabolic enzymes that use NAD or NADH as co-factors and affect the NAD/NADH ratio, NAD(H) is consumed and broken down into NAM by the poly(ADP-ribose) polymerase (PARP) family proteins, the sirtuin (SIRT) family proteins, and CD38 (Verdin E. Science 2015;350(6265):1208-13). The reduced form of nicotinamide adenine dinucleotide is referred to as NADH or NAD(H). The oxidized form of nicotinamide adenine dinucleotide is referred to as NAD⁺.

[0066] The term “nicotinamide phosphoribosyltransferase” or “NAMPT” refers to the enzyme that catalyzes the transfer of a phosphoribosyl group from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide, forming nicotinamide mononucleotide (NMN), a key NAD pathway intermediate. NAMPT is the rate-limiting enzyme in the NAD salvage pathway, a dominant source of NAD in cancer cells.

[0067] The terms “nicotinamide phosphoribosyltransferase inhibitor” or “NAMPT inhibitor” or “NAMPTi” is used in accordance with their plain and ordinary meaning and refer to inhibitors of nicotinamide phosphoribosyltransferase (NAMPT).

[0068] The term “KRAS mutation” is used in accordance with its plain and ordinary meaning

and refers to a variation or mutation in the KRAS gene. KRAS is a gene that acts as an on/off switch in cell signaling. When it functions normally, it controls cell proliferation. When it is mutated, negative signaling is disrupted. Thus, cells can continuously proliferate, and often develop into cancer. It is called KRAS because it was first identified as an oncogene in Kirsten RAt Sarcoma virus. The viral oncogene was derived from cellular genome. Thus, KRAS gene in cellular genome is called a proto-oncogene. KRAS acts as a molecular on/off switch, using protein dynamics. Once it is allosterically activated, it recruits and activates proteins necessary for the propagation of growth factors, as well as other cell signaling receptors like c-Raf and PI 3-kinase. KRAS upregulates the GLUT1 glucose transporter, thereby contributing to the Warburg effect in cancer cells. KRAS binds to GTP in its active state. It also possesses an intrinsic enzymatic activity which cleaves the terminal phosphate of the nucleotide, converting it to GDP. Upon conversion of GTP to GDP, KRAS is deactivated.

[0069] The term “TP53 mutation” is used in accordance with its plain and ordinary meaning and refers to a variation or mutation in the TP53 gene. The TP53 gene is located on chromosome 17 in humans. TP53 is a nuclear phosphoprotein with sequence-specific DNA binding activity. The TP53 protein is a negative regulator of cell proliferation and a positive regulator of apoptosis in response to DNA damaging agents. *TP53* is the most common mutated gene associated with human cancer. Li-Fraumeni syndrome is a multicancer predisposition syndrome that has constitutional *TP53* mutations.

[0070] The terms “disease” or “condition” refer to a state of being or health status of a patient or subject capable of being diagnosed and/or treated with compounds or methods provided herein. The disease may be a cancer. The disease may be pancreatic cancer.

[0071] The term "cancer" refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemias, lymphomas, carcinomas and sarcomas. Examples of cancers that may be diagnosed and/or treated with a compound or method provided herein include brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, medulloblastoma, melanoma, cervical cancer, gastric cancer, ovarian cancer, lung cancer, cancer of the head, Hodgkin's disease, and Non-Hodgkin's lymphomas. Exemplary cancers that may be diagnosed and/or treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, ovary, pancreas, rectum, stomach, and uterus. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung

adenocarcinoma, lung squamous cell carcinoma, non-small cell lung carcinoma, mesothelioma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer. In embodiments, the cancer is pancreatic cancer. In embodiments, the cancer is metastatic pancreatic cancer. In embodiments, the cancer is pancreatic adenocarcinoma. In embodiments, the cancer is metastatic pancreatic adenocarcinoma. In embodiments, the cancer is pancreatic ductal adenocarcinoma. In embodiments, the cancer is metastatic pancreatic ductal adenocarcinoma.

[0072] The term “pancreatic ductal adenocarcinoma” refers to is an epithelial tumor that arises from the cells of the pancreatic duct or ductules, for which it is named. In health, the pancreatic duct(s) serve as the conduit through which digestive enzymes and bicarbonate ion produced in acinar cells reach the small intestine. Ductal cells and acinar cells together represent the “exocrine” pancreas, from which the vast majority of pancreatic neoplasms arise.

[0073] The terms "metastasis," "metastatic," and "metastatic cancer" can be used interchangeably and refer to the spread of a proliferative disease or disorder, e.g., cancer, from one organ or another non-adjacent organ or body part. “Metastatic cancer” is also called “Stage IV cancer.” Cancer occurs at an originating site, e.g., pancreas, which site is referred to as a primary tumor, e.g., primary pancreatic cancer. Some cancer cells in the primary tumor or originating site acquire the ability to penetrate and infiltrate surrounding normal tissue in the local area and/or the ability to penetrate the walls of the lymphatic system or vascular system circulating through the system to other sites and tissues in the body. A second clinically detectable tumor formed from cancer cells of a primary tumor is referred to as a metastatic or secondary tumor. When cancer cells metastasize, the metastatic tumor and its cells are presumed to be similar to those of the original tumor. Thus, if lung cancer metastasizes to the breast, the secondary tumor at the site of the breast consists of abnormal lung cells and not abnormal breast cells. The secondary tumor in the breast is referred to a metastatic lung cancer. Thus, the phrase metastatic cancer refers to a disease in which a subject has or had a primary tumor and has one or more secondary tumors. The phrases non-metastatic cancer or subjects with cancer that is not metastatic refers to diseases in which subjects have a primary tumor but not one or more

secondary tumors.

[0074] The term “diagnosis” refers to an identification or likelihood of the presence of a particular type of cancer or outcome in a subject. The term “prognosis” refers to the likelihood or risk of a subject developing a particular outcome or particular event.

[0075] The term “biological sample” encompasses essentially any sample type obtained from a subject that can be used in a diagnostic or prognostic method described herein. The biological sample may be any bodily fluid, tissue or any other suitable sample. The definition encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as cells (e.g., cancer cells), polypeptides, or proteins. The term “biological sample” encompasses a clinical sample, but also, includes cells in culture, cell supernatants, cell lysates, blood, serum, plasma, urine, cerebral spinal fluid, biological fluid, and tissue samples. The sample may be pretreated as necessary by dilution in an appropriate buffer solution or concentrated, if desired. Any of a number of standard aqueous buffer solutions, employing one of a variety of buffers, such as phosphate, Tris, or the like, preferably at physiological pH can be used. Biological samples can be derived from patients using well-known techniques such as venipuncture, lumbar puncture, fluid sample such as saliva or urine, or tissue biopsy and the like. In embodiments, the sample is a cancer sample (e.g., containing or suspected of containing cancer cells, such as from a tumor).

[0076] The terms “treating” or “treatment” include any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable.

“Treating” or “treatment” refers to any indicia of success in the therapy or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric

evaluation. In other words, "treatment" as used herein includes any cure, amelioration, or prevention of a disease.

[0077] "Treating" or "treatment" as used herein includes prophylactic treatment. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms, fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things. The term "treating" and conjugations thereof may include prevention of an injury, pathology, condition, or disease. In embodiments, treating is preventing. In embodiments, treating does not include preventing. Treatment methods include administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by diagnostic assays (e.g., assays described herein or known in the art). In embodiments, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0078] The term "prevent" refers to a decrease in the occurrence of disease symptoms in a patient. The prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment.

[0079] The term "patient" or "subject" refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, and other non-mammalian animals. In embodiments, a subject is human.

[0080] The terms "marker" and "biomarker" are used interchangeably throughout the disclosure. As used herein, a biomarker refers generally to a protein, polypeptide, RNA, or DNA, the level or concentration of which is associated with a particular biological state. The terms "protein marker" or "polypeptide marker" refer generally to a protein or polypeptide in which the level or concentration is associated with a particular biological state. The term "RNA marker" refers generally to RNA in which the level or concentration is associated with a particular biological state.

[0081] The terms "polypeptide," "peptide" and "protein" used interchangeably herein, refer to

a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. In embodiments, detecting the concentrations of naturally occurring protein marker proteins in a biological sample is contemplated for use within diagnostic, prognostic, or monitoring methods disclosed herein.

[0082] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques.

[0083] The term “administering” as used herein refers to oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations,

intravenous infusion, transdermal patches, etc.

[0084] The term "co-administer" as used herein refers to a composition described herein administered at the same time, prior to, or after the administration of one or more other therapies. The compounds provided herein can be administered alone or can be coadministered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances.

[0085] The term "cancer model organism" as used herein refers to an organism exhibiting a phenotype indicative of cancer, or the activity of cancer causing elements, within the organism. A wide variety of organisms may serve as cancer model organisms, and include for example, cancer cells and mammalian organisms such as rodents (e.g. mouse or rat) and primates. Cancer cell lines are widely understood by those skilled in the art as cells exhibiting phenotypes or genotypes similar to in vivo cancers. Cancer cell lines as used herein includes cell lines from animals (e.g. mice) and from humans.

[0086] The terms "selective" or "selectivity" or the like of a compound refers to the compound's ability to discriminate between molecular targets.

[0087] The terms "specific", "specifically", "specificity", or the like of a compound refers to the compound's ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

[0088] The terms "nucleic acid," "nucleic acid molecule," "nucleic acid oligomer," "oligonucleotide," "nucleic acid sequence," "nucleic acid fragment," and "polynucleotide" are used interchangeably and are intended to include, but are not limited to, a polymeric form of nucleotides covalently linked together that may have various lengths, either deoxyribonucleotides or ribonucleotides, or analogs, derivatives or modifications thereof. Different polynucleotides may have different three-dimensional structures, and may perform various functions, known or unknown. Non-limiting examples of polynucleotides include a gene, a gene fragment, an exon, an intron, intergenic DNA (including, without limitation, heterochromatic DNA), messenger RNA (mRNA), transfer RNA, ribosomal RNA, a ribozyme, cDNA, a recombinant polynucleotide, a branched polynucleotide, a plasmid, a vector, isolated DNA of a sequence, isolated RNA of a sequence, a nucleic acid probe, and a primer. Polynucleotides useful in the methods of the disclosure may comprise natural nucleic acid sequences and variants thereof, artificial nucleic acid sequences, or a combination of such sequences. A polynucleotide may comprise one or more modified nucleotides, such as

methyated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Panels, assays, kits and methods of the present disclosure may include oligonucleotide probes, binding fragments thereof or other types of target-binding agents, which are specific for one or more target RNAs (e.g., an RNA expressed by a target gene).

[0089] The term “target polynucleotide” refers to a nucleic acid molecule or polynucleotide in a starting population of nucleic acid molecules having a target sequence whose presence, amount, and/or nucleotide sequence, or changes in one or more of these, are desired to be determined. In general, the term “target sequence” refers to a nucleic acid sequence on a single strand of nucleic acid. The target sequence may be a portion of a gene, a regulatory sequence, genomic DNA, cDNA, RNA including mRNA, miRNA, rRNA, or others. The target sequence may be a target sequence from a sample or a secondary target such as a product of an amplification reaction. In embodiments, the target polynucleotide is an RNA transcript (or amplification product thereof) of a gene of interest (referred to herein as a “target gene”).

[0090] An “oligonucleotide probe” or “probe” refers to a polynucleotide used for detecting or identifying its corresponding target polynucleotide in a hybridization reaction by specific hybridization with a corresponding target sequence. Thus, a nucleotide probe is hybridizable to one or more target polynucleotides, and preferably specifically hybridizable to one target polynucleotide. Oligonucleotide probes can contain a region that is perfectly complementary to one or more target polynucleotides in a sample, and may optionally contain one or more nucleotides that are not complemented by a corresponding nucleotide in the one or more target polynucleotides in a sample. By “specific hybridization,” “specifically hybridizable,” and the like is meant hybridization that is determinative of the presence of the corresponding target polynucleotide, often in a heterogeneous population of polynucleotides, which may include other target polynucleotides recognized by other probes, as well as non-target polynucleotides. Thus, under designated assay conditions, the specified oligonucleotide probe binds to a particular target polynucleotide at least two times the background and more typically more than 10 to 100 times background, or higher.

[0091] “Percentage of sequence identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions as compared to the reference sequence (which does not comprise the additions or deletions) for optimal alignment

of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (e.g., with respect to the reference sequence), and multiplying the result by 100 to yield the percentage of sequence identity. Programs for determining sequence identity are known to those skilled in the art, and include, without limitation, BLAST (as noted above, optionally using default parameters), the Needleman-Wunsch algorithm (e.g., the EMBOSS Needle aligner available at www.ebi.ac.uk/Tools/psa/emboss_needle/nucleotide.html, optionally with default settings).

[0092] The terms “identical” or percent “identity” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters, or by manual alignment and visual inspection (e.g., NCBI web site <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). In embodiments, sequences that are “substantially identical” are at least 80%, 90%, 95%, 99%, or more identical. This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. Alignment algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 10, 15, 25, or more amino acids or nucleotides in length.

[0093] An amino acid or nucleotide base “position” is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that must be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not correspond to a numbered amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the

reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0094] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence.

[0095] The term "antisense nucleic acid" as used herein refers to a nucleic acid (e.g., DNA or RNA molecule) that is complementary to at least a portion of a specific target nucleic acid and is capable of reducing transcription of the target nucleic acid (e.g. mRNA from DNA), reducing the translation of the target nucleic acid (e.g. mRNA), altering transcript splicing (e.g. single stranded morpholino oligo), or interfering with the endogenous activity of the target nucleic acid. Typically, synthetic antisense nucleic acids (e.g. oligonucleotides) are generally between 15 and 25 bases in length. Thus, antisense nucleic acids are capable of hybridizing to (e.g. selectively hybridizing to) a target nucleic acid. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid *in vitro*. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid in a cell. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid in an organism. In embodiments, the antisense nucleic acid hybridizes to the target nucleic acid under physiological conditions. Antisense nucleic acids may comprise naturally occurring nucleotides or modified nucleotides such as, e.g., phosphorothioate, methylphosphonate, and anomeric sugar-phosphate, backbone-modified nucleotides.

[0096] In the cell, the antisense nucleic acids hybridize to the corresponding RNA forming a double-stranded molecule. The antisense nucleic acids interfere with the endogenous behavior of the RNA and inhibit its function relative to the absence of the antisense nucleic acid. Furthermore, the double-stranded molecule may be degraded via the RNAi pathway. The use of antisense methods to inhibit the *in vitro* translation of genes is known in the art [88]. Further, antisense molecules which bind directly to the DNA may be used. Antisense nucleic acids may be single or double stranded nucleic acids. Non-limiting examples of antisense nucleic acids include siRNAs (including their derivatives or pre-cursors, such as nucleotide analogs), short hairpin RNAs (shRNA), micro RNAs (miRNA), saRNAs (small activating RNAs) and small nucleolar RNAs (snoRNA) or certain of their derivatives or pre-cursors.

[0097] The term "complement," as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of

nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanosine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence, only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0098] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[0099] The term “contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture. The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In embodiments, contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0100] The term “activation”, “activate”, “activating”, “activator” and the like in reference to a protein-inhibitor interaction means positively affecting (e.g. increasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the activator. In

embodiments activation means positively affecting (e.g. increasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the activator. The terms may reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease. Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein associated with a disease (e.g., a protein which is decreased in a disease relative to a non-diseased control). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein

[0101] The terms “agonist,” “activator,” “upregulator,” etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In embodiments, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist.

[0102] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments, inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0103] The terms “inhibitor,” “repressor” or “antagonist” or “downregulator” interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In

embodiments, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist. In embodiments, inhibitors of signaling pathways are provided herein. Examples of inhibitors of the IFN signaling pathway include ATR kinase inhibitors and NAMPT inhibitors.

[0104] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (e.g., ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, etc.).

[0105] The term "gene expression" refers to any step in the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the product is a functional RNA.

[0106] The term "reference value" or "control" as used herein refers to a value to which a measured quantity is compared. In embodiments, the reference value is used as a standard of comparison in evaluating experimental effects. In embodiments, a reference value is a measurement of a reference sample (e.g., non-cancer cells treated to overexpress a particular gene) as described herein. In embodiments, the reference value is a synthetic quantification standard used as a reference for assay measurements. In embodiments, a reference value is assigned to genes in order to compare measured gene expression levels and make a comparison of whether the measured value is greater, equal, or less than the reference value, which then enables a determination of increased, no change, or decreased expression level of the gene. In embodiments, a reference value is assigned to an activity level representing the collective reference expression levels of several genes (such as genes associated with a particular signature). In embodiments, reference values are pre-determined values, such as from previous measurements for which expression levels were previously measured. In embodiments, a reference value is a control value for a known sample or condition that was previously measured, or is measured in parallel with a test sample. In embodiments, a reference value is a value for a sample from a subject at an earlier time point, to which values a value for a test sample at a later time point may be compared, and which may be measured separately or simultaneously with the test sample. In embodiments, a known sample providing the reference value is a non-cancerous tissue of the same type from which a test cancer cell originated, or a cell line of the same type as a test cancer cell. In embodiments, the reference value represents a difference between two treatment conditions for the known sample (e.g., a measure in the

change of an activity level or the expression of one or more genes between a first condition in which a particular signaling pathway was induced, and a second condition in which the particular signaling pathway was not induced). In embodiments, a pathway activity increase or decrease of one standard deviation from the mean is considered significant. In embodiments, the reference value is a reference activity score. In embodiments, a reference activity score is the result of a weighted average of normalized expression levels for genes in a pathway signature that are linearly combined, and optionally scaled to between zero (0) and one (1). In embodiments, a scaled activity score of more than about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, or more of the maximum score indicates an increased activity in the corresponding pathway. In embodiments, an increased activity is indicated by a scaled activity score of more than about 0.5 of the maximum score. In embodiments, a scaled score of about zero (0) represents the activity score for a population of control cells in which the signaling pathway is not induced.

[0107] The term “associated” or “associated with” in the context of a substance, substance activity, or function associated with a disease (e.g. a protein associated disease, such as a cancer (e.g., cancer, inflammatory disease, autoimmune disease, or infectious disease)) means that the disease (e.g. cancer, inflammatory disease, autoimmune disease, or infectious disease) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease.

[0108] The term “whole transcriptome measurement” refers to methods for measuring every mRNA transcript in a sample, or suspected of being in a sample, in order to evaluate the abundance of specific RNA transcripts. Various methods for performing “whole transcriptome measurement” are available. Non-limiting examples include the use of arrays to probe for expression of all known mRNAs associated with a sample (e.g., all human genes), and the use of high-throughput sequencing methodologies to sequence all mRNA in a sample. In general, methodologies for whole transcriptome measurement are directed at identifying all genes expressed in a given sample (e.g., a particular tissue or type of cell), or measuring their expression level. In certain sequencing methodologies, all mRNAs are subjected to a common procedure that does not select for any particular target sequence, but instead non-selectively amplifies and sequences all mRNA using common structural features (e.g., presence of a poly-A tail, or adapter ligation that does not depend on the presence of any particular sequence).

[0109] Methods

[0110] Provided herein are methods of treating cancer in a patient in need thereof comprising

administering a therapeutically effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor to the patient; wherein the cancer has increased levels of interferon. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of an ATR kinase inhibitor to the patient; wherein the cancer has increased levels of interferon. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a NAMPT inhibitor to the patient; wherein the cancer has increased levels of interferon. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a PARP inhibitor to the patient; wherein the cancer has increased levels of interferon. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT inhibitor. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta. In embodiments, the cancer has an increased level of interferon relative to a control. In embodiments, the interferon is an interferon protein. In embodiments, the interferon is an interferon RNA. In embodiments, the interferon is Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0111] In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon in a sample obtained from a patient, and administering a therapeutically effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor to the patient. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon in a sample obtained from a patient, and administering a therapeutically effective amount of an ATR kinase inhibitor to the patient. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon in a sample obtained from a patient, and administering a therapeutically effective amount of a NAMPT inhibitor to the patient. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon in a sample obtained from a patient, and administering a therapeutically effective amount of a PARP inhibitor to the patient. In

embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT inhibitor. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta. In embodiments, the cancer has an increased level of interferon relative to a control. In embodiments, the interferon is an interferon protein. In embodiments, the interferon is an interferon RNA. In embodiments, the interferon is Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof. In embodiments, the Type 1 interferon is interferon-alpha. In embodiments, the Type 1 interferon is interferon-beta. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0112] Provided herein are methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor to the patient; wherein the cancer has increased levels of interferon signaling pathway activity. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of an ATR kinase inhibitor to the patient; wherein the cancer has increased levels of interferon signaling pathway activity. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising administering a therapeutically effective amount of a NAMPT inhibitor to the patient; wherein the cancer has increased levels of interferon signaling pathway activity. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT inhibitor. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta. In embodiments, the cancer has an increased level of interferon signaling pathway activity relative to a control. In embodiments, the interferon signaling pathway activity is an interferon pathway protein. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA. In embodiments, the interferon signaling pathway activity is an interferon pathway mRNA. In embodiments, the interferon is

Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof. In embodiments, the Type 1 interferon is interferon-alpha. In embodiments, the Type 1 interferon is interferon-beta. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0113] In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon signaling pathway activity in a sample obtained from a patient, and administering a therapeutically effective amount of an ATR kinase inhibitor and/or a NAMPT inhibitor to the patient. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon signaling pathway activity in a sample obtained from a patient, and administering a therapeutically effective amount of an ATR kinase inhibitor to the patient. In embodiments, the disclosure provides methods of treating cancer in a patient in need thereof comprising determining the level of interferon signaling pathway activity in a sample obtained from a patient, and administering a therapeutically effective amount of a NAMPT inhibitor to the patient. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT inhibitor. In embodiments, the methods comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta. In embodiments, the cancer has an increased level of interferon signaling pathway activity relative to a control. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA. In embodiments, the interferon signaling pathway activity is an interferon pathway mRNA. In embodiments, the interferon signaling pathway activity is an interferon pathway protein. In embodiments, the interferon signaling pathway activity is an interferon pathway protein selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway protein selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway protein selected from the group

consisting of PARP9, PARP10, PARP14, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway protein selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, and a combination of two or more thereof. In embodiments, the interferon pathway protein comprises STAT1 and MX1. In embodiments, the interferon pathway protein comprises STAT1. In embodiments, the interferon pathway protein comprises MX1. In embodiments, the interferon pathway protein comprises PARP9. In embodiments, the interferon pathway protein comprises PARP10. In embodiments, the interferon pathway protein comprises PARP14. In embodiments, the interferon pathway protein comprises PARP9, PARP10, and PARP14. In embodiments, the interferon pathway protein comprises PARP9, PARP10, PARP14, STAT1 and MX1. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, and a combination of two or more thereof. In embodiments, the interferon signaling pathway activity is an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, and a combination of two or more thereof. In embodiments, the interferon pathway RNA comprises STAT1 and MX1. In embodiments, the interferon pathway RNA comprises STAT1. In embodiments, the interferon pathway RNA comprises MX1. In embodiments, the interferon pathway RNA comprises PARP9. In embodiments, the interferon pathway RNA comprises PARP10. In embodiments, the interferon pathway RNA comprises PARP14. In embodiments, the interferon pathway RNA comprises PARP9, PARP10, and PARP14. In embodiments, the interferon pathway RNA comprises PARP9, PARP10, PARP14, STAT1, and MX1. In embodiments, the cancer has an increased level of interferon signaling pathway activity relative to a control. In embodiments, the interferon is Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0114] Provided herein are methods of classifying a cancer in a subject comprising measuring

expression levels of a plurality of target genes from a sample obtained from the patient; comparing expression levels of the plurality of target genes to a control; and classifying the cancer as responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the disclosure provides methods of classifying a cancer in a subject comprising measuring expression levels of a plurality of target genes from a sample obtained from the patient; comparing expression levels of the plurality of target genes to a control; and classifying the cancer as responsive to treatment with an ATR kinase inhibitor. In embodiments, the methods comprise classifying a cancer in a subject by measuring expression levels of a plurality of target genes from a sample obtained from the patient; comparing expression levels of the plurality of target genes to a control; and classifying the cancer as responsive to treatment with a NAMPT inhibitor. In embodiments, the cancer is classified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to the control. In embodiments, the cancer is classified as responsive to treatment with a NAMPT inhibitor when the expression levels of the plurality of target genes are increased relative to the control. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 2, 3, or 4 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 2, 3, or 4 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, and PARP14. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise PARP9, PARP10, and PARP14. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 3 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise at least 4 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes, the plurality of target genes comprise PARP9, PARP10, PARP14, STAT1, and MX1. In embodiments, the plurality of target genes comprise at least STAT1. In embodiments, the plurality of target genes comprise at least

MX1. In embodiments, the plurality of target genes comprise at least STAT1 and MX1. In embodiments, the plurality of target genes comprise at least PARP9. In embodiments, the plurality of target genes comprise at least PARP10. In embodiments, the plurality of target genes comprise at least PARP14. In embodiments, the methods comprise measure RNA expression levels from the plurality of target genes in the sample obtained from the patient. In embodiments, the methods comprise measure mRNA expression levels from the plurality of target genes in the sample obtained from the patient. In embodiments, measuring does not comprise a whole transcriptome measurement. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor. In embodiments, the methods further comprise administering an effective amount of a PARP inhibitor. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of a NAMPT inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT inhibitor. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise further administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta.

[0115] Provided herein are methods of identifying a subset of cancer patients that would be responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor comprising measuring expression levels of a plurality of target genes from a sample obtained from a patient. In embodiments, the methods of identifying a subset of cancer patients that would be responsive to treatment with an ATR kinase inhibitor comprise measuring expression levels of a plurality of target genes from a sample obtained from a patient. In embodiments, the methods of identifying a subset of cancer patients that would be responsive to treatment with a NAMPT inhibitor comprise measuring expression levels of a plurality of target genes from a sample obtained from a patient. In embodiments, the patient is identified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to the control. In embodiments, the patient is identified as responsive to treatment with a NAMPT inhibitor when the expression levels of the plurality of target genes are increased relative to the control. For measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 2, 3, or 4 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. For

measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 2, 3, or 4 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. For measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 2 or 3 genes selected from the group consisting of PARP9, PARP10, and PARP14. For measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 3 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes the plurality of target genes comprise at least 4 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. For measuring expression levels of a plurality of target genes the plurality of target genes comprise PARP9, PARP10, PARP14, STAT1, and MX1. In embodiments, the plurality of target genes comprise at least PARP9. In embodiments, the plurality of target genes comprise at least PARP10. In embodiments, the plurality of target genes comprise at least PARP14. In embodiments, the plurality of target genes comprise at least STAT1. In embodiments, the plurality of target genes comprise at least MX1. In embodiments, the plurality of target genes comprise at least STAT1 and MX1. In embodiments, the methods comprise measure RNA expression levels from the plurality of target genes in the sample obtained from the patient. In embodiments, the methods comprise measure mRNA expression levels from the plurality of target genes in the sample obtained from the patient. In embodiments, measuring does not comprise a whole transcriptome measurement. The presence of a type 1 interferon-stimulated gene (ISG) signature and/or pCHEK_{S345} indicates the subject would be responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. The presence of a type 1 interferon-stimulated gene (ISG) signature and/or pCHEK_{S345} indicates the subject would be responsive to treatment with an ATR kinase inhibitor. The presence of a type 1 interferon-stimulated gene (ISG) signature and/or pCHEK_{S345} indicates the subject would be responsive to treatment with a NAMPT inhibitor. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor. In embodiments, the methods further comprise administering an effective amount of a PARP inhibitor. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor and a PARP inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of a NAMPT inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of an ATR kinase inhibitor and a NAMPT

inhibitor. In embodiments, the methods further comprise administering an effective amount of an ATR kinase inhibitor, a NAMPT inhibitor, and a PARP inhibitor. In embodiments, the methods comprise further administering an effective amount of a NAMPT inhibitor and a PARP inhibitor. In embodiments, the methods further comprise administering to the patient an effective amount of a NAMPT inhibitor and interferon-beta.

[0116] In embodiments of the methods described herein, the sample obtained from a patient is a biological sample selected from, e.g., cells in culture, cell supernatants, cell lysates, blood, serum, plasma, urine, cerebral spinal fluid, biological fluid, and tissue samples. In embodiments, the sample is a cancer sample (e.g., containing or suspected of containing cancer cells, such as from a tumor). In embodiments, determining the level of IFN signaling pathway activity in the sample includes measuring RNA and/or protein expression of interferon-stimulated genes. In embodiments, the RNA is mRNA. Interferon-stimulated genes include one or more of the genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. Interferon-stimulated genes include one or more of the genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2. Interferon-stimulated genes include one or more of the genes selected from the group consisting of PARP9, PARP10, and PARP14. Interferon-stimulated genes include one or more of the genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway proteins for STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, STAT2, or a combination of two or more thereof. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway proteins for PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, STAT2, or a combination of two or more thereof. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway proteins for PARP9, PARP10, PARP14, or a combination of two or more thereof. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway proteins for PARP9, PARP10, PARP14, STAT1, MX1, MX2, or a combination of two

or more thereof. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for STAT1, MX1, or a combination thereof. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for STAT1 and MX1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for STAT1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for MX1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for PARP9. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for PARP10. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for PARP14. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for MX2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFIT1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFI44. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFIT3. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for OAS1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for OAS3. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for BST2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFITM1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFI27. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFI27. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for CXCL10. In embodiments, determining the level of

IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFI16. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFI30. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFIH1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFIT2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IFITM2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IRF1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IRF9. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for IRGM. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for ISG15. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for OAS2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for PSME1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for SOCS1. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA or IFN pathway protein for STAT2. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA and IFN pathway protein. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway RNA. In embodiments, the RNA is mRNA. In embodiments, determining the level of IFN signaling pathway activity in the sample includes determining the level of IFN pathway protein.

[0117] In embodiments, methods disclosed herein comprise whole transcriptome measurement. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of specific RNA transcripts including an RNA transcript selected from STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and

STAT2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of specific RNA transcripts including an RNA transcript selected from PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of specific RNA transcripts including an RNA transcript selected from PARP9, PARP10, and PARP14 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of PARP9 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of PARP10 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of PARP14 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of STAT1 RNA transcript and MX1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of STAT1 RNA transcript, MX1 RNA transcript, PARP9 RNA transcript, PARP10 RNA transcript, PARP14 RNA transcript, or a combination of two or more thereof. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of STAT1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of MX1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of MX2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFIT1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFI44 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFIT3 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of OAS1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of OAS3 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of BST2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFITM1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFI27 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of CXCL10 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFI16 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFI30 RNA transcript. In embodiments, whole transcriptome

measurement is conducted to evaluate the relative abundance of IFIH1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFIT2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IFITM2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IRF1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IRF9 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of IRGM RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of ISG15 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of OAS2 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of PSME1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of SOCS1 RNA transcript. In embodiments, whole transcriptome measurement is conducted to evaluate the relative abundance of STAT2 RNA transcript.

[0118] In embodiments, the methods include measuring the expression levels of a plurality of target genes. In embodiments, measuring expression levels of a plurality of genes does not include a whole transcriptome measurement. In embodiments, the plurality of target genes include at least one gene (e.g., at least 2, 3, 4, or 5 genes) selected from the interferon-stimulated gene signature. In embodiments, the interferon-stimulation gene signature comprises STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof. In embodiments, the interferon-stimulation gene signature comprises STAT1. In embodiments, the interferon-stimulation gene signature comprises MX1. In embodiments, the interferon-stimulation gene signature comprises STAT1 and MX1. In embodiments, the plurality of target genes include at least one gene (e.g., at least 2, 3, 4, or 5 genes) selected from the interferon-stimulated gene signature. In embodiments, the interferon-stimulation gene signature comprises PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof. In embodiments, the interferon-stimulation gene signature comprises PARP9, PARP10, PARP14, STAT1, and MX1. In embodiments, the interferon-stimulation gene signature comprises PARP9, PARP10, and PARP14. In embodiments, the interferon-stimulation gene signature comprises PARP9. In embodiments, the interferon-stimulation gene signature comprises PARP10. In embodiments, the interferon-stimulation gene signature comprises

PARP14.

[0119] Measuring gene expression may be accomplished by a number of methods known in the art including but not limited to Northern blotting, Southern blotting, Western blotting, fluorescent in situ hybridization, reverse transcriptase-polymerase chain reaction, serial analysis of gene expression (SAGE), microarray analysis, tiling arrays, NanoString assays and the like. In embodiments, isolated mRNA (or derivatives thereof, such as cDNA) is used in hybridization or amplification assays, examples of which include, but are not limited to, Southern or Northern analyses, PCR analyses, probe arrays, and NanoString Assays. One method for the detection of mRNA levels involves contacting the isolated mRNA or synthesized cDNA with an oligonucleotide probe that can hybridize to the mRNA encoded by the gene being detected. The oligonucleotide probe can be, for example, a cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250, or 500 nucleotides in length and sufficient to specifically hybridize under the assay conditions, and/or under stringent conditions, to the RNA (or corresponding cDNA) of the gene whose expression is to be measured. In embodiments, polynucleotide probes are attached to a solid support forming an array, with one or more polynucleotide probes targeting each of the RNA (or corresponding cDNA) of the genes whose expression are to be measured. In embodiments, RNA obtained from a sample is converted to complementary DNA (cDNA) in a hybridization reaction, which optionally may be further amplified prior to measuring expression (e.g., by PCR amplification). In embodiments, RNA from a sample is measured without conversion to cDNA, and/or without amplification prior to measuring expression.

[0120] In embodiments, the plurality of target genes represent an ISG signature and include at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 15, or 20 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 1 gene selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 2 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 3 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30,

IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 4 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 5 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 6 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 7 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 8 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 9 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 10 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 11 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 12 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 13 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 14 genes selected from the group consisting of STAT1, STAT2, MX1, MX2,

IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 15 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 16 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 17 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 18 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 19 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 20 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 21 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 22 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 23 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 24 genes selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 25 genes

selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least STAT1. In embodiments, the plurality of target genes includes at least MX1. In embodiments, the plurality of target genes includes at least STAT1 and MX1.

[0121] In embodiments, the plurality of target genes represent an ISG signature and include at least 1, at least 2, at least 3, at least 4, at least 5, at least 10, at least 15, at least 20, or at least 25 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 1 gene selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 3 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 4 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 5 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 6 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 7 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 8

genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 9 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 10 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 11 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 12 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 13 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 14 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 15 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 16 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 17 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 18

genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 19 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 20 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 21 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 22 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 23 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 24 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 25 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 26 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least 27 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes PARP9,

PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, and SOCS1. In embodiments, the plurality of target genes includes at least PARP9. In embodiments, the plurality of target genes includes at least PARP10. In embodiments, the plurality of target genes includes at least PARP14. In embodiments, the plurality of target genes includes at least PARP9 and PARP10. In embodiments, the plurality of target genes includes at least PARP9 and PARP14. In embodiments, the plurality of target genes includes at least PARP10 and PARP14. In embodiments, the plurality of target genes includes at least PARP9, PARP10, and PARP14. In embodiments, the plurality of target genes includes at least PARP9, PARP10, and STAT1. In embodiments, the plurality of target genes includes at least PARP9, PARP14, and STAT1. In embodiments, the plurality of target genes includes at least PARP10, PARP14, and STAT1. In embodiments, the plurality of target genes includes at least PARP9, PARP10, PARP14, and STAT1. In embodiments, the plurality of target genes includes at least PARP9, PARP10, and MX1. In embodiments, the plurality of target genes includes at least PARP9, PARP14, and MX 1. In embodiments, the plurality of target genes includes at least PARP10, PARP14, and MX. In embodiments, the plurality of target genes includes at least PARP9, PARP10, PARP14, and MX 1. In embodiments, the plurality of target genes includes at least PARP9, PARP10, STAT1, and MX1. In embodiments, the plurality of target genes includes at least PARP9, PARP14, STAT1, and MX 1. In embodiments, the plurality of target genes includes at least PARP10, PARP14, STAT1, and MX. In embodiments, the plurality of target genes includes at least PARP9, PARP10, PARP14, STAT1, and MX 1.

[0122] In embodiments, the method further includes determining an expression level in the cancer of one or more additional genes, RNA, or proteins. In embodiments, the additional genes, RNA, or proteins are selected from cGAS, STING, or a combination thereof. In embodiments, the additional genes, RNA, or proteins are selected from cGAS and STING. In embodiments, the additional genes, RNA, or proteins comprise cGAS. In embodiments, the additional genes, RNA, or proteins comprise STING. In embodiments, determining an activity level in the one or more pathways includes determining measures of expression levels of genes in cGAS and/or STING.

[0123] In embodiments, the ATR kinase inhibitors described herein are co-administered with PARP inhibitors. In embodiments, the ATR kinase inhibitors described herein are co-administered with NAMPT inhibitors. In embodiments, the ATR kinase inhibitors described herein are co-administered with one or more anticancer agents to treat cancer (e.g., pancreatic cancer). In embodiments, the ATR kinase inhibitors described herein are co-administered with

interferon. In embodiments, the ATR kinase inhibitors described herein are co-administered with one or more compounds selected from the group consisting of PARP inhibitors, NAMPT inhibitors, and interferon. In embodiments, the ATR kinase inhibitors described herein are co-administered with interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b, or a combination of two or more thereof. In embodiments, the ATR kinase inhibitors described herein are co-administered with a PARP inhibitor and an interferon. In embodiments, the ATR kinase inhibitors described herein are co-administered with a PARP inhibitor and an interferon selected from the group consisting of interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b, or a combination of two or more thereof. In embodiments, the cancer has an increased level of interferon relative to a control. In embodiments, the interferon is an interferon protein. In embodiments, the interferon is an interferon RNA. In embodiments, the interferon is Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0124] In embodiments, the NAMPT inhibitors described herein are co-administered with PARP inhibitors. In embodiments, the NAMPT inhibitors described herein are co-administered with ATR kinase inhibitors. In embodiments, the NAMPT inhibitors described herein are co-administered with one or more anticancer agents to treat cancer (e.g., pancreatic cancer). In embodiments, the NAMPT inhibitors described herein are co-administered with one or more compounds selected from the group consisting of PARP inhibitors, ATR kinase inhibitors, and interferon. In embodiments, the NAMPT inhibitors described herein are co-administered with interferon. In embodiments, the NAMPT inhibitors described herein are co-administered with interferon-beta. In embodiments, the NAMPT inhibitors described herein are co-administered with interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b, or a combination of two or more thereof. In embodiments, the NAMPT inhibitors described herein are co-administered with a PARP inhibitor and an interferon. In embodiments, the NAMPT inhibitors described herein are co-administered with a PARP inhibitor and interferon-beta. In embodiments, the NAMPT inhibitors described herein are co-administered with a PARP inhibitor and an interferon selected from the group consisting of interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b, or a combination of two or more thereof. In embodiments, the cancer has an increased level of interferon relative to a control. In embodiments, the interferon is an interferon protein. In embodiments, the interferon is an interferon RNA. In embodiments, the interferon is Type 1 interferon. In embodiments, the Type 1 interferon is interferon-alpha,

interferon-beta, or a combination thereof. In embodiments, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0125] The ATR kinase inhibitor used in the methods described herein, including all embodiments thereof, can be any known in the art. In embodiments, the ATR kinase inhibitor is berzosertib, 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol (also known as VE-821), ceralasertib, schisandrin B, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine (also known as NU6027), dactolisib, (R)-4-(2-(1H-indol-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine (also known as AZ20), caffeine, wortmannin, 2-[(3R)-3-methyl-4-morpholinyl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (also known as BAY 1895344), an analog of any one of the foregoing, or a pharmaceutically acceptable salt of any one of the foregoing. In embodiments, the ATR kinase inhibitor is berzosertib, VE-821, ceralasertib, schisandrin B, NU6027, dactolisib, AZ20, caffeine, wortmannin, an analog of any one of the foregoing, or a pharmaceutically acceptable salt of any one of the foregoing. In embodiments, the ATR kinase inhibitor is berzosertib. In embodiments, the ATR kinase inhibitor is ceralasertib. In embodiments, the ATR kinase inhibitor is schisandrin B. In embodiments, the ATR kinase inhibitor is dactolisib. In embodiments, the ATR kinase inhibitor is caffeine. In embodiments, the ATR kinase inhibitor is wortmannin. In embodiments, the ATR kinase inhibitor is VE-821. In embodiments, the ATR kinase inhibitor is NU6027. In embodiments, the ATR kinase inhibitor is AZ20. In embodiments, the ATR kinase inhibitor is BAY 1895344.

[0126] The NAMPT inhibitor used in the methods described herein, including all embodiments thereof, can be any known in the art. In embodiments, the ATR kinase inhibitor is daporinad (also known as FK866 or APO866), 4-[5-methyl-4-[[4-methylphenyl)sulfonyl]methyl]-2-oxazolyl]-N-(3-pyridinylmethyl)benzamide (also known as STF-118804), N-(4-((3,5-difluorophenyl)sulfonyl)benzyl)imidazo[1,2-a]pyridine-6-carboxamide (also known as GNE-617), N-[[4-[[3-(trifluoromethyl)phenyl)sulfonyl]phenyl]-methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (also known as GNE-618), (1Z,2E)-3-(6-aminopyridin-2-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylimidic acid (also known as KPT-9274), N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N''-4-pyridinyl-guanidine (also known as CHS-828 and GMX1778), N-[1,1'-biphenyl]-2-yl-4-(3-pyridinyl)-1H-1,2,3-triazole-1-octanamide (also known as GPP 78), 4-[[[4-(1,1-dimethylethyl)-phenyl-sulfonyl]amino]methyl]-N-3-pyridinyl-benzamide (also known as STF 31), 1-(4-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-ylmethyl)urea (also known as

SBI-797812), 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide (also known as LSN3154567 or Nampt-IN-1), N-(3-(1H-pyrazol-4-yl)propyl)-3-((4-fluorophenyl)ethynyl)-4-(pyridin-4-yl)benzamide (also known as OT-82), 4-(((7-bromo-2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl)(prop-2-yn-1-yl)amino)-N-(pyridin-3-ylmethyl)benzamide (also known as CB30865), 4-(((7-chloro-3,4-dihydro-3-methyl-2-((4-methyl-1-piperazinyl)methyl)-4-oxo-6-quinazolinyl)methyl)-2-propyn-1-ylamino)-N-(3-pyridinylmethyl)-benzamide (also known as CB300919) or an analog of any one of the foregoing. In embodiments, the NAMPT inhibitor is daporinad. In embodiments, the NAMPT inhibitor is STF-118804. In embodiments, the NAMPT inhibitor is GNE-617. In embodiments, the NAMPT inhibitor is KPT-9274. In embodiments, the NAMPT inhibitor is GMX1778. In embodiments, the NAMPT inhibitor is GP 78. In embodiments, the NAMPT inhibitor is STF 31. In embodiments, the NAMPT inhibitor is SBI-797812. In embodiments, the NAMPT inhibitor is LSN3154567. In embodiments, the NAMPT inhibitor is OT-82. In embodiments, the NAMPT inhibitor is CB30865. In embodiments, the NAMPT inhibitor is GNE-618. In embodiments, the NAMPT inhibitor is CB300919. In embodiments, the NAMPT inhibitor is LSN3154567 and/or daporinad.

[0127] The PARP inhibitor used in the methods described herein, including all embodiments thereof, can be any known in the art. In embodiments, the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, 11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)-dione (also known as CEP 9722), 10-((4-Hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-3(2H)-one (also known as E7016), or an analog of any one of the foregoing. In embodiments, the PARP inhibitor is niraparib. In embodiments, the PARP inhibitor is olaparib. In embodiments, the PARP inhibitor is rucaparib. In embodiments, the PARP inhibitor is talazoparib. In embodiments, the PARP inhibitor is vekauoarub. In embodiments, the PARP inhibitor is pamiparib. In embodiments, the PARP inhibitor is CEP 9722. In embodiments, the PARP inhibitor is E7016.

[0128] In embodiments of the methods described herein, the patient can be administered any additional anti-cancer agent. In embodiments, the additional anti-cancer agent is any anti-cancer agent used to treat pancreatic cancer. In embodiments, the additional anti-cancer agent is any anti-cancer agent used to treat pancreatic ductal adenocarcinoma. In embodiments, the additional anti-cancer drug is capecitabine, erlotinib, everolimus, fluorouracil, gemcitabine, irinotecan, leucovorin, mitomycin, nab-paclitaxel, olaparib, oxaliplatin, pembrolizumab, sunitinib, or a combination of two or more thereof. In embodiments, the methods further comprise administering to the patient radiation therapy or proton beam therapy.

[0129] The compounds described herein (e.g., ATR kinase inhibitors, NAMPT inhibitors, PARP inhibitors, anti-cancer agents) can be in the form of pharmaceutically acceptable salts. The term “pharmaceutically acceptable salts” is meant to include salts of the compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., “Pharmaceutical Salts”, Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0130] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0131] In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0132] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0133] In embodiments of the methods described herein, the cancer is an adenocarcinoma. In embodiments, the cancer has a KRAS mutation, a TP53 mutation, or a combination thereof. In embodiments, the cancer has a KRAS mutation. In embodiments, the cancer has a TP53 mutation. In embodiments, the cancer has a KRAS mutation and a TP53 mutation. In embodiments, the cancer has a KRAS mutation, a TP53, mutation, BRCA1 mutation, a BRCA2 mutation, a CDKN2A mutation, a SMAD4 mutation, a MLL3 mutation, a TGFBR2 mutation, an ARID1A mutation, a SF3B1 mutation, a PALB2 mutation, a NTRK mutation, or a combination of two or more thereof. In embodiments, the cancer has a BRCA mutation. In embodiments, the cancer has a BRCA1 mutation. In embodiments, the cancer has a BRCA2 mutation. In embodiments, the cancer has a CDKN2A mutation. In embodiments, the cancer has a SMAD4 mutation. In embodiments, the cancer has a MLL3 mutation. In embodiments, the cancer has a TGFBR2 mutation. In embodiments, the cancer has an ARID1A mutation. In embodiments, the cancer has a SF3B1 mutation. In embodiments, the cancer has a PALB2 mutation. In embodiments, the cancer has a NTRK mutation.

[0134] In embodiments of the methods described herein, the cancer is pancreatic cancer. In embodiments, the pancreatic cancer has a KRAS mutation, a TP53 mutation, or a combination thereof. In embodiments, the pancreatic cancer has a KRAS mutation. In embodiments, the pancreatic cancer has a TP53 mutation. In embodiments, the pancreatic cancer has a KRAS mutation and a TP53 mutation. In embodiments, the pancreatic cancer has a KRAS mutation, a TP53, mutation, BRCA1 mutation, a BRCA2 mutation, a CDKN2A mutation, a SMAD4 mutation, a MLL3 mutation, a TGFBR2 mutation, an ARID1A mutation, a SF3B1 mutation, a PALB2 mutation, a NTRK mutation, or a combination of two or more thereof. In embodiments, the pancreatic cancer has a BRCA mutation. In embodiments, the pancreatic cancer has a BRCA1 mutation. In embodiments, the pancreatic cancer has a BRCA2 mutation. In embodiments, the pancreatic cancer has a CDKN2A mutation. In embodiments, the pancreatic cancer has a SMAD4 mutation. In embodiments, the pancreatic cancer has a MLL3 mutation. In embodiments, the pancreatic cancer has a TGFBR2 mutation. In embodiments, the pancreatic cancer has an ARID1A mutation. In embodiments, the pancreatic cancer has a SF3B1 mutation.

In embodiments, the pancreatic cancer has a PALB2 mutation. In embodiments, the pancreatic cancer has a NTRK mutation.

[0135] In embodiments of the methods described herein, the cancer is pancreatic ductal adenocarcinoma. In embodiments, the pancreatic ductal adenocarcinoma has a KRAS mutation, a TP53 mutation, or a combination thereof. In embodiments, the pancreatic ductal adenocarcinoma has a KRAS mutation. In embodiments, the pancreatic ductal adenocarcinoma has a TP53 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a KRAS mutation and a TP53 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a KRAS mutation, a TP53, mutation, BRCA1 mutation, a BRCA2 mutation, a CDKN2A mutation, a SMAD4 mutation, a MLL3 mutation, a TGFBR2 mutation, an ARID1A mutation, a SF3B1 mutation, a PALB2 mutation, a NTRK mutation, or a combination of two or more thereof. In embodiments, the pancreatic ductal adenocarcinoma has a BRCA mutation. In embodiments, the pancreatic ductal adenocarcinoma has a BRCA1 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a BRCA2 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a CDKN2A mutation. In embodiments, the pancreatic ductal adenocarcinoma has a SMAD4 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a MLL3 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a TGFBR2 mutation. In embodiments, the pancreatic ductal adenocarcinoma has an ARID1A mutation. In embodiments, the pancreatic ductal adenocarcinoma has a SF3B1 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a PALB2 mutation. In embodiments, the pancreatic ductal adenocarcinoma has a NTRK mutation.

[0136] Dose and Dosing Regimens

[0137] The dosage and frequency (single or multiple doses) of the active agents (e.g., ATR kinase inhibitor, NAMPT inhibitor, PARP inhibitor) administered to a subject can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g. symptoms of cancer and severity of such symptoms), kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods described herein. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[0138] For any active agents described herein, the effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active agents that

are capable of achieving the methods described herein, as measured using the methods described herein or known in the art. As is known in the art, effective amounts of active agents for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0139] Dosages of the active agents may be varied depending upon the requirements of the patient. The dose administered to a patient should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the active agents. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the active agents effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0140] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active agents by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects.

[0141] In embodiments, the active agent is administered to a patient at an amount of about 0.1 mg/kg to about 500 mg/kg. In aspects, the ATR kinase inhibitor and/or NAMPT inhibitor is administered to a patient in an amount of about 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 200 mg/kg, or 300 mg/kg. It is understood that where the amount is referred to as "mg/kg," the amount is milligram per kilogram body weight of the subject being administered with the active agents. In aspects, the active agent is administered to a patient in an amount from about 1 mg to about 1,000 mg per day, as a single dose, or in a dose administered two or three times per day.

[0142] Pharmaceutical Compositions

[0143] Provided herein are pharmaceutical compositions comprising the active agents and a pharmaceutically acceptable excipient. The provided compositions are suitable for formulation and administration *in vitro* or *in vivo*. Suitable carriers and excipients and their formulations are described in Remington: The Science and Practice of Pharmacy, 21st Edition, David B. Troy, ed., Lippicott Williams & Wilkins (2005).

[0144] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the disclosure without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the disclosure. One of skill in the art will recognize that other pharmaceutical excipients are useful.

[0145] Solutions of the active compounds as free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

[0146] Pharmaceutical compositions can be delivered via intranasal or inhalable solutions or sprays, aerosols or inhalants. Nasal solutions can be aqueous solutions designed to be administered to the nasal passages in drops or sprays. Nasal solutions can be prepared so that they are similar in many respects to nasal secretions. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations and appropriate drug stabilizers, if required, may be included in the formulation. Various commercial nasal preparations are known and can include, for example, antibiotics and antihistamines.

[0147] Oral formulations can include excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills,

capsules, sustained release formulations or powders. In aspects, oral pharmaceutical compositions will comprise an inert diluent or edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 1 to about 75% of the weight of the unit. The amount of active compounds in such compositions is such that a suitable dosage can be obtained.

[0148] For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered and the liquid diluent first rendered isotonic with sufficient saline or glucose. Aqueous solutions, in particular, sterile aqueous media, are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. For example, one dosage could be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion.

[0149] Sterile injectable solutions can be prepared by incorporating the active compounds in the required amount in the appropriate solvent followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium. Vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient plus any additional desired ingredients, can be used to prepare sterile powders for reconstitution of sterile injectable solutions. The preparation of more, or highly, concentrated solutions for direct injection is also contemplated. DMSO can be used as solvent for extremely rapid penetration, delivering high concentrations of the active agents to a small area.

[0150] The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials. Thus, the composition can be in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. Thus, the compositions can be administered in a variety of unit dosage forms depending upon the method of administration. For example, unit dosage forms suitable for oral administration include, but are not limited to, powder, tablets, pills, capsules and lozenges.

[0151] Detection, Assay, and Diagnostic Methods

[0152] In embodiments, the increased level interferon or interferon pathway activity is determined by calculating the H-score for the increased level interferon or interferon pathway

activity. The H-score may be calculated for membrane interferon receptor. The H score may be calculated for tumor cells. Thus, the increased level interferon or interferon pathway activity may have an H-score. As used herein, an “H-score” or “Histoscore” is a numerical value determined by a semi-quantitative method commonly known for immunohistochemically evaluating proteins and protein expression in biological samples, such as tumor samples. The H-score may be calculated using the following formula: $[1 \times (\% \text{ cells } 1+) + 2 \times (\% \text{ cells } 2+) + 3 \times (\% \text{ cells } 3+)]$. According to this formula, the H-score is calculated by determining the percentage of cells having a given staining intensity level (i.e., level 1+, 2+, or 3+ from lowest to highest intensity level), weighting the percentage of cells having the given intensity level by multiplying the cell percentage by a factor (e.g., 1, 2, or 3) that gives more relative weight to cells with higher-intensity membrane staining, and summing the results to obtain a H-score. Commonly H-scores range from 0 to 300. Further description on the determination of H-scores in tumor cells can be found in Hirsch et al, *J Clin Oncol*, 21:3798-3807 (2003)) and John et al, *Oncogene* 28:S14-S23 (2009)). Immunohistochemistry or other methods known in the art may be used for detecting increased levels of interferon or interferon pathway activity. In embodiments, the H-score of a cancer cell is determined. In embodiments, the H-score of a non-cancer cell is determined. In embodiments, the non-cancer cell is a stromal cell. In embodiments, the H-score of a cancer cell and a non-cancer cell is determined.

[0153] In embodiments, the increased level interferon or interferon pathway activity has an H-score of at least 1 (e.g., 5, 10, 20, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 230, 240, 250, 260, 270, 280, 290, 300). In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 5. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 10. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 15. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 20. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 25. In embodiments, the elevated level of interferon or interferon pathway activity has an H-score of about 30. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 35. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 40. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 45. In embodiments, the increased level interferon or interferon pathway activity has an H-score of about 50.

[0154] In embodiments, methods described herein may include detecting a level of interferon

signaling pathway activity with a specific binding agent (e.g., an agent that binds to a protein or nucleic acid molecule). Exemplary binding agents include an antibody or a fragment thereof, a detectable protein or a fragment thereof, a nucleic acid molecule such as an oligonucleotide-polynucleotide comprising a sequence that is complementary to patient genomic DNA, mRNA or a cDNA produced from patient mRNA, or any combination thereof. In aspects, an antibody is labeled with detectable moiety, e.g., a fluorescent compound, an enzyme or functional fragment thereof, or a radioactive agent. In aspects, an antibody is detectably labeled by coupling it to a chemiluminescent compound. In aspects, the presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of chemical reaction. Non-limiting examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, thionin acridinium ester, imidazole, acridinium salt and oxalate ester.

[0155] In embodiments, a specific binding agent is an agent that has greater than 10-fold, preferably greater than 100-fold, and most preferably, greater than 1000-fold affinity for the target molecule as compared to another molecule. As the skilled artisan will appreciate the term specific is used to indicate that other biomolecules present in the sample do not significantly bind to the binding agent specific for the target molecule. In aspects, the level of binding to a biomolecule other than the target molecule results in a binding affinity which is at most only 10% or less, only 5% or less only 2% or less or only 1% or less of the affinity to the target molecule, respectively. A preferred specific binding agent will fulfill both the above minimum criteria for affinity as well as for specificity. For example, in embodiments an antibody has a binding affinity (e.g., K_d) in the low micromolar (10^{-6}), nanomolar (10^{-7} - 10^{-9}), with high affinity antibodies in the low nanomolar (10^{-9}) or pico molar (10^{-12}) range for its specific target ligand.

[0156] In embodiments, the present subject matter provides a composition comprising a binding agent, wherein the binding agent is attached to a solid support, (e.g., a strip, a polymer, a bead, a nanoparticle, a plate such as a multiwell plate, or an array such as a microarray). In embodiments relating to the use of a nucleic acid probe attached to a solid support (such as a microarray), a nucleic acid in a test sample may be amplified (e.g., using PCR) before or after the nucleic acid to be measured is hybridized with the probe. In aspects, reverse transcription polymerase chain reaction (RT-PCR) is used to detect mRNA levels. In aspects, a probe on a solid support is used, and mRNA (or a portion thereof) in a biological sample is converted to cDNA or partial cDNA and then the cDNA or partial cDNA is hybridized to a probe (e.g., on a microarray), hybridized to a probe and then amplified, or amplified and then hybridized to a probe. In aspects, a strip may be a nucleic acid-probe coated porous or non-porous solid support

strip comprising linking a nucleic acid probe to a carrier to prepare a conjugate and immobilizing the conjugate on a porous solid support. In aspects, the support or carrier comprises glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, and magnetite. In aspects, the carrier can be either soluble to some extent or insoluble for the purposes of the disclosure. In aspects, the support material may have any structural configuration so long as the coupled molecule is capable of binding to a binding agent (e.g., an antibody). In aspects, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. In aspects, the surface may be flat such as a plate (or a well within a multiwell plate), sheet, or test strip. The skilled artisan will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0157] In embodiments, a solid support comprises a polymer, to which an agent is chemically bound, immobilized, dispersed, or associated. In aspects, a polymer support may be, e.g., a network of polymers, and may be prepared in bead form (e.g., by suspension polymerization). In aspects, the location of active sites introduced into a polymer support depends on the type of polymer support. In aspects, in a swollen-gel-bead polymer support the active sites are distributed uniformly throughout the beads, whereas in a macroporous-bead polymer support they are predominantly on the internal surfaces of the macropores. In aspects, the solid support, e.g., a device, may contain an interferon signaling pathway activity binding agent.

[0158] In embodiments, detection is accomplished using an ELISA or Western blot format. In aspects, the binding agent comprises a nucleic acid (e.g., a probe or primers that are complementary for mRNA or cDNA), and the detecting step is accomplished using a polymerase chain reaction (PCR) or Northern blot format, or other means of detection. In aspects, a probe or primer is about 10-20, 15-25, 15-35, 15-25, 20-80, 50-100, or 10-100 nucleotides in length, e.g., about 10, 12, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, or 100 nucleotides in length or less than about 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, or 100 nucleotides in length.

[0159] As used herein, "assaying" means using an analytic procedure to qualitatively assess or quantitatively measure the presence or amount or the functional activity of a target entity. For example, assaying the level of a compound (such as a protein or an mRNA molecule) means using an analytic procedure (such as an in vitro procedure) to qualitatively assess or quantitatively measure the presence or amount of the compound.

[0160] In embodiments, the cells in a biological sample are lysed to release a protein or nucleic acid. Numerous methods for lysing cells and assessing protein and nucleic acid levels

are known in the art. In aspects, cells are physically lysed, such as by mechanical disruption, liquid homogenization, high frequency sound waves, freeze/thaw cycles, with a detergent, or manual grinding. Non-limiting examples of detergents include Tween 20, Triton X- 100, and sodium dodecyl sulfate. Non-limiting examples of assays for determining the level of a protein include HPLC, LC/MS, ELISA, immunoelectrophoresis, Western blot, immunohistochemistry, and radioimmuno assays. Non-limiting examples of assays for determining the level of an mRNA include Northern blotting, RT-PCR, RNA sequencing, and qRT-PCR.

[0161] In embodiments, the tumor sample can be obtained by a variety of procedures, such as surgical excision, aspiration or biopsy. In aspects, the tissue sample may be sectioned and assayed as a fresh specimen; alternatively, the tissue sample may be frozen for further sectioning. In aspects, the tissue sample is preserved by fixing and embedding in paraffin or the like.

[0162] In embodiments, once a suitable biological sample (e.g., tumor) has been obtained, it is analyzed to quantitate the expression level of each of the genes, e.g., interferon signaling pathway activity. In aspects, determining the expression level of a gene comprises detecting and quantifying RNA transcribed from that gene or a protein translated from such RNA. In aspects, the RNA includes mRNA transcribed from the gene, and/or specific spliced variants thereof and/or fragments of such mRNA and spliced variants.

[0163] In embodiments, raw expression values are normalized by performing quantile normalization relative to the reference distribution and subsequent log 10-transformation. In aspects, when the gene expression is detected using the nCounter® Analysis System marketed by Nanostring Technologies, the reference distribution is generated by pooling reported (i.e., raw) counts for the test sample and one or more control samples (preferably at least 2 samples, more preferably at least any of 4, 8 or 16 samples) after excluding values for technical (both positive and negative control) probes and without performing intermediate normalization relying on negative (background-adjusted) or positive (synthetic sequences spiked with known titrations).

[0164] In embodiments, oligonucleotides in kits are capable of specifically hybridizing to a target region of a polynucleotide, such as for example, an RNA transcript or cDNA generated therefrom. As used herein, specific hybridization means the oligonucleotide forms an anti-parallel double-stranded structure with the target region under certain hybridizing conditions, while failing to form such a structure with non-target regions when incubated with the polynucleotide under the same hybridizing conditions. The composition and length of each oligonucleotide in the kit will depend on the nature of the transcript containing the target region

as well as the type of assay to be performed with the oligonucleotide and is readily determined by the skilled artisan.

[0165] The disclosure provides a computer product comprise a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the methods described herein, including all embodiments thereof. In embodiments, the disclosure provides a computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of classifying a cancer in a patient by (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (b) comparing expression levels of the plurality of target genes to a control; and (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the disclosure provides a computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0166] The disclosure provides a system comprising computer hardware configured to perform operations comprising the methods described herein, including all embodiments thereof. In embodiments, the system comprising computer hardware configured to perform operations comprising the method of classifying a cancer in a patient by (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (b) comparing expression levels of the plurality of target

genes to a control; and (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the system comprising computer hardware configured to perform operations comprising the method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0167] The disclosure provides computer-implemented methods comprising the methods described herein, including all embodiments thereof. In embodiments, the disclosure provides computer-implemented methods comprising the method of classifying a cancer in a patient by (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (b) comparing expression levels of the plurality of target genes to a control; and (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor. In embodiments, the disclosure provides computer-implemented methods comprising the method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor and/or a NAMPT inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0168] In embodiments, the disclosure provides computer control systems that are programmed to implement the methods of the disclosure, including all embodiments thereof. A computer system can be programmed or otherwise configured to implements methods of the disclosure, including all embodiments thereof. The computer system can be integral to implementing methods provided herein, which may be otherwise difficult to perform in the absence of the computer system. The computer system can be an electronic device of a user or a computer system that is remotely located with respect to the electronic device. The electronic device can be a mobile electronic device. As an alternative, the computer system can be a

computer server.

[0169] The computer system includes a central processing unit (CPU, also "processor" and "computer processor"), which can be a single core or multi-core processor, or a plurality of processors for parallel processing. The computer system also includes memory or memory location (e.g., random-access memory, read-only memory, flash memory), electronic storage unit (e.g., hard disk), communication interface (e.g., network adapter) for communicating with one or more other systems, and peripheral devices, such as cache, other memory, data storage and/or electronic display adapters. The memory, storage unit, interface and peripheral devices are in communication with the CPU through a communication bus, such as a motherboard. The storage unit can be a data storage unit (or data repository) for storing data. The computer system can be operatively coupled to a computer network ("network") with the aid of the communication interface. The network can be the internet, an internet and/or extranet, or an intranet and/or extranet that is in communication with the internet. The network in some cases is a telecommunication and/or data network. The network can include one or more computer servers, which can enable distributed computing, such as cloud computing. The network, in some cases with the aid of the computer system, can implement a peer-to-peer network, which may enable devices coupled to the computer system to behave as a client or a server.

[0170] The CPU can execute a sequence of machine-readable instructions, which can be embodied in a program or software. The instructions may be stored in a memory location, such as the memory. The instructions can be directed to the CPU, which can subsequently program or otherwise configure the CPU to implement methods of the present disclosure. Examples of operations performed by the CPU can include fetch, decode, execute, and writeback. The CPU can be part of a circuit, such as an integrated circuit. One or more other components of the system can be included in the circuit. In some cases, the circuit is an application specific integrated circuit (ASIC).

[0171] The storage unit can store files, such as drivers, libraries and saved programs. The storage unit can store user data, e.g., user preferences and user programs. The computer system in some cases can include one or more additional data storage units that are external to the computer system, such as located on a remote server that is in communication with the computer system through an intranet or the internet.

[0172] The computer system can communicate with one or more remote computer systems through the network. For instance, the computer system can communicate with a remote computer system of a user (e.g., patient, healthcare provider, or service provider). Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's

(e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system via the network.

[0173] Methods as described herein can be implemented by way of machine (e.g., computer processor) executable code stored on an electronic storage location of the computer system, such as, for example, on the memory or electronic storage unit. The memory can be part of a database. The machine executable or machine readable code can be provided in the form of software. During use, the code can be executed by the processor. In embodiments, the code can be retrieved from the storage unit and stored on the memory for ready access by the processor. In embodiments, the electronic storage unit can be precluded, and machine-executable instructions are stored on memory.

[0174] The code can be pre-compiled and configured for use with a machine having a processor adapted to execute the code, or can be compiled during runtime. The code can be supplied in a programming language that can be selected to enable the code to execute in a precompiled or as-compiled fashion.

[0175] Aspects of the systems and methods provided herein, such as the computer system, can be embodied in programming. Various aspects of the technology may be thought of as "products" or "articles of manufacture" typically in the form of machine (or processor) executable code and/or associated data that is carried on or embodied in a type of machine readable medium. Machine-executable code can be stored on an electronic storage unit, such as memory (e.g., read-only memory, random-access memory, flash memory) or a hard disk.

[0176] "Storage" media can include any or all of the tangible memory of the computers, processors or the like, or associated modules thereof, such as various semiconductor memories, tape drives, disk drives and the like, which may provide non-transitory storage at any time for the software programming. All or portions of the software may at times be communicated through the Internet or various other telecommunication networks. Such communications, for example, may enable loading of the software from one computer or processor into another, for example, from a management server or host computer into the computer platform of an application server. Thus, another type of media that may bear the software elements includes optical, electrical and electromagnetic waves, such as used across physical interfaces between local devices, through wired and optical landline networks and over various air-links. The physical elements that carry such waves, such as wired or wireless links, optical links or the like, also may be considered as media bearing the software. As used herein, unless restricted to non-transitory, tangible "storage" media, terms such as computer or machine "readable medium"

refer to any medium that participates in providing instructions to a processor for execution.

[0177] A machine readable medium, such as computer-executable code, may take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as may be used to implement the databases, etc. Volatile storage media include dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media may take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer may read programming code and/or data. Many of these forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution.

[0178] The computer system can include or be in communication with an electronic display that comprises a user interface (UI) for providing, for example, genetic information, such as an identification of disease-causing alleles in single individuals or groups of individuals. Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface (or web interface).

[0179] Methods and systems of the present disclosure can be implemented by way of one or more algorithms. An algorithm can be implemented by way of software upon execution by the central processing unit. The algorithm can, for example, prioritize a set of two or more target genes in RNA based on an expression level of the target genes in the RNA and a control.

[0180] The medium, method, and system disclosed herein comprise one or more softwares, servers, and database modules, or use of the same. In view of the disclosure provided herein, software modules may be created by techniques known to those of skill in the art using machines, software, and languages known to the art. The software modules disclosed herein may be implemented in a multitude of ways. In embodiments, a software module comprises a file, a section of code, a programming feature, a programming structure, or combinations thereof. A

software module may comprise a plurality of files, a plurality of sections of code, a plurality of programming features, a plurality of programming structures, or combinations thereof. By way of non-limiting examples, the one or more software modules comprises a web application, a mobile application, and/or a standalone application. Software modules may be in one computer program or application. Software modules may be in more than one computer program or application. Software modules may be hosted on one machine. Software modules may be hosted on more than one machine. Software modules may be hosted on cloud computing platforms. Software modules may be hosted on one or more machines in one location. Software modules may be hosted on one or more machines in more than one location.

[0181] The medium, method, and system disclosed herein comprise one or more databases, such as the phenotypic and/or genotypic-associated database described herein, or use of the same. In embodiments, the database are used for expression levels of a plurality of target genes. Those of skill in the art will recognize that many databases are suitable for storage and retrieval of information. Suitable databases include, by way of non-limiting examples, relational databases, non-relational databases, feature oriented databases, feature databases, entity-relationship model databases, associative databases, and XML databases. In embodiments, a database is internet-based. In embodiments, a database is web-based. In embodiments, a database is cloud computing-based. A database may be based on one or more local computer storage devices.

[0182] The term “anticancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In embodiments, an anti-cancer agent is a chemotherapeutic. In embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin), triazenes (decabazine)),

anti-metabolites (*e.g.*, 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, fluorouracil, floxouridine, cytarabine), purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.*, doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin), anthracenedione (*e.g.*, mitoxantrone), substituted urea (*e.g.*, hydroxyurea), methyl hydrazine derivative (*e.g.*, procarbazine), adrenocortical suppressant (*e.g.*, mitotane, aminoglutethimide), epipodophyllotoxins (*e.g.*, etoposide), antibiotics (*e.g.*, daunorubicin, doxorubicin, bleomycin), enzymes (*e.g.*, L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (*e.g.* U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (*e.g.*, rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib, geldanamycin, 17-N-allylamino-17-demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflata; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole;

collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin;
 crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A;
 cyclopentantraquinones; cycloplatan; cypemycin; cytarabine ocfosfate; cytolytic factor;
 cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone;
 dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine;
 dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron;
 doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine;
 edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue;
 estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane;
 fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone;
 fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine;
 gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors;
 gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide;
 hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat;
 imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor
 inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin;
 ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron;
 jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim;
 lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon;
 leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine
 analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7;
 lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan;
 lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat;
 masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril;
 merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine;
 mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues;
 mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene;
 molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid
 A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple
 tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial
 cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip;
 naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic
 acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide
 antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone;
 ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin;

oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene;
 parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin;
 pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate;
 phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A;
 placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-
 triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone;
 prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C
 inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine
 nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin
 polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein
 transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re
 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide;
 roquinimex; rubiginone B1; ruboxyl; safinol; saintopin; SarCNU; sarcophytol A;
 sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense
 oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain
 antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate;
 solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine;
 splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors;
 stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide
 antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine;
 tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium;
 telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine;
 thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin
 receptor agonist; thymotrigan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine;
 titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors;
 tretinoin; triacetyluridine; tricinibine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine
 kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth
 inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system,
 erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine;
 vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, adriamycin,
 dactinomycin, bleomycin, vinblastine, cisplatin, acivicin; aclarubicin; acodazole hydrochloride;
 acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate;
 aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine;
 azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide
 dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan;

cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin I1 (including recombinant interleukin II, or rIL₂), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; tricirbine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-

XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZT-1027), LS-4559-P (Pharmacia, i.e. LS-4577), LS-4578 (Pharmacia, i.e. LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyeleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride,

aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbitux™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0183] The singular terms "a", "an", and "the" include the plural reference unless the context clearly indicates otherwise.

[0184] The term “about” means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, the term “about” means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about means the specified value.

[0185] Throughout this specification, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other

elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that no other elements are optional and may or may not be present depending upon whether or not they affect the activity or action of the listed elements.

[0186] Embodiments P1 to P41

[0187] Embodiment P1. A method of treating cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of an ATR kinase inhibitor; wherein the cancer has an increased level of interferon or interferon signaling pathway activity.

[0188] Embodiment P2. The method of Embodiment P1, wherein the cancer has an increased level of interferon, and wherein the interferon is an interferon protein or an interferon RNA.

[0189] Embodiment P3. The method of Embodiment P1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof.

[0190] Embodiment P4. The method of Embodiment P3, wherein the interferon pathway protein or the interferon pathway RNA is STAT1, MX1, or a combination thereof.

[0191] Embodiment P5. A method of treating cancer in a patient in need thereof, the method comprising: (i) determining the level of interferon or interferon signaling pathway activity in a sample obtained from a patient; and (ii) administering to the patient a therapeutically effective amount of an ATR kinase inhibitor.

[0192] Embodiment P6. The method of Embodiment P5, wherein the method comprises determining the level of interferon in the sample.

[0193] Embodiment P7. The method of Embodiment P6, wherein the interferon is an interferon protein or an interferon RNA.

[0194] Embodiment P8. The method of any one of Embodiments P5 to P7, wherein the method comprises determining the level of interferon signaling pathway activity in the sample.

[0195] Embodiment P9. The method of Embodiment P8, wherein determining the level of interferon signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for STAT1, STAT2, MX1, MX2, IFIT1, IFI44,

IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof.

[0196] Embodiment P10. The method of Embodiment P9, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for STAT1.

[0197] Embodiment P11. The method of Embodiment P9 or P10, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for MX1.

[0198] Embodiment P12. The method of any one of Embodiments P1 to P11, wherein the interferon is Type 1 interferon.

[0199] Embodiment P13. The method of Embodiment P12, wherein the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof.

[0200] Embodiment P14. The method of any one of Embodiments P1 to P13, wherein the cancer has an increased level of interferon or interferon signaling pathway activity relative to a control.

[0201] Embodiment P15. The method of any one of Embodiments P1 to P14, wherein the cancer has a KRAS mutation, a TP53 mutation, or a combination thereof.

[0202] Embodiment P16. The method of any one of Embodiments P1 to P15, wherein the cancer is pancreatic cancer.

[0203] Embodiment P17. The method of Embodiment P16, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0204] Embodiment P18. The method of any one of Embodiments P1 to P17, wherein the ATR kinase inhibitor is berzosertib, VE-821, ceralasertib, schisandrin B, NU6027, dactolisib, AZ20, caffeine, or wortmannin.

[0205] Embodiment P19. The method of Embodiment P18, wherein the ATR kinase inhibitor is berzosertib.

[0206] Embodiment P20. The method of any one of Embodiments P1 to P19, further comprising administering to the patient a therapeutically effective amount of a PARP inhibitor.

[0207] Embodiment P21. The method of Embodiment P20, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, CEP 9722, or E7016.

[0208] Embodiment P22. The method of Embodiment P21, wherein the PARP inhibitor is

olaparib.

[0209] Embodiment P23. A method of classifying a cancer in a patient, the method comprising: (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (d) comparing expression levels of the plurality of target genes to a control; and (e) classifying the cancer as responsive to treatment with an ATR kinase inhibitor.

[0210] Embodiment P24. The method of Embodiment P23, wherein the cancer is classified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to the control.

[0211] Embodiment P25. A method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0212] Embodiment P26. The method of Embodiment P25, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to a control.

[0213] Embodiment P27. The method of any one of Embodiments P23 to P26, wherein further comprising identifying the presence of a type 1 interferon-stimulated gene signature, pCHEK_{S345}, or a combination thereof in a sample obtained from the cancer patient.

[0214] Embodiment P28. The method of Embodiment P27, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

[0215] Embodiment P29. The method of any one of Embodiments P23 to P28, wherein the plurality of target genes comprises STAT1 and MX1.

[0216] Embodiment P30. The method of any one of Embodiments P23 to P29, wherein the plurality of target genes comprise at least 3 genes.

[0217] Embodiment P31. The method of Embodiment P30, wherein the plurality of target

genes comprise at least 4 genes.

[0218] Embodiment P32. The method of any one of Embodiments P23 to P31, wherein measuring does not comprise a whole transcriptome measurement.

[0219] Embodiment P33. The method of any one of Embodiments P23 to P32, wherein the cancer is pancreatic cancer.

[0220] Embodiment P34. The method of Embodiment P33, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0221] Embodiment P35. The method of any one of Embodiments P23 to P34, further comprising administering to the patient an effective amount of ATR kinase inhibitor.

[0222] Embodiment P36. The method of Embodiment P35, wherein the ATR kinase inhibitor is berzosertib, VE-821, ceralasertib, schisandrin B, NU6027, dactolisib, AZ20, caffeine, wortmannin, or an analog of any one of the foregoing.

[0223] Embodiment P37. The method of any one of Embodiments P23 to P36, further comprising administering to the patient an effective amount of a PARP inhibitor

[0224] Embodiment P38. The method of Embodiment P37, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, CEP 9722, or E7016.

[0225] Embodiment P39. A computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of any one of Embodiments P23 to P34.

[0226] Embodiment P40. A system comprising computer hardware configured to perform operations comprising the method of any one of Embodiments P23 to P34.

[0227] Embodiment P41. A computer-implemented method comprising the method of any one of Embodiments P23 to P34.

[0228] Embodiments N1 to N39

[0229] Embodiment N1. A method of treating cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of a NAMPT inhibitor; wherein the cancer has an increased level of interferon or interferon signaling pathway activity.

[0230] Embodiment N2. The method of Embodiment N1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group

consisting of PARP9, PARP10, PARP14, and a combination of two or more thereof.

[0231] Embodiment N3. The method of Embodiment N2, wherein interferon pathway protein or the interferon pathway RNA is PARP9.

[0232] Embodiment N4. Embodiment N3. The method of Embodiment N2 or N3, wherein interferon pathway protein or the interferon pathway RNA is PARP10.

[0233] Embodiment N5. The method of any one of Embodiments N2 to N4, wherein interferon pathway protein or the interferon pathway RNA is PARP14.

[0234] Embodiment N6. The method of Embodiment N1, wherein the cancer has an increased level of interferon.

[0235] Embodiment N7. A method of treating cancer in a patient in need thereof, the method comprising: (i) determining the level of interferon or interferon signaling pathway activity in a sample obtained from a patient; and (ii) administering to the patient a therapeutically effective amount of a NAMPT inhibitor.

[0236] Embodiment N8. The method of Embodiment N7, wherein the method comprises determining the level of interferon signaling pathway activity in the sample.

[0237] Embodiment N9. The method of Embodiment N8, wherein determining the level of interferon signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, or a combination of two or more thereof.

[0238] Embodiment N10. The method of Embodiment N9, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP9.

[0239] Embodiment N11. The method of Embodiment N9 or N10, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP10.

[0240] Embodiment N12. The method of Embodiment N9, N10, or N11, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP14.

[0241] Embodiment N13. The method of any one of Embodiments N1 to N12, wherein the interferon is Type 1 interferon.

[0242] Embodiment N14. The method of Embodiment N13, wherein the Type 1 interferon is

interferon-alpha, interferon-beta, or a combination thereof.

[0243] Embodiment N15. The method of any one of Embodiments N1 to N14, wherein the cancer has an increased level of interferon or interferon signaling pathway activity relative to a control.

[0244] Embodiment N16. The method of any one of Embodiments N1 to N15, wherein the cancer has a BRCA mutation, a KRAS mutation, a TP53 mutation, or a combination thereof.

[0245] Embodiment N17. The method of any one of Embodiments N1 to N16, wherein the cancer is pancreatic cancer.

[0246] Embodiment N18. The method of Embodiment N17, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0247] Embodiment N19. The method of any one of Embodiments N1 to N18, wherein the NAMPT inhibitor is daporinad, GNE-617, GNE-618, KPT-9274, CHS-828, GPP 78, STF 31, SBI-797812, LSN3154567, OT-82, CB30865, CB300919, or a combination of two or more of the foregoing.

[0248] Embodiment N20. The method of Embodiment N19, wherein the NAMPT inhibitor is daporinad or LSN3154567.

[0249] Embodiment N21. A method of classifying a cancer in a patient, the method comprising: (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, and PARP14; (d) comparing expression levels of the plurality of target genes to a control; and (e) classifying the cancer as responsive to treatment with a NAMPT inhibitor.

[0250] Embodiment N22. The method of Embodiment N21, wherein the cancer is classified as responsive to treatment with the NAMPT inhibitor when the expression levels of the plurality of target genes are increased relative to the control.

[0251] Embodiment N23. A method of identifying a cancer patient responsive to treatment with a NAMPT inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, and PARP14.

[0252] Embodiment N24. The method of Embodiment N23, wherein the patient is identified as responsive to treatment with the NAMPT inhibitor when the expression levels of the plurality of target genes are increased relative to a control.

[0253] Embodiment N25. The method of any one of Embodiments N21 to N24, further comprising identifying the presence of a type 1 interferon-stimulated gene signature, pCHEK_{S345}, or a combination thereof in a sample obtained from the cancer patient.

[0254] Embodiment N26. The method of Embodiment N25, wherein the patient is identified as responsive to treatment with the NAMPT inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

[0255] Embodiment N27. The method of any one of Embodiments N21 to N26, wherein the plurality of target genes comprise PARP9 and PARP10.

[0256] Embodiment N28. The method of any one of Embodiments N21 to N26, wherein the plurality of target genes comprise PARP9 and PARP14.

[0257] Embodiment N29. The method of any one of Embodiments N21 to N26, wherein the plurality of target genes comprise PARP10 and PARP14.

[0258] Embodiment N30. The method of any one of Embodiments N21 to N26, wherein the plurality of target genes comprise PARP9, PARP10, and PARP14.

[0259] Embodiment N31. The method of any one of Embodiments N21 to N30, wherein the cancer is pancreatic cancer.

[0260] Embodiment N32. The method of Embodiment N31, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0261] Embodiment N33. The method of any one of Embodiments N21 to N32, further comprising administering to the patient an effective amount of a NAMPT inhibitor.

[0262] Embodiment N34. The method of Embodiment N33, wherein the NAMPT inhibitor is daporinad, GNE-617, GNE-618, KPT-9274, CHS-828, GPP 78, STF 31, SBI-797812, LSN3154567, OT-82, CB30865, CB300919, or a combination of two or more of the foregoing.

[0263] Embodiment N35. The method of Embodiment N33, wherein the NAMPT inhibitor is daporinad or LSN3154567.

[0264] Embodiment N36. The method of any one of Embodiments N1-N20 and N33-N35, further comprising administering to the patient an effective amount of interferon-beta.

[0265] Embodiment N37. A computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of any one of Embodiments N21 to N32.

[0266] Embodiment N38. A system comprising computer hardware configured to perform operations comprising the method of any one of Embodiments N23 to N34.

[0267] Embodiment N39. A computer-implemented method comprising the method of any one of Embodiments N21 to N32.

[0268] Embodiments 1 to 79.

[0269] Embodiment 1. A method of treating cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof; wherein the cancer has an increased level of interferon or interferon signaling pathway activity.

[0270] Embodiment 2. The method of claim 1, comprising administering to the patient an effective amount of an ATR kinase inhibitor.

[0271] Embodiment 3. The method of claim 1, comprising administering to the patient an effective amount of an NAMPT inhibitor.

[0272] Embodiment 4. The method of claim 1, comprising administering to the patient an effective amount of an ATR kinase inhibitor and an NAMPT inhibitor.

[0273] Embodiment 5. The method of any one of claims 1 to 4, wherein the cancer has an increased level of interferon, and wherein the interferon is an interferon protein or an interferon RNA.

[0274] Embodiment 6. The method of any one of claims 1 to 4, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof.

[0275] Embodiment 7. The method of any one of claims 1 to 4, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof.

[0276] Embodiment 8. The method of claim 7, wherein the interferon pathway protein or the interferon pathway RNA is STAT1, MX1, or a combination thereof.

[0277] Embodiment 9. The method of any one of claims 1 to 4, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, and a combination of two or more thereof.

[0278] Embodiment 10. The method of any one of claims 1 to 4, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, and a combination of two or more thereof.

[0279] Embodiment 11. A method of treating cancer in a patient in need thereof, the method comprising determining the level of interferon or interferon signaling pathway activity in a sample obtained from a patient; and administering to the patient a therapeutically effective amount of an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof.

[0280] Embodiment 12. The method of claim 11, comprising administering to the patient an effective amount of the ATR kinase inhibitor.

[0281] Embodiment 13. The method of claim 11, comprising administering to the patient the effective amount of an NAMPT inhibitor.

[0282] Embodiment 14. The method of claim 11, comprising administering to the patient the effective amount of an ATR kinase inhibitor and an NAMPT inhibitor.

[0283] Embodiment 15. The method of any one of claims 11 to 14, wherein the method comprises determining the level of interferon in the sample.

[0284] Embodiment 16. The method of any one of claims 11 to 14, wherein the method comprises determining the level of interferon in the sample.

[0285] Embodiment 17. The method of any one of claims 11 to 14, wherein the method comprises determining the level of interferon signaling pathway activity in the sample.

[0286] Embodiment 18. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof.

[0287] Embodiment 19. The method of claim 17, wherein determining the level of interferon

signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof.

[0288] Embodiment 20. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for STAT1.

[0289] Embodiment 21. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for MX1.

[0290] Embodiment 22. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, or a combination of two or more thereof.

[0291] Embodiment 23. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, STAT1, MX1, or a combination of two or more thereof.

[0292] Embodiment 24. The method of any one of claims 1 to 23, wherein the interferon is Type 1 interferon.

[0293] Embodiment 25. The method of claim 24, wherein the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof.

[0294] Embodiment 26. The method of any one of claims 1 to 25, wherein the cancer has an increased level of interferon or interferon signaling pathway activity relative to a control.

[0295] Embodiment 27. The method of any one of claims 1 to 26, wherein the cancer has a BRCA mutation, a KRAS mutation, a TP53 mutation, or a combination thereof.

[0296] Embodiment 28. The method of any one of claims 1 to 27, wherein the cancer is pancreatic cancer.

[0297] Embodiment 29. The method of claim 28, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0298] Embodiment 30. The method of any one of claims 1, 2, 4-12, and 14-29, wherein the ATR kinase inhibitor is berzosertib, 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-

dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol, ceralasertib, schisandrin B, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine, dactolisib, (R)-4-(2-(1H-indol-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine, caffeine, wortmannin, or 2-[(3R)-3-methyl-4-morpholinyl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine.

[0299] Embodiment 31. The method of claim 30, wherein the ATR kinase inhibitor is berzosertib.

[0300] Embodiment 32. The method of any one of claims 1, 3-11, and 13-29, wherein the NAMPT inhibitor is daporinad, 4-[5-methyl-4-[(4-methylphenyl)sulfonyl]methyl]-2-oxazolyl]-N-(3-pyridinylmethyl)benzamide, N-(4-((3,5-difluorophenyl)sulfonyl)benzyl)imidazo[1,2-a]pyridine-6-carboxamide, N-[4-[[3-(trifluoromethyl)phenyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, (1Z,2E)-3-(6-aminopyridin-2-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylimidic acid, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N''-4-pyridinyl-guanidine, N-[1,1'-biphenyl]-2-yl-4-(3-pyridinyl)-1H-1,2,3-triazole-1-octanamide, 4-[[[4-(1,1-dimethylethyl)phenyl]sulfonyl]amino]-methyl]N-3-pyridinyl-benzamide, 1-(4-(((1R,5S)-8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-ylmethyl)urea, 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinolinyl]-1-propanesulfonamide, N-(3-(1H-pyrazol-4-yl)propyl)-3-((4-fluorophenyl)ethynyl)-4-(pyridin-4-yl)benzamide, 4-(((7-bromo-2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl)(prop-2-yn-1-yl)amino)-N-(pyridin-3-ylmethyl)benzamide, 4-(((7-chloro-3,4-dihydro-3-methyl-2-((4-methyl-1-piperazinyl)methyl)-4-oxo-6-quinazolinyl)methyl)-2-propyn-1-ylamino)-N-(3-pyridinylmethyl)-benzamide, or a combination of two or more of the foregoing.

[0301] Embodiment 33. The method of claim 32, wherein the NAMPT inhibitor is daporinad or 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinolinyl]-1-propanesulfonamide.

[0302] Embodiment 34. The method of any one of claims 1 to 33, further comprising administering to the patient a therapeutically effective amount of a PARP inhibitor.

[0303] Embodiment 35. The method of claim 34, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, 11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)dione, or 10-((4-Hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-3(2H)one.

[0304] Embodiment 36. The method of claim 35, wherein the PARP inhibitor is olaparib.

[0305] Embodiment 37. A method of classifying a cancer in a patient, the method comprising: (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (b) comparing expression levels of the plurality of target genes to a control; and (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor.

[0306] Embodiment 38. The method of claim 37, wherein the cancer is classified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to the control.

[0307] Embodiment 39. A method of classifying a cancer in a patient, the method comprising: (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2; (b) comparing expression levels of the plurality of target genes to a control; and (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof.

[0308] Embodiment 40. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0309] Embodiment 41. The method of any one of claims 37 to 40, wherein the plurality of target genes comprise STAT1 and MX1.

[0310] Embodiment 42. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, and PARP14.

[0311] Embodiment 43. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1.

[0312] Embodiment 44. The method of any one of claims 39 to 43, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof when the expression levels of the plurality of target genes are increased relative to the control.

[0313] Embodiment 45. The method of claim 44, comprising classifying the cancer as responsive to treatment with a NAMPT inhibitor.

[0314] Embodiment 46. The method of claim 44, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor.

[0315] Embodiment 47. The method of claim 44, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor and a NAMPT inhibitor.

[0316] Embodiment 48. A method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0317] Embodiment 49. The method of claim 48, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to a control.

[0318] Embodiment 50. A method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0319] Embodiment 51. The method of claim 50, wherein the plurality of target genes comprise at least 2 genes from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

[0320] Embodiment 52. The method of any one of claims 48 to 51, wherein the plurality of target genes comprise STAT1 and MX1.

[0321] Embodiment 53. The method of claim 50, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, and PARP14.

[0322] Embodiment 54. The method of claim 50, wherein the plurality of target genes comprises PARP9, PARP10, PARP14, STAT1, and MX1.

[0323] Embodiment 55. The method of any one of claims 50 to 54, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof when the expression levels of the plurality of target genes are increased relative to a control.

[0324] Embodiment 56. The method of any one of claims 48 to 55, further comprising identifying the presence of a type 1 interferon-stimulated gene signature, pCHEK_{S345}, or a combination thereof in a sample obtained from the cancer patient.

[0325] Embodiment 57. The method of claim 55, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

[0326] Embodiment 58. The method of claim 55, wherein the patient is identified as responsive to treatment with a NAMPT inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

[0327] Embodiment 59. The method of any one of claims 37 to 58, wherein the plurality of target genes comprise at least 3 genes.

[0328] Embodiment 60. The method of claim 59, wherein the plurality of target genes comprise at least 4 genes.

[0329] Embodiment 61. The method of any one of claims 37 to 60, wherein measuring does not comprise a whole transcriptome measurement.

[0330] Embodiment 62. The method of any one of claims 37 to 61, wherein the cancer has a BRCA mutation, a KRAS mutation, a TP53 mutation, or a combination thereof.

[0331] Embodiment 63. The method of any one of claims 37 to 61, wherein the cancer is pancreatic cancer.

[0332] Embodiment 64. The method of claim 63, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

[0333] Embodiment 65. The method of any one of claims 37 to 64, further comprising administering to the patient an effective amount of ATR kinase inhibitor.

[0334] Embodiment 66. The method of claim 65, wherein the ATR kinase inhibitor is berzosertib, 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol, ceralasertib, schisandrin B, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine, dactolisib, (R)-4-(2-(1H-indol-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine, caffeine,

wortmannin, or 2-[(3R)-3-methyl-4-morpholinyl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine.

[0335] Embodiment 67. The method of claim 65, wherein the ATR kinase inhibitor is berzosertib.

[0336] Embodiment 68. The method of any one of claims 37 to 67, further comprising administering to the patient an effective amount of a NAMPT inhibitor.

[0337] Embodiment 69. The method of claim 68, wherein the NAMPT inhibitor is daporinad, 4-[5-methyl-4-[[[(4-methylphenyl)sulfonyl]methyl]-2-oxazolyl]-N-(3-pyridinylmethyl)benzamide, N-(4-((3,5-difluorophenyl)sulfonyl)benzyl)imidazo[1,2-a]pyridine-6-carboxamide, N-[[4-[[3-(trifluoromethyl)phenyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, (1Z,2E)-3-(6-aminopyridin-2-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylimidic acid, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N''-4-pyridinyl-guanidine, N-[1,1'-biphenyl]-2-yl-4-(3-pyridinyl)-1H-1,2,3-triazole-1-octanamide, 4-[[[[4-(1,1-dimethylethyl)phenyl]sulfonyl]amino]methyl] N-3-pyridinyl-benzamide, 1-(4-(((1R,5S)-8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-ylmethyl)urea, 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide, N-(3-(1H-pyrazol-4-yl)propyl)-3-((4-fluorophenyl)ethynyl)-4-(pyridin-4-yl)benzamide, 4-(((7-bromo-2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl)(prop-2-yn-1-yl)amino)-N-(pyridin-3-ylmethyl)benzamide, 4-(((7-chloro-3,4-dihydro-3-methyl-2-((4-methyl-1-piperazinyl)methyl)-4-oxo-6-quinazoliny)methyl)-2-propyn-1-ylamino)-N-(3-pyridinylmethyl)-benzamide, or a combination of two or more of the foregoing.

[0338] Embodiment 70. The method of claim 68, wherein the NAMPT inhibitor is daporinad or 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide.

[0339] Embodiment 71. The method of any one of claims 37 to 70, further comprising administering to the patient a therapeutically effective amount of a PARP inhibitor.

[0340] Embodiment 72. The method of claim 71, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, 11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)dione, or 10-((4-hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-3(2H)one.

[0341] Embodiment 73. The method of claim 71, wherein the PARP inhibitor is olaparib.

[0342] Embodiment 74. A computer program product comprising a machine-readable medium

storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of any one of claims 11 to 73.

[0343] Embodiment 75. A computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of any one of claims 37 to 64.

[0344] Embodiment 76. A system comprising computer hardware configured to perform operations comprising the method of any one of claims 11 to 73.

[0345] Embodiment 77. A system comprising computer hardware configured to perform operations comprising the method of any one of claims 37 to 64.

[0346] Embodiment 78. A computer-implemented method comprising the method of any one of claims 11 to 73.

[0347] Embodiment 79. A computer-implemented method comprising the method of any one of claims 37 to 64

EXAMPLES

[0348] Example 1: IFN signaling in PDAC tumors

[0349] Amongst metabolites critical for cancer cell proliferation, nucleotides are particularly important as they are required for a variety of biological processes including nucleic acid (RNA and DNA) biosynthesis. A balanced and sufficient supply of deoxyribonucleotide (dNTP) pools is essential to sustain pancreatic ductal adenocarcinoma (PDAC) cell proliferation and is maintained by the coordinated activity of *de novo* biosynthetic and salvage pathways.

[0350] The KRAS oncogene is an established positive regulator of *de novo* nucleotide biosynthesis and pharmacological inhibition of pyrimidine biosynthesis using dihydroorotate dehydrogenase (DHODH) inhibitors has been proposed as a treatment strategy for PDAC (Ref. 19). Additionally, inhibition of lysosome function has been shown to restrict dNTP pools in PDAC cells by limiting aspartate availability, which is critically required for the *de novo* synthesis of both pyrimidine and purine nucleotides (Ref. 20). To resolve the DNA replication stress that results from dNTP insufficiency, cancer cells rely on the replication stress response signaling pathway (Ref. 21). The proximal mediator of this response, ataxia telangiectasia and Rad3-related protein (ATR) initiates a signaling cascade which slows DNA replication by suppressing origin firing, promotes replication fork stabilization and activates the G2/M

checkpoint (Ref. 22).

[0351] Importantly, ATR has been shown to promote nucleotide biosynthesis and salvage via activation of rate-limiting enzymes in these pathways: ribonucleotide reductase (RNR) and deoxycytidine kinase (dCK) (Ref. 23). ATR is recruited and activated by replication protein A (RPA)-bound single stranded DNA, which can arise at stalled replication forks and also occurs following DNA end resection during the early stages of homologous recombination for DNA double strand break repair. CHEK1, an established substrate of ATR, serves to inhibit cyclin-dependent kinase (CDK) activity through the inhibition of the phosphatase CDC25A. ATR inhibitors berzosertib and ceralasertib are currently being evaluated in clinical trials in combination with chemotherapy, DNA damaging therapy (PARP inhibitors) or immunotherapy (immune checkpoint blockade) for multiple cancer types including PDAC (Ref. 22).

Additionally, ATR inhibitors may be particularly effective for the treatment of tumor cells with oncogenic signaling driven by activation KRAS mutations and mutant TP53. ATR has been shown to mitigate DNA damage triggered by mutant RAS activation in tumor cells (Refs. 24-25). Mutant TP53 has been implicated in similar phenotypes (Ref. 26). The links between other hallmarks of PDAC, including cytokine signaling, and the replication stress response pathway remain unexplored. Despite the marked enrichment of interferon (IFN) signaling in PDAC tumors, its impact on tumor cell signaling, metabolism and response to therapy is poorly understood.

[0352] In the experiments described herein, it was determined that PDAC primary patient-, patient-derived xenograft- and cell line xenograft-tumors exhibit a type I IFN response signature (**FIG. 2**). Data demonstrated that a transcriptional type I interferon (IFN) response signature is enriched in The Cancer Genome Atlas (TCGA) PDAC specimens with a range of expression observed among individual samples. Consistently, data showed that IFN signaling is detectable in a subset of PDAC patient-derived and cell line xenografts. In these models, a requirement for PDAC cell cGAS/STING pathway activity was defined for tumor IFN signaling.

[0353] Data demonstrated that constitutive type I IFN signaling in xenograft tumors was dependent on PDAC cell cGAS/STING pathway functionality. In vitro, IFN signaling triggers replication stress and alters nucleotide metabolism in PDAC cells. Using a chemical genomics high-throughput screening approach, it was determined that type I IFN signaling renders PDAC cells addicted to replication stress response signaling. Experiments showed that inhibiting this pathway at the level of ATR induces catastrophic DNA damage and cell death in cells exposed to IFN. PARP inhibitors further sensitize PDAC cells to ATR inhibition together with type I IFN signaling. Collectively, this work begins to define the crosstalk between cytokine signaling,

stress response networks and metabolism in PDAC and identifies a targetable, tumor cell collateral dependency resulting from STING-driven IFN signaling.

[0354] IFN signaling is constitutive in a subset of PDAC tumors

[0355] Type I IFNs are produced by epithelial and immune cells and have been linked to the regulation of cancer cell proliferation, apoptosis and immune-recognition via the transcriptional regulation of effector IFN-stimulated genes (Ref. 8). According to the TCGA dataset, pancreatic adenocarcinoma ranks among cancers exhibiting the greatest increase in transcript enrichment of a previously defined IFN response signature relative to organ specific normal tissue controls (normalized for CD4-positive cell infiltration as previously described; **FIGS. 1A-1B**) (Refs. 27-28). Furthermore, a subset of PDAC tumors in the TCGA collection exhibit a particularly high enrichment of genes contained within this signature with a correlation observed amongst these genes (**FIG. 3A**). In contrast, no such correlation was observed in the PDAC CCLE cell line RNAseq dataset derived from *in vitro* samples (**FIG. 1C**). Consistent with TCGA mRNA expression data, a subset of surgical PDAC specimens exhibit high levels of STAT1 protein notably localized to the tumor cell compartment (**FIG. 3B**).

[0356] To model these findings, subcutaneous xenografts of 33 primary patient-derived PDAC samples and 17 established PDAC cell lines were established in NSG mice. A subset of primary patient-derived and cell line-derived PDAC xenograft tumors were found to express high levels of IFN-stimulated genes STAT1 and MX1 while a minority scored as negative (**FIGS. 2A-2C**). Because of the lack of IFN species cross reactivity, these data suggest that IFN-stimulated gene expression in xenograft tumors is driven by a tumor cell autonomous mechanism. One explanation for the lack of IFN-stimulated gene expression in a subset of xenograft tumors is low expression or impaired activity of IFN receptors or downstream kinases, a characteristic of some tumor cells and an established mechanism of acquired resistance to immune checkpoint blockade (Refs. 29-30).

[0357] To investigate this possibility, a panel of PDAC cell lines was treated with type I IFN (IFN β) *in vitro* and all models responded to IFN β by upregulating STAT1 expression, including those scoring as STAT/MX1 low when grown as xenograft tumors (**FIG. 3A**). Using immunoblot analysis, data demonstrated that MX1 and STAT1 were expressed at high levels in lysates prepared from DANG xenograft tumors compared to cell culture samples. Supplementing these cultures with recombinant IFN β restored STAT1 and MX1 to levels observed in tumor samples (**FIG. 3C**). Collectively, these results indicate that IFN signaling is constitutive in PDAC tumors and is driven by a tumor cell-autonomous mechanism.

[0358] Type I IFN signaling activates the replication stress response pathway in PDAC cells

[0359] Because IFNs impair cancer cell proliferation *in vitro*, it was hypothesized that IFN exposure triggers adaptive signaling alterations in PDAC cells that can be exploited for the treatment of IFN-signaling high tumors (Ref. 8). To systematically profile such mechanisms, an nLC-MS/MS phospho-proteomics analysis of SUIT2 PDAC cells 24 hours following IFN β treatment was applied (**FIG. 3D**). There were 1,077 significantly altered proteins identified (among 9,350 detected, 1% FDR), many of which were enriched in pathways related to established IFN functions which validated the approach (**FIG. 3B**), and 911 significantly altered phosphopeptides (among 17,368 detected, 0.1% FDR).

[0360] Kinase substrate enrichment analysis (KSEA) of the significantly altered phosphopeptides identified enriched phosphorylation of ATM/ATR, HIPK2, and MAPK1/3 (ERK1/2) substrates following treatment (**FIG. 3D**) (Ref. 31). While activation of the MAPK pathway by type I IFN has been reported, little is known about the connection between IFN signaling and the replication stress response pathway mediated by ATR (Refs. 32-33). Increased phosphorylation of CHEK1_{S317}, an established substrate of ATR, was detected in the phospho-proteomics dataset. This finding was confirmed using immunoblot analysis in which pCHEK1_{S345} was observed 12 hours after the addition of IFN β to PDAC cell culture (**FIGS. 3E-3F**).

[0361] ATR activation is a compensatory response to replication stress, caused by any obstacle to DNA replication, and results in decreased proliferation and cell cycle arrest in S-phase (Ref. 21). Consistently, data showed that IFN treatment resulted in both impaired proliferation (**FIG. 3F**) and induced S-phase arrest in SUIT2 cells (**FIG. 3G**). This analysis was expanded to a panel of PDAC cell lines and observed varying degrees of IFN-induced pCHEK1_{S345} (**FIG. 3I**). A similar pattern of heterogeneity was observed in the induction of S-phase accumulation (**FIG. 3J**). pCHEK1 induction appears to predict IFN-induced S-phase arrest in this panel. The co-existence of pCHEK1_{S345} and IFN markers was validated in subsets of surgical PDAC specimens and several cases were observed in which high levels of both markers were apparent in serial sections of a single specimen (**FIGS. 3K, 3C, 3D**). Taken together, the results indicated that type I IFN signaling induces replication stress in PDAC cells, suggesting a potential vulnerability of PDAC tumor exhibiting constitutive type I IFN signaling.

[0362] IFN signaling restricts nucleotide pools

[0363] An established cause of replication stress is an insufficient or imbalanced supply of the substrates for DNA replication (dNTPs) (Ref. 21). A targeted LC-MS/MS approach was applied

to: (i) evaluate IFN β -induced alterations in total dNTP abundance and (ii) evaluate the contribution of stable isotope [$^{13}\text{C}_6$] glucose to dNTP pools, an indicator of *de novo* synthesis (**FIG. 4A**). Data demonstrated that IFN treatment triggers in a decrease in dCTP, dTTP, dATP and dTTP pools in both SUIT2 and YAPC cells (**FIGS. 4B-4C**). To systematically investigate the cause of this metabolic reprogramming, IFN-induced alterations in the expression of nucleotide-metabolism genes were evaluated in the nLC-MS/MS proteomics dataset obtained for **FIG. 3D**. Notably, the expression of proteins that catabolize nucleotides and nucleosides, including sterile alpha-motif and histidine-aspartate domain-containing protein 1 (SAMHD1), thymidine phosphorylase (TYMP), and cytosolic 5'-nucleotidase 3A (NT5C3A), exhibited significant upregulation in IFN β -treated cells (**FIGS. 4E, 5A**). Additionally, the data demonstrated a significant down-regulation of dihydrofolate reductase (DHFR) and thymidylate synthase (TYMS) which are required for *de novo* dNTP biosynthesis. Taken together, these observations suggested a model in which type I IFNs restrict dNTP pools via the combination of impaired biosynthesis and enhanced catabolism (**FIG. 4F**).

[0364] SAMHD1 emerged as a potential mediator of IFN-induced replication stress as it has been previously linked to the regulation of cell cycle progression and functions as a central mediator of dNTP homeostasis by catalyzing the phosphohydrolysis of dNTP to deoxyribonucleosides (dN) which are effluxed into the environment (Refs. 34-35). Recently, SAMHD1 has been shown to possess a novel moonlighting function which is to promote DNA repair by acting as a molecular scaffold for CtIP at replication forks (Ref. 35). Interestingly, this secondary function of SAMHD1 negatively regulates cytosolic DNA sensing pathways and autocrine IFN signaling explaining the observation that mutational inactivation of SAMHD1 is associated with development of the autoimmune interferonopathy Aicardi-Goutieres Syndrome (Ref. 36).

[0365] To investigate the role of SAMHD1 in IFN-induced nucleotide pool restriction, experiments were undertaken to generate SUIT2 SAMHD1 knockout cells using CRISPR/Cas9 (**FIG. 4B**). dNs produced by phosphohydrolysis were either effluxed from cells, re-enter metabolism via the actions of nucleoside kinases dCK and TK1 or catabolized via deaminases (CDA and ADA) or phosphorylases (PNP and TYMP). It was reasoned that upregulation of SAMHD1 expression would result in increased dNTP phosphohydrolysis and nucleoside efflux in PDAC cells. To test this, a previously described LC-MS/MS assay was used to evaluate the contribution of [$^{13}\text{C}_6$]glucose to dNTP pools, extracellular dNs and newly replicated DNA in SUIT2 parental and SAMHD1 knockout cells (**FIG. 5C**) (Ref. 23). In parental cells, IFN treatment resulted in a 2-fold decrease in dCTP pools and a 3-fold increase in dC efflux (**FIG.**

5D). At baseline, SAMHD1 knockout cells had a nearly 3-fold greater labeled dCTP pool than parental cells and in this model IFN failed to induce dCTP pool decreases or enhance dC efflux. A similar pattern was found in the evaluation of the dATP pool but it was determined that IFN was still capable of decreasing this pool in SAMHD1 knockout cells, albeit by a small degree. Interestingly, efflux of the purine nucleoside deoxyadenosine (dA) was not detected in this model. Then, it was hypothesized that the nucleoside kinase dCK could maintain dCTP pools in the presence of IFN by recycling SAMHD1-produced nucleosides thereby preventing dC efflux. To test this hypothesis, the analysis was expanded to include an evaluation of SUIT2 dCK knockout cells alongside parental and SAMHD1 knockout cells (**FIG. 5C**). Results demonstrated that dCK knockout decreased dCTP pools and increased dC efflux at baseline and amplified IFN-induced dCTP pool depletion and dC efflux. Expectedly, dCK knockout did not influence dATP pool alterations induced by IFN.

[0366] It was determined that IFN impaired the contribution of [$^{13}\text{C}_6$]glucose to the dC and dA compartment of DNA in each of the isogenic lines indicating that while SAMHD1 is a critical mediator of IFN-induced intracellular dNTP pool alterations and dN efflux, it is not solely responsible for impaired DNA replication in this model (**FIG. 5E**). SAMHD1 induction and dNTP pool reduction were not a transient response to acute IFN exposure and were sustained and detectable following 21 days of chronic exposure (**FIGS. 5F-5G**). Collectively, these results demonstrated that SAMHD1 is a critical mediator of IFN-induced alterations in dNTP abundance and dN efflux but that is not solely responsible for IFN-induced replication defects.

[0367] The purine nucleosides dA and dG produced by SAMHD1-mediated dNTP phosphohydrolysis can either be recycled by dCK or catabolized by the combined actions of ADA and PNP. It was reasoned that the inability to detect dA nucleoside efflux in SUIT2 cells is because of its rapid catabolism by these enzymes (**FIG. 4A**). Results showed that [$^{13}\text{C}_6$]glucose-derived dG was only detectable in cells co-treated with the PNP inhibitor BCX-1777 and was enhanced by IFN β (**FIG. 4B**). Additionally, it was determined that SAMHD1 expression was required for dG efflux in SUIT2 cells (**FIG. 4B**).

[0368] While dCK can accept dC, dA and dG, salvage of thymidine (dT) requires the nucleoside kinase thymidine kinase 1 (TK1). dCK and TK1 have been well studied for their role in nucleoside salvage (i.e., the scavenging and trapping of environmental nucleosides) but their cell autonomous role in preventing efflux is unexplored (Ref. 37). Utilizing a combination of a small molecule dCK inhibitor developed by our group (DI-82) and CRISPR/Cas9 knockout of TK1 we found that both pyrimidine deoxyribonucleoside kinases prevent efflux of [$^{13}\text{C}_6$]glucose labeled pyrimidine nucleosides at baseline as efflux was elevated in knockout cells (**FIGS. 4D-**

4G) (Ref. 23). Results demonstrated that while IFN triggered an increase in dC efflux, dT efflux was decreased. It was hypothesized that this decrease reflects enhanced dT catabolism by TYMP, which is induced by IFN. These results indicated that IFN triggers a metabolic shift in PDAC cells from an anabolic to a catabolic phenotype mediated by SAMHD1 and that nucleoside kinases counteract SAMHD1, and potentially TYMP activities. Interestingly, these findings suggested that a substrate cycle exists between SAMHD1 and dCK/TK1, which could serve to fine-tune dNTP pool sizes or to promote a futile cycle of ATP consumption.

[0369] The cGAS/STING pathway drives autocrine type I IFN signaling in PDAC tumors

[0370] The observation that patient-derived and cell xenograft PDAC tumors exhibited IFN signaling biomarker enrichment suggested that tumor cells produce IFN as IFN is species-restricted. In epithelial cells, type I IFN production can be initiated downstream of cytosolic nucleic acid sensor activation triggered by pathogen or mis-localized self DNA (**FIG. 1**). One such sensor is cyclic GMP-AMP synthase (cGAS), which binds ssDNA (single-stranded) and dsDNA (double-stranded) and in turn activates stimulator of interferon genes (STING) via production of the cyclic dinucleotide 2'-3'-cGAMP. In contrast to other cancers in which cGAS and STING are suppressed by mutational inactivation or epigenetic silencing, cGAS and STING promoters are generally hypo-methylated in PDAC and STING is transcriptionally up-regulated in PDAC tumors compared to normal pancreas (**FIG. 6A**) (Ref. 38). Moreover, IHC staining of the PDAC tissue microarray used in these studies revealed detectable STING expression in tumor cells at varying levels in >90% of samples, a finding consistent with a previous report (**FIG. 6B**) (Ref. 39). To evaluate the functionality of the cGAS/STING pathway in tumor cells, a panel of PDAC cell lines was transfected with IFN stimulatory DNA (ISD, a cGAS ligand) and induction of the IFN β transcript was measured using RT-PCR. Results showed that ISD triggered an increase in the IFN β transcript only in a subset of lines (**FIG. 6C**). It was reasoned that cell lines not responsive to ISD are defective in either cGAS or STING expression. However, results demonstrated that there is no correlation between cGAS or STING protein levels and ISD response in this panel and several cell lines were identified, including SUIT2, which were ISD non-responders but expressed both cGAS and STING at levels comparable to ISD-responsive cells (**FIG. 6D**). In SUIT2 cells, it was found that despite their lack of response to ISD, direct activation of STING via transfection with a bisphosphorothioate 2'-3'-cGAMP analog (cGAMP) triggered an increase in IFN β transcript levels (**FIG. 6E**). This finding suggested that in SUIT2 cells cGAS is mis-localized or inhibited by a post-translational mechanism of which several have been described (Ref. 40). Expectedly, cGAMP transfection triggered rapid phosphorylation of IRF3_{S139}, which is mediated by TBK1 downstream of

STING-dependent cGAMP sensing, and phosphorylation of STAT1 which was temporally followed by induction of STAT1 and MX1 protein expression (**FIGS. 6F-6G**). Additionally, cGAMP transfection triggered secretion of IFN β protein into culture supernatants in STING-proficient DANG cells (**FIG. 6H**). Inhibition of JAK1 using ruxolitinib (RUX) abrogated cGAMP induced STAT1 phosphorylation and interferon stimulated gene induction, further indicating that interferon stimulated gene expression initiated by STING functions via an autocrine/paracrine mechanism (**FIGS. 6F-6G**). Consistent with the *in vitro* observation, STAT1 and MX1 proteins were highly expressed in untreated xenograft tumors derived from the STING pathway-active DANG cells. STAT1 and MX1 protein levels in DANG tumors were comparable to their levels observed in cell culture following 24 hour treatment with IFN, a finding which indicated that cell culture can mask a constitutive endogenous IFN response (**FIG. 1C**). Furthermore, MX1 and STAT1 were expressed at low levels in xenograft tumors derived from STING pathway-inactive SUI2 cells (**FIG. 7A**). Collectively, these results indicated that the cGAS/STING pathway drives constitutive IFN signaling in xenograft tumors and that profiling of cGAS and STING expression is not sufficient to predict pathway functionality in PDAC cells.

[0371] IFN signaling modulates PDAC cell proliferation and nucleotide metabolism *in vivo*

[0372] To model the IFN-high and -low conditions observed in PDAC patient specimens in an isogenic system, SUI2 cells were engineered to express a previously described constitutively active STING mutant (STING^{R248M}) or a GFP control conditionally in the presence of doxycycline (**FIGS. 5A, 7B**) (Ref. 41). Activation of STING^{R248M} resulted in impaired cell proliferation in 3D cultures, similar to findings herein with recombinant IFN (**FIG. 5B**). Experiments confirmed that this model recapitulated IFN exposure by performing immunoblot analysis of IFN stimulated in gene expression following doxycycline treatment which was comparable to treatment with recombinant IFN (**FIG. 5C**). Pharmacological inhibition of JAK abrogated IFN stimulated gene induction mediated by the STING^{R248M} transgene.

[0373] To determine if these phenotypes occur *in vivo*, SUI2-STING^{R248M} cells were implanted subcutaneously in NCG mice (NOD-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/NjuCrl; Coisogenic Immunodeficient) and provided doxycycline-supplemented diet. Results showed that STING^{R248M} induction significantly impaired xenograft tumor growth. Immunoblot analysis of explanted tumors was performed and results demonstrated that doxycycline treatment induced STING, IFN stimulated gene expression and phosphorylation of CHEK1.

[0374] To compliment these findings and to determine if endogenously produced IFN, mediated by STING, impairs tumor growth *in vivo*, STING was knocked out using

CRISPR/Cas9 in DANG cells which exhibit constitutive IFN signaling when grown as xenograft tumors (**FIG. 3C; 7C**). In this loss-of-function model, STING knockout abrogated xenograft tumor expression of MX1 and STAT1 as determined by IHC staining (**FIG. 7D**). Results showed that STING knockout promoted DANG tumor growth, completely blocked expression of MX1 and resulted in decreased CHEK1 phosphorylation in tumors (**FIGS. 5F-5G**). Collectively, these findings provide a link between STING activity, PDAC cell IFN signaling, tumor growth and replication stress *in vitro* and *in vivo*.

[0375] To validate this findings, a second STING knockout isogenic cell line system was generated in HS766T which stably express a firefly luciferase (fLUC)-linked IFN stimulated response element (ISRE) reporter to non-invasively track type I IFN signaling activity in xenograft PDAC tumors. Under cell culture conditions, only STING-proficient HS766T cells exhibit reporter ISRE promoter activation following 2'-3'-cGAMP transfection while both isogenic lines were responsive to IFN β (**FIG. 7E**). Consistently, STING proficient HS766T ISRE-fLUC tumors exhibited a higher luminescence intensity when compared to STING knockout isogenic tumors (**FIG. 7F**) and substantially decreased levels of pSTAT1_{Y701}, STAT1, and MX1 (**FIG. 7G**).

[0376] The proliferation of STING isogenic models was further investigated using an orthotopic system in which PDAC cells were injected into the pancreata of immunodeficient mice. For this model, SUI2-STING^{R248M} cells were engineered to constitutively express a fLUC reporter that allows for non-invasive monitoring of tumor burden using bioluminescence imaging. Experiments showed that activation of STING using doxycycline resulted in impaired growth of orthotopic PDAC tumors (**FIG. 5H**). Immunoblot analysis of orthotopic tumor explants was performed and results showed enrichment of IFN stimulated gene expression in STING^{R248M} active tumors (**FIG. 5I**). Down-regulation of the nucleotide biosynthetic genes DHFR and TYMS in STING^{R248M} tumors was observed, consistent with *in vitro* observations (**FIG. 4D**). Collectively, these results demonstrated that the cGAS/STING signaling pathway was intact in a subset of PDAC models and that its activity in tumor cells was a non-redundant contributor to cell type I IFN signaling in PDAC xenograft tumors.

[0377] Next, experiments were undertaken to ascertain if IFN signaling mediated by STING triggers metabolic alterations *in vivo*. It was hypothesized that the induction of TYMP by IFN could be leveraged for the detection of STING-active tumors using positron emission tomography (PET) as environmental thymidine levels have been shown to influence [¹⁸F]fluorothymidine ([¹⁸F]FLT) PET probe accumulation in tumors (Refs. 42-43). TYMP is a key metabolic enzyme which degrades dT into thymine and 2-deoxy-alpha-D-ribose 1-

phosphate and depletes free dT pools (**FIG. 8A**). Additionally, TYMP has also been identified as a positive regulator of angiogenesis by promoting the growth and proliferation of endothelial cells (Ref. 44). Both thymidine and [^{18}F]FLT require phosphorylation by thymidine kinase 1 (TK1) for their intracellular accumulation, however, the affinity of dT for TK1 greatly exceeds that of [^{18}F]FLT⁴³. [^{18}F]FLT is not a substrate for TYMP but its accumulation is a surrogate marker of its activity: [^{18}F]FLT accumulation is a function of both TK1 expression and dT levels (which are mediated by TYMP). In this model, IFN-dependent depletion of dT will result in increased accumulation of the [^{18}F]FLT PET probe in tumors. To test this hypothesis the impact of IFN treatment on [^{18}F]FLT uptake was evaluated under varying dT concentrations (**FIG. 8B**). Results demonstrated that dT competitively inhibited [^{18}F]FLT uptake but treatment with IFN prevented this effect. To confirm a role for TYMP in this phenotype, TYMP knockdown cells were generated using shRNA in SUIT2 cells (**FIG. 8C**). Results demonstrated that both knockdown of TYMP and treatment with a JAK inhibitor impaired IFN-induced [^{18}F]FLT uptake in SUIT2 cells in the presence of dT (**FIG. 8D**). It was determined that type II IFN (IFN γ) elicited similar induction of TYMP in SUIT2 cells and that YAPC cells are deficient for TYMP at baseline and in the presence of either IFN β or IFN γ (**FIG. 8E**). Data showed that IFNs induced [^{18}F]FLT uptake in a TYMP-dependent manner (**FIG. 8F**) and that IFN did not enhance [^{18}F]FLT uptake in TYMP-deficient YAPC cells (**FIG. 8G**).

[0378] Using PET imaging of tumor bearing mice, it was determined that [^{18}F]FLT accumulation was significantly increased after doxycycline treatment in STING^{R248M} tumors compared to GFP expressing isogenic controls (**FIG. 5J**). Experiments confirmed that this alteration was specific to [^{18}F]FLT and not the consequence of global metabolic reprogramming as [^{18}F]FDG uptake in the same animal model was unaffected by IFN signaling (**FIG. 5K**). Additionally, [^{18}F]FLT and [^{18}F]FDG imaging of NCG mice bearing bilateral SUIT2-GFP and -STING^{R248M} tumors was performed and data showed that [^{18}F]FLT accumulation was significantly enriched in STING tumors whereas no impact on [^{18}F]FDG accumulation was observed. The data indicated that STING induced metabolic reprogramming was locally confined (**FIG. 8H**). Consistently, data showed that STING^{R248M} induction does not alter nucleotide metabolism systemically as significant differences in plasma dT levels were not observed in mice bearing either SUIT2-GFP or -STING^{R248M} tumors treated with doxycycline (**FIG. 8I**). In summary, the data confirmed that IFN signaling driven by STING reprograms tumor cell metabolism both *in vitro* and *in vivo*.

[0379] The replication stress response pathway is a collateral dependency triggered by IFN signaling in a subset of PDAC cells

[0380] To compliment the phosphoproteomic profiling and with the goal of systematically identifying signaling pathway co-dependencies triggered by IFN in tumor cells, a high-throughput 430 compound chemical genomics screen was applied using SUI2 cells treated $\pm$ IFN (**FIG. 6A**). Inhibitors of key replication stress response effectors, including ATR (ceralasertib) and CHEK1 (LY2603618, PF-477736 and AZD-7762), scored among top hits and exhibited significantly increased activity in SUI2 cells treated with IFN β . Expectedly, JAK kinase inhibitors (LY278544, tofacitinib and ruxolitinib) which block type I IFN signaling abrogated the anti-proliferative effects of IFN β in our screen. These hits were consistent with the phosphoproteomics results described herein and identified the replication stress response pathway as an IFN β -induced co-dependency in PDAC cells.

[0381] The replication stress response pathway is initiated by ATR which phosphorylates and activates downstream effectors CHEK1 and WEE1 in response to any obstacle to DNA replication. Small molecule inhibitors of these kinases have entered clinical trials in various cancers combined with genotoxic chemotherapy, PARP inhibitors or immunotherapy (**FIG. 17A**) (Ref. 22). To validate the screen, the interaction between IFN β and berzosertib was evaluated in an anchorage independent growth assay and results showed that while single agents had a cytostatic effect only the combination completely prevented PDAC cell proliferation (**FIG. 6B**). Using Cell Titer Glo, results showed synergy between IFN β and inhibitors of each of the replication stress response pathway kinases ATR, CHEK1 and WEE1 (**FIG. 17B**). Results demonstrated a synergistic increase in cleaved PARP and cleaved caspase 3 in cells co-treated with IFN and either of two ATR inhibitors berzosertib or ceralasertib (**FIG. 17C**). Collectively, these results confirmed that the replication stress response pathway, and not ATR or CHEK1 alone, is an IFN-induced co-dependency in PDAC cells.

[0382] Next, experiments were undertaken to directly measure ssDNA abundance, an established consequence of replication fork stalling and replication stress, by evaluating F7.26 ssDNA-specific antibody cross-reactivity (Ref. 23). Both IFN and ATRi triggered ssDNA accumulation alone and combination treatment resulted in the greatest degree of induction (**FIGS. 6C, 10A**). Flow cytometry analysis was performed of pH2A.X_{S139} to determine if combination treatment induces DNA damage (**FIG. 6D**). While only inducing a 3% increase alone, IFN β increased the percentage of pH2A.X_{S139} positive cells from 33% to 72% when berzosertib was present. Interestingly, data showed that while the percentage of pH2A.X_{S139} positive cells was synergistically increased in the combination group, the overall pH2A.X_{S139} intensity decreased compared to berzosertib treatment alone. This observation was reminiscent of previous findings that pan-nuclear pH2AX, as opposed to foci accumulation, was a marker

for replication catastrophe (**FIG. 10B**) (Ref. 45). In addition, apoptosis was synergistically induced by IFN β and berzosertib as determined by AnnexinV/PI flow cytometry (**FIGS. 6E, 10C**).

[0383] To determine if mitotic entry was required for the lethal effects of IFN β +berzosertib, cells were treated simultaneously with a CDK4/6 inhibitor (CDK4/6i) which expectedly arrested SUIT2 cells in G1 (**FIG. 10D**). Data demonstrated that CDK4/6i treatment did not alter IFN stimulated gene expression but completely prevented IFN β +VE822-induced H2AX_{S139} phosphorylation and cleaved PARP accumulation (**FIG. 10D**). Taken together, these data indicated that mitotic entry is required for synergy between IFN β and ATRi.

[0384] The findings were expanded to a panel of PDAC cell lines and data showed a heterogeneous degree of sensitivity to IFN, berzosertib and the combination using live-cell imaging (**FIG. 6F**). Models with the highest degree of synergy exhibited highest pCHEK1_{S345} induction by IFN β (**FIG. 3I**). Furthermore, IFN and berzosertib synergistically induced S-phase accumulation selectively in lines in which an anti-proliferative synergy was observed (**FIG. 6G**). A synergistic interaction was identified between IFN β and berzosertib on proliferation inhibition and S-phase accumulation in A13A primary PDAC cultures (**FIGS. 10E-10F**) whereas no significant anti-proliferative effect nor S-phase arrest was observed in the non-transformed human pancreatic ductal epithelial cells (HPDE; **FIGS. 10G-10H**).

[0385] Type I IFN and ATR signaling collaboratively control PDAC cell nucleotide metabolism

[0386] As ATR has been shown to regulate both *de novo* and scavenging nucleotide biosynthesis by transcriptional and post-translational mechanisms, it was reasoned that berzosertib could enhance dNTP restriction triggered by IFN²³. Consistent with previous work in leukemia data showed that berzosertib treatment down-regulated the expression of nucleotide biosynthetic genes, TYMS, RRM1 and RRM2, and the nucleoside kinase TK1 in a dose dependent manner in the presence of IFN (**FIG. 11C**) (Ref. 23). This analysis was expanded to a panel of PDAC cell lines representative of the heterogeneity in synergy between IFN and berzosertib. Data demonstrated that the berzosertib alone only triggered down-regulation of RRM1, RRM2, TK1 and TYMS in cell lines in which synergy between IFN and berzosertib was observed (**FIG. 7A**). Furthermore, data demonstrated that IFN potentiated the down-regulation of these genes selectively in “sensitive” models. To investigate the mechanism of down-regulation, RT-PCR analysis of nucleotide metabolism gene expression following treatment with IFN $\pm$ berzosertib (**FIG. 11B**) was performed. Data demonstrated that IFN alone decreased the levels of TYMS transcript, consistent with the findings in **FIG. 4**, and induced upregulation of

RRM2 and TK1 transcripts which is likely the consequence of S-phase arrest as the expression of these genes is restricted to S-phase. Berzosertib treatment resulted in decreased levels of TYMS, TK1, RRM1 and RRM2 transcripts. This down-regulation is likely not an artifact of cell cycle alterations as treated cells significantly accumulated in S-phase (**FIG. 6G**). ATR has been previously associated with the transcriptional control of these genes via stabilization of their transcription factor, E2F1 (Ref. 46). The anti-proliferative effects of IFN have also been linked to their ability to down-regulate E2F activity (Ref. 47). In addition to regulating transcription, ATR has been demonstrated to promote RRM2 protein stability by preventing its phosphorylation on T33 by CDK1 which positively regulates its degradation mediated by the SCF^{Cyclin F} ubiquitin ligase complex (Ref. 48). Data herein demonstrated that supplementation with a proteasome inhibitor partially rescued ATRi-mediated down regulation of TYMS, TK1, RRM1 and RRM2 both alone and in the presence of IFN (**FIG. 11C**). These results indicated that ATR coordinates nucleotide metabolism by both promoting of gene transcription and preventing protein degradation.

[0387] Using LC-MS/MS analysis, results demonstrated that both IFN and berzosertib decreased dCTP pool abundance with the lowest levels observed in the combination treatment group (**FIG. 7B**). To evaluate the impact of IFN and berzosertib on replication dynamics, an LC-MS/MS assay previously used was adapted to track the incorporation of glucose-derived or nucleoside-derived nucleotides using stable isotope tracers (Ref. 23). Data showed that both IFN and berzosertib decreased the total degree of deoxycytidine labeling in DNA (DNA-C) mediated by the *de novo* pathway ($[^{13}\text{C}_6]$ glucose-derived nucleosides; **FIG. 7C**). Furthermore, the greatest degree of inhibition was observed in cells treated with both IFN and berzosertib. Collectively, these results indicated that IFN β primarily restricts dNTP abundance by initiating nucleotide and nucleoside catabolism whereas ATR inhibition limits dNTP biosynthesis via down-regulation of the expression of anabolic genes, including both *de novo* pathway genes and nucleoside salvage kinases. This down-regulation is likely mediated by ATRi-mediated impairment of E2F1 transcription factor activity.

[0388] STING activation triggers a collateral dependency on ATR

[0389] To determine if tumor cell-autonomous IFN signaling drives a collateral dependency on ATR, the sensitivity of the SUIT2-STING^{R248M} cells to berzosertib was evaluated using live cell imaging of 3D cultures. Data demonstrated that both DOX treatment (STING activation) and berzosertib impaired sphere growth the combination completely prevented proliferation (**FIGS. 8A, 8B**). A second conditional STING^{R248M} model was generated using YAPC cells to expand these findings and confirmed doxycycline treatment induces STING and interferon

stimulated gene expression that is dependent on JAK activity (**FIG. 12A**). Results showed similar synergy between STING activation and berzosertib in this model using 2D cultures (**FIG. 12B**). Signaling through JAK is essential for this synergy as supplementation with ruxolitinib restored the proliferation of combination treated cells (**FIG. 12C**). To test this model *in vivo*, SUIT2 TetR fLuc cells were engineered with either the STINGR248M transgene, an ATR targeting shRNA, or the combination. These cells were injected into the pancreas of NCG mice and tumor burden was monitored using bioluminescence imaging following doxycycline treatment. Knockdown of ATR using shRNA impaired the proliferation of SUIT2-STING^{R248M} cells *in vivo* while ATR knockdown had no effect on tumor growth alone (**FIGS. 8C-8E**). Collectively, these results indicated that STING-driven IFN signaling triggers a collateral dependency on ATR *in vitro* and *in vivo* and suggest that ATR inhibitors may exhibit increased activity against tumors exhibiting constitutive IFN signaling.

[0390] PARP inhibitors synergize with IFN and ATR inhibitors

[0391] ATR inhibitors (ATRi) have progressed into phase I and phase II clinical trials in combination with chemotherapy, radiation or PARP inhibitors. DNA repair by homologous recombination (HR) is required for resolution of PARP inhibitor-induced DNA damage and thus PARP inhibitors have been shown to be particularly effective against HR-deficient tumors such as BRCA1/2-deficient breast and pancreatic cancer (Ref. 6). Additionally, mediators of HR, including BRCA1 and CtIP are known targets of E2F1 and down-regulated by ATRi in PDAC cells (**FIG. 13A**). It was reasoned that IFN/ATRi treatment would induce a HR-deficient like cellular state and serve as an effective approach to sensitive PDAC cells to PARP inhibitors. Data showed that ATR inhibition sensitized PDAC cells to olaparib, a response which was amplified by IFN supplementation (**FIG. 13B**). Experiments were conducted using pH2AX_{S139} flow cytometry to evaluate the extent of DNA damage in treated cells and data showed the highest levels in SUIT2 cells treated with berzosertib and olaparib in the presence of IFN β (**FIG. 13C**). Annexin V/PI analysis revealed that type I IFN signaling increases apoptosis-induction by the berzosertib/olaparib combination in SUIT2 cells (**FIG. 13D**). To expand these findings, the effects of the berzosertib/olaparib combination SUIT2, DANG, and in the primary PDAC culture model A13A were evaluated and results showed that berzosertib and olaparib synergize to impair proliferation in the presence of IFN β across all models tested (**13C**). Using Annexin V/PI flow cytometry, data showed a synergistic induction of apoptosis by the combination of IFN, berzosertib and olaparib in the primary A13A model. Collectively, these results suggested that constitutive IFN signaling driven by STING in combination with an ATR inhibitor may trigger an HR deficiency-like phenotype that may render tumor cells particularly vulnerable to

PARP inhibitor combinations.

[0392] IFNs reprogram nucleotide metabolism in PDAC cancer-associated fibroblasts

[0393] In addition to constitutive inflammatory cytokine signaling, a heterotypic cellular microenvironment is a hallmark of PDAC. Among the cell types present in the PDAC microenvironment, cancer associated fibroblasts (CAFs) are particularly important and as they constitute the bulk of the majority of tumors and influence response to therapy (Ref. 49). CAF and macrophage-derived nucleosides have been shown to influence the activity of anti-metabolite chemotherapy gemcitabine by competing with dCK for phosphorylation (Ref. 50).

[0394] Having observed that IFNs promote dC efflux in tumor cells, experiments were to be conducted to determine whether a similar phenotype can be observed in CAF cultures (**FIG. 14A**). An immortalized human PDAC CAF culture was treated with IFN β and robust up-regulation of pSTAT1_{Y701} and SAMHD1 was observed (**FIG. 14B**). Results showed that CAF cells overproduce dC and efflux *de novo* produced dC into the media. [¹³C₆]glucose labeled-derived dC levels were nearly 3-fold higher when CAFs were exposed to IFN β (**FIG. 14C**). These results indicated that PDAC CAFs, like tumor cells, phosphohydrolyze dNTPs via a mechanism presumably mediated by SAMHD1. While some nucleoside-analog chemotherapies, including cytarabine, have been shown to be inactivated by SAMHD1 directly by phosphohydrolysis of their triphosphate forms, gemcitabine-triphosphate (dFdCTP) is resistant to this mechanism (Ref. 51). SAMHD1 can promote gemcitabine resistance indirectly by increasing dC levels in the microenvironment thereby increasing competition for phosphorylation by dCK. Thus, it is hypothesized that PDAC tumors exhibiting high IFN signaling are poorly responsive to gemcitabine because of increased levels of microenvironmental SAMHD1-derived nucleosides. In addition to preventing antimetabolite activity CAF-derived, nucleosides can be utilized as a nutrient source in PDAC cells.

[0395] Experiments described herein define the causes and consequences of IFN signaling in PDAC tumors. Data demonstrated that the cGAS/STING pathway is active in a subset of PDAC cells and is required for constitutive type I IFN signaling in PDAC tumors. Orthogonal phosphoproteomics and chemical genomics approaches implicated the replication stress response pathway as an IFN-induced collateral dependency in PDAC cells. Pharmacological inhibition of replication stress response kinases ATR, CHEK1 or WEE1 induced replication catastrophe in IFN β -treated PDAC cell lines and primary cells but not in non-transformed cells. ATR inhibition impaired nucleotide metabolism by restricting the expression of rate limiting nucleotide biosynthetic enzymes. Finally, it was determined that IFN β signaling sensitizes PDAC cells to the clinically viable combination of small molecule ATR and PARP inhibitors.

[0396] In addition to mutations in KRAS and TP53, chronic inflammation is a hallmark feature of PDAC tumors. This low grade inflammatory response observed has been termed “para-inflammation” and is a defined transcriptional signature resembling a type I IFN response (Ref. 28). Among TCGA datasets PDAC ranks highest in terms of para-inflammation signature enrichment which is a negative prognostic factor in this disease (Ref. 28). Type I IFN production is induced by the activation of cytosolic or endosomal pathogen sensing pathways including the cGAS-STING pathway which initiates type I IFN production in epithelial, stromal, endothelial and immune cells in response to accumulation of cytosolic ssDNA and dsDNA. The cGAS-STING pathway is tightly regulated by transcriptional and post-translational mechanisms and indirectly by proteins which control the levels of cytosolic ssDNA and dsDNA, including SAMHD1, TREX1, and RPA/RAD51 (Ref. 52). Importantly, mutational inactivation of several of these proteins results in Aicardi-Goutieres Syndrome (AGS), an early onset inflammatory disorder characterized and aberrantly high systemic levels of type I IFNs. Additionally, germ-line STING gain of function mutations have been associated with a lupus-like autoimmune disease in humans (Ref. 53).

[0397] STING agonists are being evaluated as immune stimulating anti-cancer vaccines and analogs of the endogenous STING ligand 2'-3'-cGAMP which overcome its susceptibility to hydrolysis by ENPP1 are in development (Ref. 54-55) Interestingly, covalent STING inhibitors have also been described and may be useful tools to reprogram cytokine signaling in inflamed PDAC tumors (Ref. 56). cGAS and/or STING are down-regulated in various cancers, including colorectal cancer and melanoma, and thus this pathway has been classified as tumor suppressive (Ref. 57, 58). cGAS and STING down-regulation appear to be primarily mediated by epigenetic mechanisms and treatment with DNA de-methylating agents can restore pathway functionality in some cases. PDAC is an exception as cGAS and STING exhibit decreased promoter methylation in patient samples (Ref. 38). Consistently, STING expression in PDAC appears to be elevated compared to normal pancreas and STING has previously been shown to be expressed extensively in both the cancer cell and stromal compartments of tumors, a finding confirmed in this study (Ref. 39). It has been proposed that tumors exhibiting low cGAS-STING expression may be especially vulnerable to oncolytic virus therapy. Consistently, data herein showed a high degree of concordance between the PDAC cell lines identified as ISD responders/non-responders and those previously reported to be resistant/sensitive to oncolytic virus therapy (Ref. 59). Regarding the discrepancy between basal interferon-stimulated gene expression in cGAS/STING proficient cells *in vitro* and *in vivo*, it is possible that these lines constitutively secrete minimal amounts of IFN that is diluted in culture media and removed with passaging. A second explanation is that the cGAS ligand responsible for constructive activation

is absent *in vitro* and only produced when PDAC cells are grown *in vivo*. In addition to the cGAS/STING pathway, other stimuli and pathways, such as TLR agonists and the NF- κ B pathway, also activate type I IFN production and their contributions to type I IFN production in PDAC remains unclear (Ref. 60). As STING activation has been shown mediate to inflammation-induced carcinogenesis, it may be that STING activation plays a role in the development or progression of a subset of PDAC tumors.

[0398] Paradoxically, IFNs have been shown to exert both pro- and anti-tumor functions. *in vitro*, IFNs are well studied for their ability to restrict cancer cell proliferation. However, IFN regulated genes also have been investigated in the context of a IFN DNA damage resistance gene expression signature (IRDS) which is associated with resistance to chemotherapy and radiation (Ref. 10). Additionally, chronic IFN pathway agonism has been associated with resistance to immune checkpoint blockade (Ref. 61). It is possible that constitutive STING-driven IFN signaling is a mechanism by which PDAC cells condition an immunosuppressive microenvironment. In this model, tumor cells in the PDAC microenvironment may hijack the pro-tumor functions of IFNs and mitigate their anti-tumor effects by activating compensatory signaling and metabolic pathways (i.e. ATR and dCK).

[0399] Tumor cell vulnerabilities elicited by IFN signaling have not been systematically evaluated. However, IFN treatment has been shown to amplify the cytotoxic effects of MEK inhibitors in a subset of melanoma cell lines exhibiting low basal IFN signaling pathway activity (Ref. 62). In addition, multiple groups have independently demonstrated that IFN signaling induces a collateral dependency on ADAR to prevent dsRNA-mediated proliferation inhibition driven by PKR activity, a finding that is limited by the current lack of clinically viable ADAR inhibitors (Refs. 63-64). Experiments herein identified an additional dependency driven by IFN signaling that is immediately actionable.

[0400] Herein experiments demonstrated three major consequences of type I IFN signaling in PDAC cells: induction of nucleotide catabolism, cell cycle delay in S-phase and activation of the replication stress response. Multiple IFN-stimulated genes have been annotated in each of these processes, rendering the identification of a single mediator of these phenotypes a significant challenge. Moreover, several of IFN-relegated metabolic genes have moonlighting functions; SAMHD1 possesses both metabolic (dNTP hydrolase) and DNA repair (CtIP scaffold) functions (Refs. 35, 65). SAMHD1 induction by type I IFN signaling could reduce dNTP abundance and simultaneously facilitate DNA repair. The K312 residue in SAMHD1 is essential for its dNTPase function, whereas T592, which is phosphorylated by cyclin-dependent kinases (CDKs), is critical for its role in end resection (Ref. 35). Future studies incorporating the

investigation of SAMHD1 mutants (K312A or T592A) will further define the specific function of SAMHD1 in the IFN signaling impact on PDAC cells.

[0401] IFN signaling has been reported to regulate metabolism in macrophages and dendritic cells however, the impact of IFNs on tumor cell metabolism has not yet been systematically evaluated (Refs. 18, 66-67). Early work on IFNs demonstrated that they influence nucleotide metabolism nucleic acid biosynthesis in tumor cells and here we build on this foundation and characterize molecular mediators of this phenotype (Ref. 68). Findings herein demonstrated that IFN signaling in cell culture and *in vivo* PDAC models triggers a shift in nucleotide metabolism toward a predominately catabolic phenotype. Interestingly, dT catabolism has been identified as a stress response to starvation in cancer cells which provides carbon for glycolysis via the actions of TYMP and DR5P aldolase (DERA) (Ref. 69). IFN may promote this process and catabolized nucleotides and nucleosides serve as a carbon source for other biochemical processes to fuel PDAC cell progression. Additionally, the restriction of thymidine pools resulting from IFN-induced up-regulation of TYMP can be leveraged using [¹⁸F]FLT PET/CT. It was anticipated that [¹⁸F]FLT PET would have utility as a pharmacodynamic biomarker for STING agonists as well as other IFN-stimulating immunotherapies such as immune checkpoint blockade.

[0402] In addition to the cell autonomous effects, IFNs may also play an important role in regulating the landscape and composition of the metabolic synapse between tumor cells and immune cells (Ref. 16). Evidence for the competition between cancer cells and immune cells for nucleosides in tumor microenvironment is provided by the observation that nucleoside kinases and transporters, such as dCK, uridine-cytidine kinase 2 (UCK2) and SLC29A1 are up-regulated in T-cells following activation (Refs. 70-72). Additionally, purine efflux triggered by IFN signaling may have local immunosuppressive effects (Ref. 73). These observations justify the investigation of nucleotide metabolism-related IFN regulated genes in the context of immunotherapy in PDAC as well as other cancers with constitutive type I IFN signaling.

[0403] In this study, a range of response to the IFN β /ATRi combination was observed in our human PDAC models. This variation may be reflective of the well-documented genomic, transcriptional and metabolic heterogeneity of PDAC cells (Refs. 4, 7, 74). Genomic alterations previously linked to ATR inhibitor sensitivity in PDAC, such as mutations of KRAS, TP53, ATM or ARID1A, may also influence response to endogenous IFN β and ATRi therapy (Ref. 75). Similar heterogeneity has been documented in melanoma cell lines where type I IFN treatment enhanced the cytotoxic response of MEK inhibition only in a subset of cell lines (Ref. 62). Potentially related is the observation that hyper-activating JAK2V617F mutations have

been linked to replication stress in myeloproliferative neoplasms (Ref. 76).

[0404] Findings herein have high translational significance as ATR inhibitors and IFN-inducing therapies (such as immune checkpoint blockade and TLR agonists) are being evaluated in the clinic. Interestingly, ATR inhibition has been shown to enhance the efficacy of immune checkpoint blockade in pre-clinical models (Ref. 77). Collectively, our work defines the intersection between cytokine signaling, nucleotide metabolism and replication stress in PDAC and rationalizes the use of an IFN-related transcriptional signature to stratify patients for the ATR inhibitor/PARP inhibitor combinations currently being evaluated for the treatment of solid tumors.

[0405] Experimental Model and Subject Details

[0406] Cell culture: All cell cultures were maintained in antibiotic free DMEM +10% FBS at 37°C in 5% CO₂. Mycoplasma contamination was monitored using the PCR-based Venor Mycoplasma kit. PDAC cell lines were acquired either from commercial vendors ATCC or from collaborators. Cell line identity was independently authenticated by PCR. For anchorage-independent culture PDAC cells were grown on tissue-culture plates treated with poly(2-hydroxyethyl methacrylate (poly-HEMA) (Ref. 78). Briefly, Poly-HEMA was dissolved at 20 mg/mL concentration in 95% Ethanol and then added to the plate to fully cover growth area and dried overnight. Plates were sterilized by UV irradiation for two hours.

[0407] Drugs: Stocks were prepared in DMSO or H₂O and diluted fresh in cell culture media for treatments. The nonhydrolyzable bisphosphorothioate 2'-3'-cGAMP analog (2'-3'-cGAMP) and ISD were complexed with Lipofectamine 3000 before treatment.

[0408] In vivo mouse studies: All animal studies were approved by the UCLA Animal Research Committee (ARC). 4-6 week-old female NCG (CRL572; Charles River Laboratories) mice were injected subcutaneously on the flanks with 0.5x10⁶ cells resuspended 1:1 in PBS:matrigel. For orthotopic studies 3x10⁴ cells were resuspended 1:1 in PBS:matrigel and injected into the pancreata of NCG mice.

[0409] Patient samples: PDAC samples were collected from surgical tumor resection UCLA patients.

[0410] Method Details

[0411] Live cell imaging: For live cell imaging cells were plated at 2x10³ cells / well in either ultra-low attachment or treated flat-bottom clear 96-well plates. After 24-72 hour treatments were added and cell proliferation was tracked using the IncuCyte Zoom live-cell imaging system. Images were acquired at 3 hour intervals over the indicated time periods.

[0412] LC-MS/MS DNA measurements: Cells were transferred into DMEM without glucose and supplemented with 10% dialyzed FBS containing the following labeled substrates: precursors for de novo [$^{13}\text{C}_6$]glucose at 11 mM and [$^{13}\text{C}_{10}, ^{15}\text{N}_2$]dT at 5 μM . Genomic DNA was extracted using the Quick-gDNA MiniPrep kit and hydrolyzed to nucleosides using the DNA Degradase Plus kit following manufacturer-supplied instructions. In the final step of DNA extraction, 50 μL of water was used to elute the DNA into 1.5 mL microcentrifuge tubes. A nuclease solution (5 μL ; 10X buffer/DNA Degradase PlusTM/water, 2.5/1/1.5, v/v/v) was added to 20 μL of the eluted genomic DNA in an HPLC injector vial. The samples were incubated overnight at 37°C. For genomic DNA and media analysis, an aliquot of the hydrolyzed DNA or media samples (20 μL) were injected onto a porous graphitic carbon column (Thermo Fisher Scientific Hypercarb, 100 x 2.1 mm, 5 μm particle size) equilibrated in solvent A (water 0.1% formic acid, v/v) and eluted (200 $\mu\text{L}/\text{min}$) with an increasing concentration of solvent B (acetonitrile 0.1% formic acid, v/v) using min/%B/flow rates ($\mu\text{L}/\text{min}$) as follows: 0/0/200, 5/0/200, 10/15/200, 20/15/200, 21/40/200, 25/50/200, 26/100/700, 30/100/700, 31/0/700, 34/0/700, 35/0/200. The effluent from the column was directed to the Agilent Jet Stream ion source connected to the triple quadrupole mass spectrometer (Agilent 6460) operating in the multiple reaction monitoring (MRM) mode using previously optimized settings. The peak areas for each nucleosides and nucleotides (precursor→fragment ion transitions) at predetermined retention times were recorded using the software supplied by the instrument manufacturer (Agilent MassHunter).

[0413] RT-PCR: Total RNA was isolated from cells using the Zymo Quick-RNA MiniPrep kit. Reverse transcription was performed using the High Capacity cDNA Reverse Transcription kit (Life Technologies). Quantitative PCR was performed using EvaGreen qPCR Master Mix (Lamda Biotech). RNA expression values were normalized and calculated as relative expression to control. Primers used are reported in **FIG. 23**.

[0414] Immunohistochemistry (IHC): Formalin-fixed, paraffin-embedded tumor samples were incubated at 60°C for 1 hour, deparaffinized in xylene, and rehydrated with graded alcohol washes. Slides were then boiled in 0.01 M sodium citrate buffer for 15 minutes followed by quenching of endogenous peroxidase with 3% hydrogen peroxide for antigen retrieval. After 1 hour of blocking with 5% donkey serum at room temperature, primary antibodies were added and incubated overnight at 4°C. Biotin-conjugated anti-rabbit secondary antibody (1:500 Jackson Labs) was added and developed using Elite Vectastain ABC kit.

[0415] Immunoblot analysis: PBS-washed cell pellets were resuspended in cold RIPA buffer supplemented with protease and phosphatase inhibitors. Protein lysates were normalized using

BCA assay, diluted using RIPA and 4x laemmli loading dye, resolved on 4-12% Bis-Tris gels and electro-transferred to nitrocellulose membranes. After blocking with 5% nonfat milk in TBS + 0.1% Tween-20 (TBS-T), membranes were incubated overnight in primary antibodies diluted (per manufactures instructions) in 5% BSA in TBS-T. Membranes were washed with TBST-T and incubated with HRP-linked secondary antibodies prepared at a 1:2500 dilution in 5% nonfat dry milk in TBS-T. HRP was activated by incubating membranes by incubating membranes with mixture of SuperSignal Pico and SuperSignal Femto ECL reagents (100:1 ratio). Exposure of autoradiography film was used for detection.

[0416] Tumor tissue homogenization: Snap-frozen tumor tissue was transferred to Omni Hard Tissue homogenization vials. 750 µl of tissue Lysis buffer spiked with 1x protease and phosphatase inhibitor cocktails were added to each vial. Vials were homogenized using an Omni Bead Ruptor Elite (8 cycles of 15 seconds on, 30 seconds off, speed 8) chilled to 4°C. Tissue homogenates were cleared by centrifugation at 12,000xg for 10 minutes at 4°C. Cleared lysates were normalized using the BCA method and prepared for immunoblot analysis as described for cell culture samples.

[0417] Immuno-fluorescence microscopy: Cells cultured on coverslips were fixed with 4% (w/v) paraformaldehyde in PBS for 15 min., permeabilized with 0.2% (v/v) Triton X-100, blocked with 3% (w/v) BSA in PBS for 30 min., and then incubated with primary antibodies containing 1% (w/v) BSA and 0.1% (w/v) saponin in PBS for overnight, washed with PBS then incubated with fluorescence secondary antibodies for 1 hour. Following washing, cells were stained with DAPI, washed with PBS, and mounted onto microscope slides and imaged using a NIKON fluorescence microscope.

[0418] Clonogenic survival and viability analysis: For crystal violet staining, PDAC cells were plated in 6-well plates at 1×10^4 cells/well and treated as described. Following treatment cells were fixed by incubating in 4% PFA in PBS for 15 min. at room temperature. Plates were subsequently washed with PBS and stained with 0.1% crystal violet in H₂O for 15 min. at room temperature.

[0419] For anchorage-dependent CellTiter-Glo analysis cells were plated at 1×10^3 cells / well in at 50 µl / well in white opaque 384-well plates and treated as described. Following incubation 50 µl of CellTiter-Glo reagent (Diluted 1:5 in dH₂O) was added to each well, plates incubated at room temperature for 5 min. and luminescence was measured using a BioTek microplate luminescence reader.

[0420] For anchorage-independent culture Cell Titer Glo analysis cells were plated at 5×10^3

cells / well in at 100 μ l /well poly-HEMA treated 96-well plates and treated as described. Following incubation 100 μ l of 3D CellTiter-Glo reagent (Diluted 1:5 in dH₂O) was added to each well, plates incubated at room temperature for 5 m and luminescence was measured.

[0421] Flow cytometry: All flow cytometry data were acquired on five-laser BD LSRII, and analyzed using FlowJo software.

[0422] AnnexinV/PI: Treated PDAC cells were washed with PBS and incubated with AnnexinV and propidium iodide diluted in 1x Annexin binding buffer.

[0423] Propidium iodide cell cycle analysis: Treated PDAC cells were washed with PBS and suspended in cell cycle staining solution (100 μ g/ml propidium iodide; 20 μ g/ml Ribonuclease A; 1 mg/ml sodium citrate; 0.3% Triton-X 100 prepared in dH₂O).

[0424] EdU: PDAC cells were pulsed with 10 μ M EdU for 2 hour, washed twice with PBS, and released in fresh media containing 5 μ M deoxyribonucleosides. Cells were collected 4 hour following release in fresh media, fixed with 4% paraformaldehyde and permeabilized using saponin perm/wash reagent (Invitrogen), and then stained with azide-AlexaFluor 647 by Click reaction. The total DNA content was assessed by staining with FxCycle-Violet at 1 μ g/mL final concentration. The cell cycle durations were calculated using equations for multiple time-point measurements according to previously published methods (CITE).

[0425] pH2A.X_{S139}: Cells were harvested, fixed, permeabilized with cytofix/cytoperm for 15 minutes on ice, prior to staining with a phospho-Histone H2A.X_{S139} antibody conjugated to FITC (1:800 dilutions in perm/wash) for 20 minutes at room temperature shielded from light. Subsequently, cells were washed and stained with 0.5 mL of DAPI for DNA content before analysis.

[0426] Protein kinase inhibitor phenotypic screen: A library of 430 protein kinase inhibitors (SelleckChem Cat. L1200) was arrayed in polypropylene 384-well plates at 200x concentrations covering a 7-point concentration range (corresponding to 1x concentrations: 5 μ M, 1.65 μ M, 550nM, 185nM, 61.5nM, 20.6nM, 6.85nM). 25 μ l per well of growth media with or without 200 U/mL IFN β supplementation (for a final concentration of 100 U/mL) was plated in opaque-white 384-well plates using a BioTek multidrop liquid handler. Protein kinase inhibitors were added by 250 nL pin-tool transfer (BioMek FX, Beckman-Coulter) and inhibitor/media mixtures were incubated at room temperature for 30 m. 25 μ L of a 40,000 cells/mL SUIT2 suspension (for 1000 cells / well) was subsequently added to each well. After 72 h, 50 μ L of CellTiter-Glo reagent diluted 1:4 in dH₂O was added to each well and luminescence was measured using a Wallac plate reader (Perkin Elmer). Each condition was assayed in duplicate (n=2) and %

proliferation values were calculated by normalizing experimental wells to plate negative controls and averaging replicate values. Composite IFN β synergy scores for each test compound were defined as the sum of the Synergy Score (% proliferation inhibition observed - % proliferation inhibition expected) between IFN β and individual protein kinase inhibitor concentrations across the 7-point concentration range. Z factor scores for individual assay plates were calculated using eight positive and eight negative control wells on each plate. All plates gave a Z factor > 0.5.

[0427] CRISPR/Cas9 knockout cell line generation: All gRNA sequences were cloned into LentiCrisprV2. Lipofectamine 3000 was used to transfect PDAC cells with 1 μ g/ml gRNA-specific LentiCrisprV2 vectors. Following puromycin selection cells were singly cloned.

[0428] shRNA knockdown cell line generation: For generation of stable knockdown cell lines PDAC cells were transduced with lentivirus harvested from HEK293FT cells in the presence of polybrene. Following transduction cells underwent antibiotic selection and knockdown efficiency was confirmed using immunoblot analysis. For virus production lentiviral vectors and packaging plasmids (psPAX2, pMD2G) at a 2:1:1 ratio were transfected into FT293 cells using polyethylenimine. Lentivirus-containing supernatants were filtered through a 0.45 μ m filter prior to use.

[0429] Bioluminescence Imaging: Mice were anesthetized with 2% isoflurane prior to intraperitoneal injection of 100 μ L (50 mg/mL) D-luciferin. Images were acquired on an IVIS 100 Bioluminescence Imaging scanner 10 minutes after D-luciferin administration.

[0430] IFN β ELISA: Cells were plated at 250k cells/well in treated 24-well tissue culture plates and allowed to seed overnight. 2'-3'-cGAMP was complexed with Lipofectamine3000 in Optimem at a 1:1:2 cGAMP:lipofectamine3000:Optimem ratio. Before transfection cells were washed with PBS, 400 μ L of culture media was added to each well and 100 μ L of complexed 2'-3'-cGAMP was added drop-wise for a final concentration of 25 μ g/mL. Media was collected, centrifuged for 4 m at 450xg at 4C at indicated time points. ELISA analysis was performed per manufacturer's instructions.

[0431] Statistical analyses: Data are presented as mean $\pm$ SD with number of biological replicates indicated. Comparisons of two groups were calculated using indicated unpaired or paired two-tailed Student's t-test and P values less than 0.05 were considered significant. For some experiments, generated mean normalized values (ratios from two groups, treated to untreated) were compared to the hypothetical value 1 (indicating equal values between treated and untreated), calculated using one-sample t-test, and P values less than 0.05 were considered significant. Comparisons of more than two groups were calculated using one-way ANOVA

followed by Bonferroni's multiple comparison tests, and P values less than 0.05/m, where m is the total number of possible comparisons, were considered significant.

[0432] Example 2

[0433] Emerging evidence suggests that intratumoral interferon (IFN) signaling can trigger targetable vulnerabilities. A hallmark of pancreatic ductal adenocarcinoma (PDAC) is its extensively reprogrammed metabolic network, in which NAD and its reduced form NADH are critical cofactors. Here, we show that IFN signaling, present in a subset of PDAC tumors, substantially lowers NAD(H) levels through upregulating the expression of NAD-consuming enzymes PARP9, PARP10, and PARP14. This mechanism has not been previously delineated. Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme in the NAD salvage pathway, a dominant source of NAD in cancer cells. We found that IFN-induced NAD consumption increased dependence upon NAMPT for its role in recycling NAM to salvage NAD pools, thus sensitizing PDAC cells to pharmacologic NAMPT inhibition. Their combination decreased PDAC cell proliferation and invasion *in vitro* and suppressed orthotopic tumor growth and liver metastases *in vivo*.

[0434] Pancreatic ductal adenocarcinoma (PDAC) is the major type of pancreatic cancer with a median overall survival of less than one year (1). In addition to an aggressive tumor biology and late stage at diagnosis, the poor prognosis of PDAC is due to its resistance to current therapies. In recent years, studies have profiled its extensively reprogrammed metabolic network and characterized its extreme tumor microenvironment (2-5). These studies have identified PDAC cells' dependence on glycolysis (2,6), lipogenesis (2,7), glutamine metabolism (8,9), alanine metabolism, and tricarboxylic acid cycle/oxidative phosphorylation (10,11). Strategies targeting each of these specific metabolic pathways have been attempted but have not been successfully translated into clinical therapeutics. However, all of these re-wired metabolic pathways rely on nicotinamide adenine dinucleotide (NAD), or its reduced form NADH, as co-factors.

[0435] NAMPT inhibitors showed promising potency in a variety of pre-clinical tumor models including pancreatic cancer (15-18). Two NAMPT inhibitors, FK866 (19) and CHS-828 (20,21), have been tested in clinical trials, where lack of objective responses and dose-limiting toxicity suggest it is necessary to identify subsets of tumors with high sensitivity to NAMPT inhibition. Multiple studies have examined intracellular factors that affect cancer cell sensitivity to NAMPT inhibition, such as NAMPT levels (22), nicotinic acid phosphoribosyltransferase (NAPRT) levels (23), PPM1D mutations (15), and CD38 levels (24). We hypothesized that, in addition to intracellular factors, the tumor microenvironment also impacts PDAC cell NAD(H) levels and thus the sensitivity to NAMPT inhibitors.

[0436] In this study, we found that type I interferons (IFNs) lower PDAC cell NAD(H) levels through the upregulation of NAD(H) consuming enzymes PARP9, PARP10, and PARP14 (PARP9/10/14). Unlike their better studied relatives PARP1 and PARP2, which catalyze poly-ADP-ribosylation (PARylation), PARP9/10/14 catalyze the transfer of a single unit of ADP ribose to their targets, a process referred to as monoADP-ribosylation (MARylation) (25). The roles of PARP9/10/14 in mediating NAD depletion in PDAC cells have not been previously explored. We further hypothesized that IFN-mediated NAD depletion caused by the upregulation of PARP9/10/14 sensitizes PDAC cells to NAMPT inhibitors, which we confirmed in both *in vitro* and *in vivo* PDAC models.

[0437] Type I IFN in the tumor microenvironment reduces NAD(H) levels in PDAC cells.

[0438] We hypothesized that in a subset of PDAC tumors, certain cytokine(s) in the PDAC tumor microenvironment impact tumor NAD(H) levels. To test this hypothesis, we cultured Panc 03.27 cells with the supplementation of individual cytokines that have been previously reported as present in the PDAC tumor microenvironment (26-30) (**FIG. 24A**). Among them, only IFN β supplementation significantly reduced NAD levels in PDAC cells. To further examine the effect of IFN β on reducing NAD levels, we supplemented IFN β in the culture medium of a panel of PDAC cell lines (**FIGS. 24B-24C**). With the exception of Hs 766T cells, all PDAC cell lines tested showed significantly reduced NAD levels. In addition, IFN β also significantly reduced NADH, the reduced form of NAD, in our panel of PDAC cell lines (again with the exception of Hs 766T). It is important to note that while IFN β reduced the total abundance of NAD(H), it did not significantly affect the NAD/NADH ratio.

[0439] To further support these findings, we extracted cellular metabolites of four PDAC cell lines (Panc 03.27, HPAF-II, CFPAC-1, and SUIT2) from cultured cells and xenograft tumors (**FIGS. 24D-24E**). NAD levels were significantly lower in xenograft tumors compared to cultured cells (Panc 03.27, HPAF-II, and CFPAC-1) (**FIGS. 24D-24E**), regardless of 2D or 3D culture methods. No significant difference in NAD levels was detected between cultured SUIT2 cells and SUIT2 xenograft tumors. We performed immunohistochemistry (IHC) staining of IFN β signaling markers MX1 and STAT1 in our xenograft tumors derived from PDAC cell lines Panc 03.27, HPAF-II, CFPAC-1, and SUIT2 (**FIG. 24F**). While Panc 03.27, HPAF-II and CFPAC-1 tumors were positive for MX1 and STAT1, SUIT2 tumors were negative for the IFN β markers. These results confirm that IFN β signaling is present in the PDAC tumors that demonstrated a decrease in their NAD levels and absent in PDAC tumors without a decrease in NAD levels. Given the lack of interspecies IFN cross-reactivity, we are also able to conclude that the IFN β -positive xenograft PDAC tumors engaged in autocrine type I IFN signaling. And we recognize that SUIT2 cells

represent a subset of PDAC tumors which do not produce IFN β *in vivo* (**FIG. 24F**), but do have an intact IFN β signaling pathway and respond to supplemented IFN β *in vitro* (**FIGS. 24B-24C**).

[0440] IFN β increases the expression of NAD(H) consuming enzymes PARP9, PARP10, and PARP14, leading to a reduction in cellular NAD(H) levels.

[0441] IFNs signal by stimulating the expression of certain genes, known as interferon-stimulated genes (ISGs) (31). We hypothesized that IFN β reduced NAD(H) levels through upregulating the expression of genes for NAD(H) consuming enzymes. To test this hypothesis, we profiled the mRNA levels of all reported NAD(H) consuming enzymes, including 16 PARP family members, 7 SIRT family members, and CD38, in two PDAC cell lines (Panc 03.27 and SUIT2), with and without IFN β supplementation (**FIG. 25A**). In both cell lines, the mRNA levels of PARP9, PARP10, and PARP14 were substantially upregulated by IFN β , and the mRNA level of CD38 was increased only in Panc 03.27 cells (**FIG. 25A**). We examined the effect of IFN β on the protein levels of PARP9, PARP10, PARP14, and CD38 in Panc 03.27 and SUIT2 cells, as well as three additional PDAC cell lines (T3M4, HPAF-II, and Hs766T) (**FIG. 25B**). PARP9, PARP10, and PARP14 protein levels were increased by IFN β in all PDAC cell lines tested except for Hs766T, and CD38 protein levels were not affected by IFN β (**FIG. 25B**). These data indicate that the up-regulation of PARP9/10/14 expression mediates the reduction of NAD(H) levels induced by IFN β . They also indicated that Hs 766T did not show reduced NAD(H) levels with IFN β supplementation (**FIG. 24F**) because of the lack of upregulation of PARP9/10/14 protein levels in these cells (though these cells expressed the marker ISG MX1 in response to IFN β , demonstrating an intact IFN β signaling pathway) (**FIG. 25B**).

[0442] To evaluate the discrete contributions of PARP9, PARP10 and PARP14 to IFN-induced NAD depletion, we knocked down their expression individually in both Panc 03.27 and SUIT2 cells using shRNA. Analysis of protein levels after knockdown demonstrated an intact IFN β signaling pathway but appropriate lack of up-regulation of each of the corresponding enzymes (**FIGS. 26A-26B**). We found that knockdown of each gene partially mitigated the effect of IFN β treatment on NAD/NADH depletion, but did not completely rescue either NAD or NADH levels, indicating that these ISGs may function in concert to deplete NAD(H) pools in PDAC cells (**FIGS. 26C-26D**).

[0443] Among the PDAC tumor samples in the Cancer Genome Atlas (TCGA) dataset, we observed a correlation between IFN β signaling marker mRNA levels (STAT1 and MX1) and PARP9/10/14 mRNA levels (**FIG. 26G**). There is a minor subset of PDAC tumors with high PARP9, PARP10, or PARP14 levels but without high STAT1/MX1 levels, suggesting that PARP9/10/14 can occasionally be induced by factors other than type I IFN signaling. 16% of all

TCGA PDAC tumors exhibit high PARP9/10/14 levels in association with high STAT1/MX1 levels (**FIG. 26G**). There was no significant difference in disease progression between the PARP9/10/14 high and low subsets of PDAC patients. We also confirmed the association between high or low levels of ISGs MX1 and STAT1 and high or low levels of PARP9, PARP10, and PARP14 within cancer cells in PDAC patient-derived xenograft (PDX) models using IHC staining (**FIG. 26H**). We therefore hypothesized that IFN signaling-induced upregulation of PARP9/10/14 causing increased NAD consumption would sensitize these tumor cells to further NAD-depleting therapies.

[0444] NAD(H) consumption via upregulation of PARP9/10/14 results in increased dependency of these tumors on NAMPT, therefore sensitizing them to NAMPT inhibition.

[0445] NAMPT mediates the rate-limiting step in the NAD(H) salvage pathway, which is the dominant source of NAD(H) supply in cancer cells and most normal tissues (13). We hypothesized that type I IFN signaling, which increases NAD(H) consumption through upregulating PARP9/10/14 expression, increases the dependency of these tumors on NAMPT to recycle NAM and regenerate NAD(H), thus sensitizing them to treatment with NAMPT inhibitors. To test this hypothesis, we first examined the effect of combining IFN β and an NAMPT inhibitor (NAMPTi) FK866 on NAD and NADH levels in PDAC cells. In both Panc 03.27 and SUI2, the combination of IFN β and NAMPTi reduced NAD and NADH levels to a significantly lower levels compared to either IFN β or NAMPTi alone, supporting our hypothesis that these cells are reliant upon NAMPT to maintain NAD pools via NAM recycling in the setting of PARP9/10/14 upregulation by IFN β (**FIGS. 27A-27B**).

[0446] We hypothesized that the NAD(H) depletion induced by this combination therapy would cause dysfunction of known NAD(H)-requiring metabolic pathways. NAD(H) is a co-factor of complex I for mitochondrial respiration and glyceraldehyde-3-P dehydrogenase (GPDA) and lactate dehydrogenase (LDH) in glycolysis. We examined the mitochondrial oxygen consumption rate (OCR) and the extracellular acidification rate (ECAR), a measure of glycolytic reserve, in PDAC cells exposed to IFN β and NAMPTi, both alone and in combination. The combination of IFN β and NAMPTi significantly reduced OCR and ECAR more than either IFN β or NAMPTi alone (**FIGS. 27C-27D**). Additionally, this reduction in OCR and ECAR was rescued by supplementation with nicotinamide riboside (NR) (**FIGS. 27C-27D**), which bypasses the NAMPT step in the salvage pathway for NAD(H) synthesis (14), demonstrating the on-target effect of this therapy. A consequence of NAD(H) depletion, reduced OCR, and decreased glycolytic reserve is ATP depletion. To determine ATP depletion, we examined the Thr172 phosphorylation of AMPK, a cellular energy sensor. IFN β and NAMPTi

together triggered AMPK phosphorylation, and this was again rescued by NR supplementation (**FIG. 27E**).

[0447] Yet another consequence of NAD(H) depletion is DNA damage, because the activities of the critical DNA repair enzymes in the PARP and Sirtuin families are NAD(H) dependent. The NAD(H)-dependent PARP and Sirtuin families are critical players in DNA repair (32,33). PARP family activity can be monitored by measuring PAR abundance (34). PAR abundance was substantially reduced by IFN β and NAMPTi and this reduction was rescued by NR supplementation (**FIG. 27F**). We observed that IFN β and NAMPTi together increased H2A.X phosphorylation, a marker of DNA damage, which was also rescued by NR supplementation (**FIG. 27G**). Given these observations, we hypothesized that the NAD(H) reduction by IFN β and NAMPTi together would result in increased PDAC cell apoptosis, which was confirmed by Annexin V/propidium iodide quantification by flow cytometry (**FIG. 27H**). This was also rescued by NR supplementation (**FIG. 27H**). Finally, it has been demonstrated that NAD(H) depletion results in decreased malignant cell invasion (35). And we found that IFN β and NAMPTi together inhibited the invasion of PDAC cells, whereas neither IFN β nor NAMPTi significantly affected PDAC cell invasion as single agents, and at the molecular level, IFN β and NAMPTi down-regulated the protein levels of epithelial cell markers E-cadherin and N-cadherin.

[0448] Taken together, our results confirmed that IFN β sensitized PDAC cells to NAMPTi, with NAD(H) depletion resulting in cytotoxicity and metabolic dysfunction due to a multifactorial model including DNA damage, impaired DNA repair activity of the PARP and Sirtuin family members, and decreased mitochondrial respiration and glycolytic reserve (**FIG. 27J**). To further support our finding that increased NAD(H) consumption by IFN β sensitizes PDAC cells to NAMPTi, we tested two chemically different NAMPTi inhibitors FK866 and LSN3154567 (17) in a viability assay in a panel of PDAC cell lines and primary PDAC cultures (A2.4 and AM1283) with and without IFN β supplementation. Except for Hs 766T, which we previously found does not upregulate PARP9/10/14 and lower NAD(H) levels when supplemented with IFN β (**FIGS. 24F and 25B**), all PDAC cell lines and primary cultures showed lower IC50 values of FK866 and LSN3154567 in the presence of IFN β , both in standard 2D culture and anchorage-independent 3D culture (**FIGS. 28A-28B, FIG. 31**). In both 2D and 3D cultures, the increased cytotoxicity of NAMPTi by IFN β was rescued by NR supplementation (**FIGS. 27C-27D**), confirming that this phenotype was due to on-target NAD(H) depletion.

[0449] PDAC is characterized by the presence of abundant desmoplastic stroma primarily

composed of cancer-associated fibroblasts (CAFs), which support PDAC cell survival and chemoresistance (36-39). Therefore, we tested the effect of the IFN β /NAMPTi combination side-by-side on the growth of spheroids with SUIT2/GFP cancer cells alone and spheroids with both SUIT2/GFP cancer cells and CAF/mCherry stromal cells. In both spheroid models, the IFN β /NAMPTi combination suppressed spheroid growth better than either IFN β or NAMPTi alone (**FIGS. 28E-28F**). Taken together, our results indicate that the presence of IFN β sensitizes PDAC cells to the cytotoxicity of NAMPTi in an NAD(H)-dependent manner.

[0450] Inactivation of Type I IFN signaling promotes resistance to NAMPT inhibitors.

[0451] Having demonstrated the IFN β -induced, PARP9/10/14-mediated sensitization to NAMPTi of PDAC cells *in vitro*, we hypothesized that type I IFN signaling is required to see this effect *in vivo*. We profiled a broad panel of PDAC xenograft models for *in vivo* type I IFN signaling based on IHC analyses of the type I IFN ISG MX1 (**FIGS. 29A-29B**). We found a subset of xenograft tumors that stained positive for MX1, which we termed IFN-positive PDAC xenografts, and another subset which did not stain for MX1, which we termed IFN-negative. We selected a representative IFN-positive PDAC xenograft PATU8988T and used CRISPR-Cas9 to knockout (KO) the type I IFN receptor IFNAR1. To confirm that PARP9, PARP10, and PARP14 expression was mediated by type I IFN signaling, we also examined protein levels of those enzymes and found that IFNAR1 KO abolished the increased expression of MX1, PARP9, PARP10, and PARP14 after IFN β treatment seen in WT cells (**FIG. 29C**).

[0452] In order to compare the efficacy of NAMPTi in *in vivo* PDAC tumor models with and without type I IFN signaling, we utilized this PATU8988T model with its IFNAR1 KO isogenic line as a loss-of-function control. After orthotopic PATU8988T WT and IFNAR1 KO tumors were established, mice were randomized to either be treated with vehicle control or NAMPTi (**FIG. 29D**). After 3 weeks of treatment, PDAC tumors with intact type I IFN signaling and treated with NAMPTi (representing the combination group) were significantly smaller, both based on weekly bioluminescent imaging (BLI) (**FIG. 29E**) and endpoint tumor weights (**FIG. 29F**), than both IFNAR1 KO tumors treated with NAMPTi (representing the NAMPTi only treatment group), and WT untreated tumors (representing the type I IFN only treatment group). Our results confirmed that increased PARP9/10/14 expression, NAD(H) reduction, growth inhibition, and enhanced sensitivity to NAMPTi *in vivo* are mediated by type I IFN signaling.

[0453] Increased IFN signaling downstream of STING activation sensitizes tumors to NAMPTi.

[0454] Type I IFN production by cancer cells is frequently driven by the activation of STING due to genomic instability (40). In order to compare the efficacy of NAMPTi in *in vivo* PDAC

tumor models with controllable type I IFN signaling, we established a gain-of-function PDAC SUIT2 model of autocrine type I IFN signaling with doxycycline (DOX)-inducible expression of an active STING^{R284M} mutant (41). DOX exposure stimulated the expression of ISGs STAT1 and MX1 as well as PARP9, PARP10, and PARP14 (**FIG. 30A**), indicating the activation of type I IFN signaling in the presence of DOX. DOX exposure significantly lowered NAD(H) levels in SUIT2-STING^{R284M} cells (**FIG. 30B**). To confirm that PARP9, PARP10, and PARP14 expression was mediated by autocrine type I IFN signaling in these models, we used CRISPR-Cas9 to knockout (KO) type I IFN receptor IFNAR1. In the presence of DOX, IFNAR1 KO abolished STING^{R284M}-mediated expression of STAT1, MX1, PARP9, PARP10, and PARP14. IFNAR1 KO did not significantly affect the proliferation of SUIT2-STING^{R284M} cells in the absence of DOX. In the presence of DOX, IFNAR1 KO rescued the growth inhibitory effect of STING^{R284M} and the effect of STING^{R284M} on sensitizing SUIT2 cells to NAMPTi.

[0455] We implanted orthotopic SUIT2-STING^{R284M} cells and once tumors were established, mice were randomized to either a vehicle control or DOX-containing diet (to activate type I IFN signaling) and also to be treated with either a vehicle control or NAMPTi (**FIG. 30C**). After a 3-week treatment, PDAC tumors with type I IFN signaling (DOX diet) and treated with NAMPTi were significantly smaller than IFN-negative (control diet) tumors treated with NAMPTi, as well as smaller than tumors with type I IFN signaling alone (**FIGS. 30D-30E**). In addition to suppressing primary orthotopic tumor growth, NAMPTi and type I IFN signaling together resulted in a decreased number and size of liver metastases (**FIGS. 30F-30G**), a common feature of clinical PDAC. During the treatment period, the dosage of NAMPTi we used was well tolerated by the animals. Immunoblot analyses of tumor homogenates revealed activation of autocrine type I IFN signaling and expression of PARP9/10/14 in samples collected from animals on DOX-diet (**FIG. 30H**). Our results indicate that NAMPTi is more effective in suppressing both tumor growth and liver metastases of PDAC tumors with active type I IFN signaling. And taken together, our results support our hypothesis that the sensitization to NAMPTi seen with type I IFN signaling is dependent upon PARP9/10/14-mediated NAD(H) depletion leading to an increased dependence upon NAMPT for salvage of NAD(H) pools.

[0456] Discussion

[0457] Chronic inflammation, a defining characteristic of PDAC tumors, has been linked to elevated levels of cytokines produced by tumor, stromal, and immune cells (42). Of the inflammatory cytokines in the PDAC tumor microenvironment (43,44), interferons (IFNs) are amongst the most important given their high prevalence and ability to regulate the expression of thousands of genes (45,46) with both tumor supportive (47-49) and suppressive phenotypes

(45,49). Emerging evidence suggests that IFN signaling also triggers targetable vulnerabilities in cancer cells (50). Unlike IFN γ that is mainly produced by activated T cells, type I IFNs can be produced by multiple cell types in the PDAC tumor microenvironment, including tumor cells themselves with autocrine circuitries (31,51). While the signaling and immunomodulatory effects of type I IFNs have been described, their impact on tumor cell metabolism remains poorly understood. In this study, we identified an effect of type I IFN, which is present in a subset of PDAC tumors, on reducing tumor cell NAD(H) levels and sensitizing PDAC cells to NAMPTi through stimulating the expression of PARP9, PARP10, and PARP14.

[0458] PARP1 and PARP2 are the founding members in the PARP family and have been extensively studied for their DNA repair activity. Compared to PARP1 and PARP2, the roles of PARP9, PARP10, and PARP14 are less well characterized. Our data showed that silencing of PARP9, PARP10, or PARP14 partially rescued IFN β -induced NAD(H) reduction. Both PARP10 and PARP14 have broad spectra ADP-ribosylation substrates identified in protein microarrays (52), which are consistent with their NAD(H) consumption in our observations. In contrast, PARP9 lacks catalytic activity (53), but it interacts with other PARP family members, and regulate their expression and activity (54). In addition, PARP9 also promotes cellular response to IFNs (54). These indirect effects of PARP9 may explain our observation that PARP9 silencing reduced IFN β -induced NAD(H) consumption. Previous clinical trials of NAMPTi for cancer treatment suggest that its clinical success requires the identification of cancer subsets with high sensitivity to NAD(H) reduction. While the salvage pathway for NAD(H) supply has been extensively studied and explored for cancer treatment, the significance of NAD(H) consumption has not yet been comprehensively examined. We found that upregulation of PARP9/10/14 by type I IFN lowered NAD(H) levels, increased dependency on NAMPT to prevent severe depletions of NAD pools, and sensitized PDAC cells to NAMPTi treatment which then resulted in the suppression of both glycolysis and mitochondrial respiration, impaired DNA repair, and the induction of apoptosis.

[0459] Autocrine type I IFN signaling is regulated by STING. Our gain-of-function model of type I IFN signaling suggest that small-molecule STING agonists are potentially able to upregulate PARP9/10/14 levels in IFN signaling negative PDAC tumors and sensitize them to NAMPTi therapy. While many STING agonists requires intratumoral injection (55), which cannot be practically applied for clinical PDAC treatment, a recent study reported a potent STING agonist with systemic anti-cancer activity (56). Our research indicates that the use of systemic STING agonists should be examined as a strategy to sensitize tumors to NAMPTi.

[0460] In conclusion, our studies demonstrated that the upregulation of PARP9/10/14 is the

mechanism by which type 1 IFN signaling leads to increased NAD(H) consumption in PDAC tumors. This NAD(H) consumption resulted in increased dependence upon NAMPT for the cycling of NAM to salvage NAD pools, thus sensitizing these tumors to treatment with NAMPTi.

[0461] Materials and Methods

[0462] Cell Culture. Panc 03.27, HPAF-II, Hs 766T, CFPAC-1, SU.86.86, PANC-1, BxPC-3 and SW 1990 were purchased from American Type Culture Collection (ATCC). DAN-G and YAPC were provided by Dr. David Dawson, University of California, Los Angeles (UCLA). AM1283 cultures were derived from a PDX model provided by the National Cancer Institute (NCI). A2.4 cultures were provided by Memorial Sloan Kettering Cancer Center (MSKCC). Primary human cancer-associated fibroblasts (CAFs) were established from surgical PDAC specimens by a previously described protocol (58) and verified by wild-type KRAS status and α -smooth muscle actin expression as described (59). SUIT2, T3M4 and PATU 8988T were purchased from Research Resource Identifiers (RRIDs). All cells were between passages 3 and 20 and cultured in DMEM with 10% FBS and 1% Penicillin/Streptomycin at 37 °C in 5% CO₂ incubator. Cells were routinely authenticated and checked for Mycoplasma contamination using the MycoAlert kit (Lonza).

[0463] Antibodies and drugs. Vinculin (#3901S), MX1 (#37849S), STAT1 (#14994S), pH2A.X Ser139(#9718S), STING (#13647S), CD38 (#14637S), E-cadherin (#3195S), N-cadherin (#14215S), AMPK α (#5832), pAMPK α Thr172 (#2535), anti-rabbit secondary antibody HRP (#7074S) and anti-mouse secondary antibody (#7076S) were purchased from Cell Signaling Technology. Also used were PARP-14 (Santa Cruz, #sc-377150), PARP10 (Novus, #NB100-2157), PARP9 (Proteintech, #17535-1-AP) and PAR (Trevigen, #4336-APC-050). IFN β (#11415-1), IL-6 (#11605-2) and TGF β 3 (#11627-1) were purchased from PBL Assay Science. TNF α (#210TA020) was purchased from R&D. EGF (#E9644), FGF (#11123149001), MCSF (#GF053) and GM-CSF (#GF413) were purchased from Sigma Aldrich. IL-10 (#200-10), LIF(#300-05) and PDGF (#100-13A) were purchased from PeproTech. FK866 ((E) - Daporinad, #HY-50876) was purchased from Med Chem Express (MCE). Nicotinamide riboside (#23132) was purchased from Cayman Chemical.

[0464] NAD/NADH Assay. NAD/NADH levels were measured by the NAD/NADH-Glo Assay (Promega, #G9071) was used. Cells were seeded in 96-well plates (2D culture) or poly(2-hydroxyethyl methacrylate)-coated (20 mg/ml in 95% ethanol, Sigma, #P3932) 96-well plates (3D culture) for 24 h. Then cells were lysed with 50 μ L of D-PBS and 50 μ L of 0.2 N NaOH solution with 1% DTAB. The lysates were centrifuged at 4 °C 14,000 g and the supernatant was

collected. A BCA Protein Assay Kit (Pierce, #23227) was used to measure the protein concentration of the lysates. To measure NAD, 20 i.iL lysate was added to 384-well plate (Greiner bio-one, #781098), treated with 10 i.iL 0.4 N HCL and heat quenched at 60 °C for 15 min. This was then neutralized with 10 i.iL Trizma base solution. NADH samples alone were heat quenched in the same manner as the NAD samples, followed by the addition of 20 i.iL HCL/Trizma solution. An equal volume of NAD/NADH-Glo Detection Reagent was added to each well and incubated at room temperature for 30 min. The luminescence was measured by Synergy H1 Hybrid Multi-Mode Reader (BioTek). The sample NAD/NADH levels based on luminescence intensity were calculated based on the NAD/NADH standard curves. The final data (i.imol NAD(H)/g protein) were adjusted based on BCA results.

[0465] pH2A.X assay. Cells were harvested, fixed, and permeabilized with cytofix/cytoperm (BD biosciences, #554722) for 15 min on ice, and then stained with a phospho-Ser139 H2A.X antibody conjugated to fluorochrome FITC (EMD Millipore, #05-636, 1:800 dilutions in perm/wash) at room temperature in the dark for 20 min. Finally, cells were washed and then stained with 0.5 mL of DAPI (Invitrogen, #D1306) for DNA content before the acquisition of data by flow cytometry. 5-ethynyl2-deoxyuridine (EdU) cell cycle profiling. Panc 03.27 cells were pulsed with 10 μ M EdU (Invitrogen) for 2 h, washed twice with PBS, and then released in fresh media containing 5 μ M deoxyribonucleosides. 4 h following release in fresh media, the cells were collected and then fixed with 4% paraformaldehyde. They were permeabilized using saponin perm/wash reagent (Invitrogen). Cells were then stained with azide-Alexa Fluor 647 by Click reaction (Invitrogen; Click-iT EdU Flow cytometry kit, #C10634). Total DNA content was assessed by staining with FxCycle-Violet (Invitrogen, #F10347) at 1 μ g/mL final concentration. Flow cytometry data were acquired on five-laser LSRII cytometers (BD), and analyzed using FlowJo software (Tree Star). The cell cycle durations were then calculated using equations for multiple time-point measurements according to previously published methods (60).

[0466] Western Blot. Cells were lysed in cold RIPA lysis buffer with protease and phosphatase inhibitors (Thermo Scientific). The lysates were subsequently normalized using a BCA assay, then diluted using RIPA buffer and 6 x laemmli loading dye. Protein extracts were resolved on SDS-PAGE and then electrotransferred to an Immun-Blot Nitrocellulose membrane (Bio-Rad, #1620115). After blocking using 5% nonfat milk in TBS + 0.1% Tween-20 (TBS-T), membranes were probed with the indicated primary antibodies at 4 °C overnight. After incubation, the membranes were washed with TBS-T and then probed with horseradish peroxidase (HRP)-conjugated secondary antibodies at room temperature for 1h. Blots were

developed using Immobilon Forte Western HRP Substrate (Millipore, #WBLUF0500) and imaged on the LI-COR Odyssey imaging system.

[0467] Seahorse respirometry assay. Respirometry assays were performed as described (61). Panc 03.27 and SUI2 cells were plated into an XF96 microplate at a density of 20,000 cells per well. FK866, nicotinamide riboside (NR), and human IFN β were added to the cell culture 24 hours prior to the measurement and again injected into the experimental medium prior to respirometry measurement. The mitochondrial stress test conditions included injection of 2 μ M oligomycin, 0.9 μ M FCCP, 2 μ M antimycin A and rotenone. Oxygen consumption rates were all normalized to cellular protein content per well.

[0468] Kinetic proliferation assay. For mono-culture, cells were seeded at 1,000 cells / well in ultra-low attachment (ULA) round bottom 96-well plates (Corning, #7007). For co-culture, PDAC cells labeled with GFP were seeded at 1,000 cells / well and CAF cells labeled with mCherry at 8,000 cells / well. Drugs were added after 72 h incubation, and the IncuCyte Zoom live-cell imaging system was used to track cell proliferation. Images were taken with white light, green fluorescence, and red fluorescence were taken every 3 hours for 5 days. Proliferation was measured using a combination of the size of the cell spheroids and the total measured green and red fluorescence at each time point.

[0469] Knock down. For generation of stable knockdown cell lines, PDAC cells were transduced with a lentivirus harvested from HEK293FT cells in the presence of polybrene. Following transduction, cells underwent antibiotic selection and knockdown efficiency was confirmed using immunoblot analysis. For inducible PARP9, PARP10, and PARP14 knockdown, PARP9 shRNA oligonucleotides (shPARP9 (SEQ ID NO:1) and (SEQ ID NO:2); (SEQ ID NO:3) and (SEQ ID NO:4), (SEQ ID NO:5) and (SEQ ID NO:6) PARP10 shRNA oligonucleotides (shRNA10 (SEQ ID NO:7) and (SEQ ID NO:8); (SEQ ID NO:9) and (SEQ ID NO:10); (SEQ ID NO:11) and (SEQ ID NO:12) and PARP14 shRNA oligonucleotides (shPARP14 (SEQ ID NO:13) and (SEQ ID NO:14) and (SEQ ID NO:15) and (SEQ ID NO:16); (SEQ ID NO:17) and (SEQ ID NO:18) were annealed and ligated into pENTR/H1/TO vector (Invitrogen #K4920-00) following BLOCK-iT Inducible H1 RNAi Entry Vector Kit manual. Resulting shRNA constructs were recombined into pLentipuro/BLOCK-iT-DEST using Gateway LR Clonase II (Invitrogen #11791-020). Recombinant lentiviruses were packaged in 293T cells by co-transfecting each of lentivirus plasmid with packaging vectors containing the gag/pol, rev and vsvg genes. Lentivirus was harvested 48 hours after transfection and added to subconfluent Panc0327 and SUI2 cells with polybrene for 16 hours. After 48hr cells were selected in puromycin for 1 week. Doxycycline induction of knockdown is controlled by the Tet

repressor (TetR) protein expressed from the pLenti0.3/EF/GW/IVS-Kozak-TetR-P2A-Bsd vector. Knockdown was induced with 50 ng/mL doxycycline for at least 72hrs.

[0470] IFN receptor knock out. Three sgRNA sites were designed for the IFNAR1 gene. The recombinant plasmids of Lentiviral vector2-IFNAR1-sgRNA were constructed. The constructed vectors were transfected into PATU8988T and SUI2-mSTING cells with Lipofectamine 3000. 24 hours later, cells were treated with puromycin for 3 days. The two gRNAs (#1: (SEQ ID NO:19) and #2: (SEQ ID NO:20) with the best knockout effect were selected. Following puromycin selection, cells were singly cloned. Single cell cloning was performed with limited dilution of cells into 96-well plates. At least 2 single clones of each gRNA were confirmed as knockout ones with genomic DNA PCR and TIDE In/del analysis after Sanger sequencing.

[0471] Quantitative real-time PCR (qRT-PCR). Total RNA was isolated from cells using the Zymo Quick-RNA MiniPrep kit. Reverse transcription was performed using the High Capacity cDNA Reverse Transcription kit (Life Technologies). Quantitative PCR was performed using EvaGreen qPCR Master Mix (Lamda Biotech). RNA expression values were normalized and calculated as relative expression to control. Primer sequences used for qRT-PCR for each gene are as follows: SIRT1 (Forward primer (FP)-(SEQ ID NO:21), Reverse Primer (RP)- (SEQ ID NO:22); SIRT2 (FP-(SEQ ID NO:23), RP-(SEQ ID NO:24); SIRT3 (FP-(SEQ ID NO:25), RP-(SEQ ID NO:26); SIRT4 (FP-(SEQ ID NO:27), RP-(SEQ ID NO:28); SIRT5 (FP-(SEQ ID NO:29), RP-(SEQ ID NO:30); SIRT6 (FP-(SEQ ID NO:31), RP-(SEQ ID NO:32); SIRT7 (FP-(SEQ ID NO:33), RP-(SEQ ID NO:34); PARP1 (FP-(SEQ ID NO:35), RP-(SEQ ID NO:36); PARP2 (FP-(SEQ ID NO:37), RP-(SEQ ID NO:38); PARP3 (FP-(SEQ ID NO:39), RP-(SEQ ID NO:40); PARP4 (FP-(SEQ ID NO:41), RP-(SEQ ID NO:42); PARP5a (FP-(SEQ ID NO:43), RP-(SEQ ID NO:44); PARP5b (FP-(SEQ ID NO:45), RP-(SEQ ID NO:46); PARP6 (FP-(SEQ ID NO:47), RP-(SEQ ID NO:48); PARP7 (TIPARP) (FP-(SEQ ID NO:49), RP-(SEQ ID NO:50); PARP8 (FP-(SEQ ID NO:51), RP-(SEQ ID NO:52); PARP9 (FP-(SEQ ID NO:53), RP-(SEQ ID NO:54); PARP10 (FP-(SEQ ID NO:55), RP-(SEQ ID NO:56); PARP11 (FP-(SEQ ID NO:57), RP-(SEQ ID NO:58); PARP12 (FP-(SEQ ID NO:59), RP-(SEQ ID NO:60)); PARP14 (FP-(SEQ ID NO:61), RP-(SEQ ID NO:62)); PARP15 (FP-(SEQ ID NO:63), RP-(SEQ ID NO:64)); PARP16 (FP-(SEQ ID NO:65), RP-(SEQ ID NO:66)); CD38 (FP-(SEQ ID NO:67), RP-(SEQ ID NO:68)); CD73 (NT5E) (FP-(SEQ ID NO:69), RP-(SEQ ID NO:70)).

[0472] Immunohistochemistry. Formalin-fixed, paraffin-embedded tumor samples were incubated at 60°C for 1h, deparaffinized in xylene, and rehydrated with graded alcohol washes. Slides were then boiled in 0.01 M sodium citrate buffer for 15 m followed by quenching of endogenous peroxidase with 3% hydrogen peroxide for antigen retrieval. After 1 h of blocking

with 5% donkey serum at room temperature, primary antibodies were added and incubated overnight at 4°C. Biotin-conjugated anti-rabbit secondary antibody (1:500 Jackson Labs) was added and developed using Elite Vectastain ABC kit.

[0473] Mice. NCG mice (NOD-Prkdc^{em26Cd52}Il2rg^{em26Cd22}/NjuCrl) were purchased from Charles River. Mice used for orthotopic implantation were males 6 to 8 weeks of age.

[0474] Orthotopic implantation and tumor imaging. Cells were trypsinized and washed twice in PBS. Mice were anesthetized with Isothesia (Isoflurane) solution (Henry Schein Animal Health, #029405). After shaving and swabbing with a sterile alcohol pad followed by povidone-iodide scrub, a 0.5 cm incision was made on the left lateral abdomen. The tail of the pancreas was located. Cells (SUIT2 3×10^4 cells, Panc 03.27 2×10^5 cells) in 30 μ L FBS-free DMEM and Matrigel (1:1) were injected into the tail of the pancreas with an insulin syringe (BD, #08290-3249-11). The abdominal and skin incisions were closed with 5-0 coated VICRYL sutures (Ethicon, #J385H). 100 μ g Carporfen (Zoetis, Rimadyl, #141-199) was injected immediately after surgery and on POD1. To monitor tumor growth, mice were injected intraperitoneally with 50 mg/kg D-Luciferin (BioVision, #7903) and imaged with the IVIS Lumina III imaging system (PerkinElmer). Data were analyzed using Living Image v4.5 software.

[0475] Viability assay. For 2D anchorage-dependent CellTiter-Glo analysis, cells were plated at 1×10^3 cells / well in 50 μ L / well in white opaque 384-well plates and treated as described. Following incubation, 50 μ L of CellTiter-Glo reagent (Diluted 1:5 in dPBS) was added to each well. The plates were incubated at room temperature for 5 min and luminescence was measured using a BioTek microplate luminescence reader.

[0476] For 3D anchorage-independent culture CellTiter-Glo analysis, cells were plated at 1×10^3 cells / in 50 μ L / well in white opaque 384-well plates previously coated with poly-HEMA and treated as described. Following incubation, 50 μ L of 3D CellTiter-Glo reagent (Diluted 1:5 in dPBS) was added to each well. The plates were then shaken using a BioTek microplate reader for 5 min and then incubated at room temperature for 25 min, after which luminescence was measured using a BioTek microplane luminescence reader.

[0477] Invasion assay. Approximately 1×10^5 cells were suspended in 300 μ L serum-free DMEM and added into the upper chamber of Transwell plate (Corning BioCoat Matrigel Invasion Chamber, catalog 354480). 500 μ L DMEM with 10% FBS were added in the lower chamber. After 48h incubation, the cells were fixed in 4% paraformaldehyde and permeabilized with 0.5% Triton-100X, then stained with Hematoxylin. A cotton swab was used to remove cells on the upper surface of the filter manually. The invasion cells images were taken by 10 X

magnification microscope in 5 random non-overlapping fields, then counted using ImageJ software. Statistics. Data were presented as means $\pm$ SD with indicated biological replicates. Comparisons of two groups were calculated using indicated unpaired or paired two-tailed Student's t-test and P values <0.05 were considered significant. All statistical analyses were performed in Graphpad Prism 8.0.

[0478] All patents, patent applications, articles and publications mentioned herein, both supra and infra, are hereby expressly incorporated herein by reference in their entireties.

[0479] Informal Sequence Listing

[0480] SEQ ID NO:1

CACCGCATATACTTCACCAAGAACCTTCAAGAGAGGTTCTTGGTGAAGTATATGC-3'

[0481] SEQ ID NO:2

AAAAGCATATACTTCACCAAGAACCTCTCTTGAAGGTTCTTGGTGAAGTATATGC

[0482] SEQ ID NO:3

CACCGGGACATCCGTTAAATATTGTTTCAAGAGAACAAATATTTAACGGATGTCCC-3'

[0483] SEQ ID NO:4

AAAAGGGACATCCGTTAAATATTGTTCTCTTGAAACAATATTTAACGGATGTCCC

[0484] SEQ ID NO:5

CACCGGGTAGGTAGATACCAAATGATTCAAGAGATCATTGTTGATCTACCTACCC-3'

[0485] SEQ ID NO:6

AAAAGGGTAGGTAGATACCAAATGATCTCTTGAATCATTGTTGATCTACCTACCC

[0486] SEQ ID NO:7

CACCGGCAGATCACGAACTACATGGTTCAAGAGACCATGTAGTTCGTGATCTGCC-3'

[0487] SEQ ID NO:8

AAAAGGCAGATCACGAACTACATGGTCTCTTGAACCATGTAGTTCGTGATCTGCC-3'

[0488] SEQ ID NO:9

CACCGGAGTTGTACCTGGAGAATGATTCAAGAGATCATTCTCCAGGTACAACCTCC-3'

[0489] SEQ ID NO:10

AAAAGGAGTTGTACCTGGAGAATGATCTCTTGAATCATTCTCCAGGTACAACCTCC-3'

[0490] SEQ ID NO:11

CACCGCTCTGTTGTTTGAATAAACGTTCAAGAGACGTTTATTCAAACAACAGAGC-3'

[0491] SEQ ID NO:12

AAAAGCTCTGTTGTTTGAATAAACGTCTCTTGAACGTTTATTCAAACAACAGAGC-3'

[0492] SEQ ID NO:13

CACCGCAGATGTGTATAAAGCAAAGTTCAAGAGACTTTGCTTTATACACATCTGC-3'

[0493] SEQ ID NO:14

AAAAGCAGATGTGTATAAAGCAAAGTCTCTTGAACTTTGCTTTATACACATCTGC-3'

[0494] SEQ ID NO:15

CACCGCATTGAAGTTGAGAACAAAGTTCAAGAGACTTTGTTCTCAACTTCAATGC-3'

[0495] SEQ ID NO:16

AAAAGCATTGAAGTTGAGAACAAAGTCTCTTGAACTTTGTTCTCAACTTCAATGC-3'

[0496] SEQ ID NO:17

CACCGCACCATCCAAGTTTATTTGTTTCAAGAGAACAAATAAACTTGGATGGTGC-3'

[0497] SEQ ID NO:18

AAAAGCACCATCCAAGTTTATTTGTTCTCTTGAAACAAATAAACTTGGATGGTGC-3'

[0498] SEQ ID NO:19 GCACTAGGGTCGTCGCGCCC

[0499] SEQ ID NO:20 GCTCGTCGCCGTGGCGCCAT

[0500] SEQ ID NO:21 ATGCTCGCCTTGCTGTAGAC

[0501] SEQ ID NO:22 TGTTGCAAAGGAACCATGACAC

[0502] SEQ ID NO:23 TGCGGAACTTATTCTCCCAGA

[0503] SEQ ID NO:24 GAGAGCGAAAGTCGGGGAT

[0504] SEQ ID NO:25 GACATTCGGGCTGACGTGAT

[0505] SEQ ID NO:26 ACCACATGCAGCAAGAACCTC

[0506] SEQ ID NO:27 AGCCTCCATTGGGTTATTTGTG

[0507] SEQ ID NO:28 TCTGGTATCCCCGATTCGGT

[0508] SEQ ID NO:29 GCCATAGCCGAGTGTGAGAC

[0509] SEQ ID NO:30 CAACTCCACAAGAGGTACATCG

[0510] SEQ ID NO:31 CCCACGGAGTCTGGACCAT

[0511] SEQ ID NO:32 CTCTGCCAGTTTGTCCCTG

[0512] SEQ ID NO:33 AGAAGCGTTAGTGCTGCCG

[0513]	SEQ ID NO:34	GAGCCCGTCACAGTTCTGAG
[0514]	SEQ ID NO:35	CGGAGTCTTCGGATAAGCTCT
[0515]	SEQ ID NO:36	TTTCCATCAAACATGGGCGAC
[0516]	SEQ ID NO:37	AGCAAGATGAATCTGTGAAGGC
[0517]	SEQ ID NO:38	CACTGAAGTTCCTCTGGGCA
[0518]	SEQ ID NO:39	CCGCATCATGCCACATTCTG
[0519]	SEQ ID NO:40	CCAACTCAGTGTCTGGGTC
[0520]	SEQ ID NO:41	AGGTTTTGCAGAATCATCACAGT
[0521]	SEQ ID NO:42	CCTCACATTACCAAGTTTGCTCA
[0522]	SEQ ID NO:43	TGGACGCGGCAAACGTAAAT
[0523]	SEQ ID NO:44	AAGCGGGATGAGACCTCCAT
[0524]	SEQ ID NO:45	TCTTGGACTTGAGCACCTAATG
[0525]	SEQ ID NO:46	CTCTTCCTCCACAGACTGAAAC
[0526]	SEQ ID NO:47	TCCTCCGGACAGAACCTATT
[0527]	SEQ ID NO:48	CCAGCCCAAATCCTTCCTTAT
[0528]	SEQ ID NO:49	CTCCGCCTCCGCGAC
[0529]	SEQ ID NO:50	TAGCTCCAAGTCTCCTCAG
[0530]	SEQ ID NO:51	TGTGCTAGTTACTACAGAGCCA
[0531]	SEQ ID NO:52	CCCCATCATAGTTCACCTGCC
[0532]	SEQ ID NO:53	TGGCAAGGAAAAAGGAGCGA
[0533]	SEQ ID NO:54	AGCTCTTGAGTTGGAGGCAC
[0534]	SEQ ID NO:55	CCTTCTACGACACCCTGGAC
[0535]	SEQ ID NO:56	ATACACGCCCTTCCCGTAGA
[0536]	SEQ ID NO:57	GGAAGCGAATCCAGAGATGTT
[0537]	SEQ ID NO:58	GCTGCTTTCCAGTGGTGAGA
[0538]	SEQ ID NO:59	TACGTGTCTCCCCAGGATGT
[0539]	SEQ ID NO:60	GCGTGCGGTAAAGAGGTTC

[0540] SEQ ID NO:61 CACGGTGGCAAGCAAGTTTA
 [0541] SEQ ID NO:62 CCATTTCGATTGACGTGTGGC
 [0542] SEQ ID NO:63 TCCGACCCCCAGAGAACTTA
 [0543] SEQ ID NO:64 TGACAATGACATCGGCCAG
 [0544] SEQ ID NO:65 GTGCAGGGAAGGCAGAGTTT
 [0545] SEQ ID NO:66 GGCTGTATATGAGGGCCAGG
 [0546] SEQ ID NO:67 CAACTCTGTCTTGGCGTCAGT
 [0547] SEQ ID NO:68 CCCATACACTTTGGCAGTCTACA
 [0548] SEQ ID NO:69 CCAGTACCAGGGCACTATCTG
 [0549] SEQ ID NO:70 TGGCTCGATCAGTCCTTCCA

[0550] References for Background and Example 1

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CLAIMS

What is claimed is:

1. A method of treating cancer in a patient in need thereof, the method comprising administering to the patient an effective amount of an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof; wherein the cancer has an increased level of interferon or interferon signaling pathway activity.
2. The method of claim 1, comprising administering to the patient an effective amount of an ATR kinase inhibitor.
3. The method of claim 1, comprising administering to the patient an effective amount of an NAMPT inhibitor.
4. The method of claim 1, comprising administering to the patient an effective amount of an ATR kinase inhibitor and an NAMPT inhibitor.
5. The method of claim 1, wherein the cancer has an increased level of interferon, and wherein the interferon is an interferon protein or an interferon RNA.
6. The method of claim 1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof.
7. The method of claim 1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and a combination of two or more thereof.
8. The method of claim 7, wherein the interferon pathway protein or the interferon pathway RNA is STAT1, MX1, or a combination thereof.
9. The method of claim 1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon

pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, and a combination of two or more thereof.

10. The method of claim 1, wherein the cancer has an increased level of interferon signaling pathway activity, wherein the interferon signaling pathway activity is an interferon pathway protein or an interferon pathway RNA selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, and a combination of two or more thereof.

11. A method of treating cancer in a patient in need thereof, the method comprising:
- (i) determining the level of interferon or interferon signaling pathway activity in a sample obtained from a patient; and
 - (ii) administering to the patient a therapeutically effective amount of an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof.

12. The method of claim 11, comprising administering to the patient an effective amount of the ATR kinase inhibitor.

13. The method of claim 11, comprising administering to the patient the effective amount of an NAMPT inhibitor.

14. The method of claim 11, comprising administering to the patient the effective amount of an ATR kinase inhibitor and an NAMPT inhibitor.

15. The method of claim 11, wherein the method comprises determining the level of interferon in the sample.

16. The method of claim 15, wherein the interferon is an interferon protein or an interferon RNA.

17. The method of claim 11, wherein the method comprises determining the level of interferon signaling pathway activity in the sample.

18. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof.

19. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprises determining the level of interferon pathway RNA or interferon pathway protein for STAT1, STAT2, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, or a combination of two or more thereof.

20. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for STAT1.

21. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for MX1.

22. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, or a combination of two or more thereof.

23. The method of claim 17, wherein determining the level of interferon signaling pathway activity in the sample comprising determining the level of interferon pathway RNA or interferon pathway protein for PARP9, PARP10, PARP14, STAT1, MX1, or a combination of two or more thereof.

24. The method of claim 11, wherein the interferon is Type 1 interferon.

25. The method of claim 24, wherein the Type 1 interferon is interferon-alpha, interferon-beta, or a combination thereof.

26. The method of claim 11, wherein the cancer has an increased level of interferon or interferon signaling pathway activity relative to a control.

27. The method of claim 11, wherein the cancer has a BRCA mutation, a KRAS mutation, a TP53 mutation, or a combination thereof.

28. The method of claim 11, wherein the cancer is pancreatic cancer.

29. The method of claim 28, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

30. The method of claim 11, wherein the ATR kinase inhibitor is berzosertib, 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol, ceralasertib, schisandrin B, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine, dactolisib, (R)-4-(2-(1H-indol-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine, caffeine, wortmannin, or 2-[(3R)-3-methyl-4-morpholinyl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine.

31. The method of claim 30, wherein the ATR kinase inhibitor is berzosertib.

32. The method of claim 11, wherein the NAMPT inhibitor is daporinad, 4-[5-methyl-4-[[[(4-methylphenyl)sulfonyl]methyl]-2-oxazolyl]-N-(3-pyridinylmethyl)benzamide, N-(4-((3,5-difluorophenyl)sulfonyl)benzyl)imidazo[1,2-a]pyridine-6-carboxamide, N-[[4-[[3-(trifluoromethyl)phenyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, (1Z,2E)-3-(6-aminopyridin-2-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylimidic acid, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N''-4-pyridinyl-guanidine, N-[1,1'-biphenyl]-2-yl-4-(3-pyridinyl)-1H-1,2,3-triazole-1-octanamide, 4-[[[[4-(1,1-dimethylethyl)phenyl]sulfonyl]amino]-methyl]N-3-pyridinylbenzamide, 1-(4-(((1R,5S)-8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-ylmethyl)urea, 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide, N-(3-(1H-pyrazol-4-yl)propyl)-3-((4-fluorophenyl)ethynyl)-4-(pyridin-4-yl)benzamide, 4-(((7-bromo-2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl)(prop-2-yn-1-yl)amino)-N-(pyridin-3-ylmethyl)benzamide, 4-(((7-chloro-3,4-dihydro-3-methyl-2-((4-methyl-1-piperazinyl)methyl)-4-oxo-6-quinazolinyl)methyl)-2-propyn-1-ylamino)-N-(3-pyridinylmethyl)-benzamide, or a combination of two or more of the foregoing..

33. The method of claim 32, wherein the NAMPT inhibitor is daporinad or 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide.

34. The method of claim 11, further comprising administering to the patient a therapeutically effective amount of a PARP inhibitor.

35. The method of claim 34, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, 11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)dione, or 10-((4-

Hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-3(2H)one.

36. The method of claim 35, wherein the PARP inhibitor is olaparib.

37. A method of classifying a cancer in a patient, the method comprising:

- (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2;
- (b) comparing expression levels of the plurality of target genes to a control; and
- (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor.

38. The method of claim 37, wherein the cancer is classified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to the control.

39. A method of classifying a cancer in a patient, the method comprising:

- (a) measuring expression levels of a plurality of target genes in RNA from a sample obtained from the patient, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2;
- (b) comparing expression levels of the plurality of target genes to a control; and
- (c) classifying the cancer as responsive to treatment with an ATR kinase inhibitor, an NAMPT inhibitor, or a combination thereof.

40. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

41. The method of claim 39, wherein the plurality of target genes comprise STAT1 and MX1.
42. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, and PARP14.
43. The method of claim 39, wherein the plurality of target genes comprise at least 2 genes selected from the group consisting of PARP9, PARP10, PARP14, STAT1, and MX1.
44. The method of claim 39, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof when the expression levels of the plurality of target genes are increased relative to the control.
45. The method of claim 44, comprising classifying the cancer as responsive to treatment with a NAMPT inhibitor.
46. The method of claim 44, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor.
47. The method of claim 44, comprising classifying the cancer as responsive to treatment with an ATR kinase inhibitor and a NAMPT inhibitor.
48. A method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.
49. The method of claim 48, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the expression levels of the plurality of target genes are increased relative to a control.
50. A method of identifying a cancer patient responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof, the method comprising measuring expression levels of a plurality of target genes in a sample obtained from the cancer patient, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, PARP14, STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15,

OAS2, PSME1, SOCS1, and STAT2.

51. The method of claim 50, wherein the plurality of target genes comprise at least 2 genes from the group consisting of PARP9, PARP10, and PARP14.

52. The method of claim 50, wherein the plurality of target genes comprise at least 2 genes from the group consisting of STAT1, MX1, MX2, IFIT1, IFI44, IFIT3, OAS1, OAS3, BST2, IFITM1, IFI27, CXCL10, IFI16, IFI30, IFIH1, IFIT2, IFITM2, IRF1, IRF9, IRGM, ISG15, OAS2, PSME1, SOCS1, and STAT2.

53. The method of claim 50, wherein the plurality of target genes comprise STAT1 and MX1.

54. The method of claim 50, wherein the plurality of target genes comprises PARP9, PARP10, PARP14, STAT1, and MX1.

55. The method of any claim 50, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor, a NAMPT inhibitor, or a combination thereof when the expression levels of the plurality of target genes are increased relative to a control.

56. The method of claim 50, further comprising identifying the presence of a type 1 interferon-stimulated gene signature, pCHEK_{S345}, or a combination thereof in a sample obtained from the cancer patient.

57. The method of claim 55, wherein the patient is identified as responsive to treatment with an ATR kinase inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

58. The method of claim 55, wherein the patient is identified as responsive to treatment with a NAMPT inhibitor when the presence of the type 1 interferon-stimulated gene signature, pCHEK_{S345}, or the combination thereof is identified.

59. The method of claim 39, wherein the plurality of target genes comprise at least 3 genes.

60. The method of claim 59, wherein the plurality of target genes comprise at least 4 genes.

61. The method of claim 39, wherein measuring does not comprise a whole transcriptome measurement.

62. The method of claim 39, wherein the cancer has a BRCA mutation, a KRAS mutation, a TP53 mutation, or a combination thereof.

63. The method of claim 39, wherein the cancer is pancreatic cancer.

64. The method of claim 63, wherein the pancreatic cancer is pancreatic ductal adenocarcinoma.

65. The method of claim 39, further comprising administering to the patient an effective amount of ATR kinase inhibitor.

66. The method of claim 65, wherein the ATR kinase inhibitor is berzosertib, 2-(aminomethyl)-6-[4,6-diamino-3-[4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxyoxane-3,4,5-triol, ceralasertib, schisandrin B, 4-cyclohexylmethoxy-2,6-diamino-5-nitrosopyrimidine, dactolisib, (R)-4-(2-(1H-indol-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine, caffeine, wortmannin, or 2-[(3R)-3-methyl-4-morpholinyl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine.

67. The method of claim 65, wherein the ATR kinase inhibitor is berzosertib.

68. The method of claim 39, further comprising administering to the patient an effective amount of a NAMPT inhibitor.

69. The method of claim 68, wherein the NAMPT inhibitor is daporinad, 4-[5-methyl-4-[[[(4-methylphenyl)sulfonyl]methyl]-2-oxazolyl]-N-(3-pyridinylmethyl)benzamide, N-(4-((3,5-difluorophenyl)sulfonyl)benzyl)imidazo[1,2-a]pyridine-6-carboxamide, N-[[4-[[3-(trifluoromethyl)phenyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, (1Z,2E)-3-(6-aminopyridin-2-yl)-N-((5-(4-(4,4-difluoropiperidine-1-carbonyl)phenyl)-7-(4-fluorophenyl)benzofuran-2-yl)methyl)acrylimidic acid, N-[6-(4-chlorophenoxy)hexyl]-N'-cyano-N"-4-pyridinyl-guanidine, N-[1,1'-biphenyl]-2-yl-4-(3-pyridinyl)-1H-1,2,3-triazole-1-octanamide, 4-[[[[4-(1,1-dimethylethyl)phenyl]sulfonyl]amino]methyl] N-3-pyridinylbenzamide, 1-(4-(((1R,5S)-8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)phenyl)-3-(pyridin-4-ylmethyl)urea, 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide, N-(3-(1H-pyrazol-4-yl)propyl)-3-((4-fluorophenyl)ethynyl)-4-(pyridin-4-yl)benzamide, 4-(((7-bromo-2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl)(prop-2-yn-1-yl)amino)-N-(pyridin-3-ylmethyl)benzamide, 4-(((7-chloro-3,4-dihydro-3-methyl-2-((4-methyl-1-piperazinyl)methyl)-4-oxo-6-

quinazoliny)methyl)-2-propyn-1-ylamino)-N-(3-pyridinylmethyl)-benzamide, or a combination of two or more of the foregoing.

70. The method of claim 68, wherein the NAMPT inhibitor is daporinad or 2-hydroxy-2-methyl-N-[1,2,3,4-tetrahydro-2-[2-(3-pyridinyloxy)acetyl]-6-isoquinoliny]-1-propanesulfonamide.

71. The method of claim 39, further comprising administering to the patient a therapeutically effective amount of a PARP inhibitor.

72. The method of claim 71, wherein the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, vekauoarub, pamiparib, 11-methoxy-2-((4-methylpiperazin-1-yl)methyl)-4,5,6,7-tetrahydro-1H-cyclopenta[a]pyrrolo[3,4-c]carbazole-1,3(2H)dione, or 10-((4-hydroxypiperidin-1-yl)methyl)chromeno[4,3,2-de]phthalazin-3(2H)one.

73. The method of claim 71, wherein the PARP inhibitor is olaparib.

74. A computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of claim 37.

75. A computer program product comprising a machine-readable medium storing instructions that, when executed by at least one programmable processor, cause the at least one programmable processor to perform operations comprising the method of claim 37.

76. A system comprising computer hardware configured to perform operations comprising the method of claim 37.

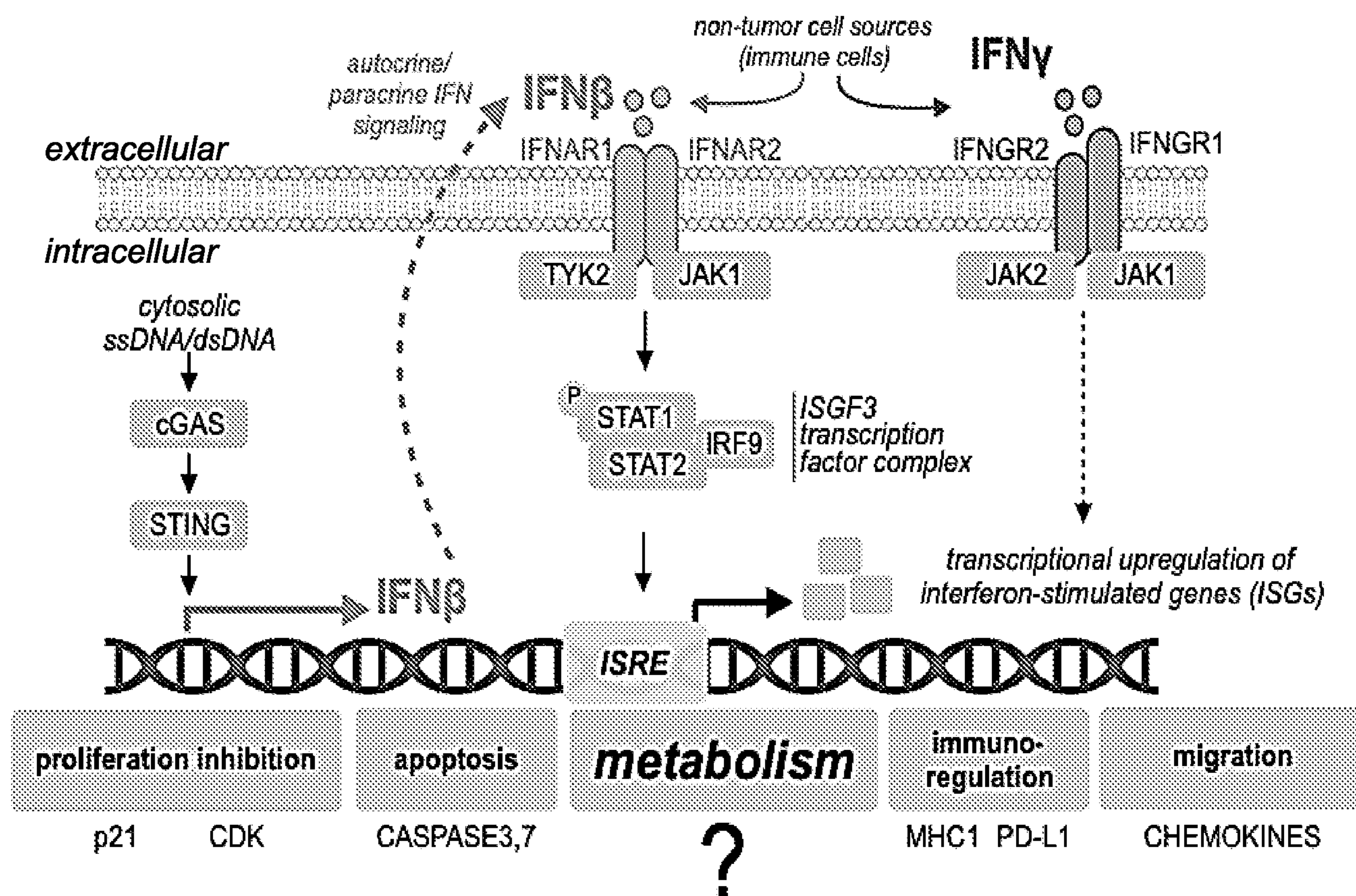


FIG. 1

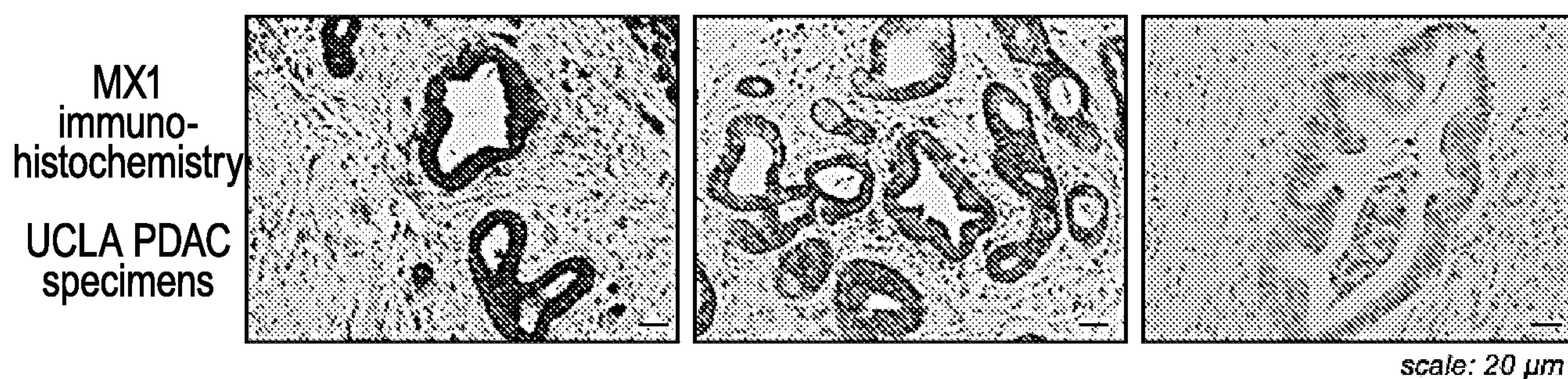


FIG. 2

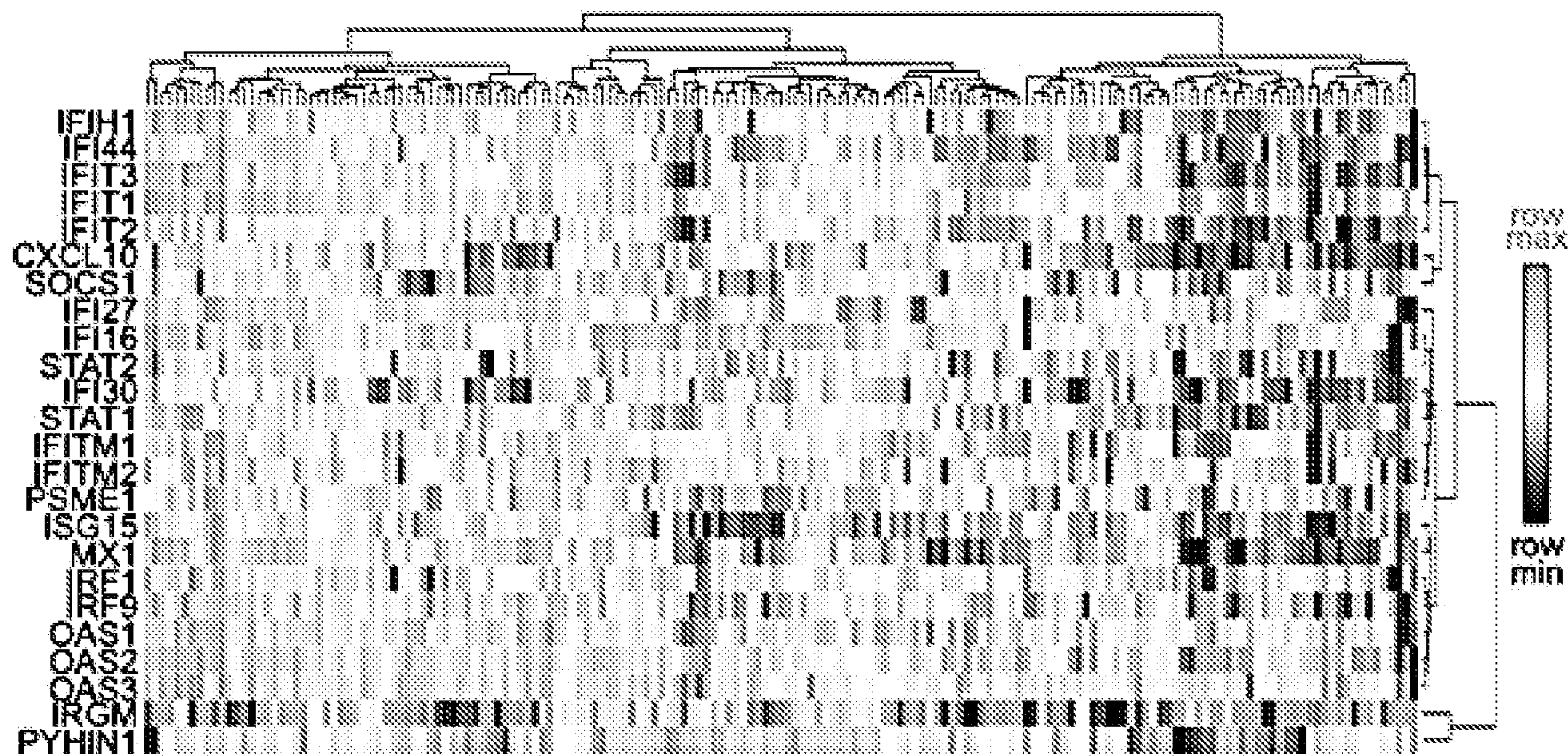


FIG. 3A

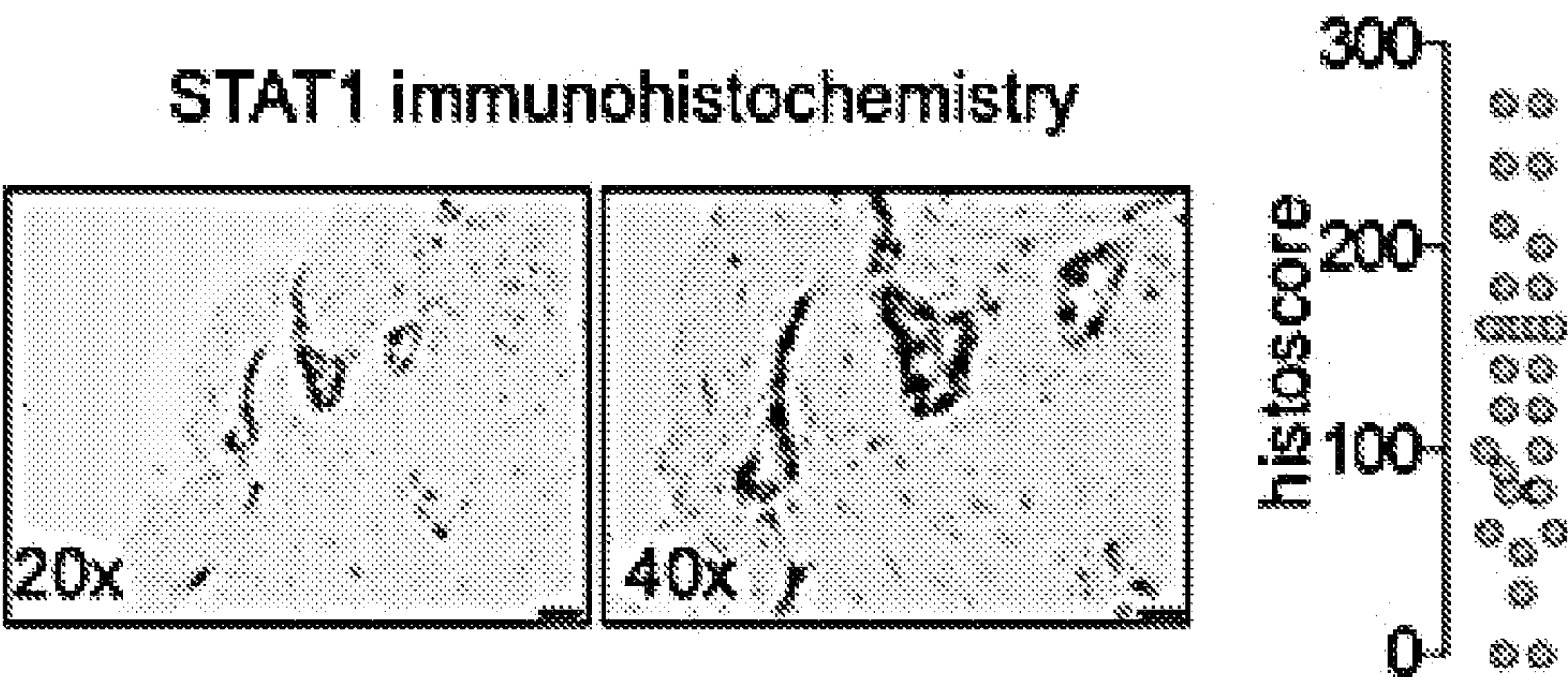


FIG. 3B

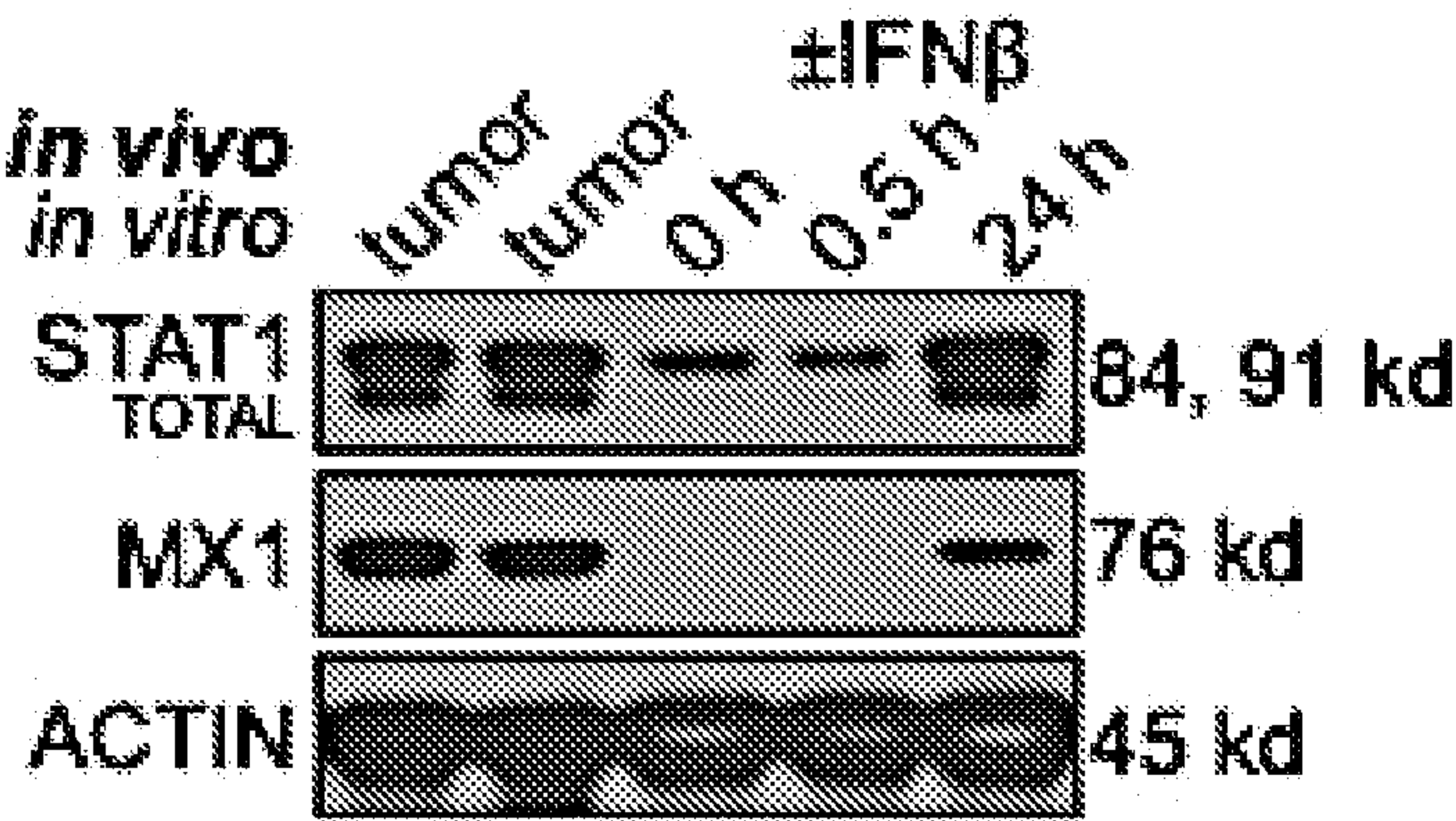


FIG. 3C

nLC-MS/MS proteomics/
phosphoproteomics

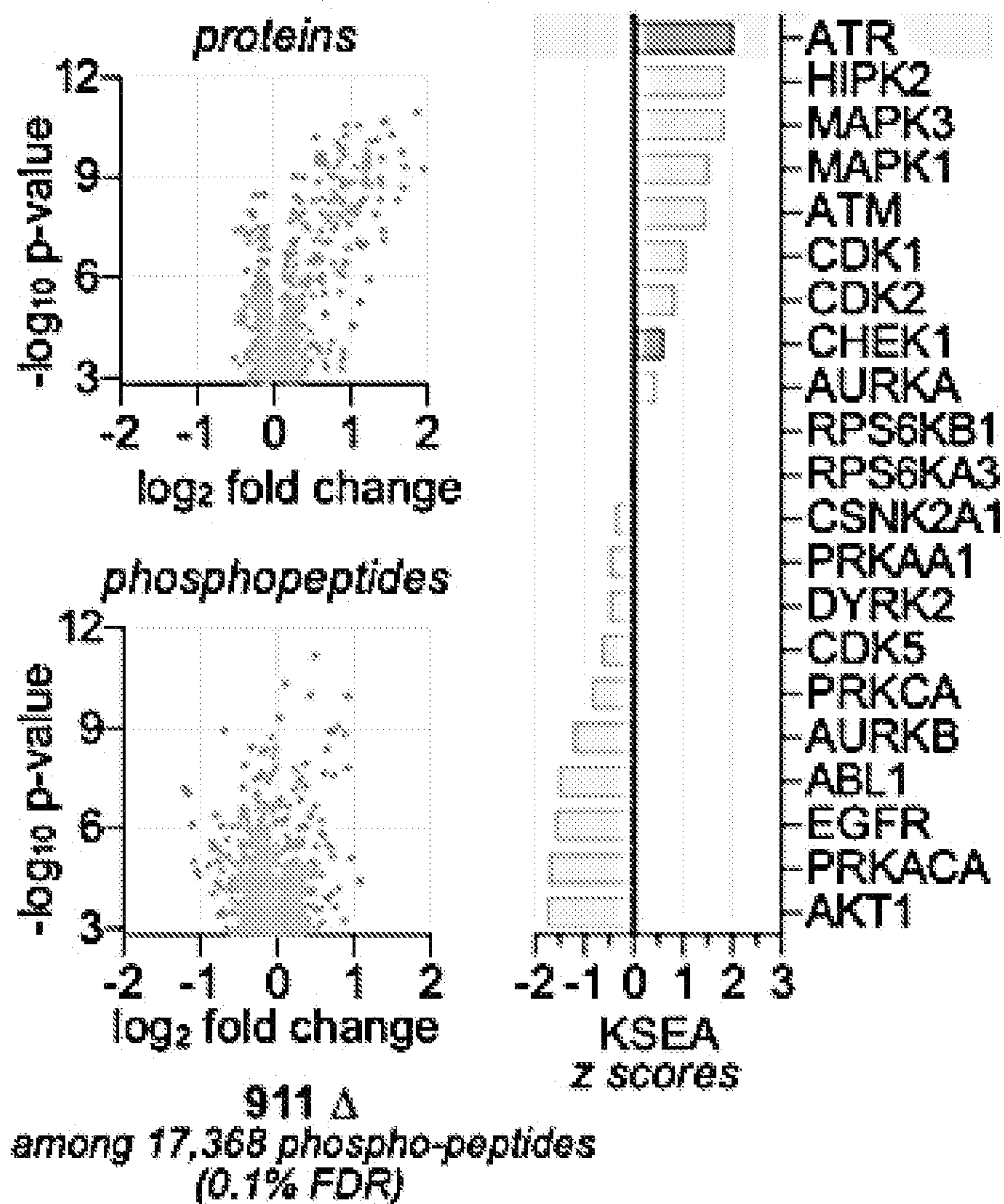


FIG. 3D

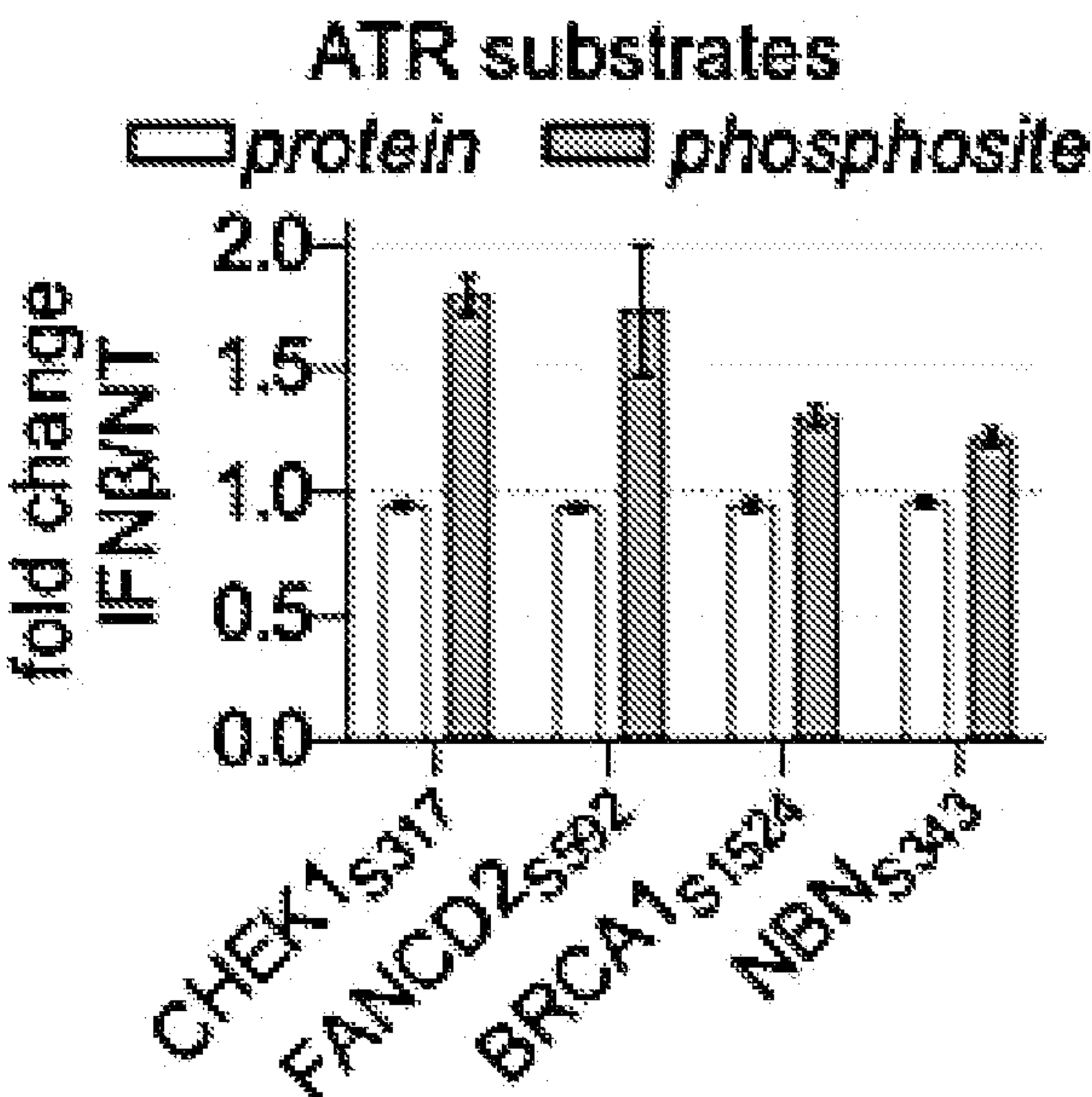


FIG. 3E

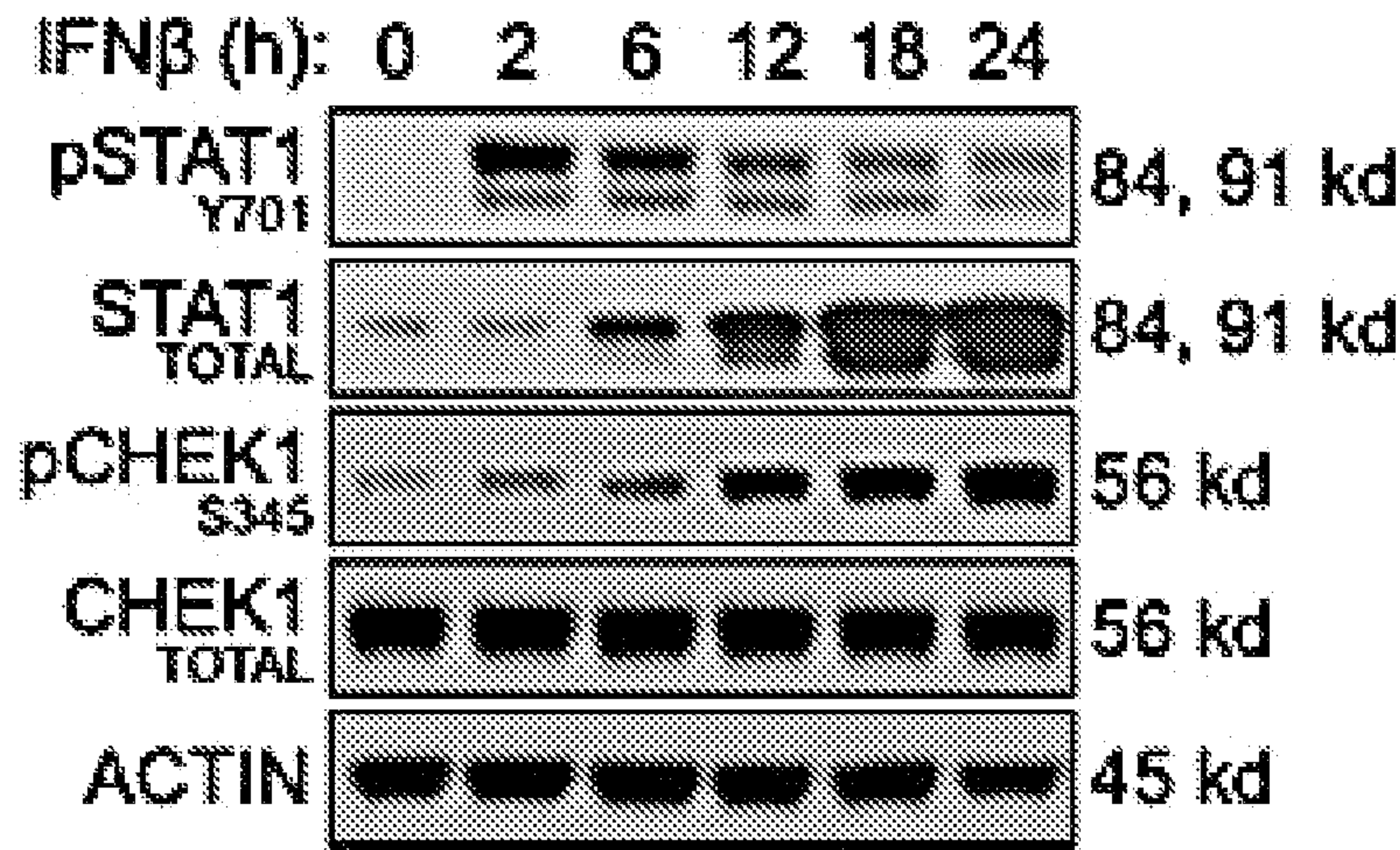


FIG. 3F

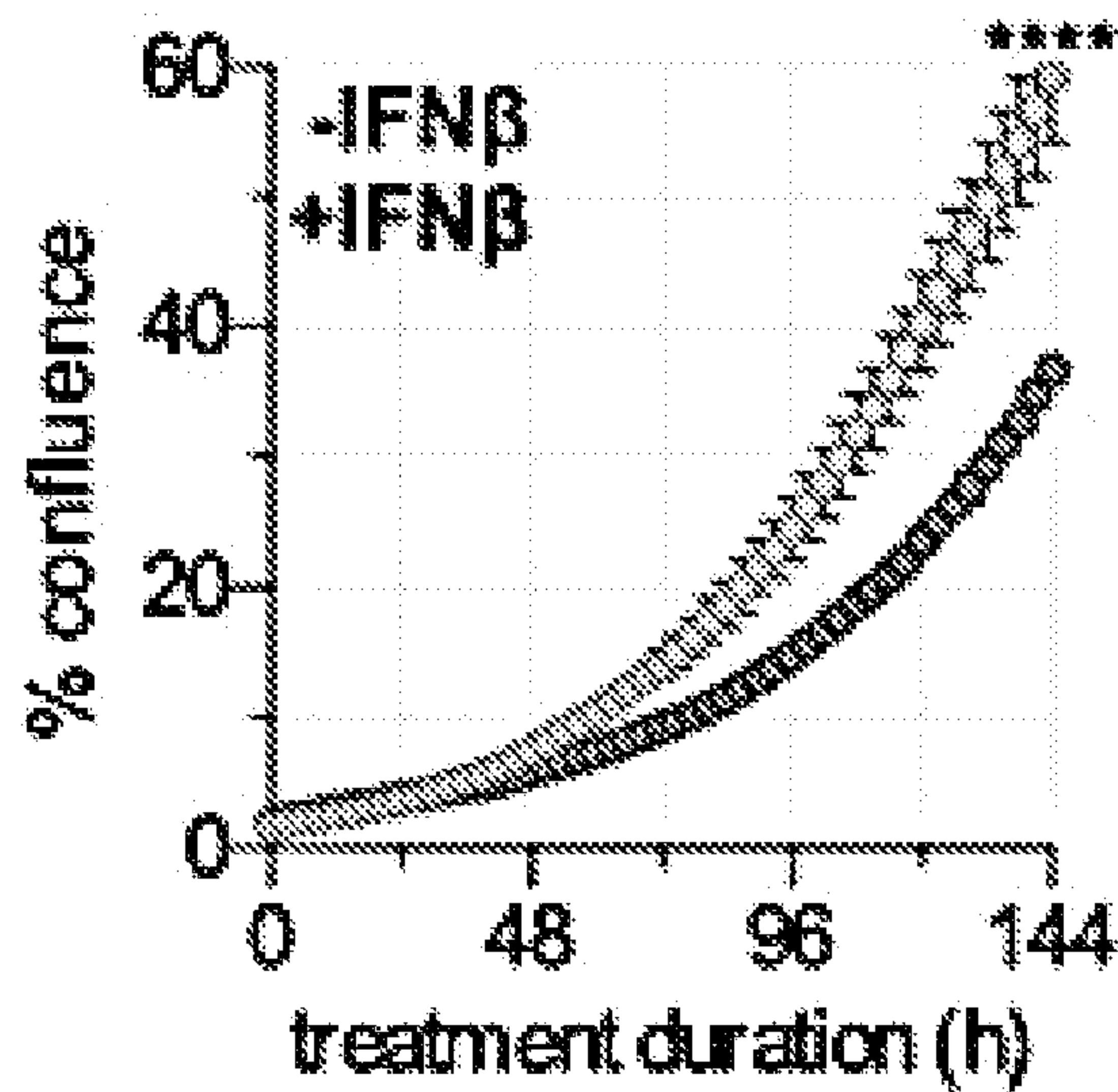


FIG. 3G

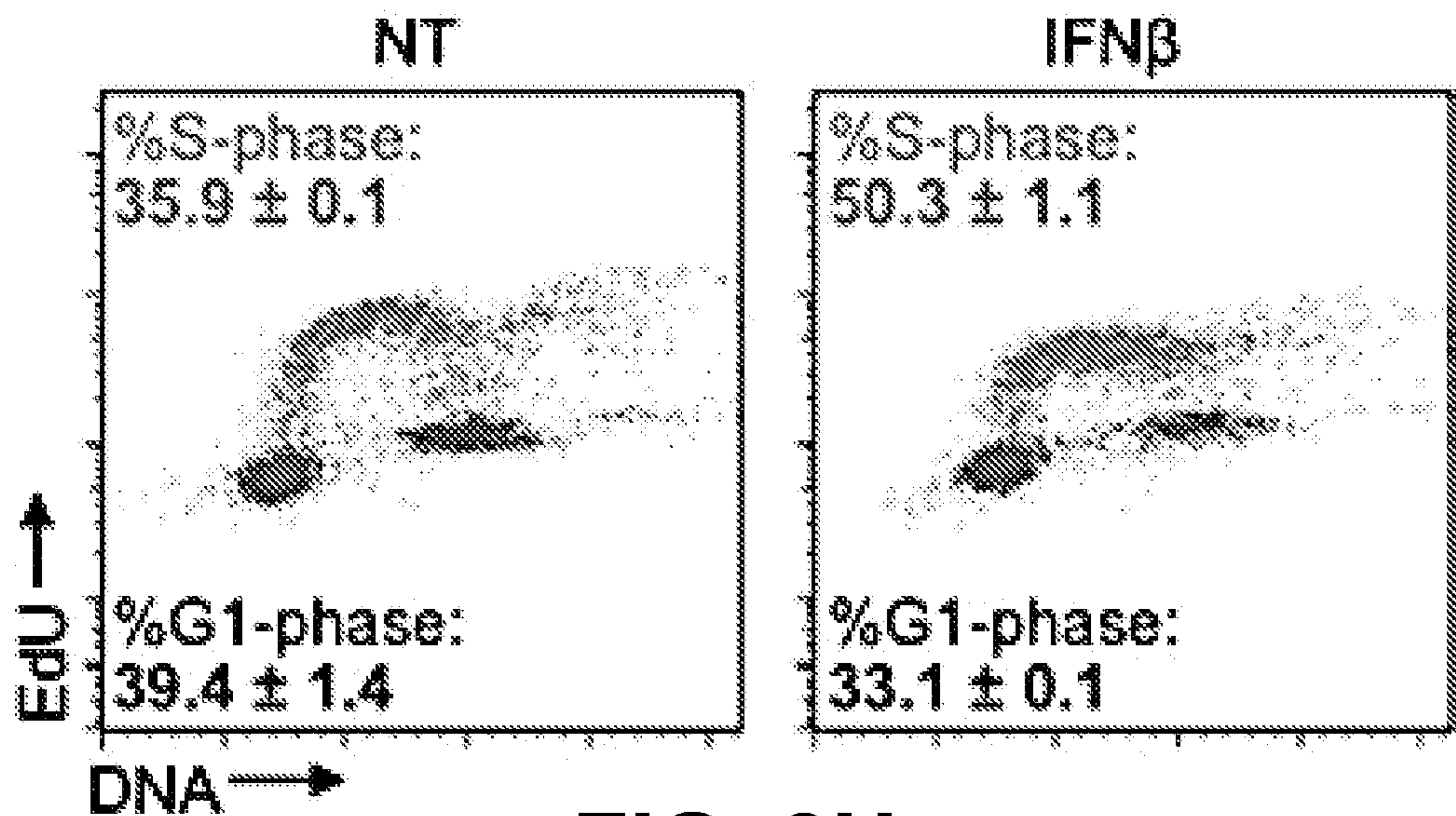


FIG. 3H

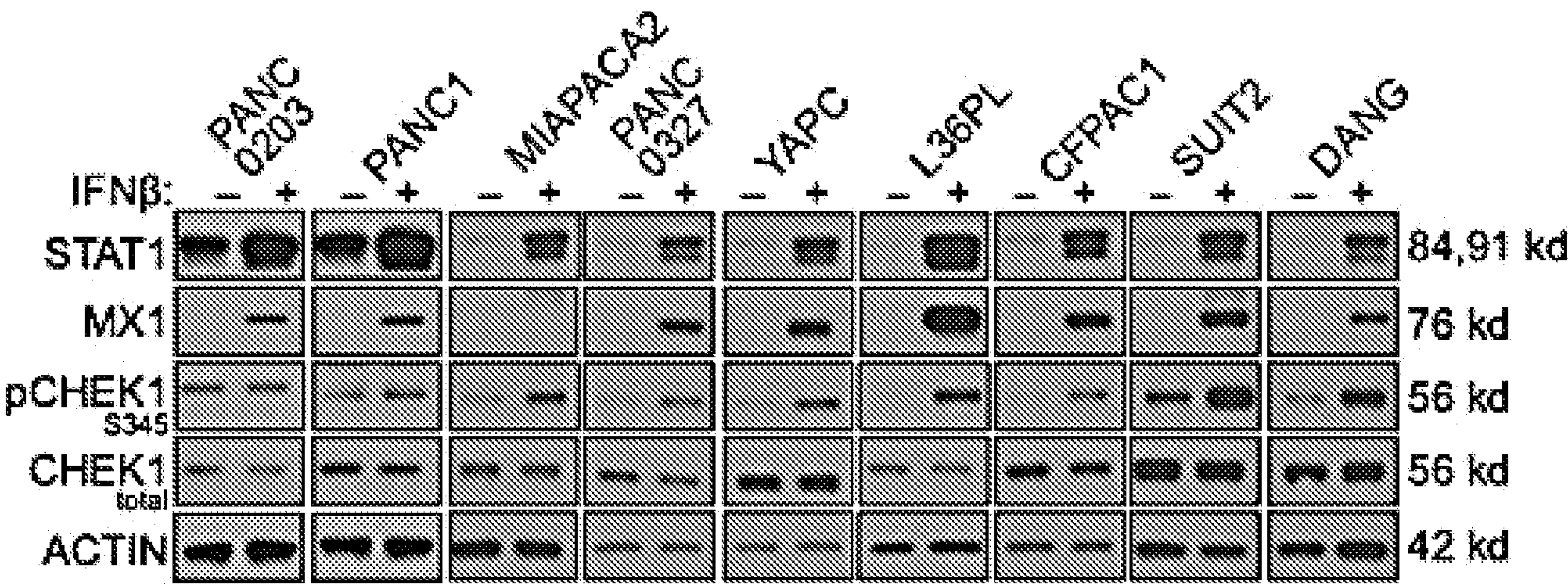


FIG. 3I

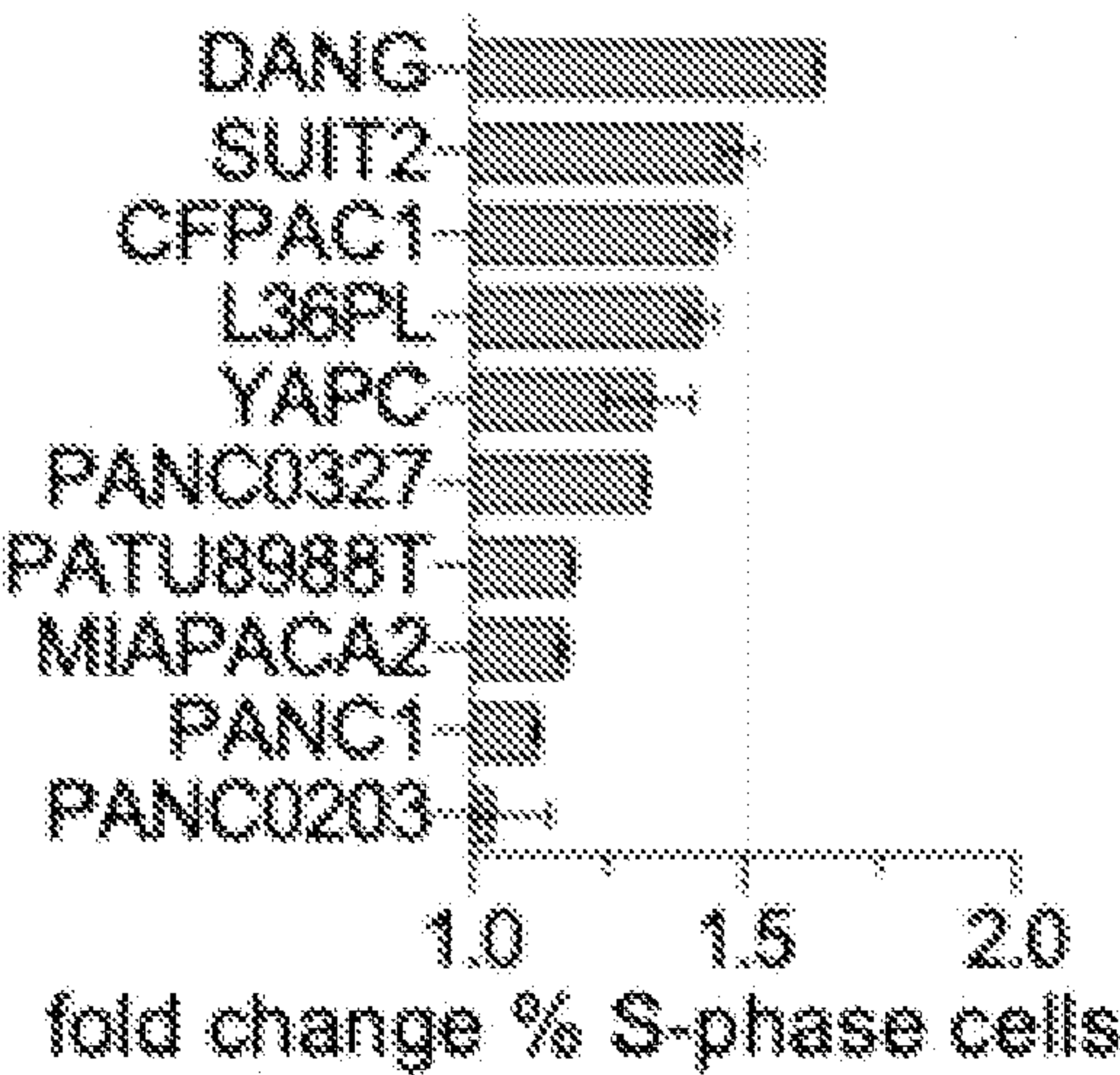


FIG. 3J

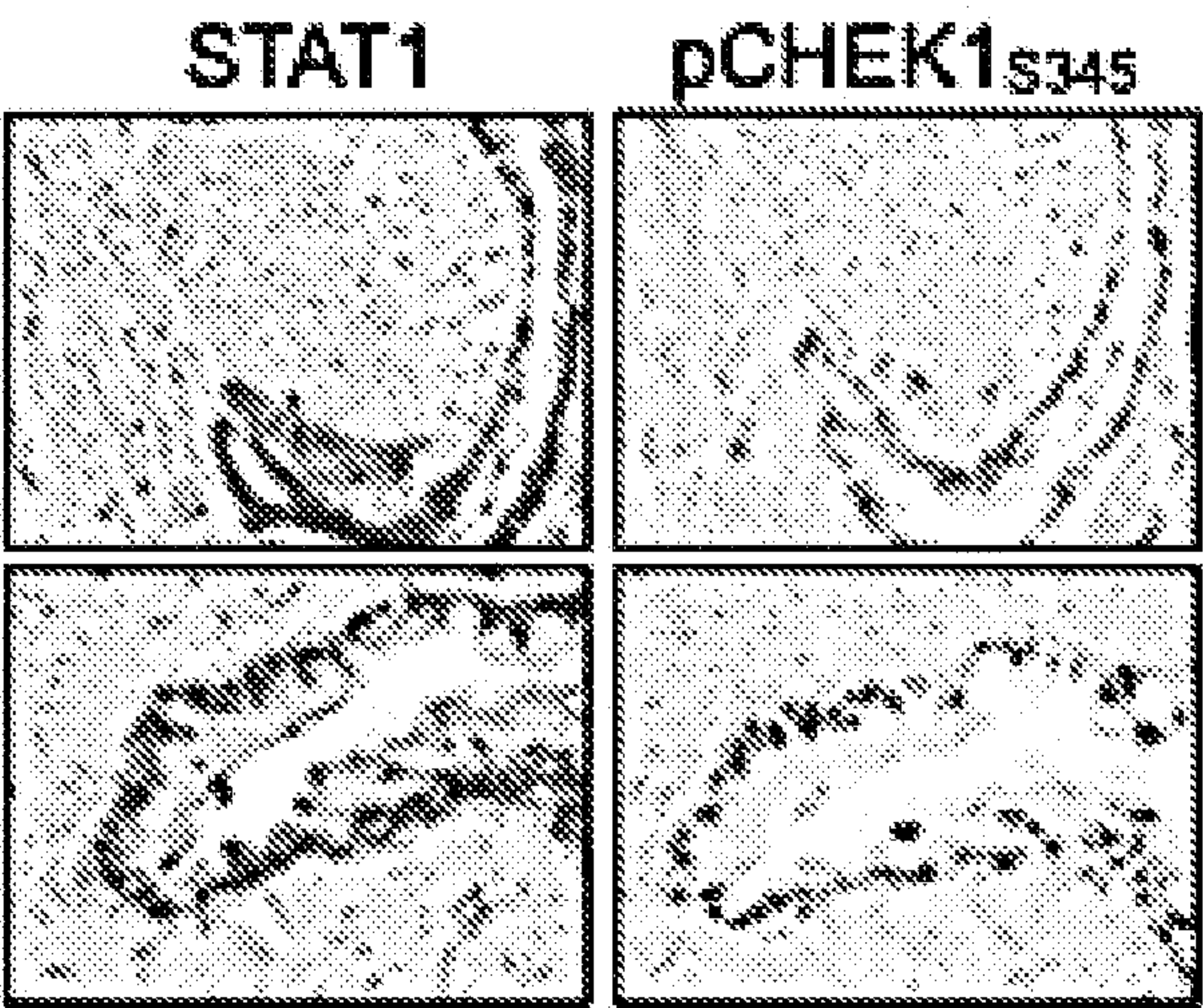


FIG. 3K

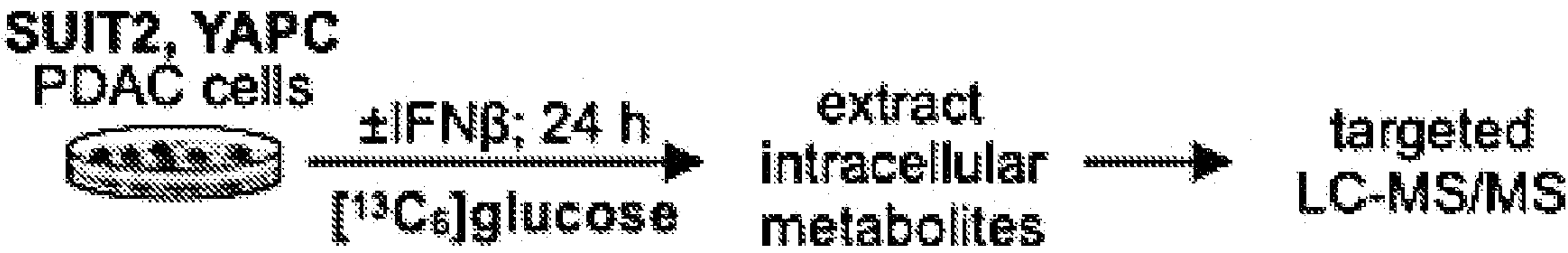


FIG. 4A

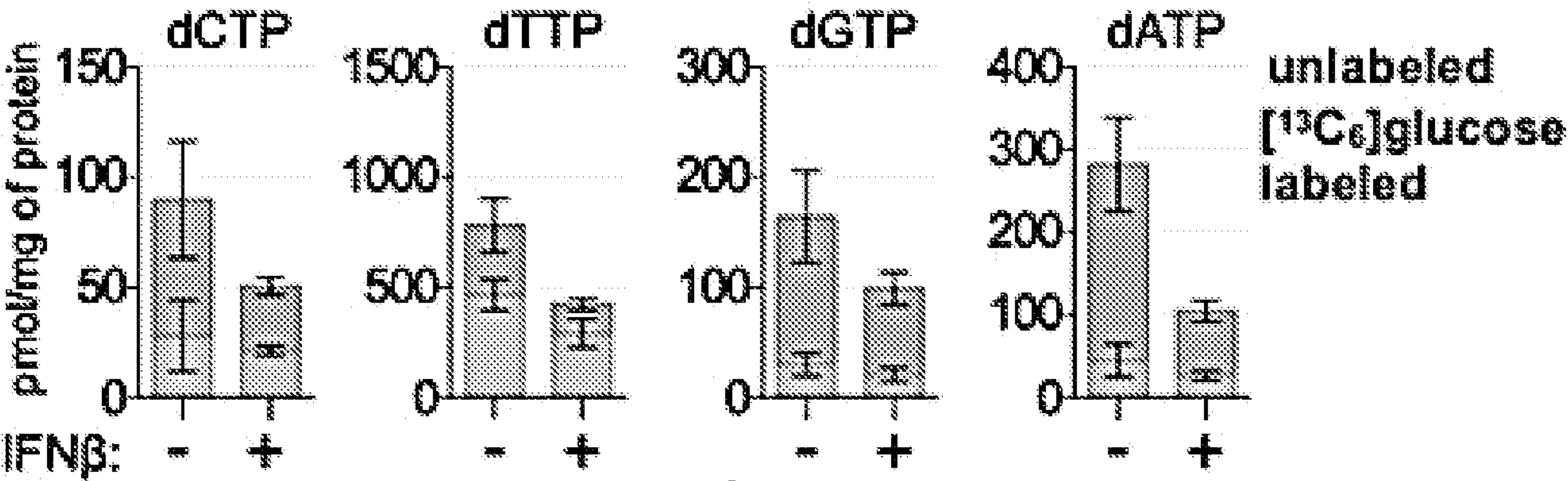


FIG. 4B

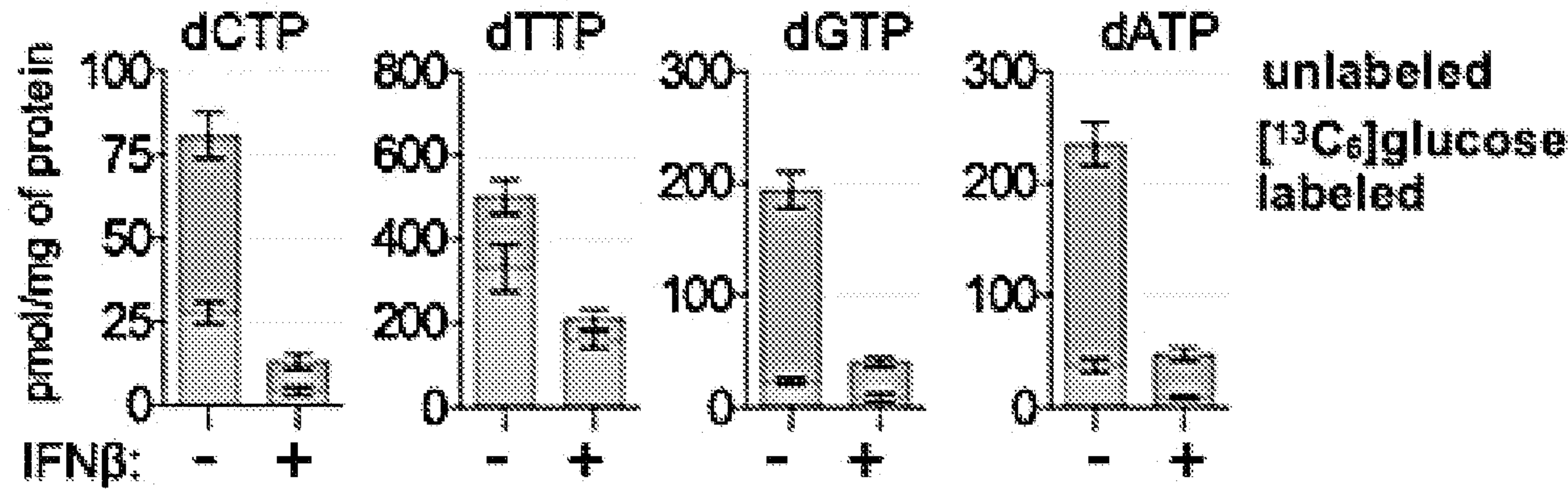


FIG. 4C

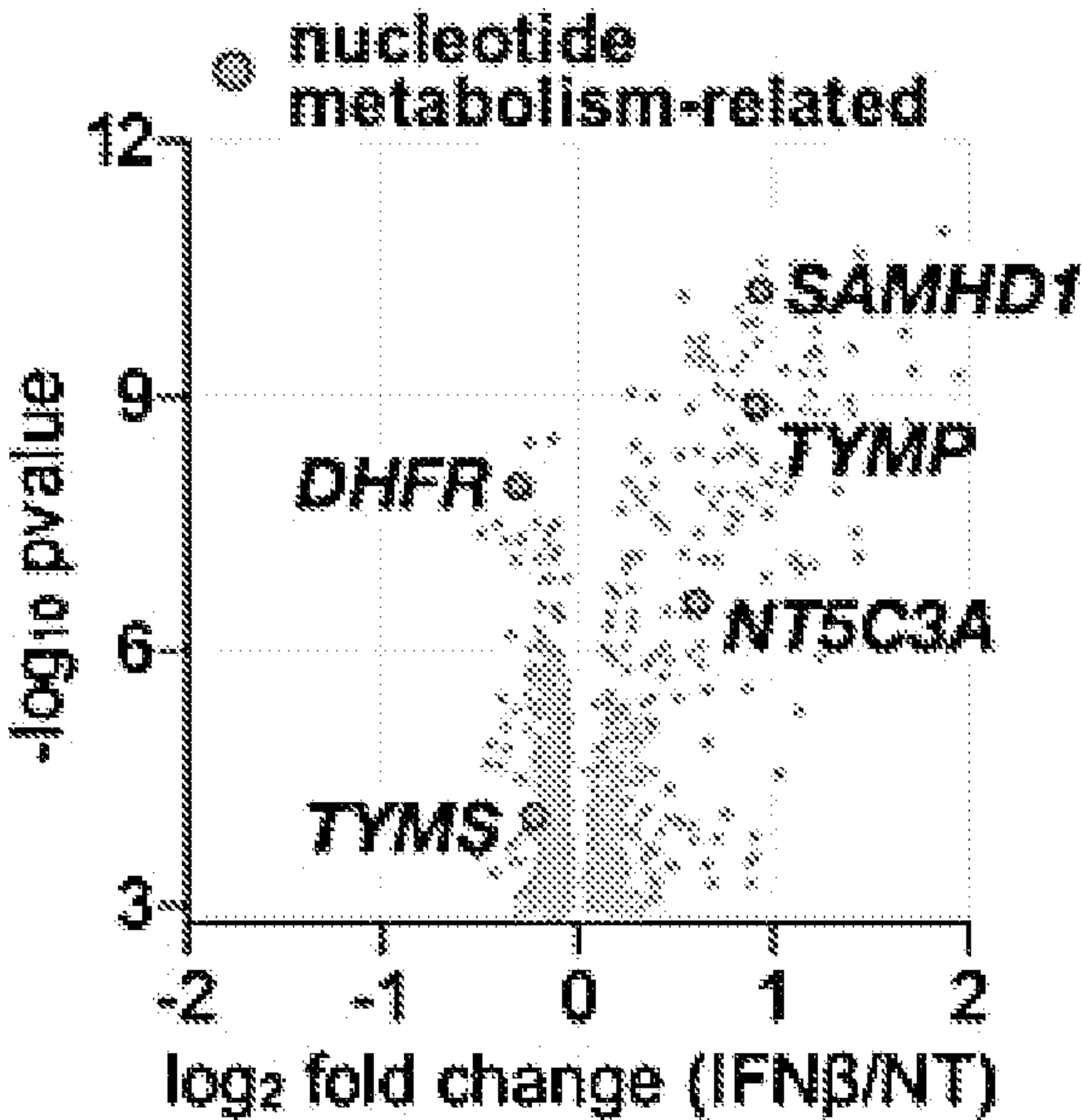


FIG. 4D

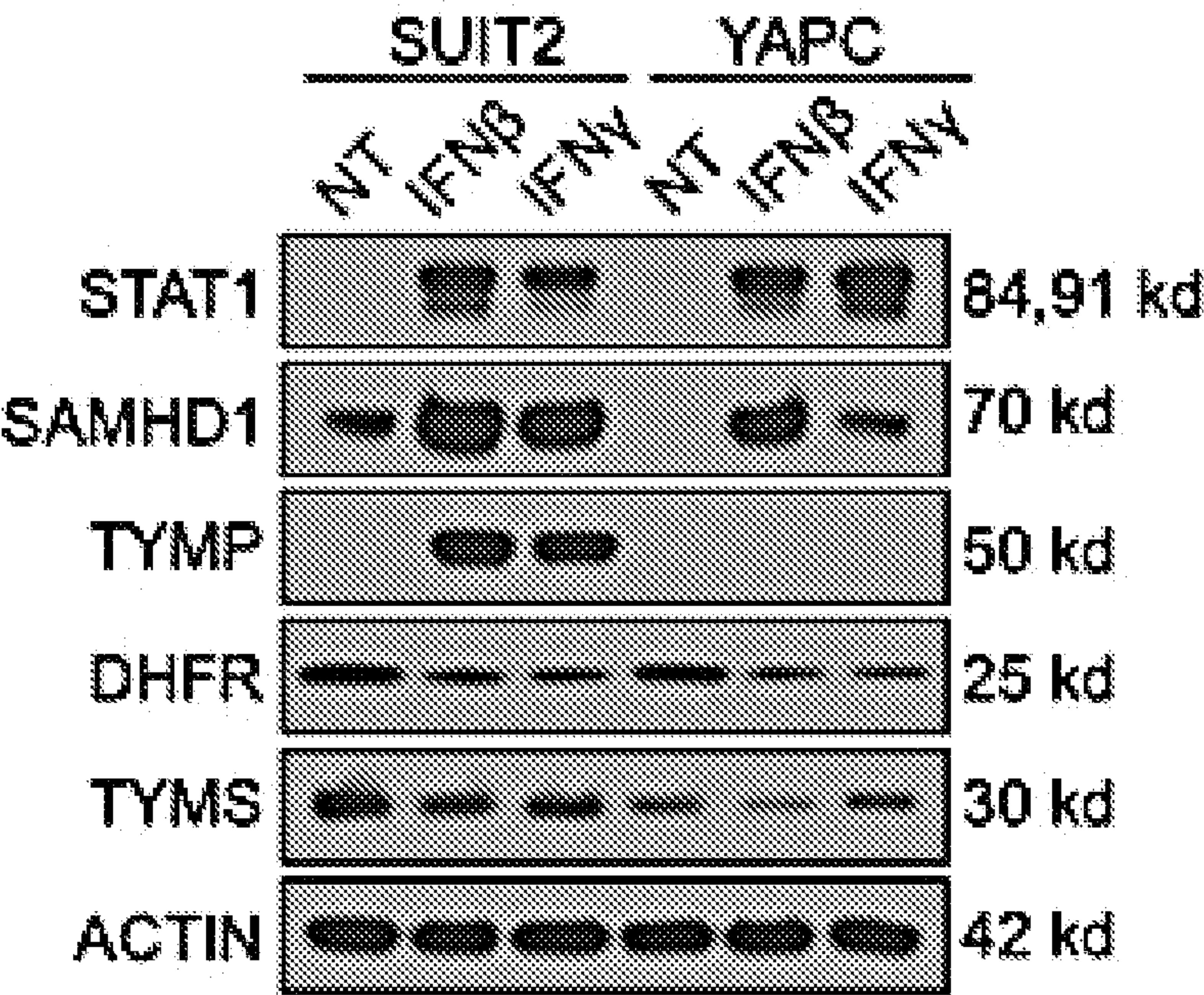


FIG. 4E

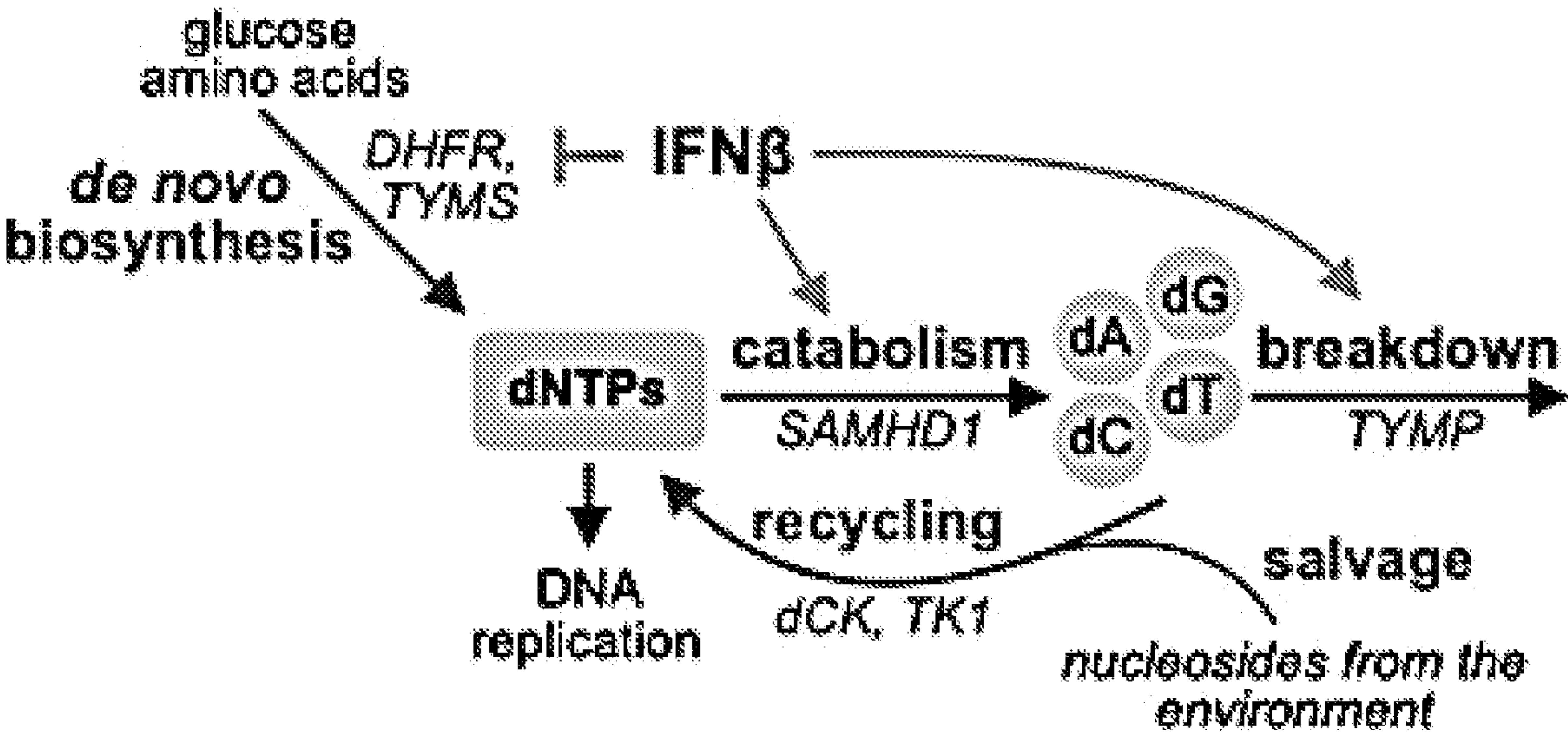


FIG. 4F

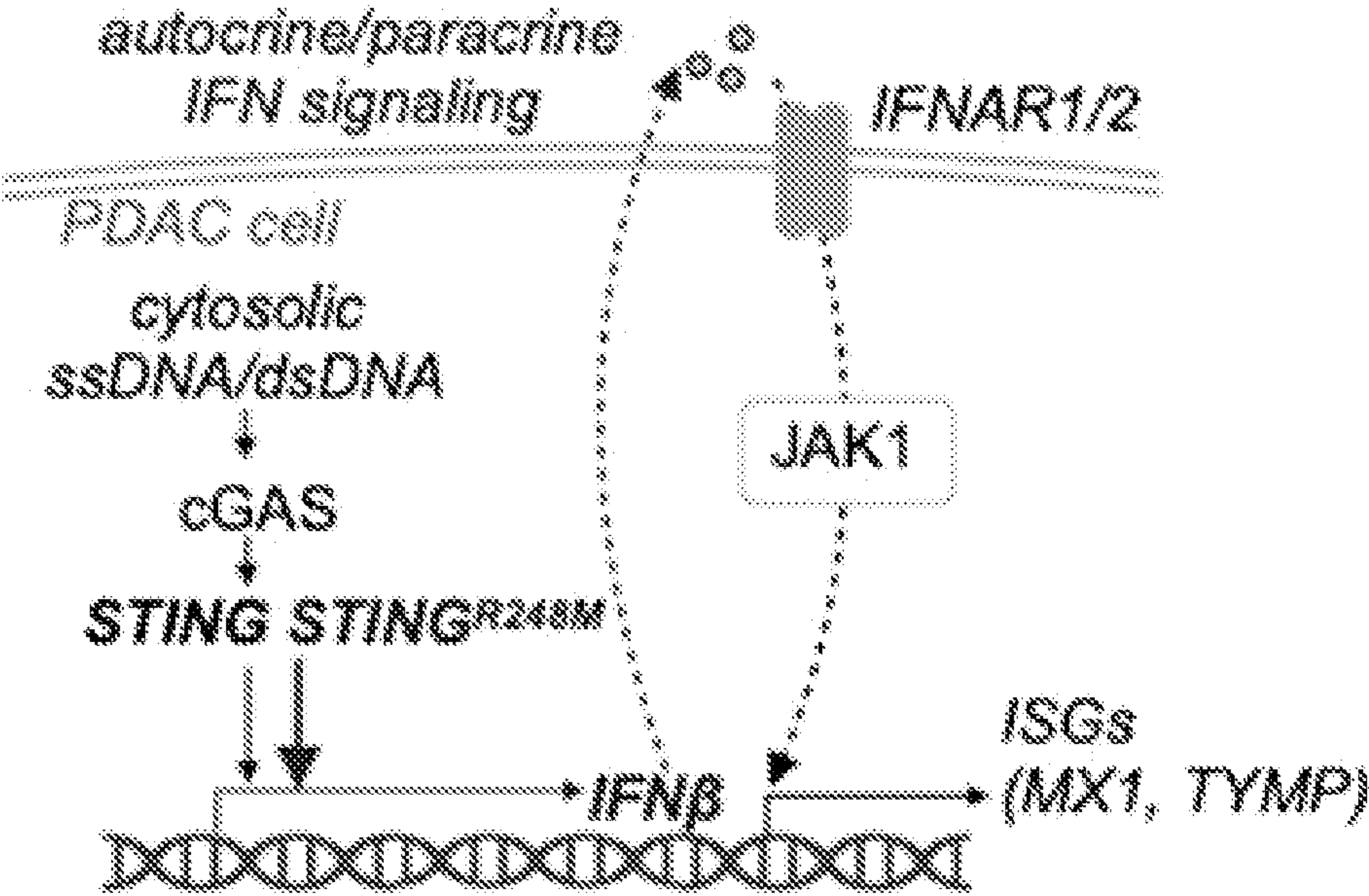


FIG. 5A

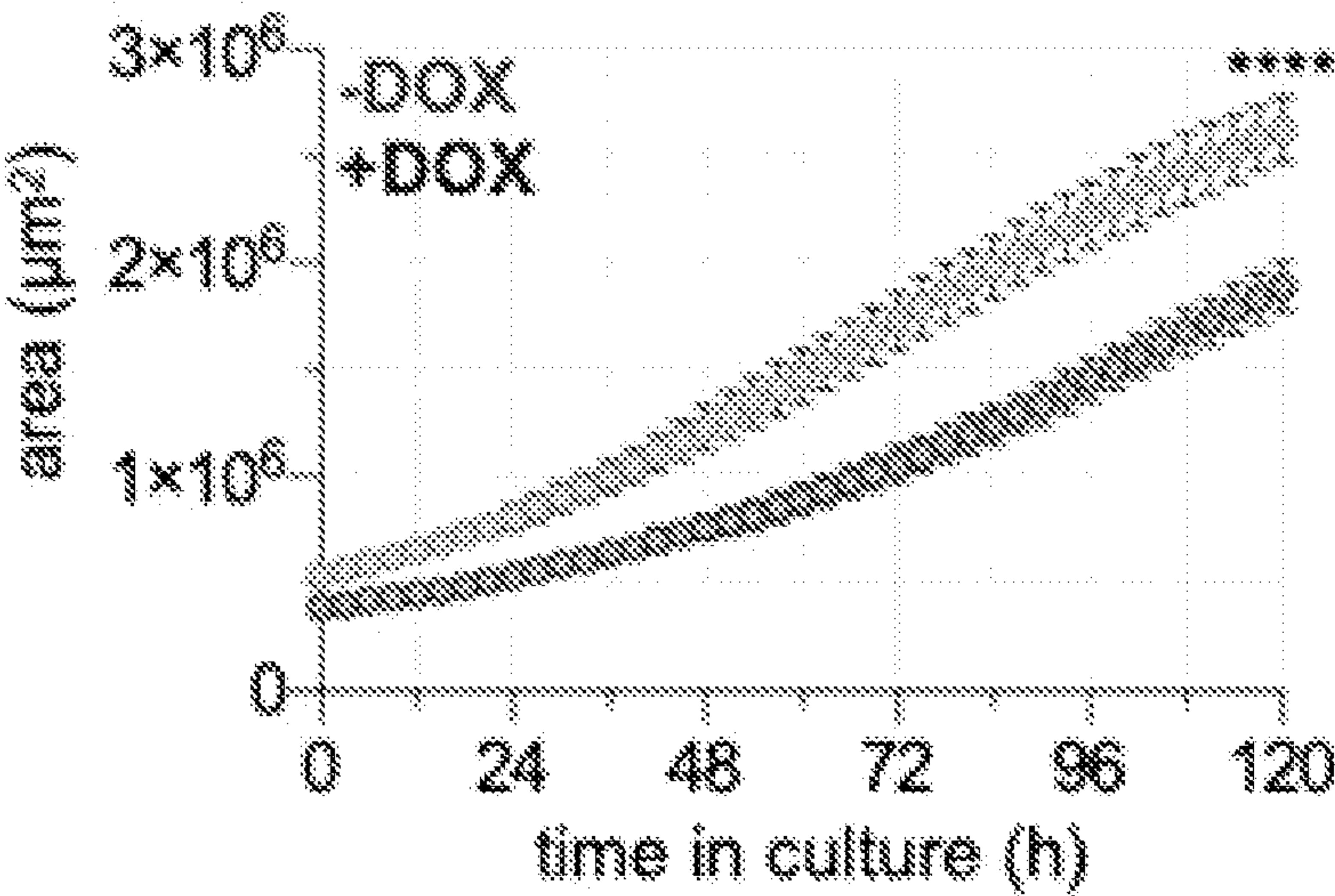


FIG. 5B

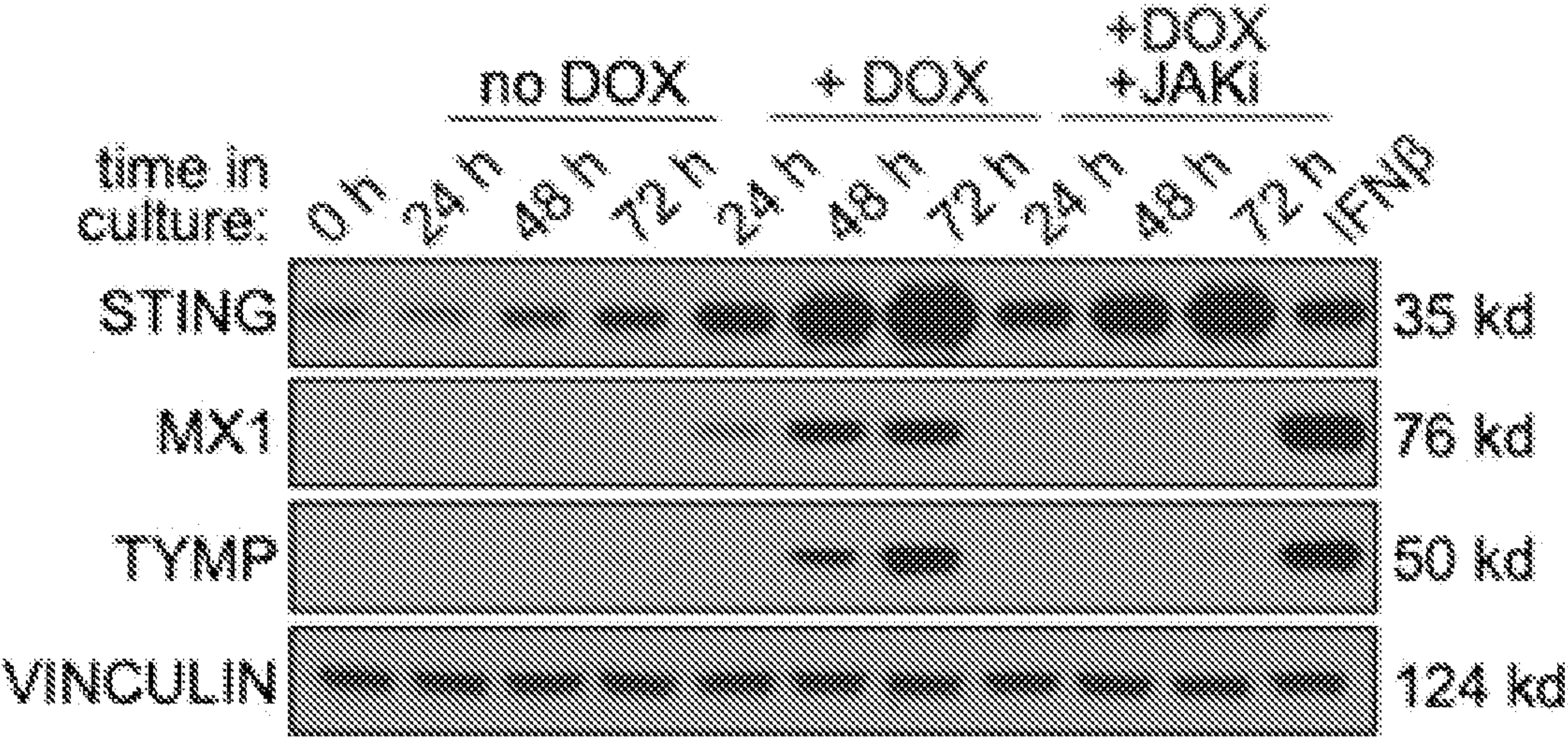


FIG. 5C

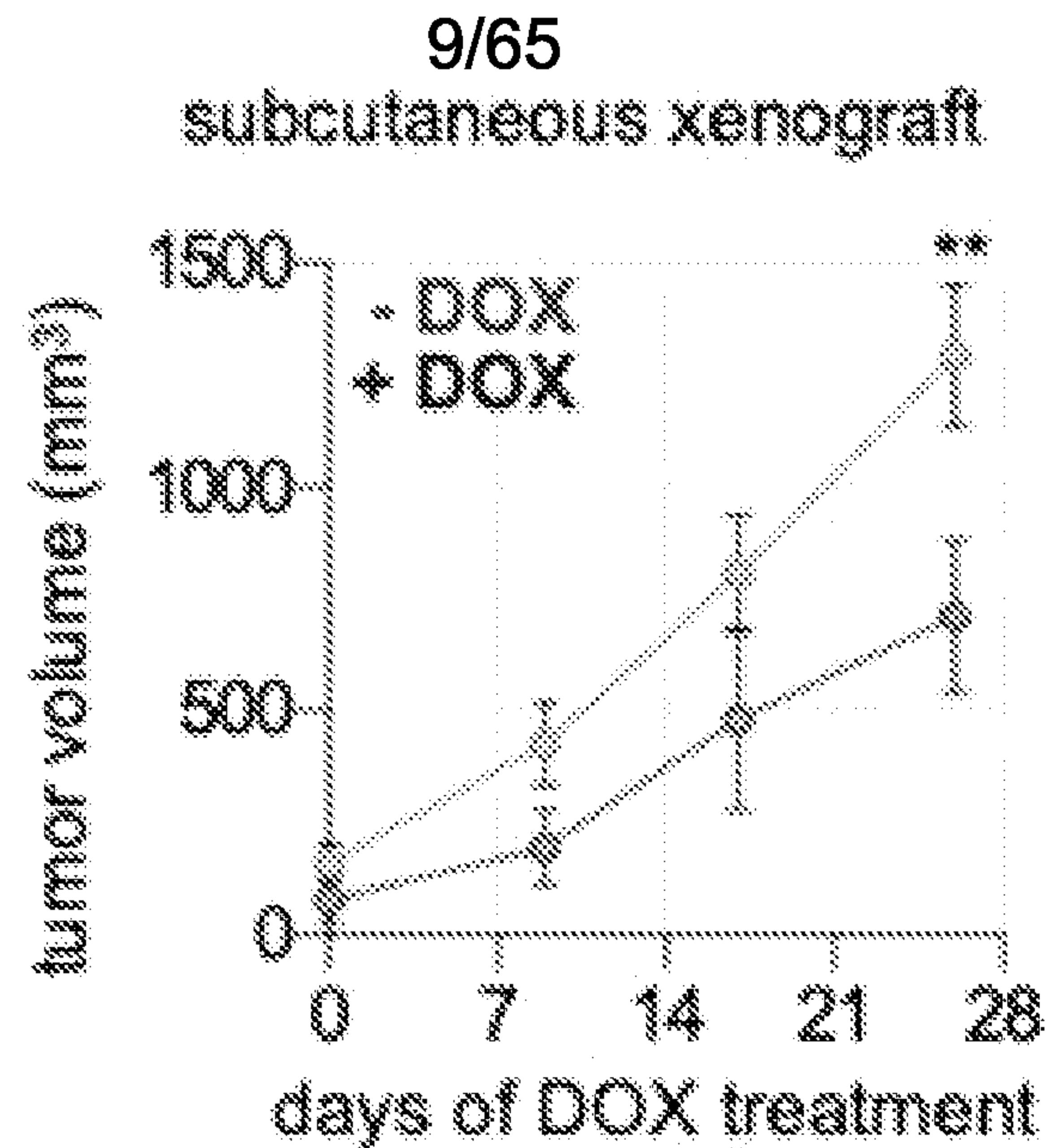


FIG. 5D

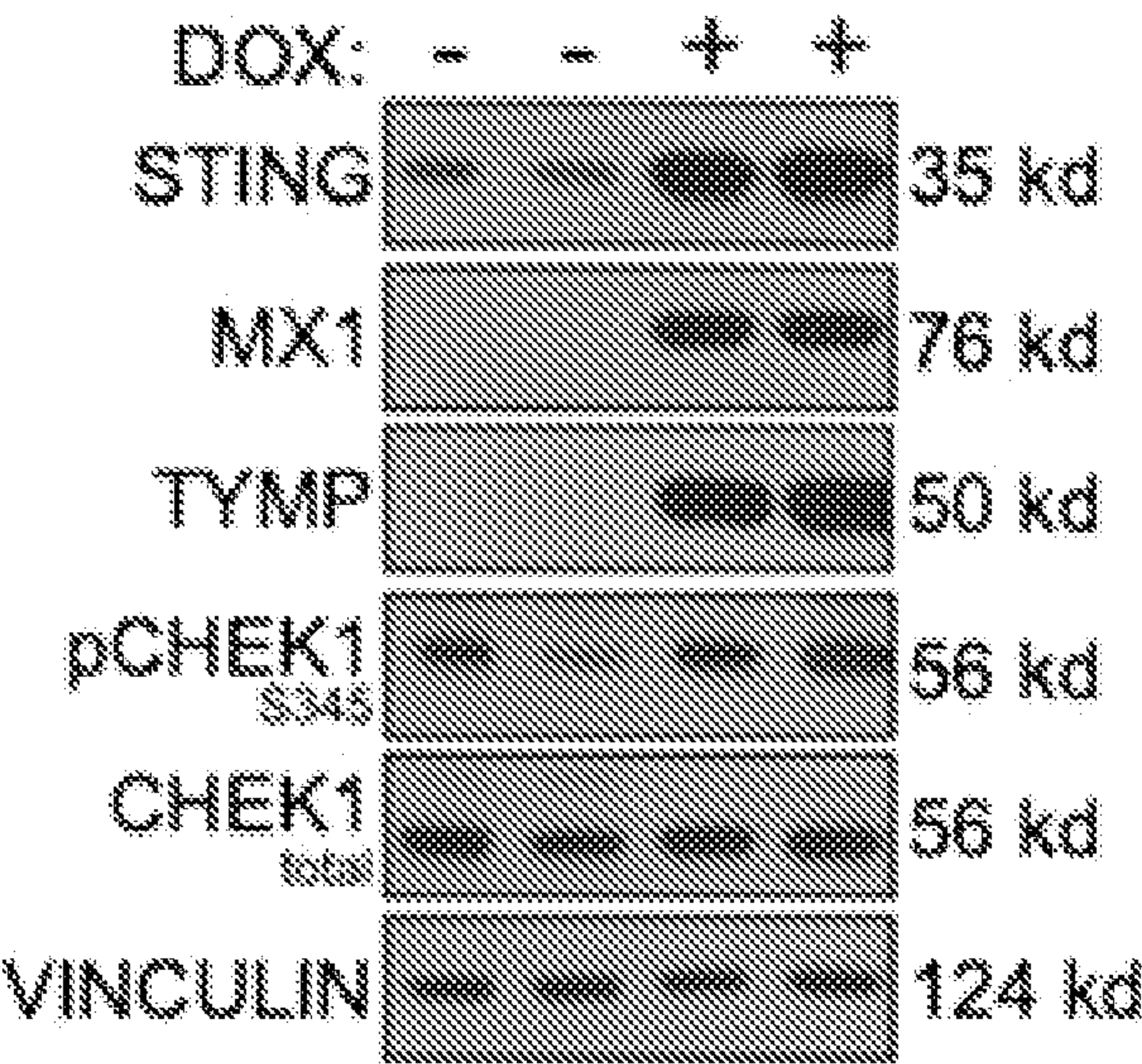


FIG. 5E

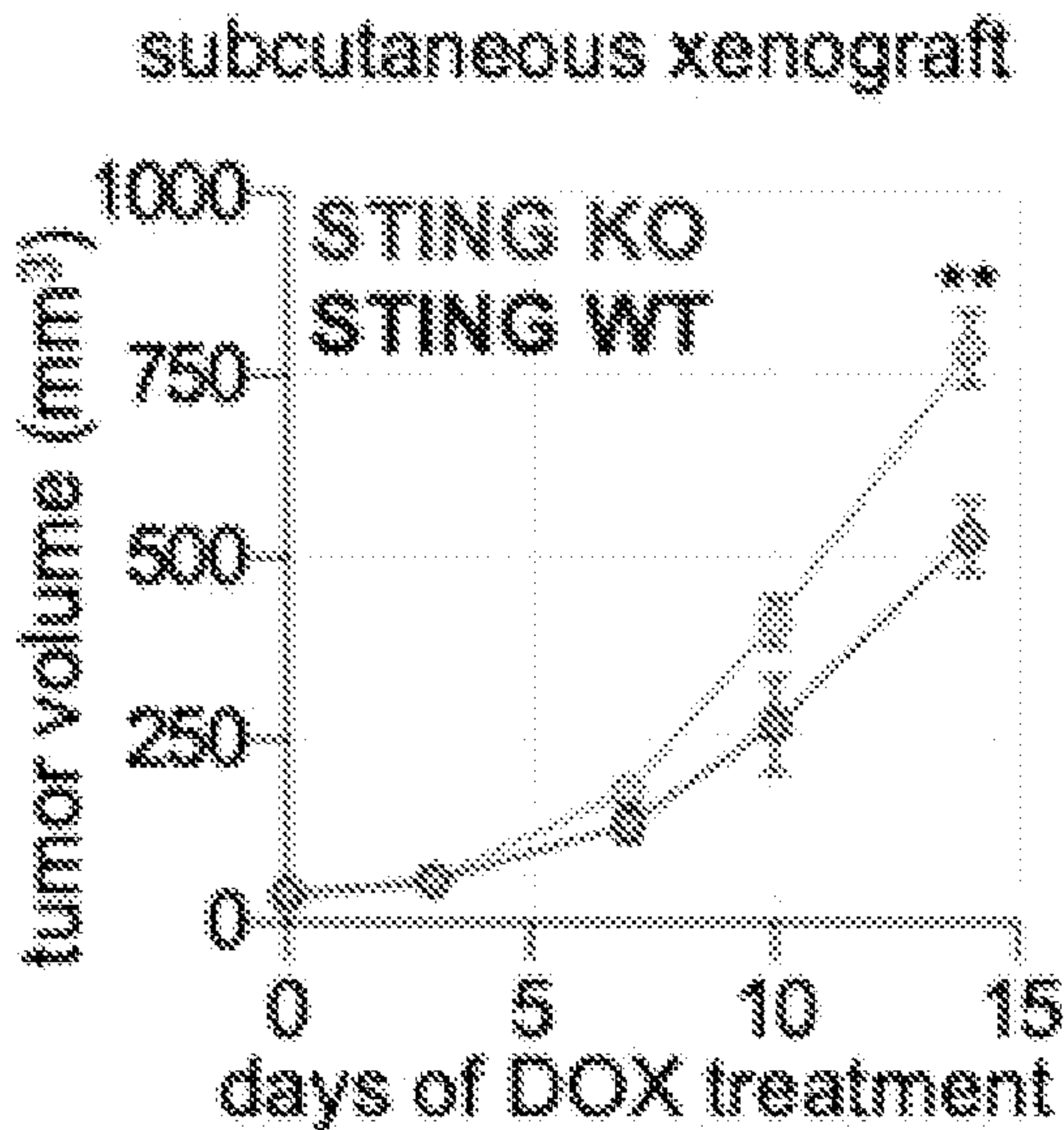


FIG. 5F

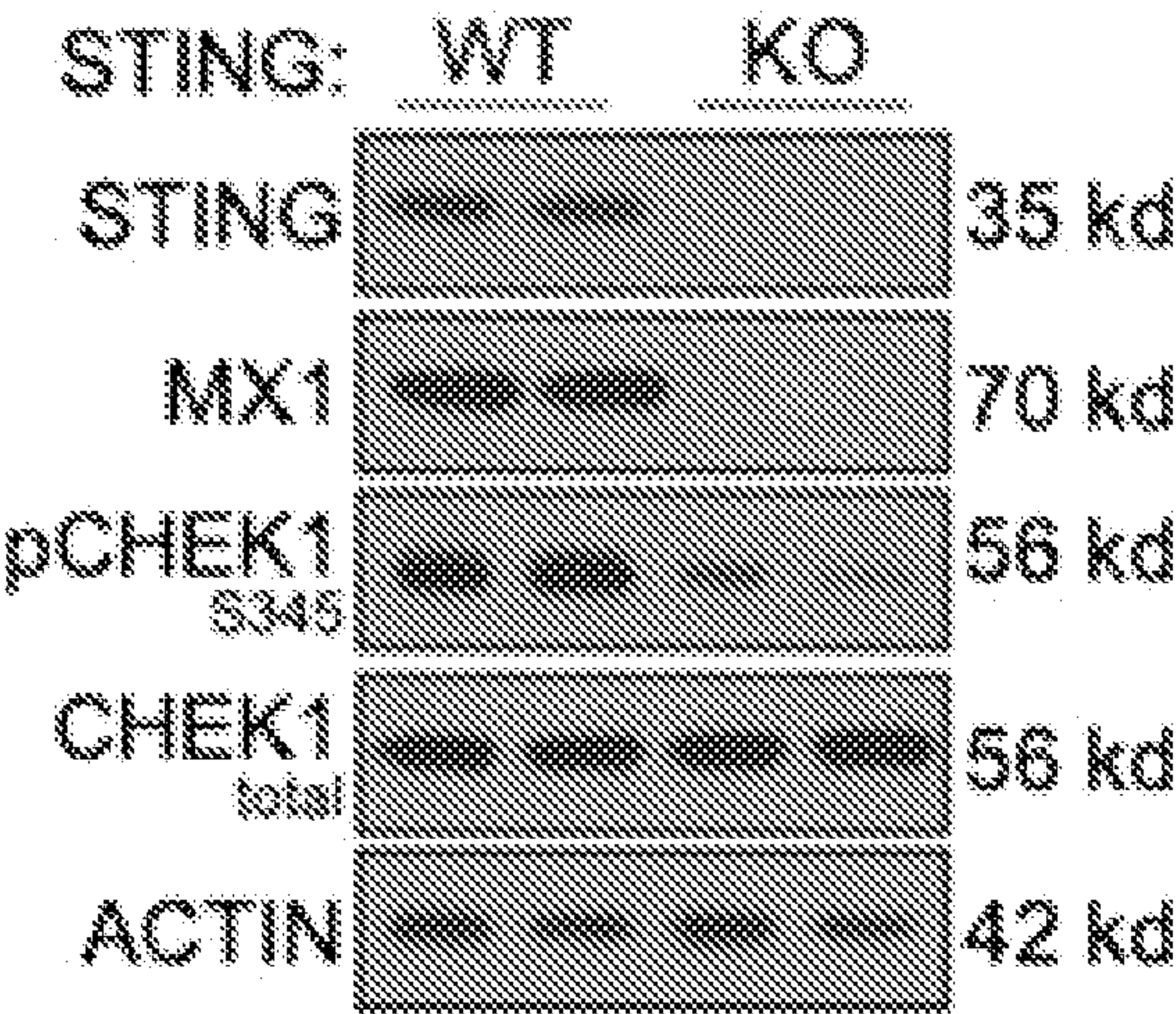


FIG. 5G

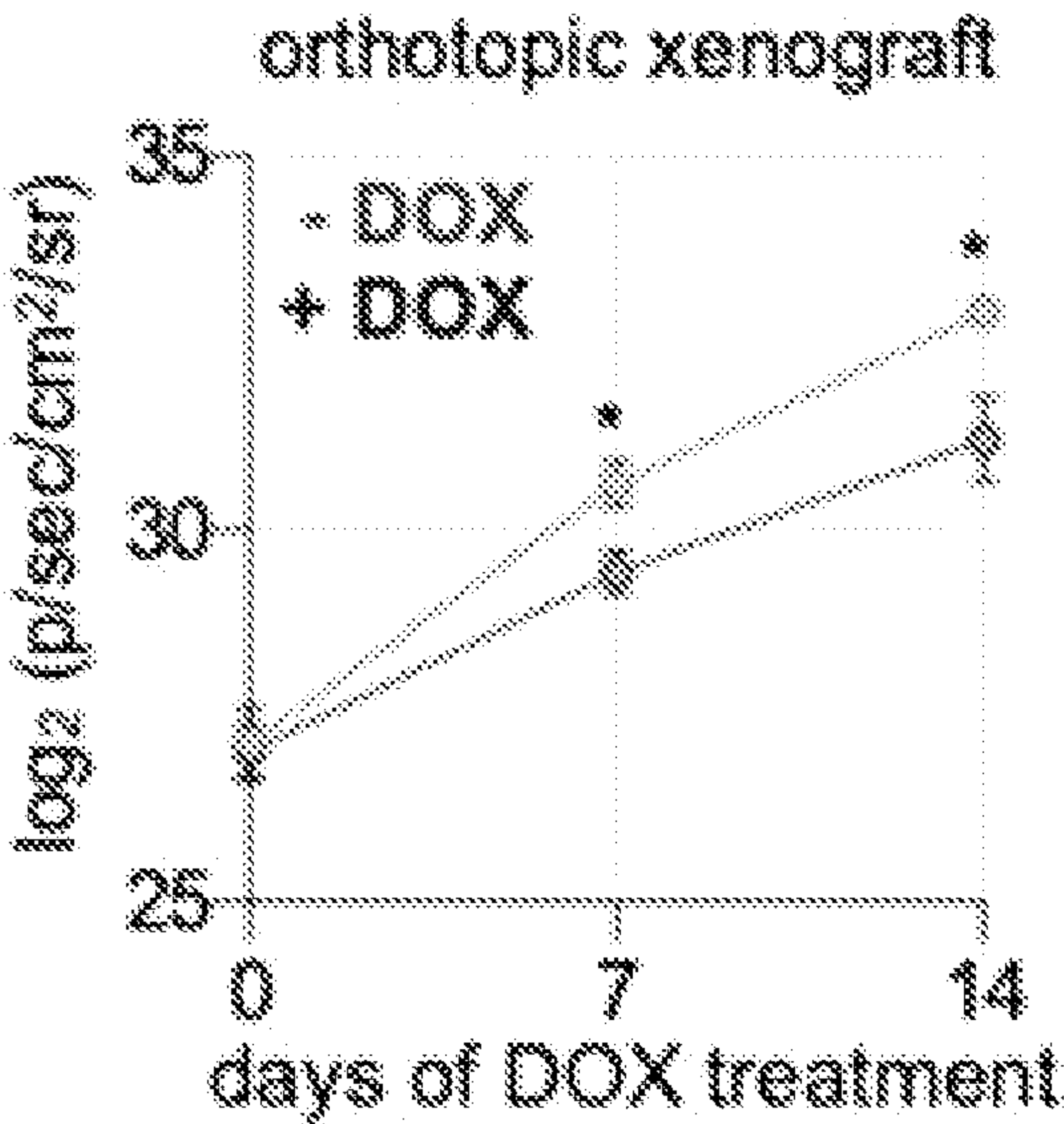


FIG. 5H

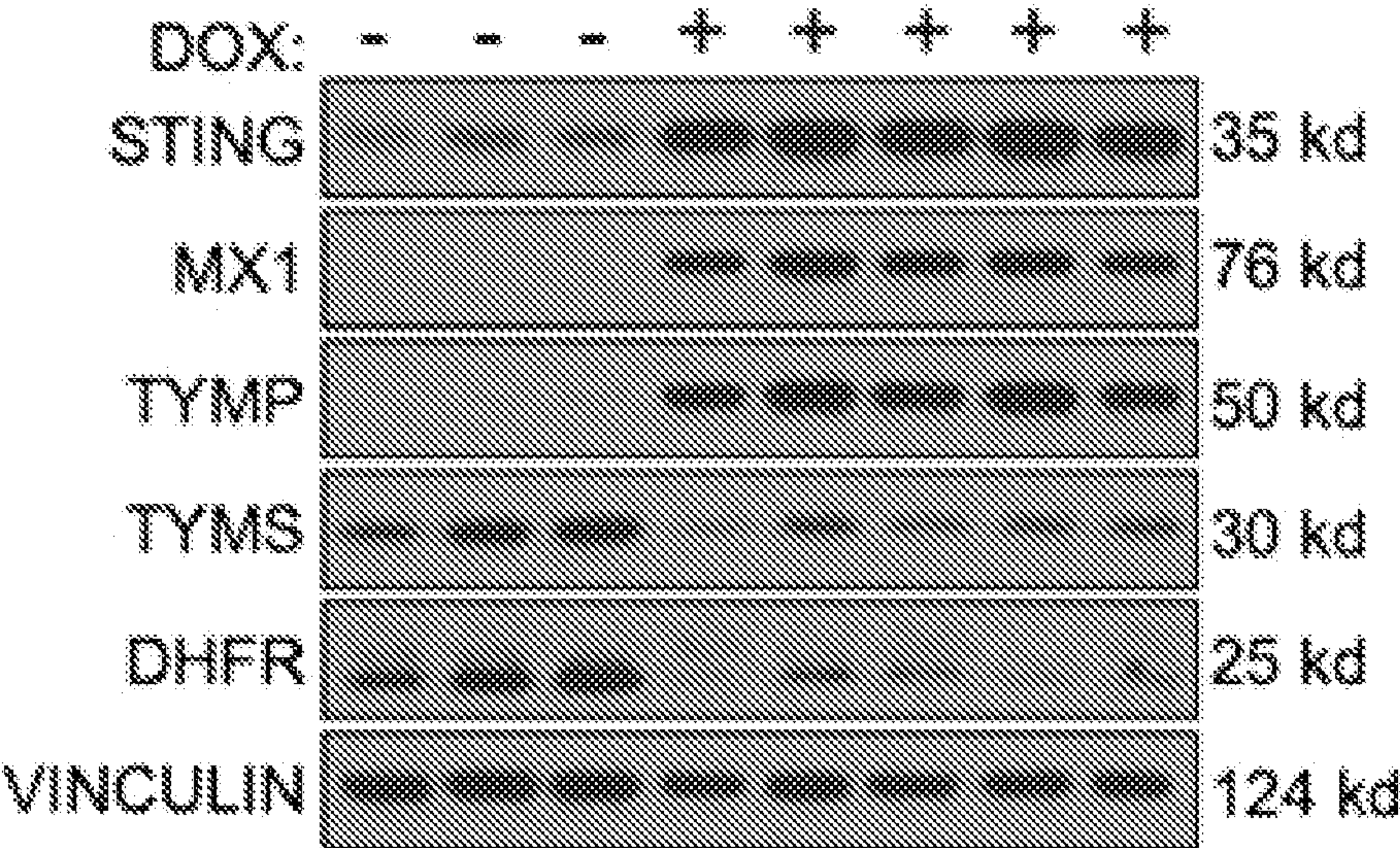


FIG. 5I

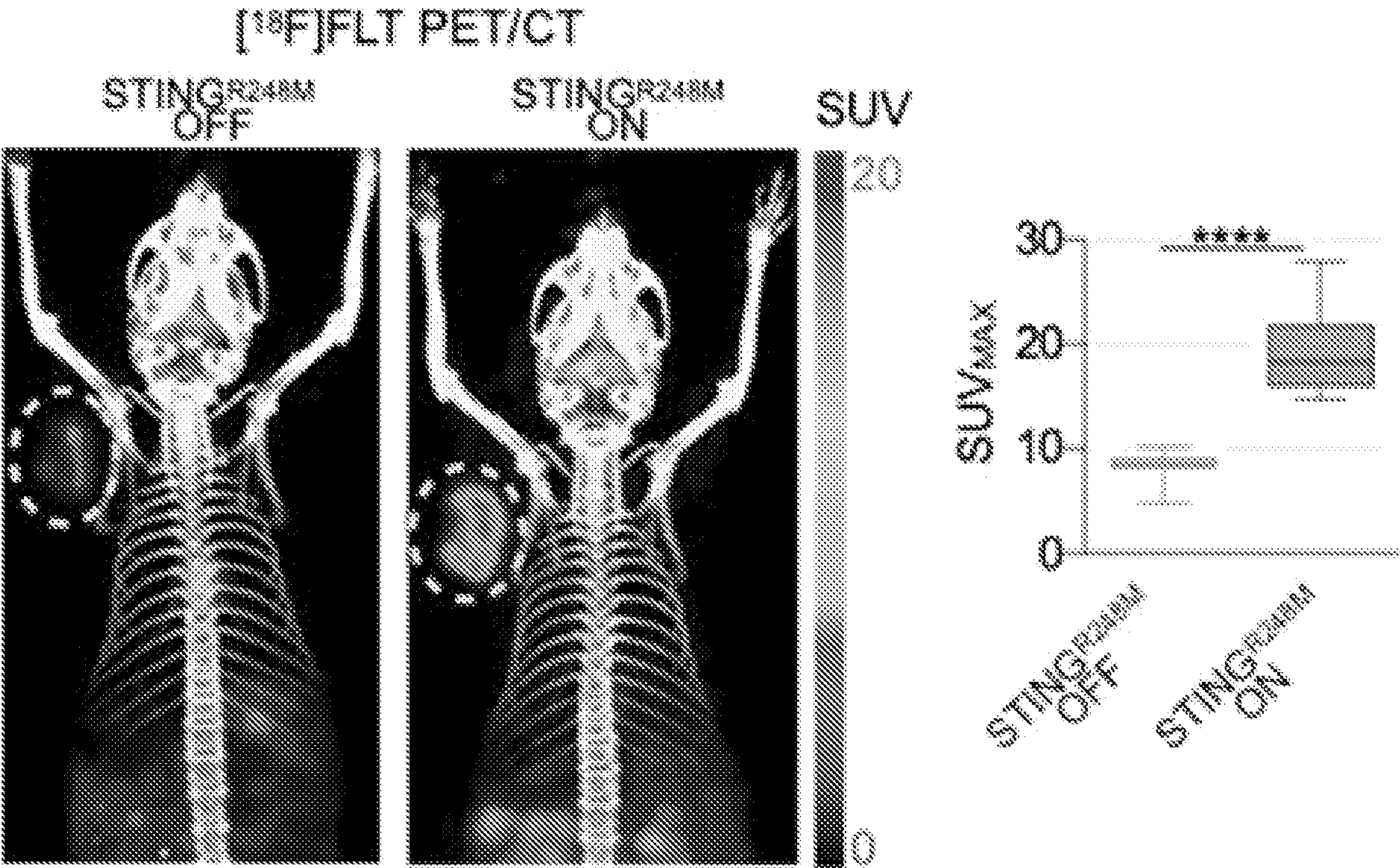


FIG. 5J

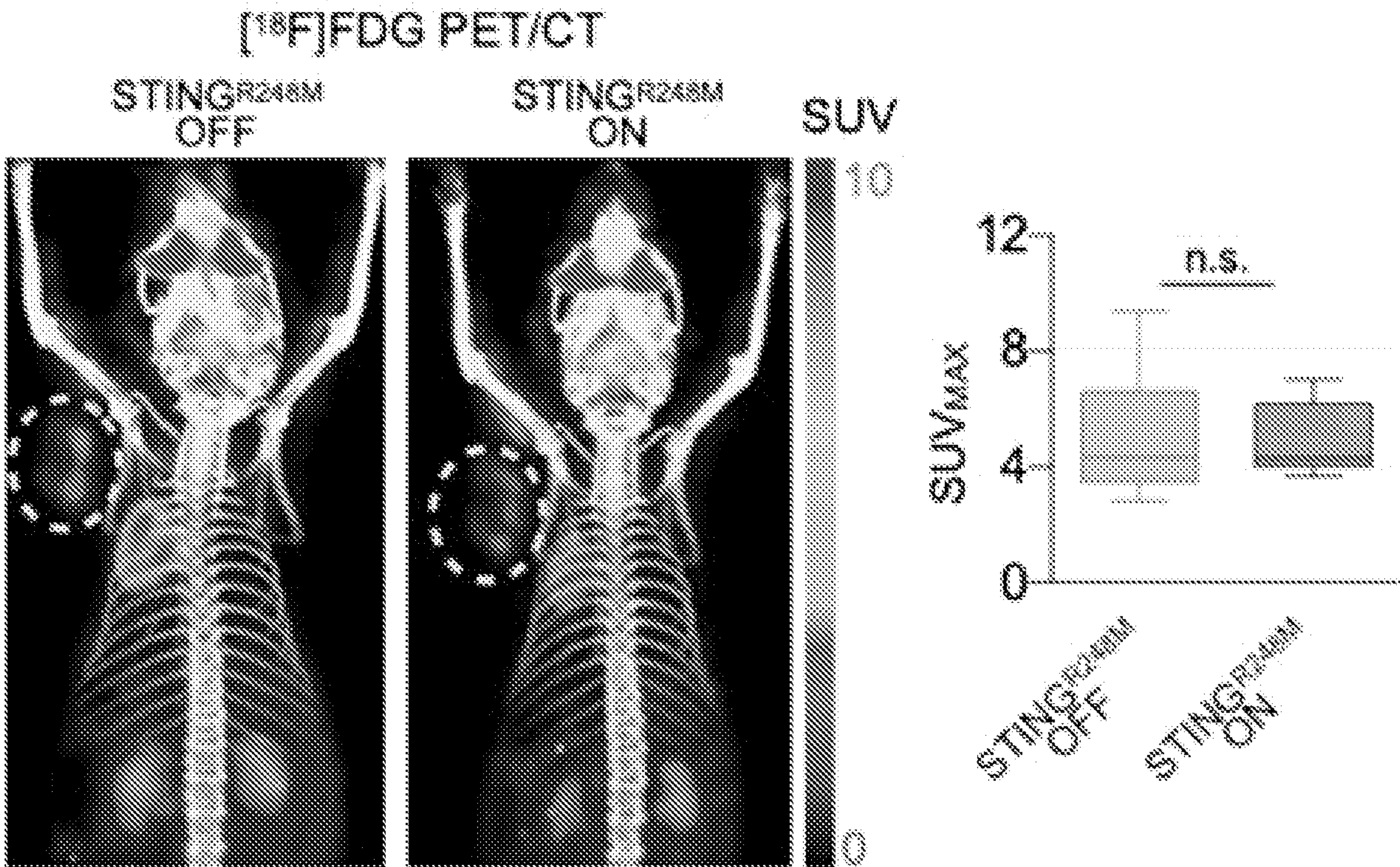


FIG. 5K

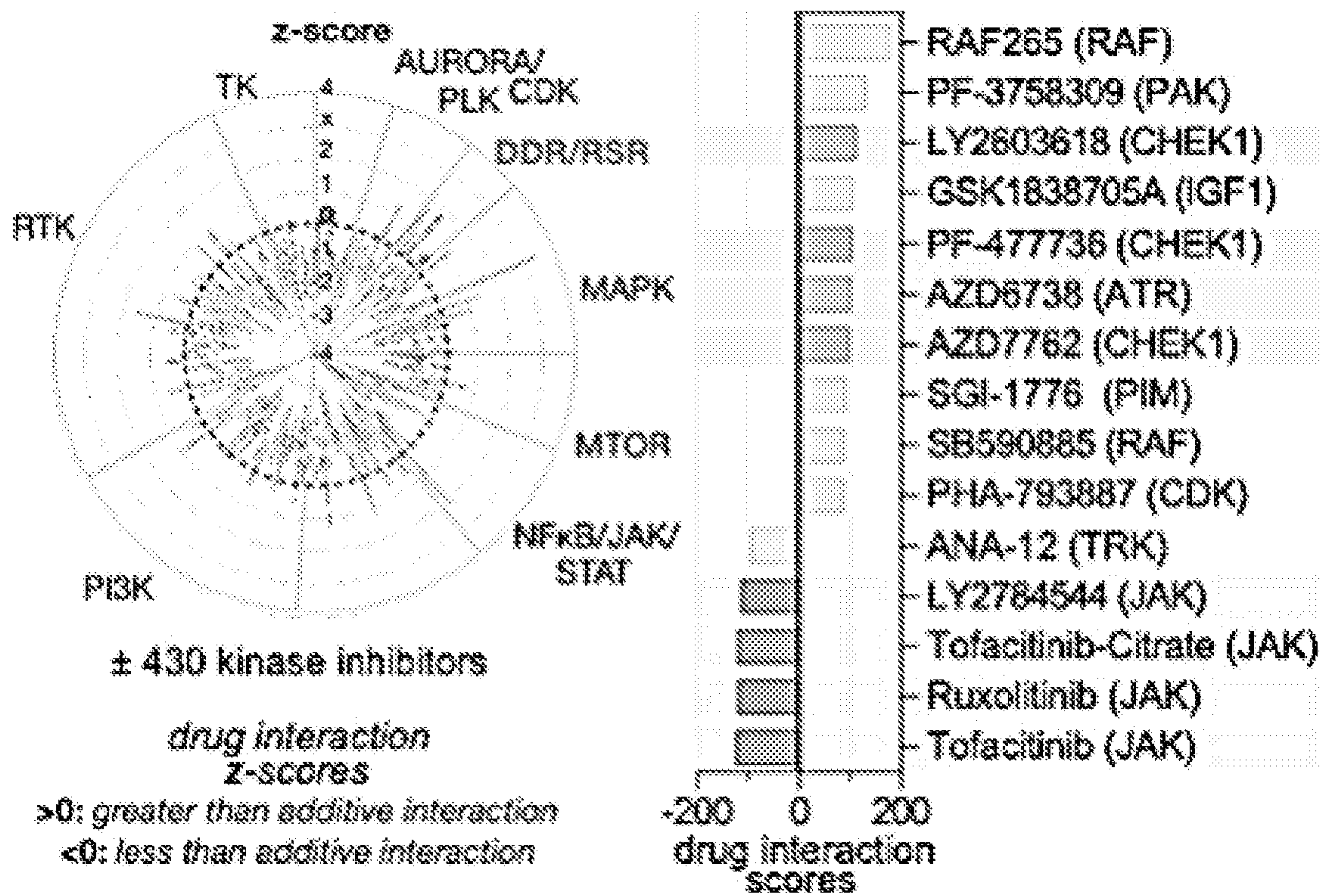


FIG. 6A

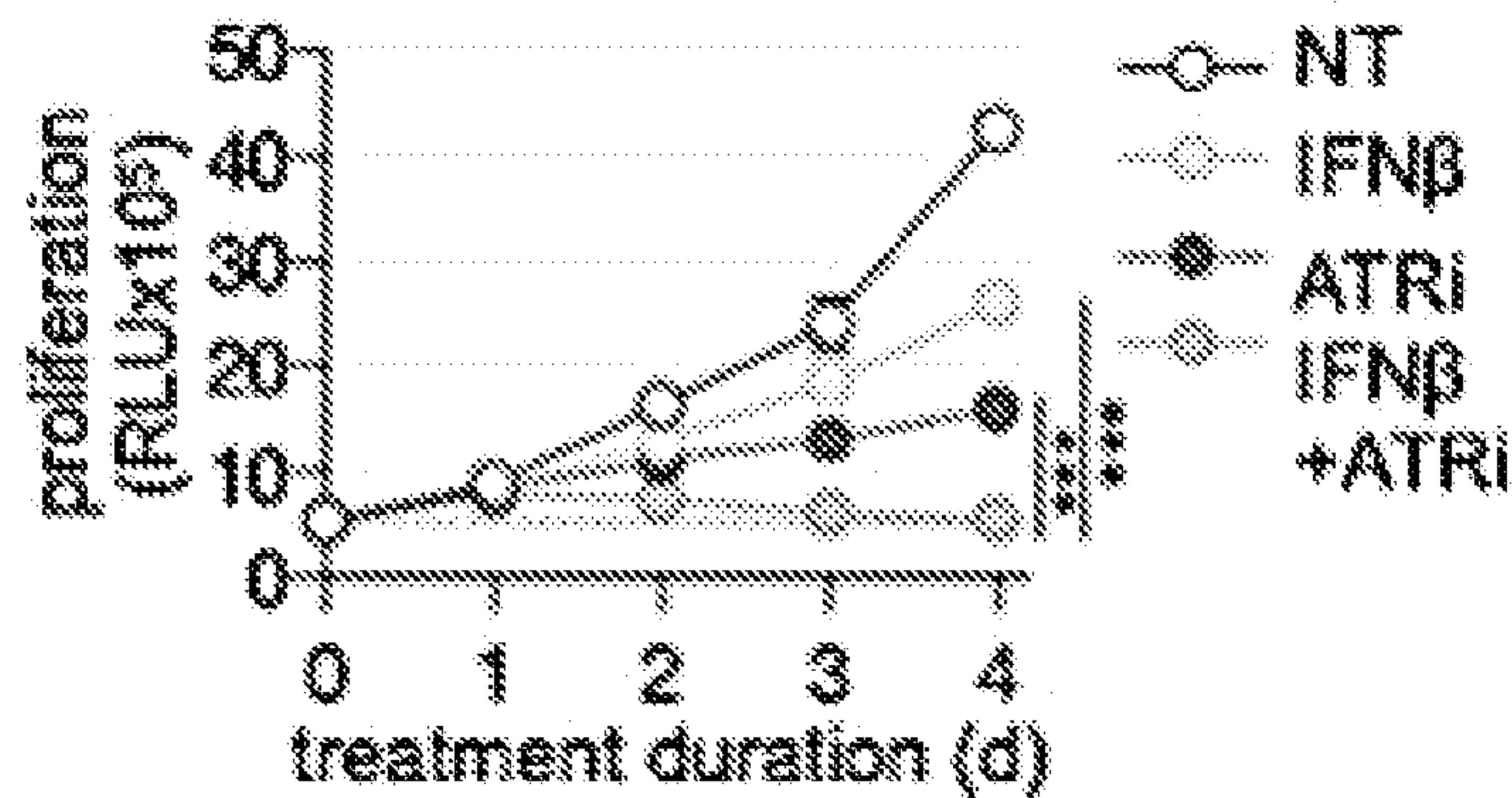


FIG. 6B

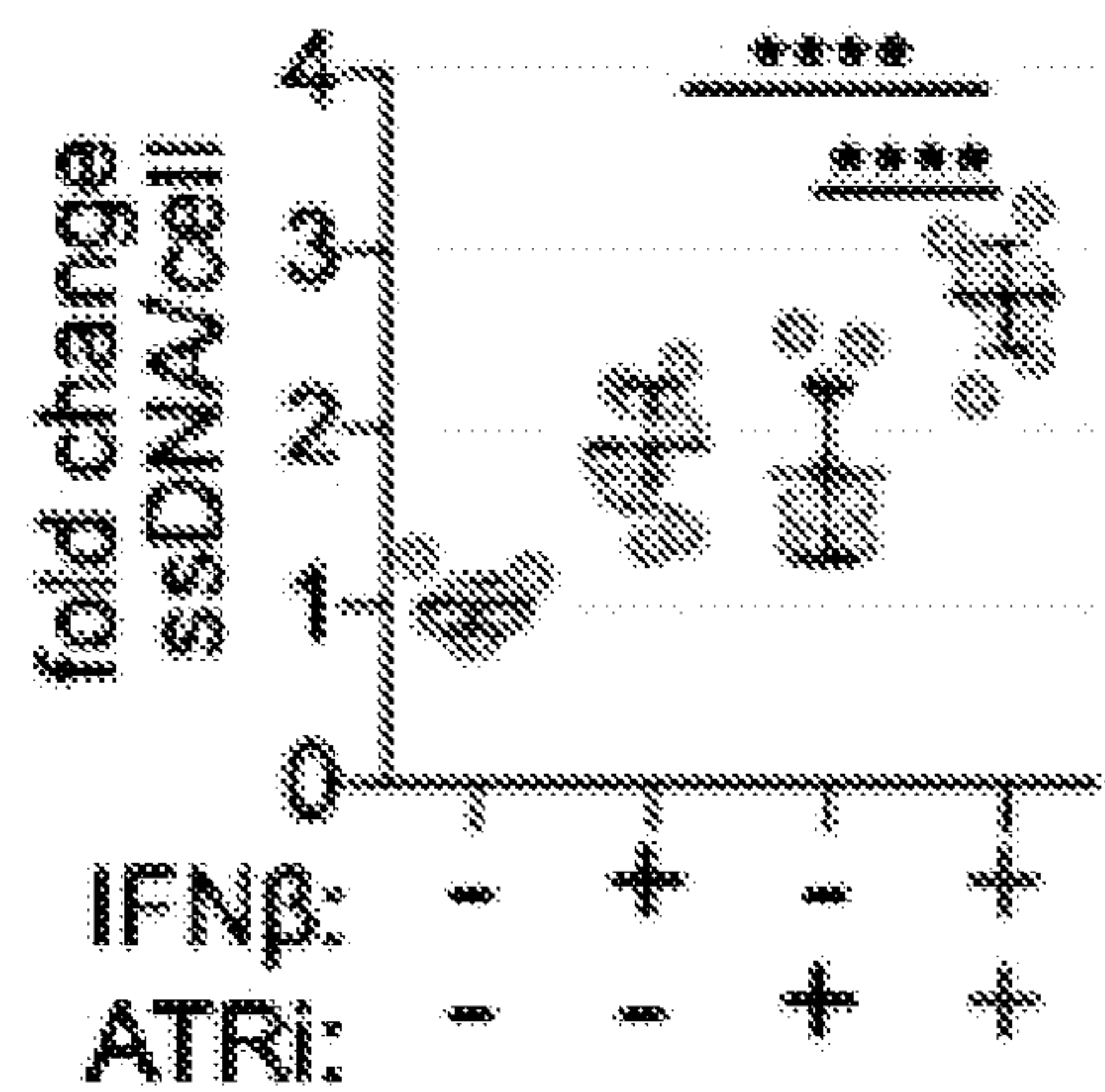


FIG. 6C

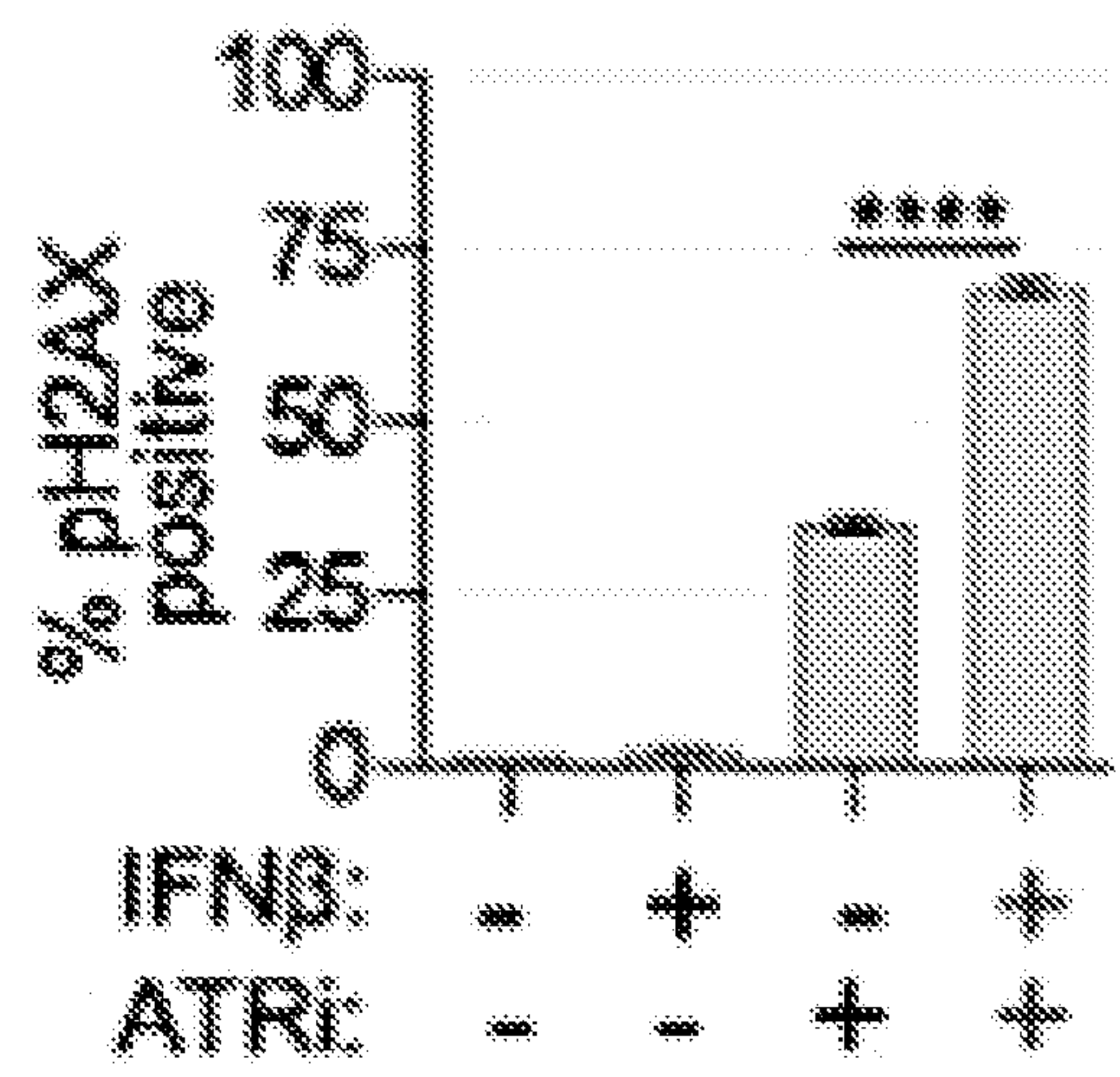


FIG. 6D

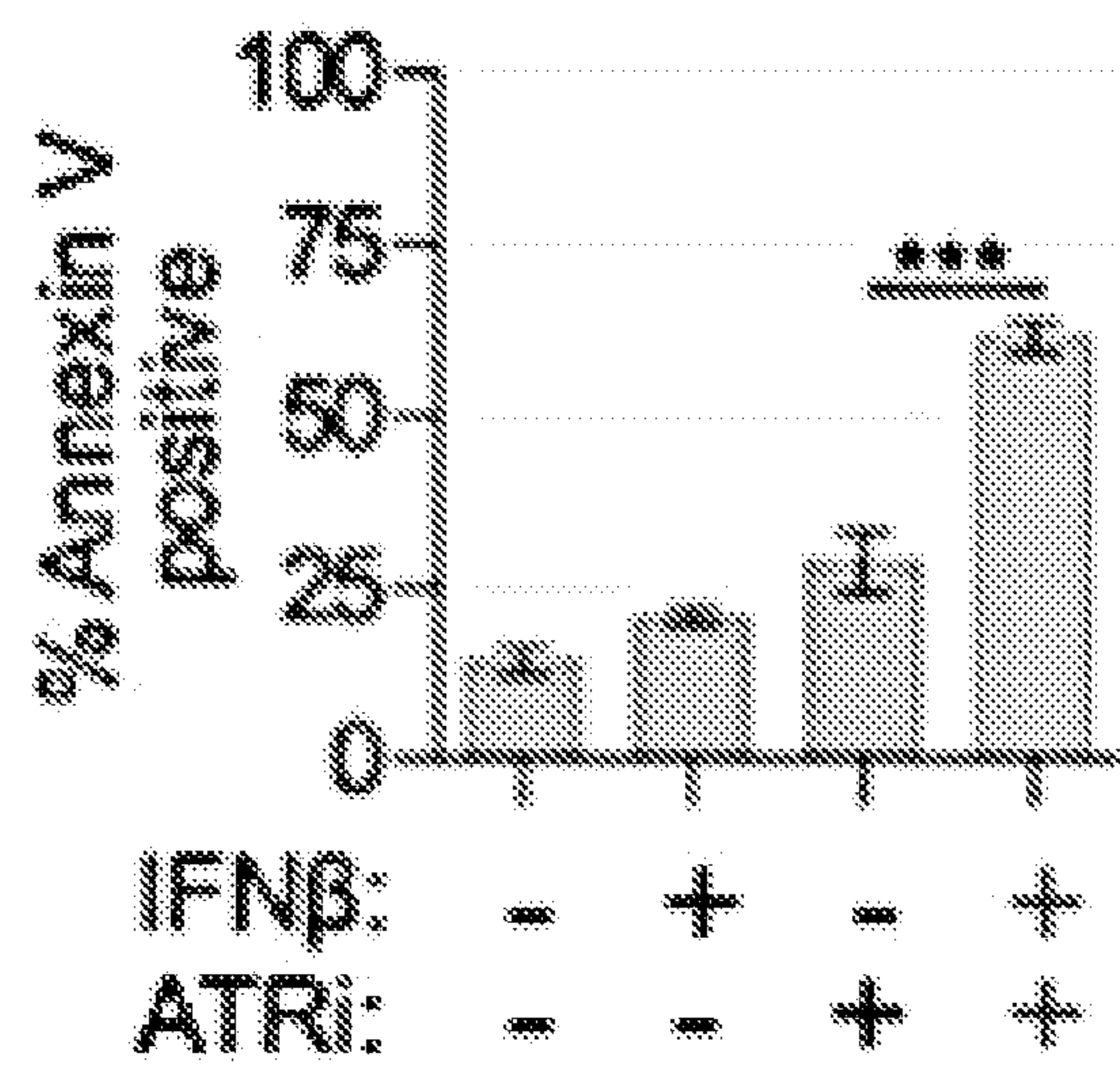


FIG. 6E

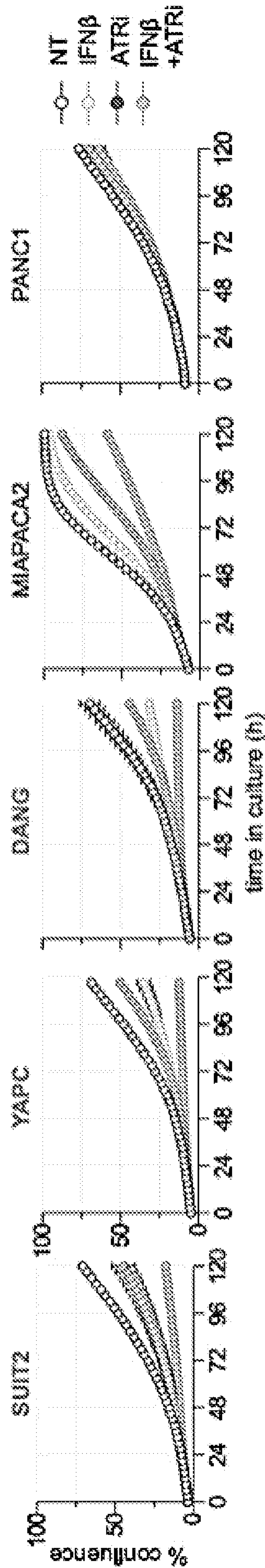


FIG. 6F

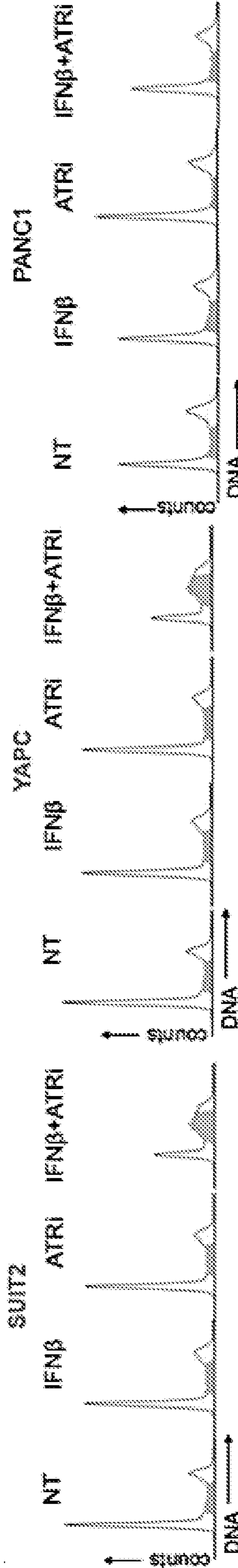


FIG. 6G

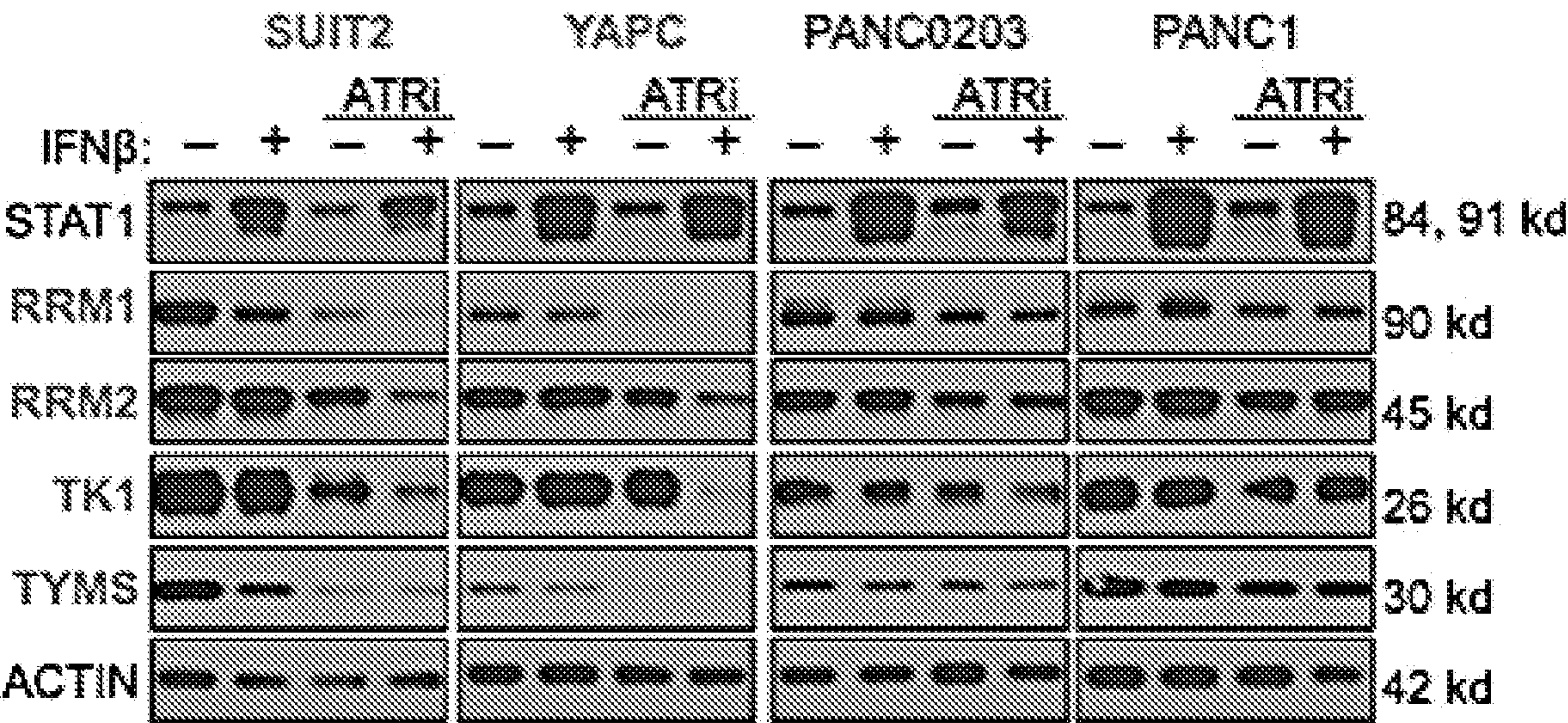


FIG. 7A

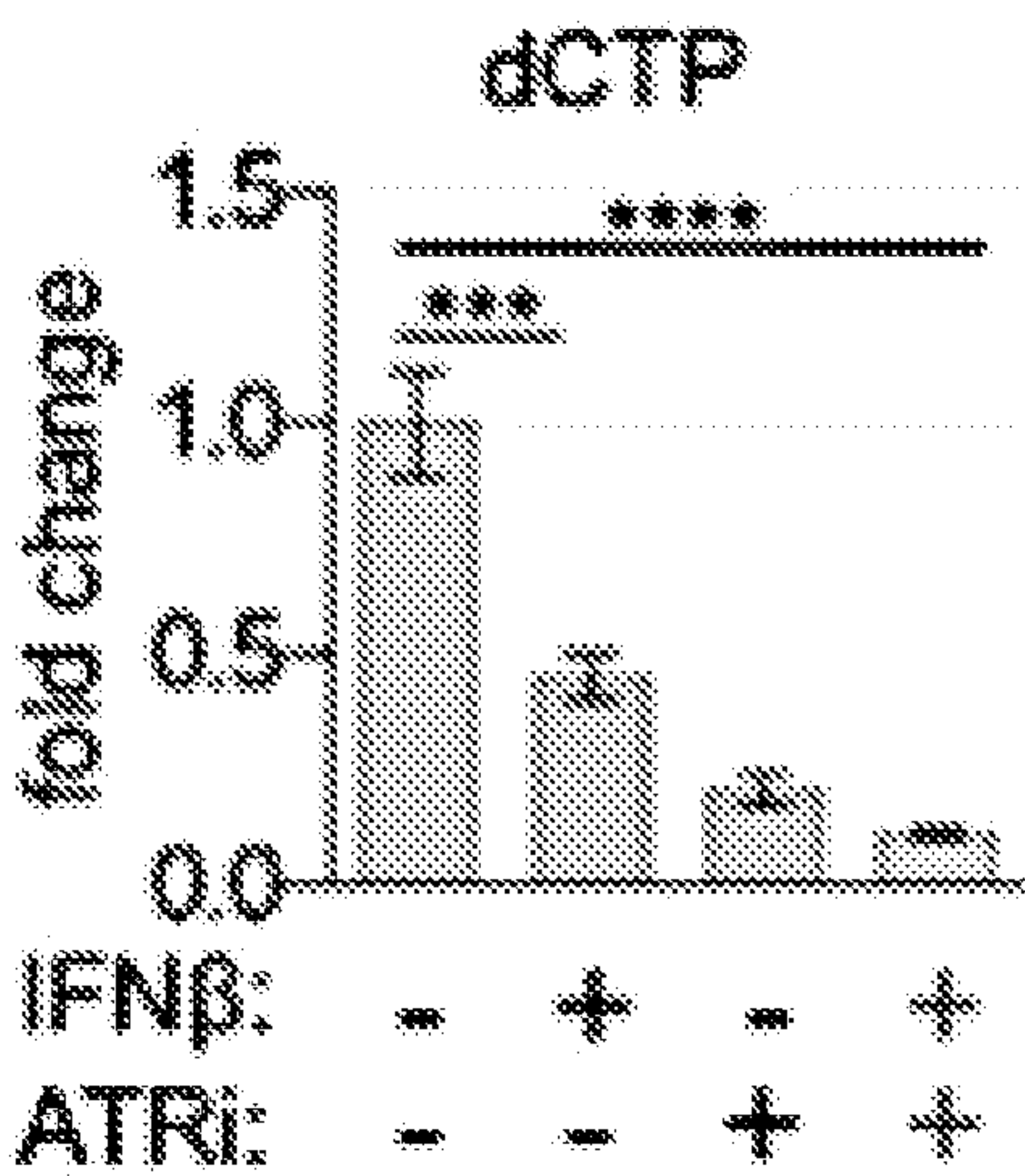


FIG. 7B

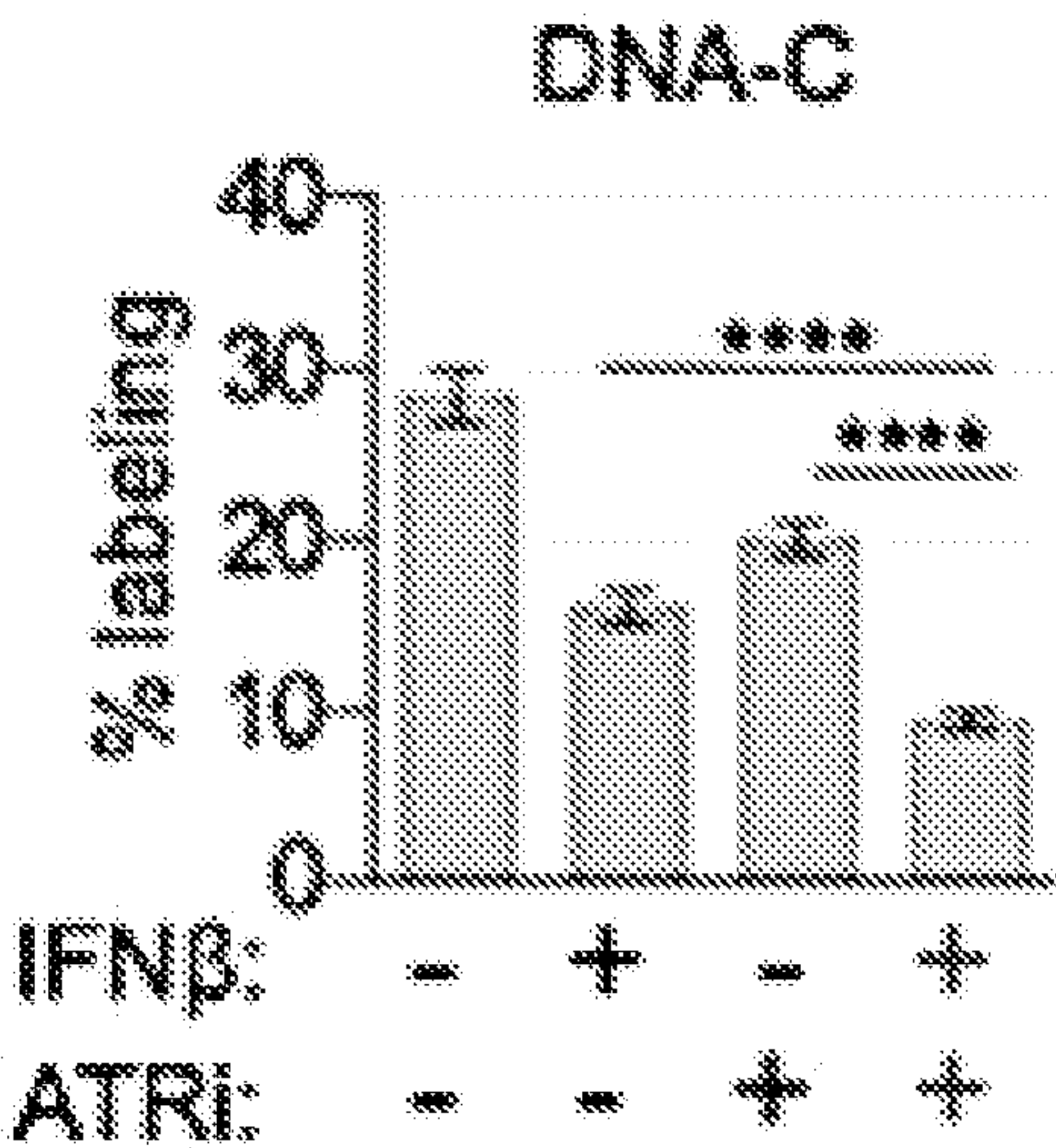
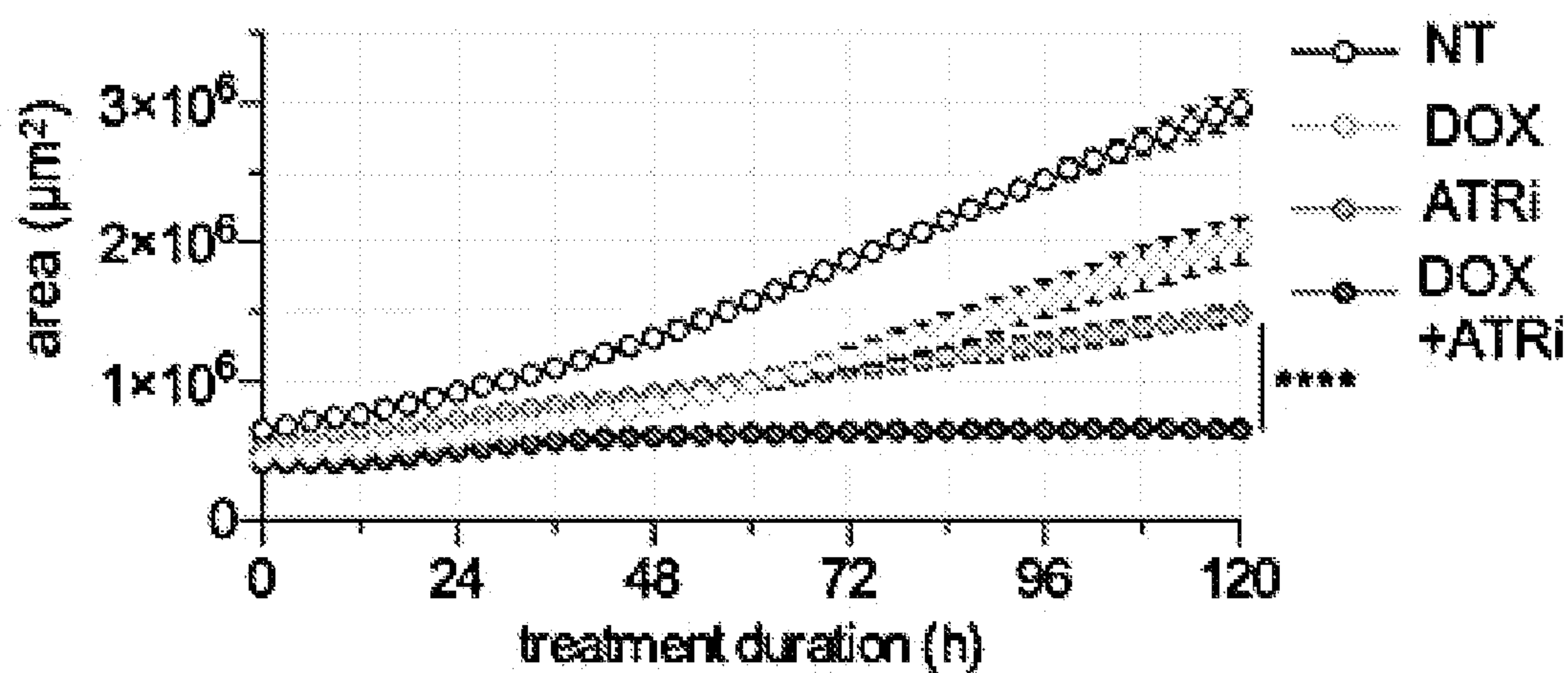
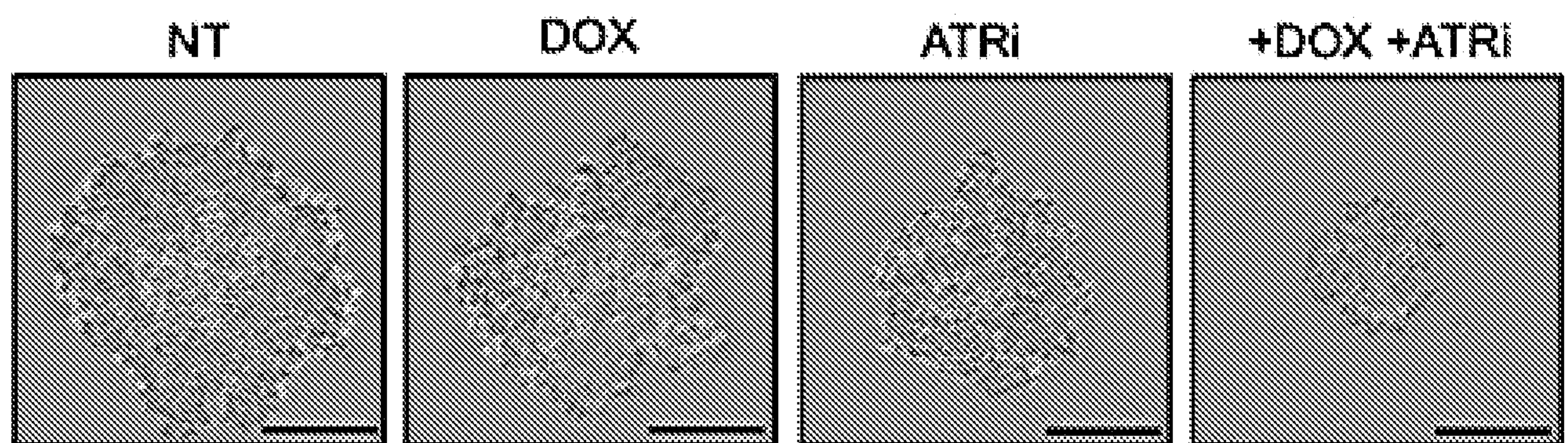
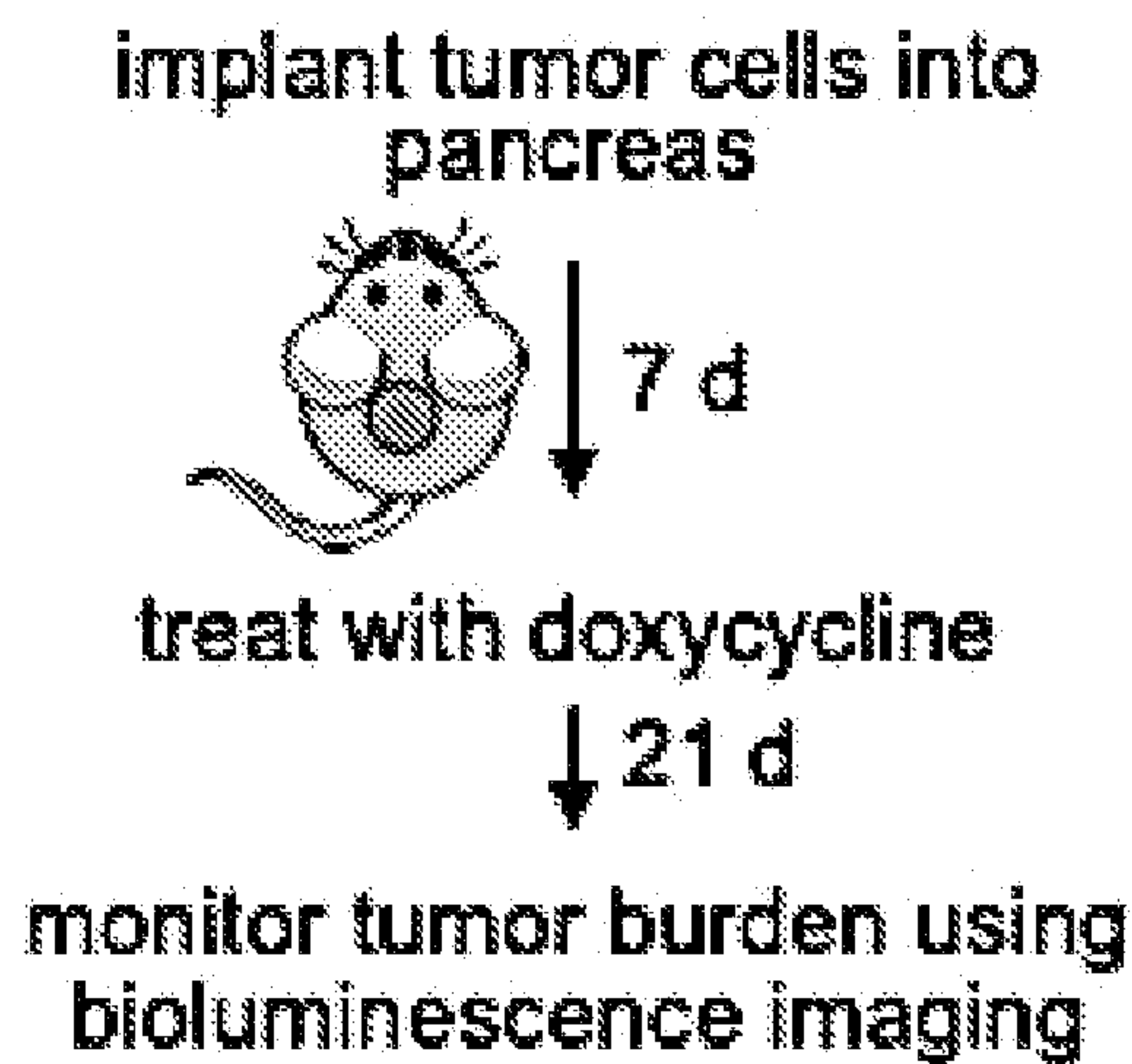


FIG. 7C

**FIG. 8A**scale: 800 μm **FIG. 8B****FIG. 8C**

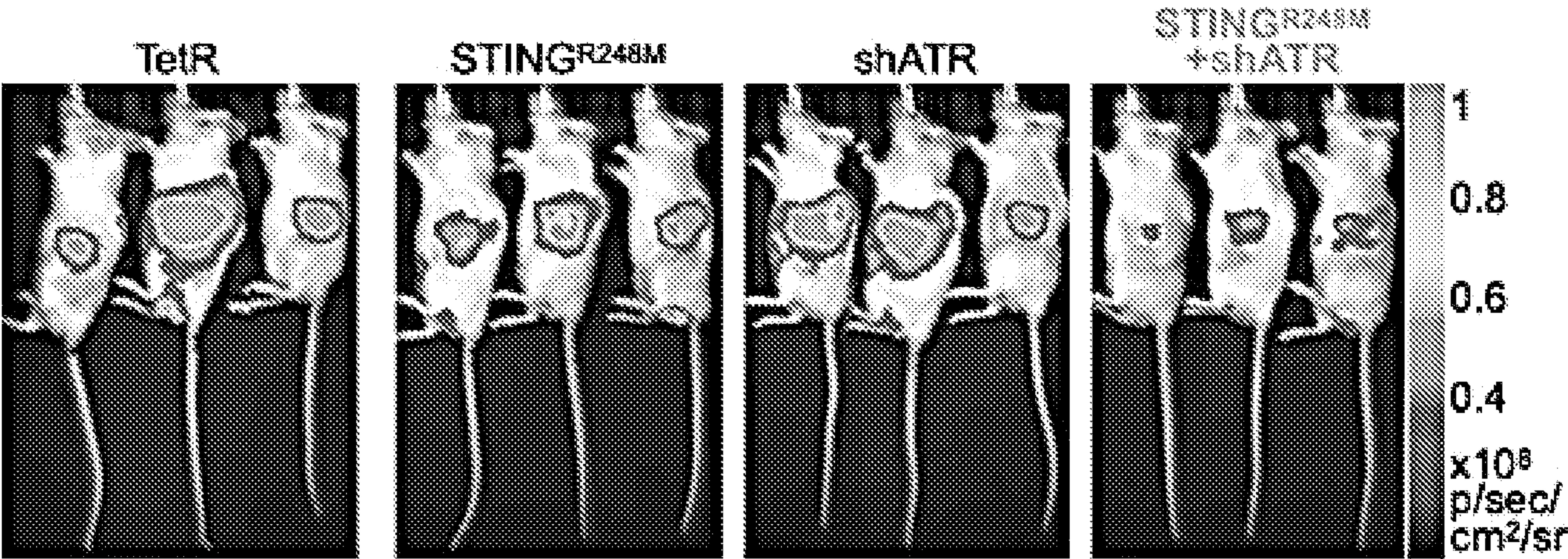


FIG. 8D

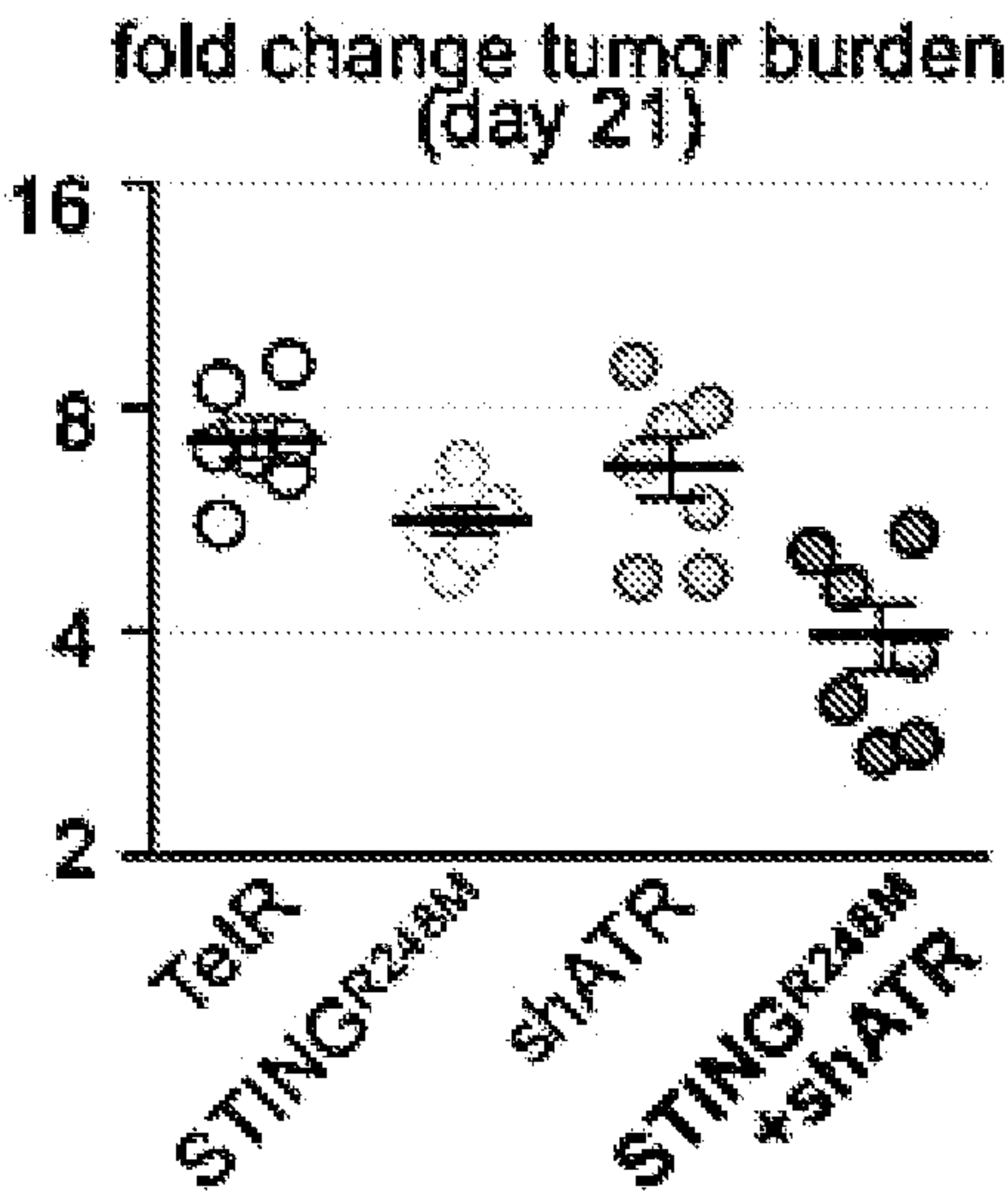


FIG. 8E

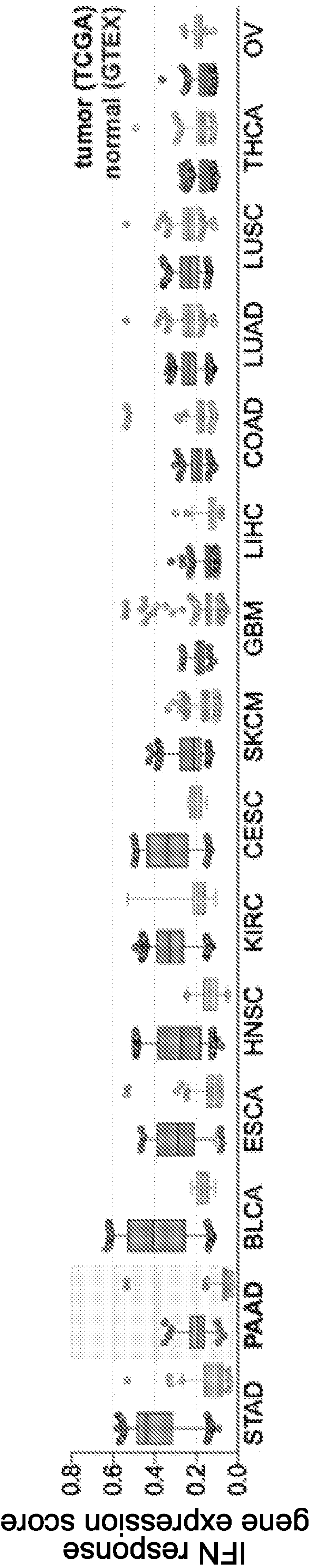


FIG. 9A

dataset	ID	<i>n</i>	median
BLCA	Bladder Urothelial Carcinoma	426	0.41
GTEX-bladder		9	0.18
CESC	Cervical squamous cell carcinoma and	309	0.34
GTEX-cervix		10	0.21
COAD	Colon adenocarcinoma	331	0.20
GTEX-colon		308	0.18
ESCA	Esophageal carcinoma	195	0.29
GTEX-esophagus		273	0.13
GBM	Glioblastoma multiforme	171	0.19
GTEX-brain		850	0.14
HNSC	Head and Neck squamous cell carcinoma	564	0.27
GTEX-salivary		55	0.13
KIRC	Kidney renal clear cell carcinoma	603	0.33
GTEX-kidney		28	0.20
LIHC	Liver hepatocellular carcinoma	421	0.14
GTEX-liver		110	0.12
LUAD	Lung adenocarcinoma	574	0.24
GTEX-lung		288	0.24
LUSC	Lung squamous cell carcinoma	548	0.23
GTEX-lung		288	0.24
OV	Ovarian serous cystadenocarcinoma	427	0.16
GTEX-ovary		88	0.19
PAAD	Pancreatic adenocarcinoma	183	0.19
GTEX-pancreas		167	0.06
SKCM	Skin Cutaneous Melanoma	470	0.21
GTEX-skin		557	0.16
STAD	Stomach adenocarcinoma	450	0.44
STEC-stomach		175	0.09
THCA	Thyroid carcinoma	571	0.16
GTEX-thyroid		279	0.17

FIG. 9B

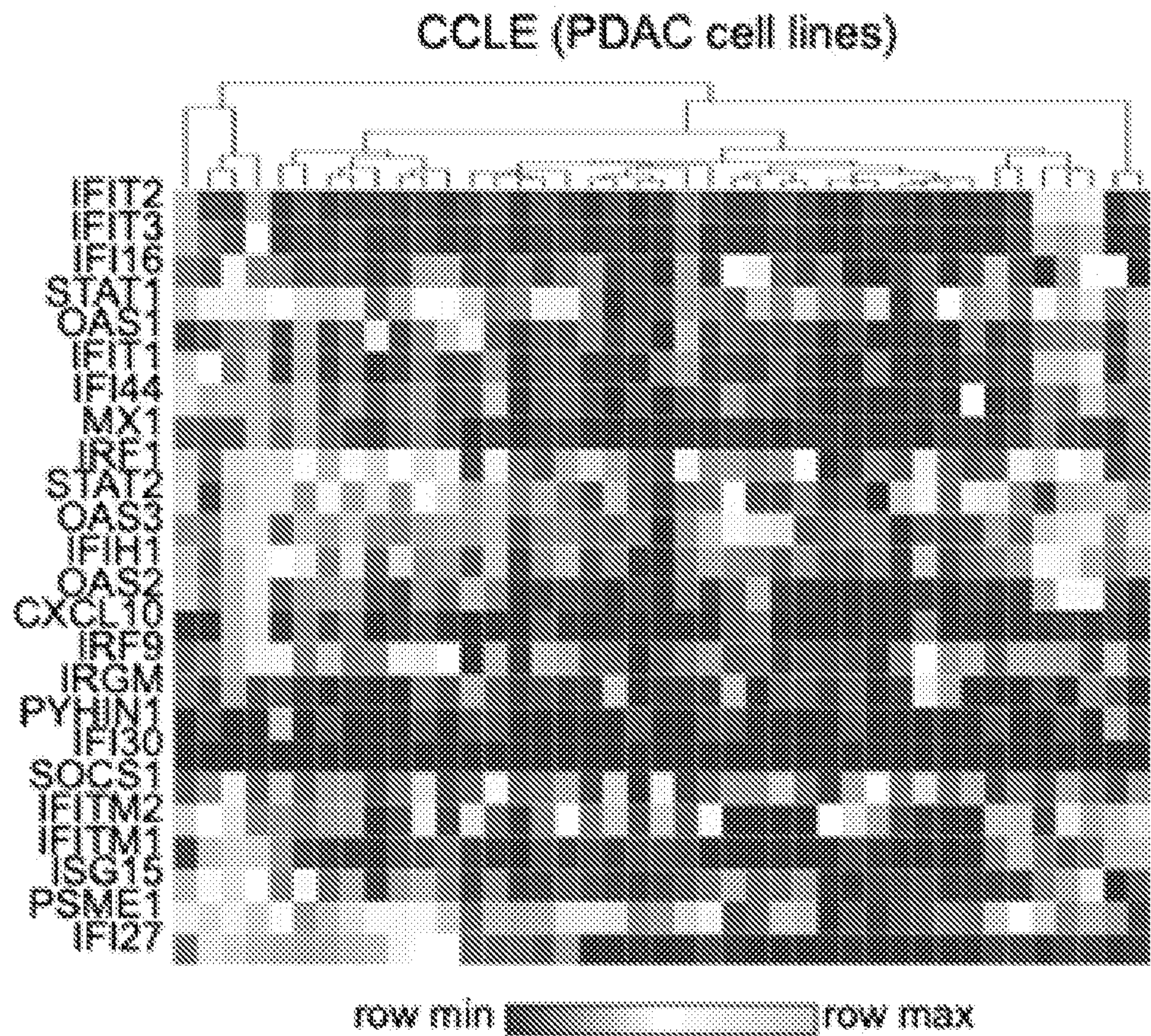


FIG. 9C

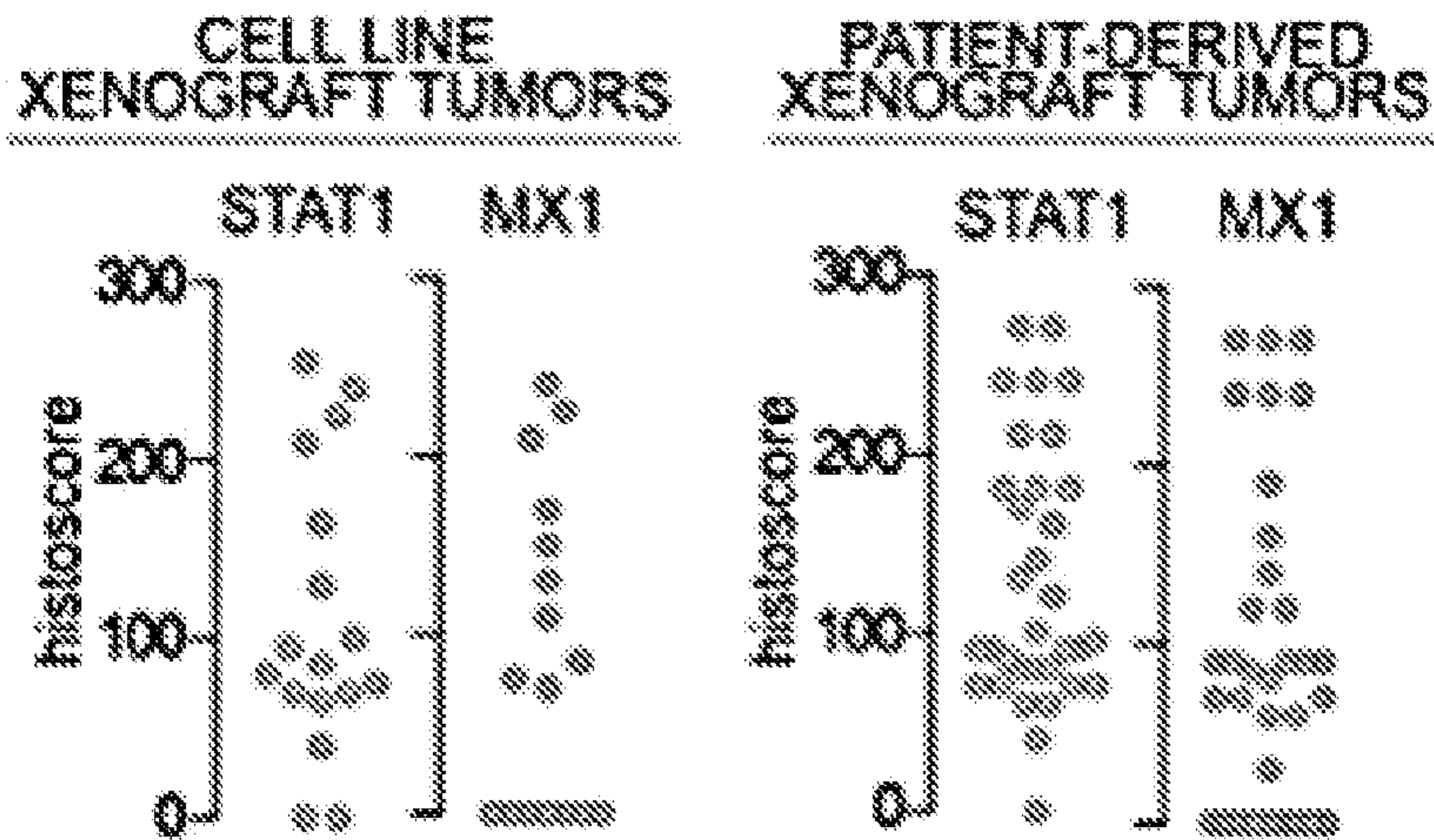


FIG. 10A

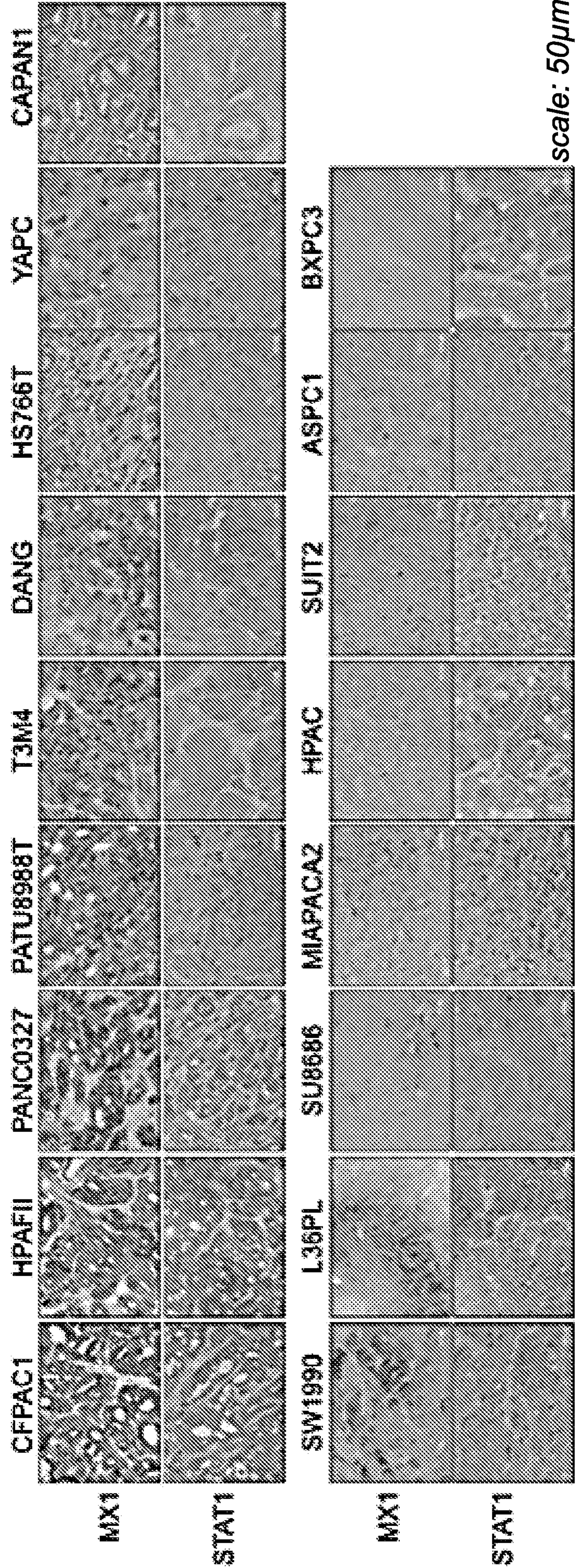


FIG. 10B

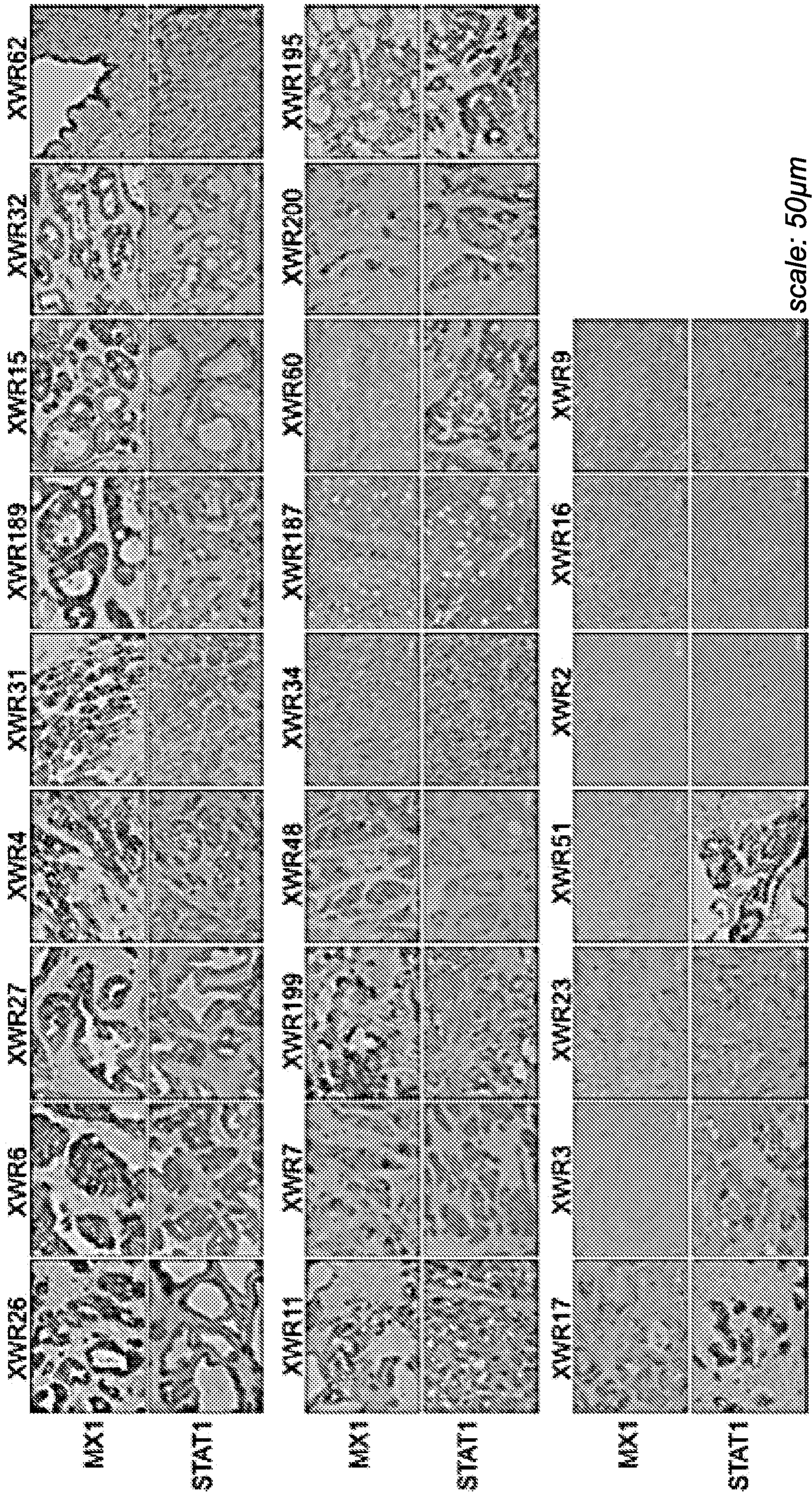


FIG. 10C

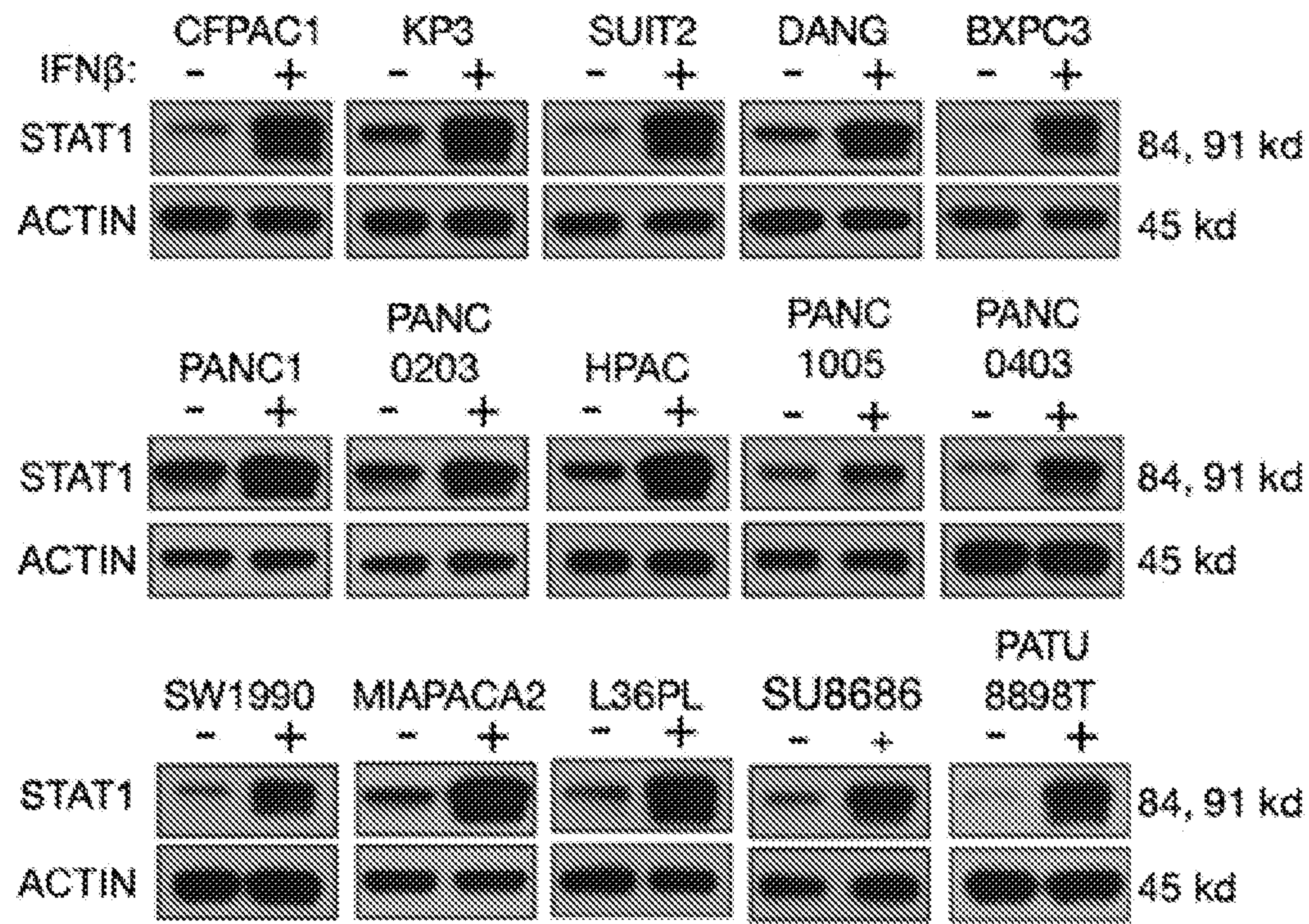


FIG. 11A

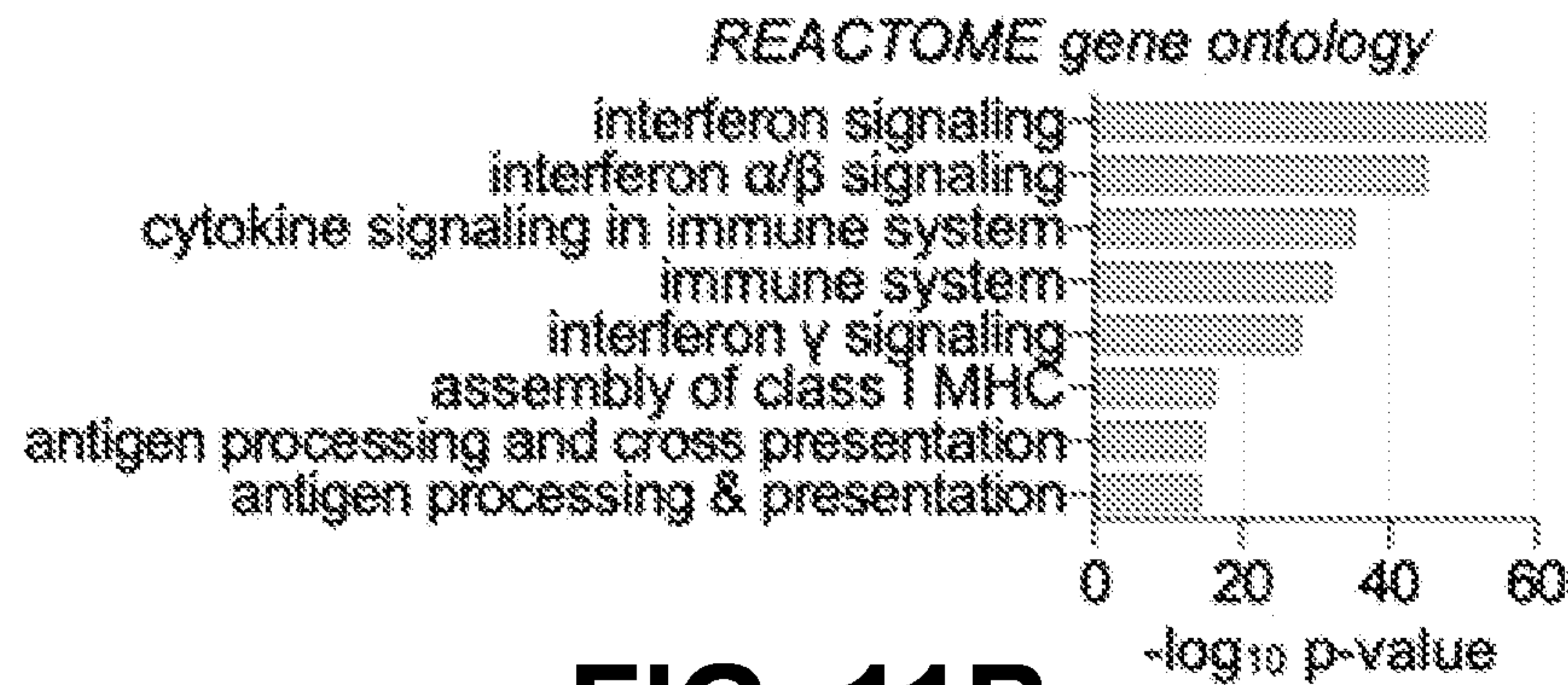


FIG. 11B

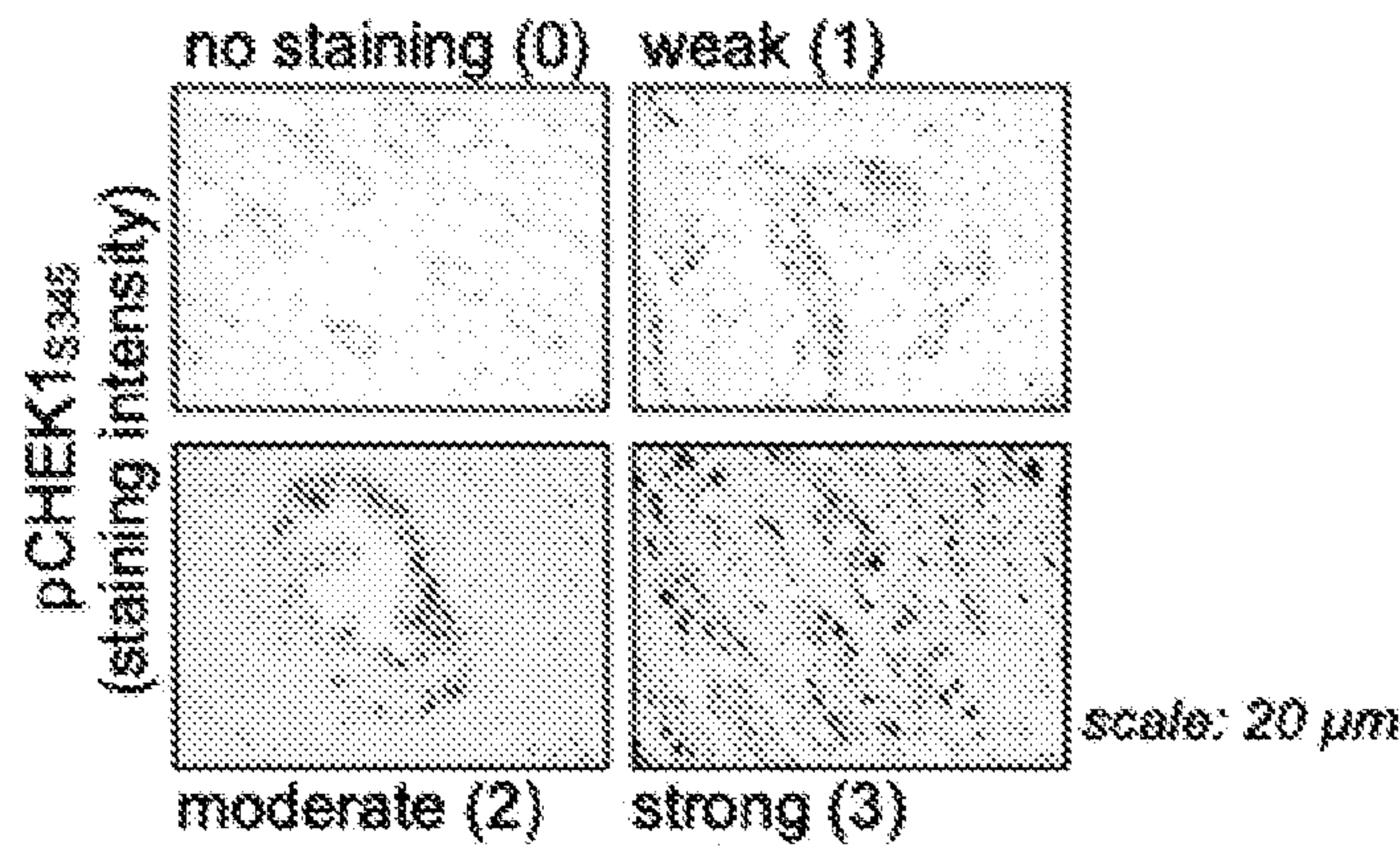


FIG. 11C

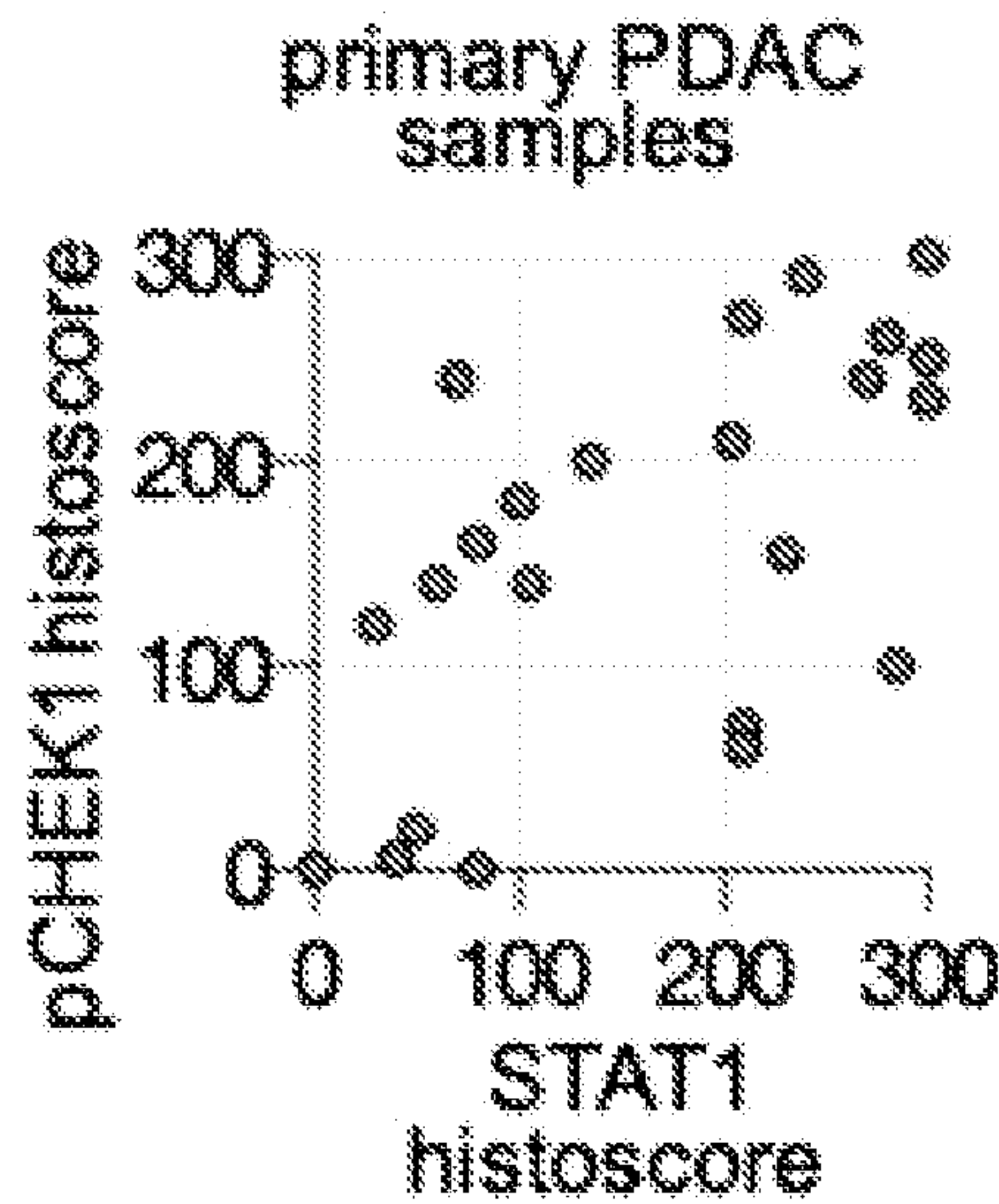


FIG. 11D

gene ID	metabolic role	substrate(s)	product(s)
<i>SAMHD1</i>	dNTP triphosphohydrolase	dCTP, dTTP, dGTP, dATP	dC, dT, dG, dA; +PPP
<i>NT5C3A</i>	pyrimidine nucleotidase	UMP, CMP	rU, rC; +P
<i>TYMP</i>	thymidine phosphorylase	dT	thymine + 2-deoxy-alpha-D-ribose 1-phosphate

FIG. 12A

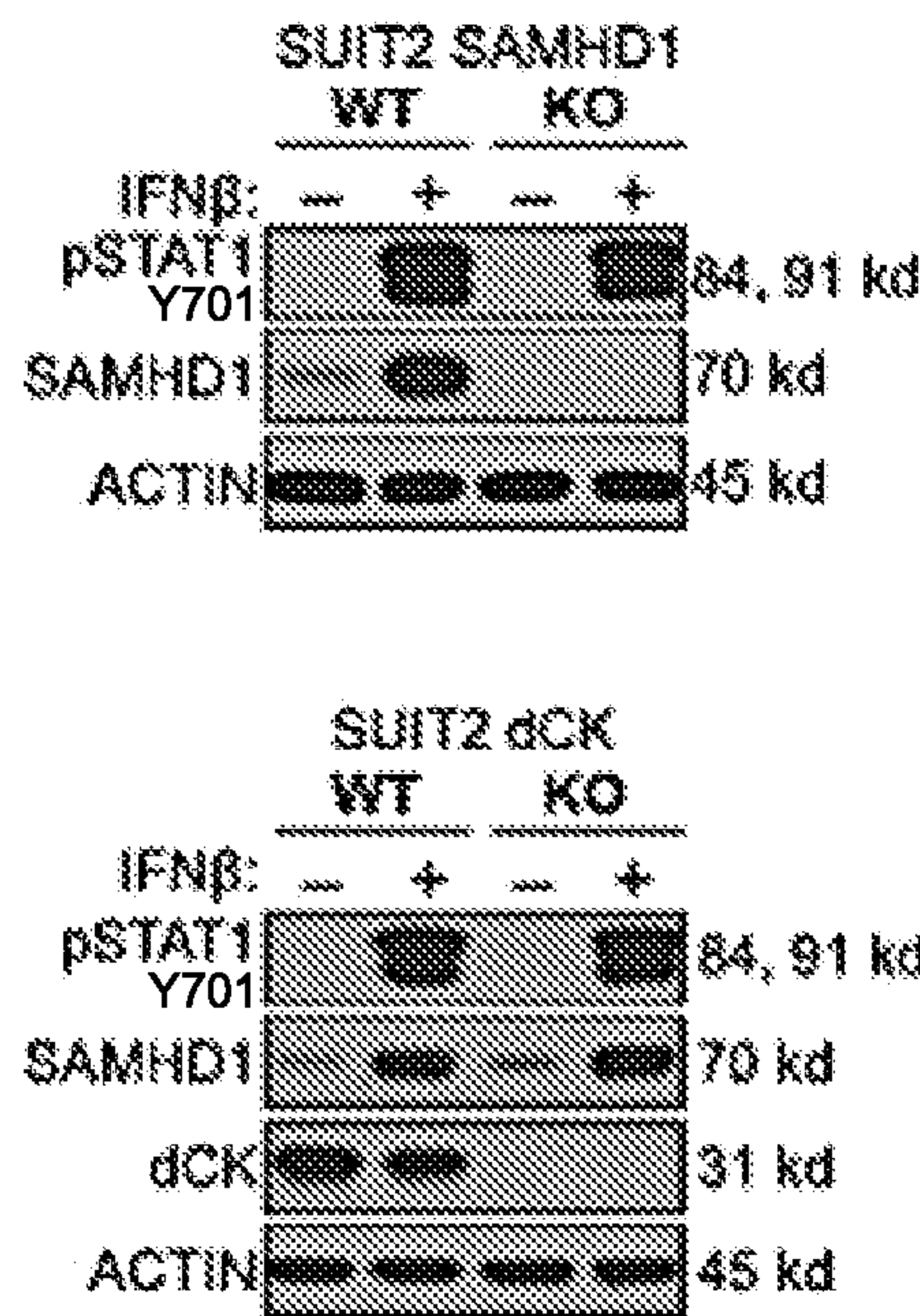


FIG. 12B

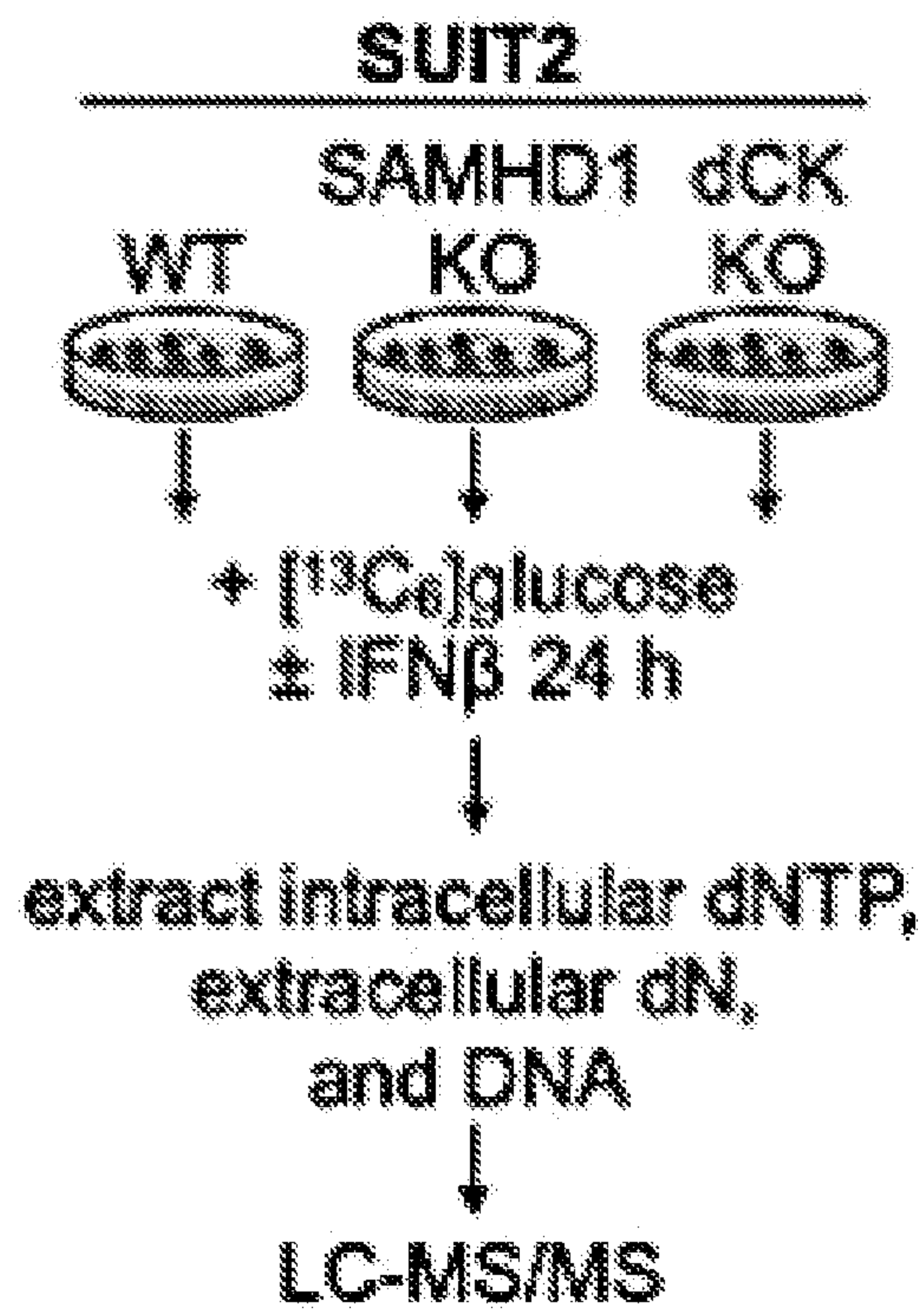


FIG. 12C

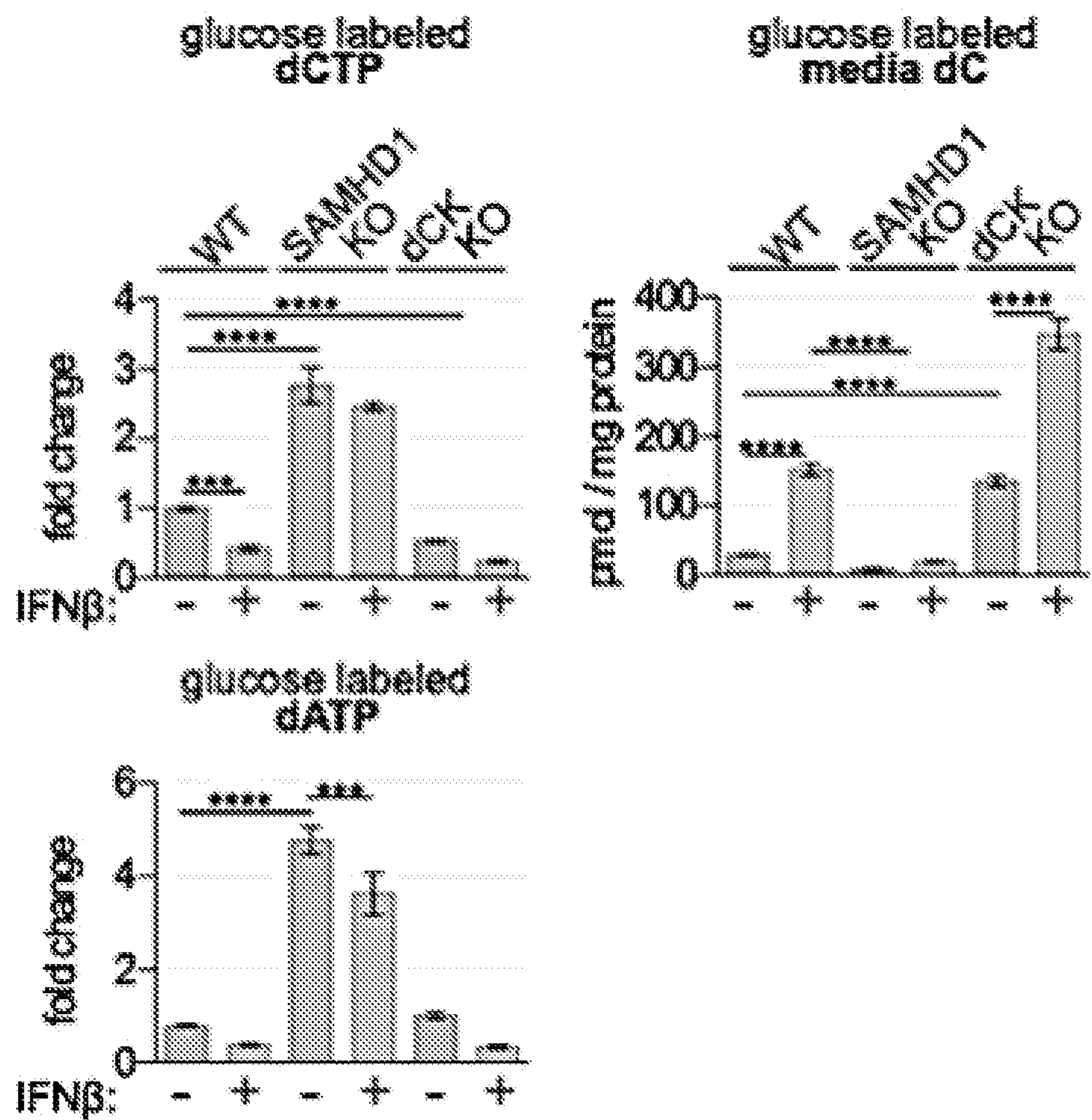


FIG. 12D

26/65

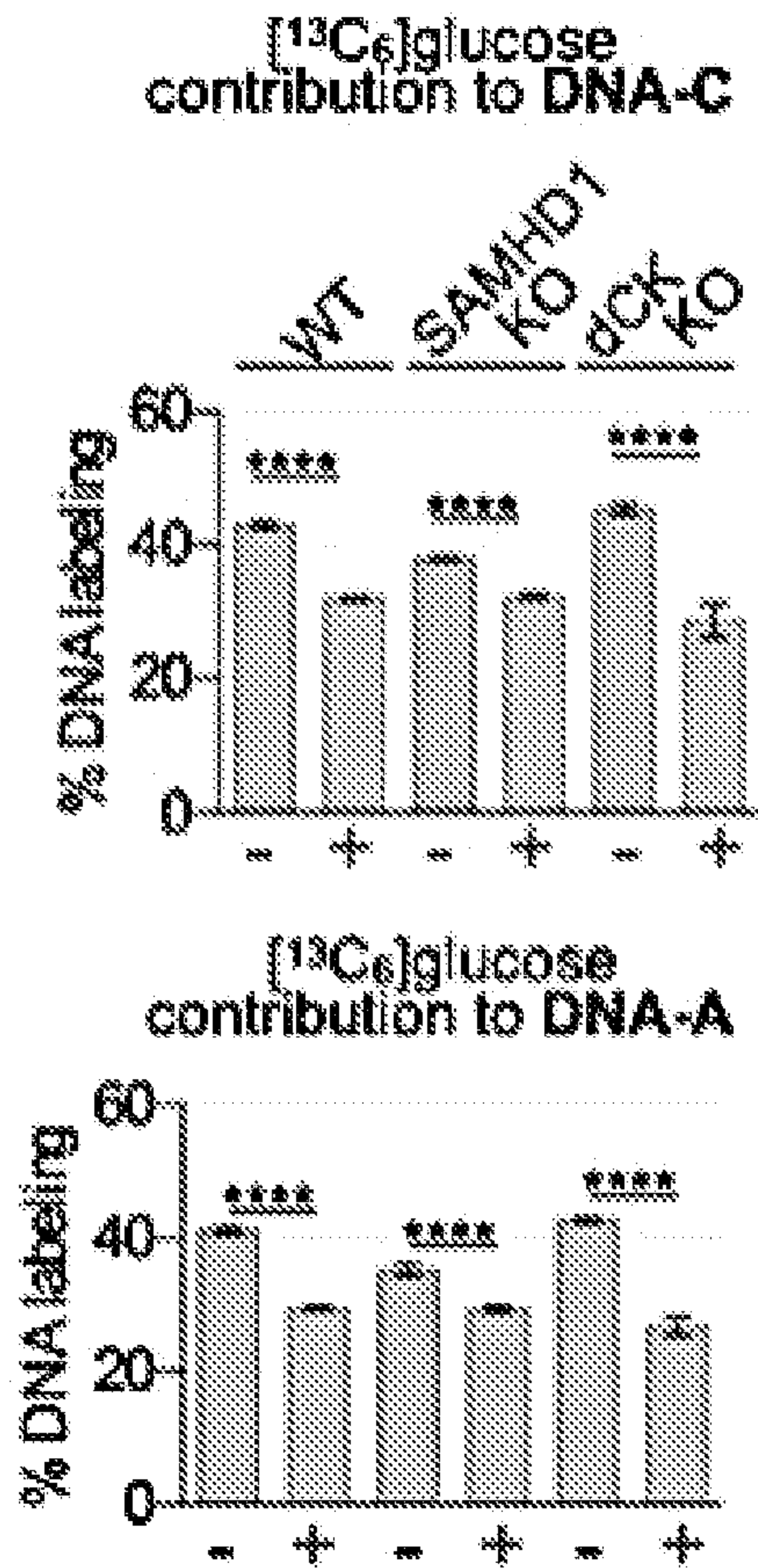


FIG. 12E

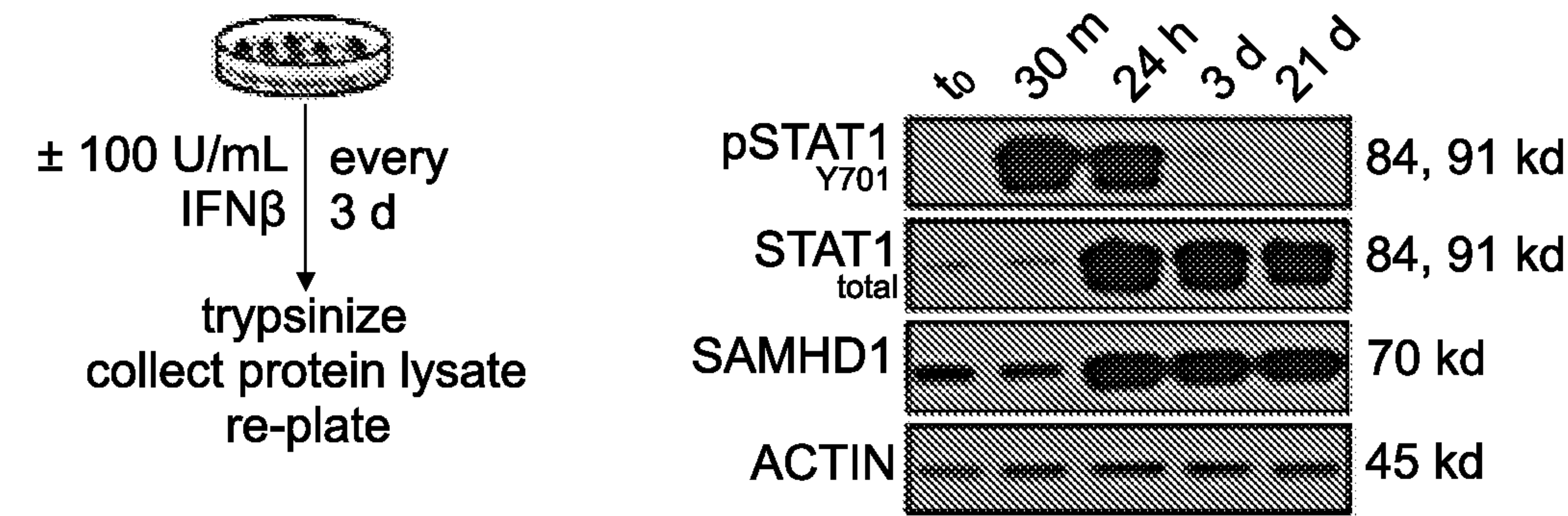


FIG. 12F

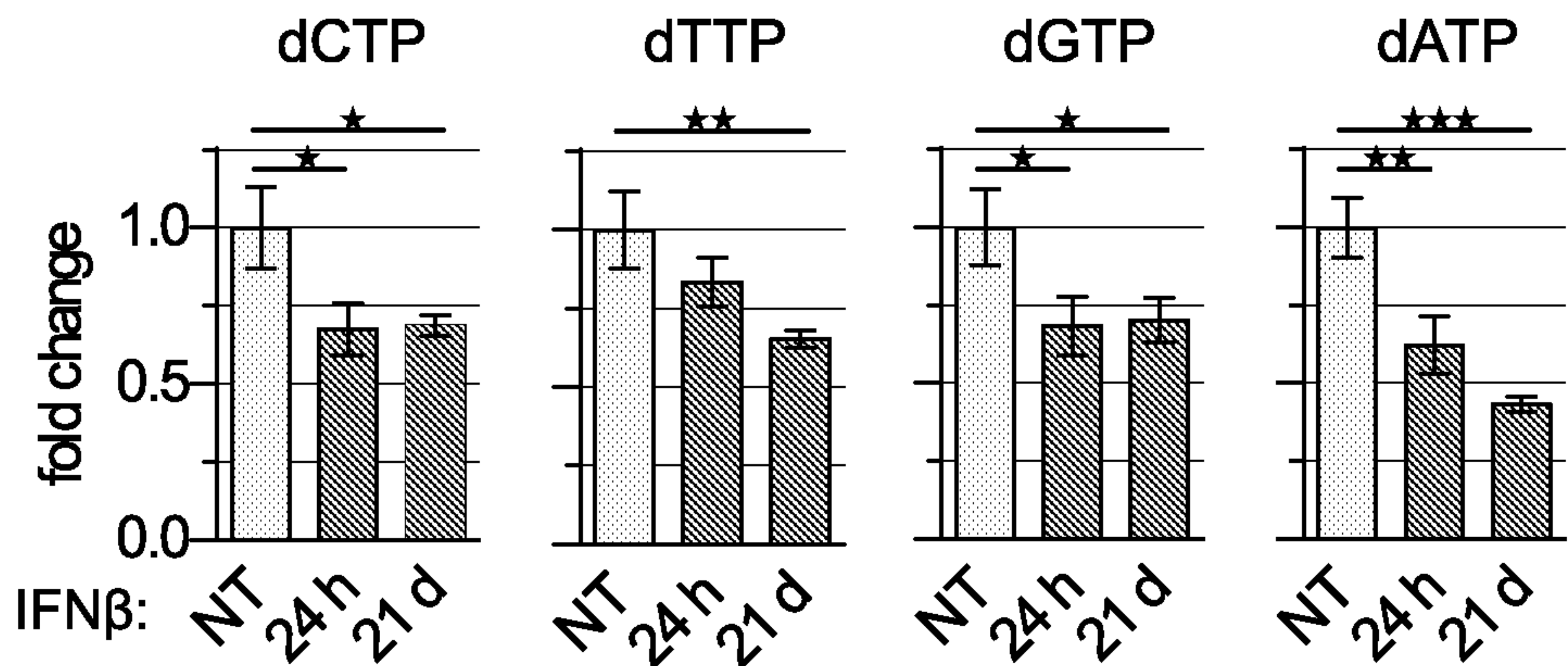


FIG. 12G

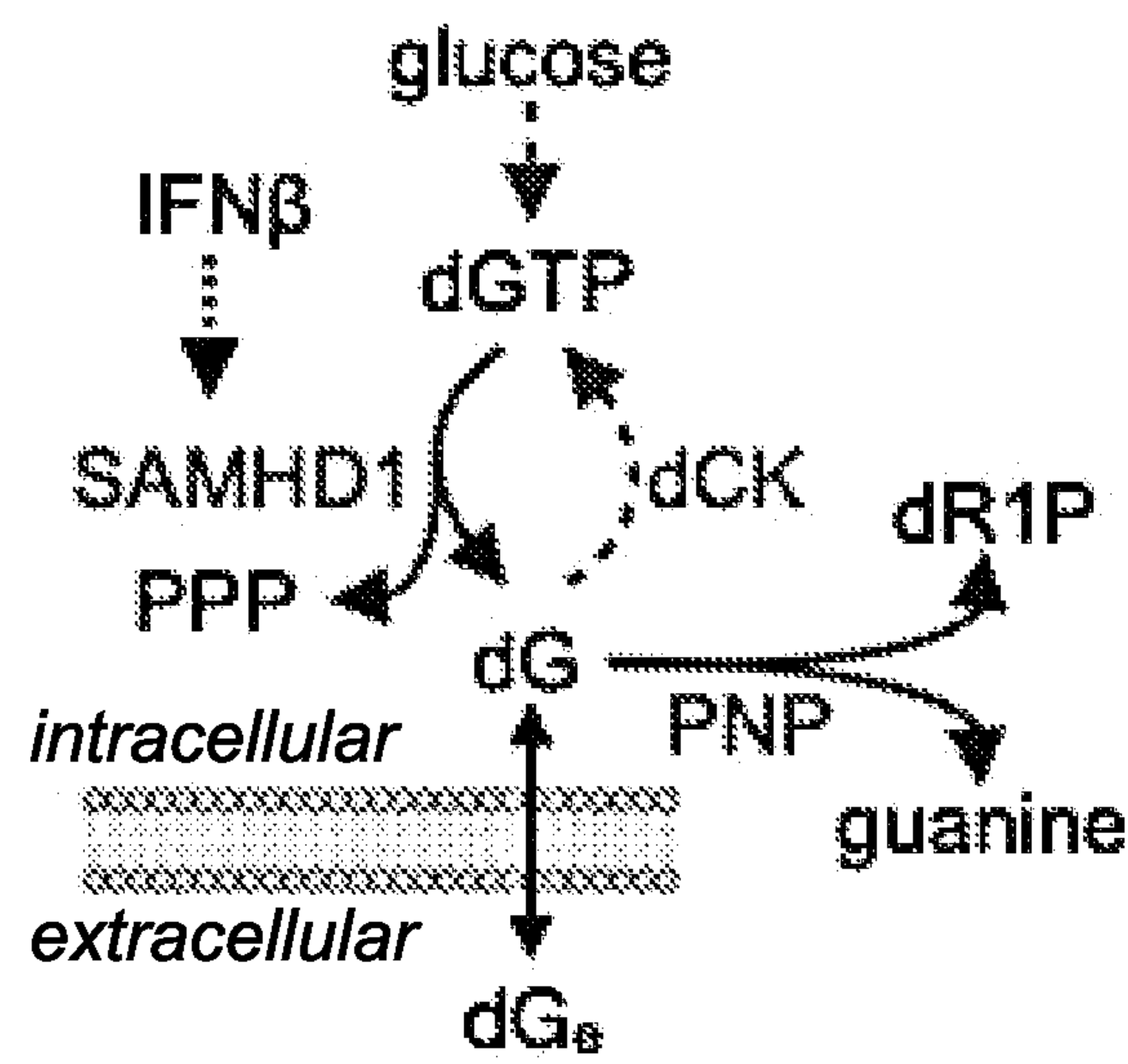


FIG. 13A

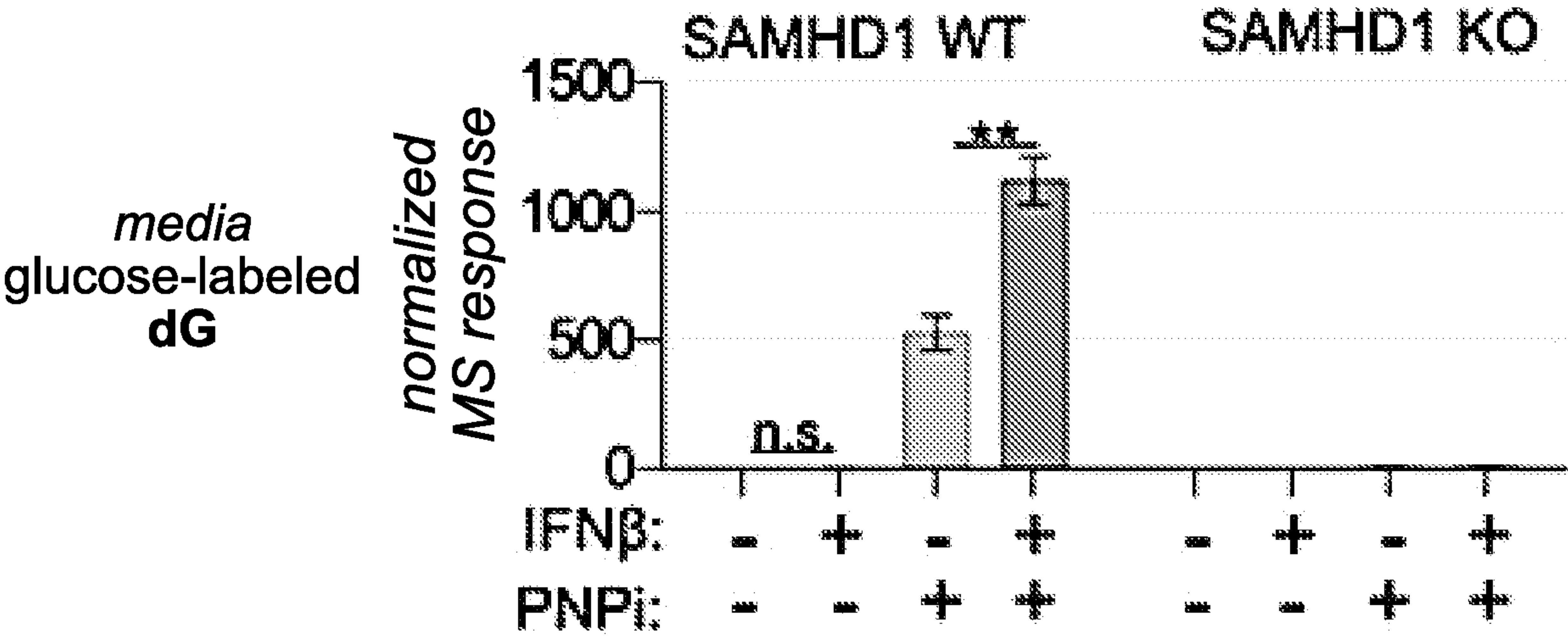


FIG. 13B

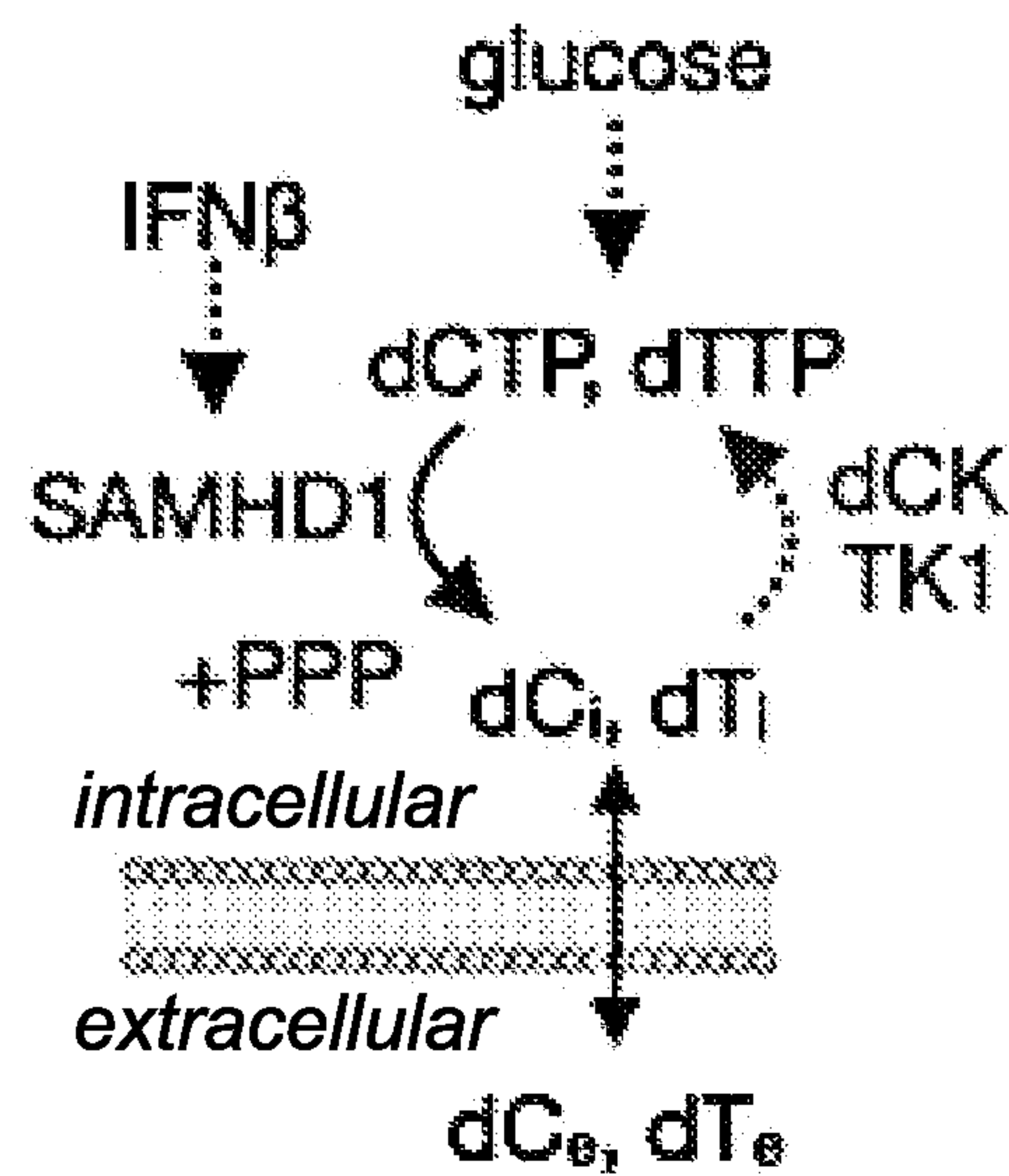


FIG. 13C

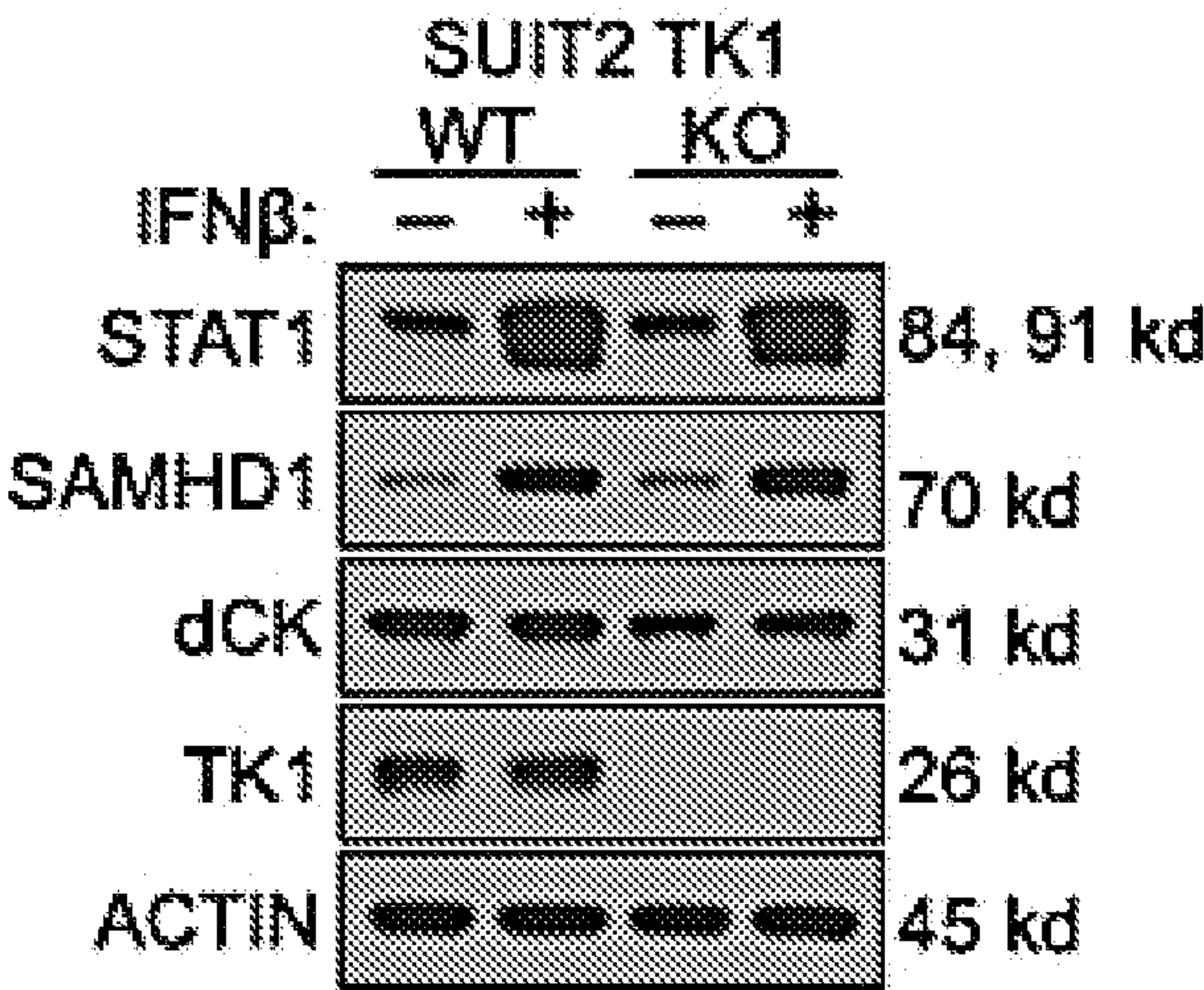


FIG. 13D

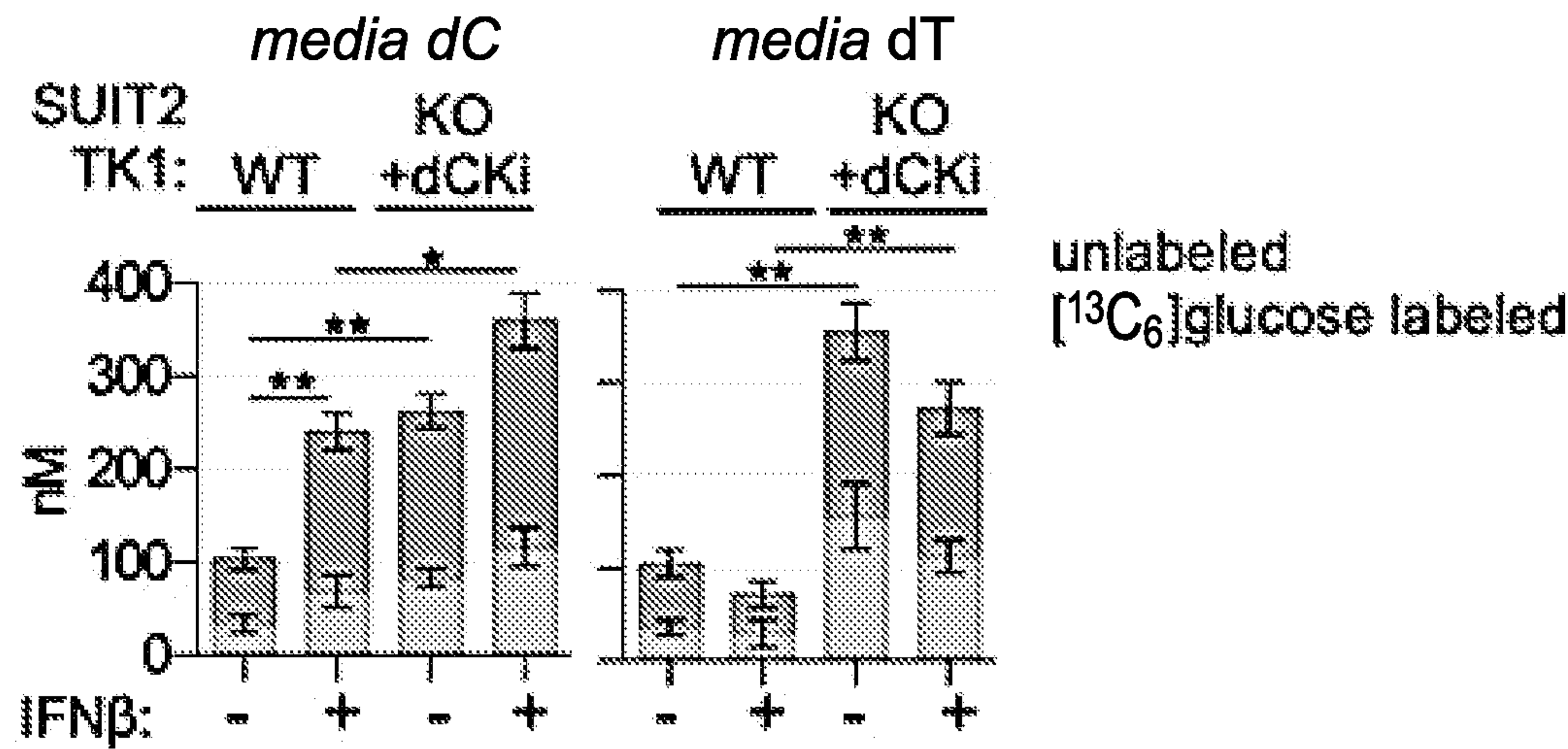


FIG. 13E

Efflux (fmol/h/cell) x10 ⁻³	WT		pyrimidine salvage deficient	
	-IFN β	+IFN β	-IFN β	+IFN β
dC	10.1 $\pm$ 0.80	28.9 $\pm$ 4.15	21.3 $\pm$ 2.22	36.1 $\pm$ 4.95
dT	10.2 $\pm$ 0.68	8.52 $\pm$ 0.28	30.5 $\pm$ 5.16	27.4 $\pm$ 4.05

FIG. 13F

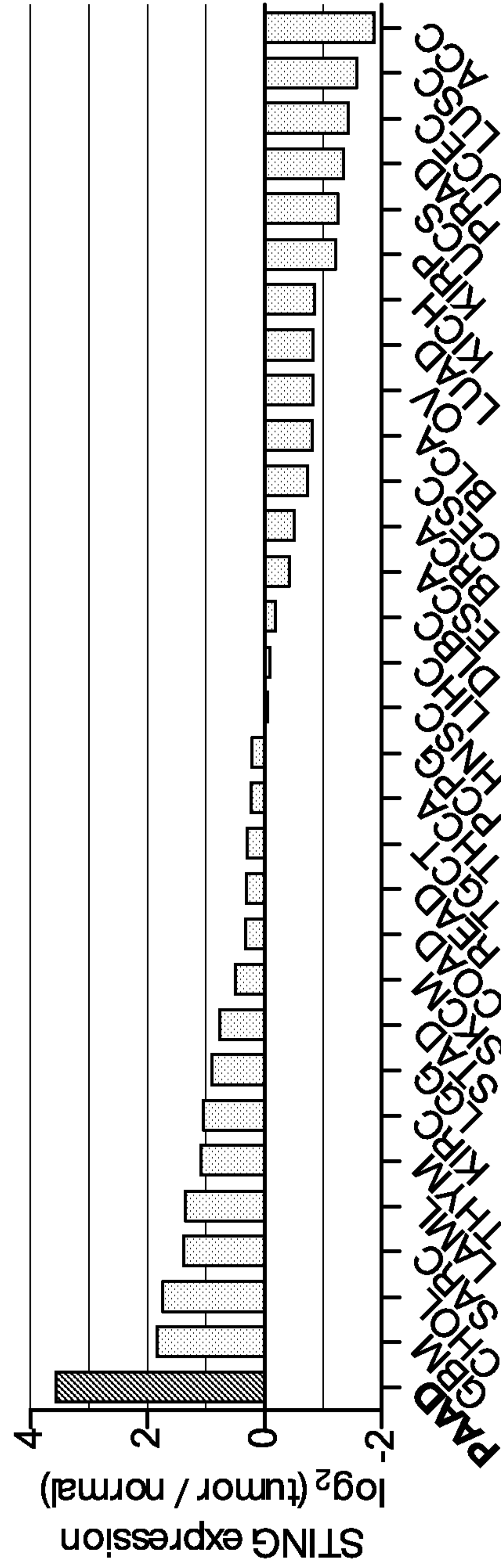


FIG. 14A

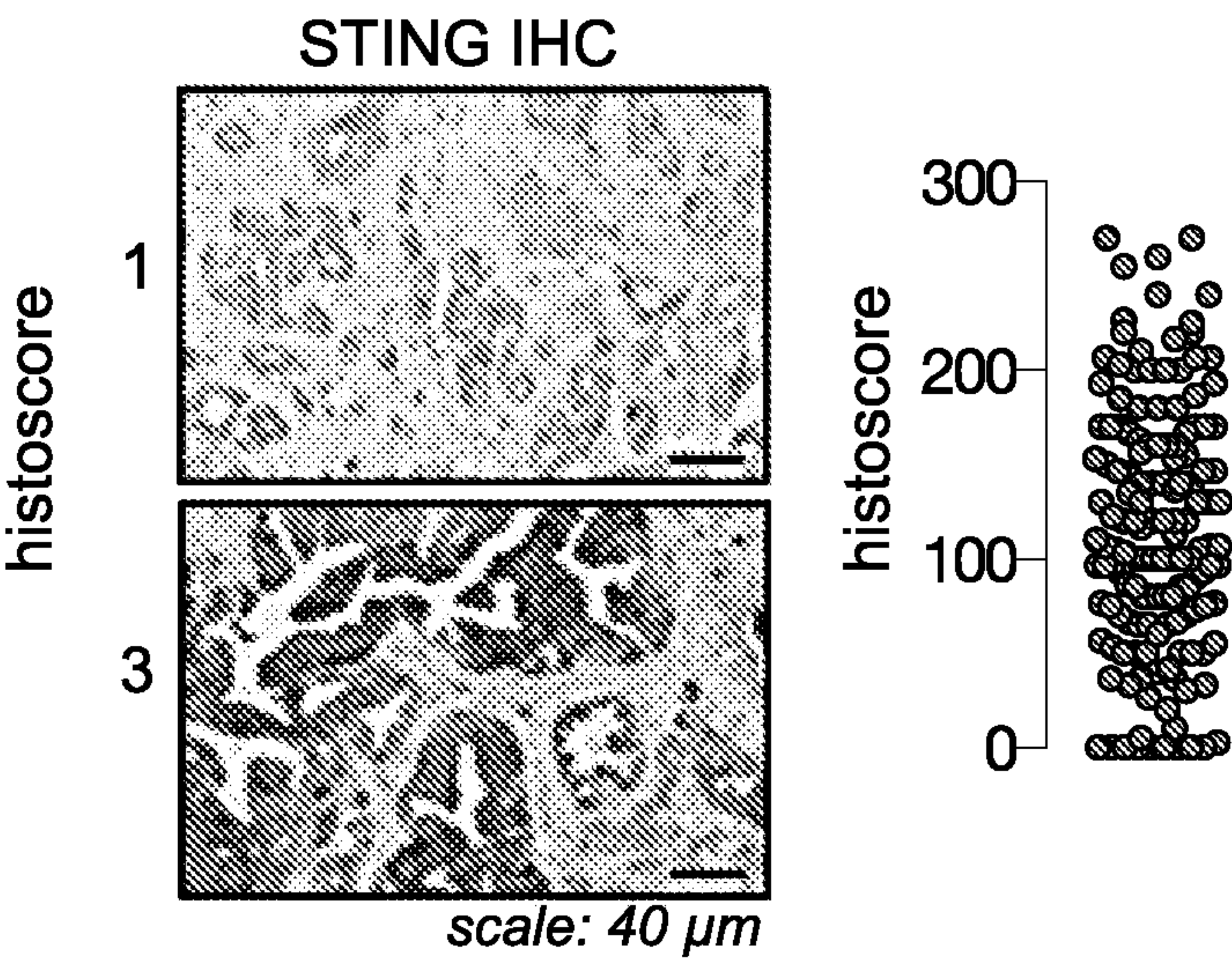


FIG. 14B

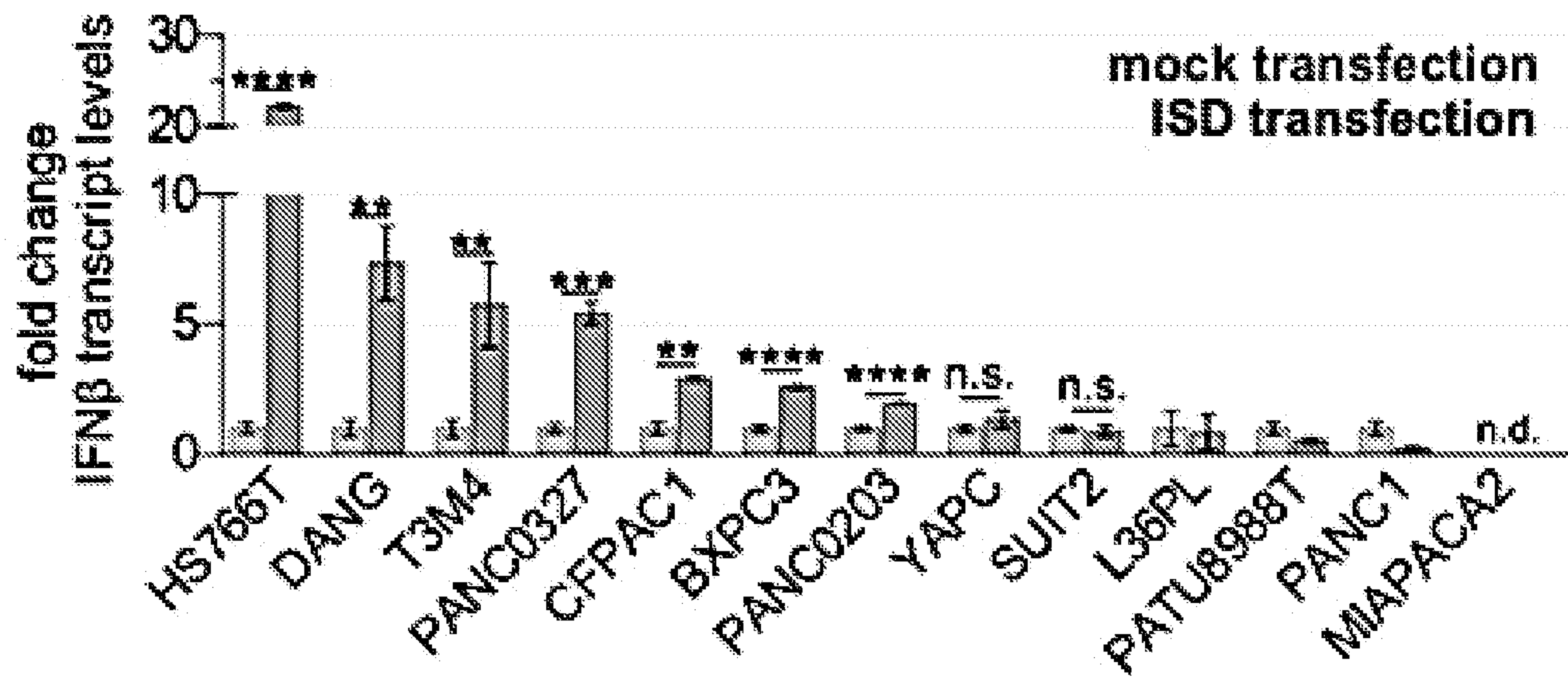


FIG. 14C

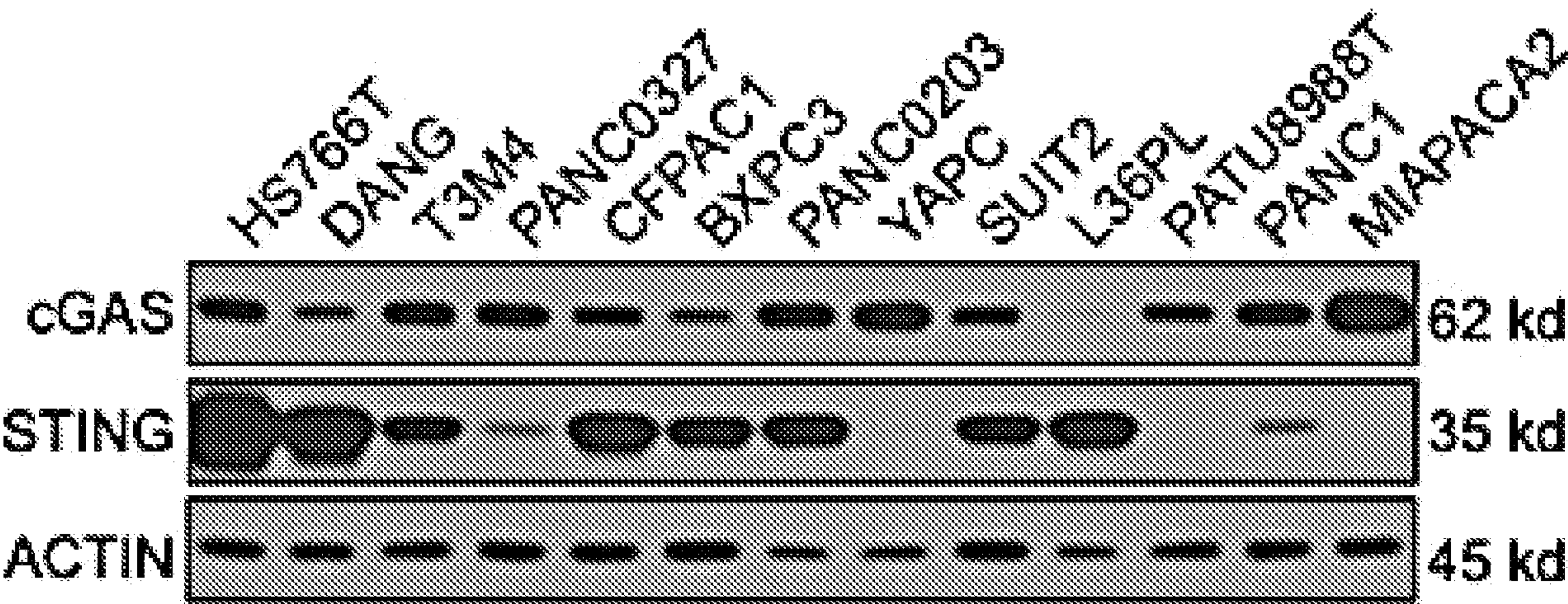


FIG. 14D

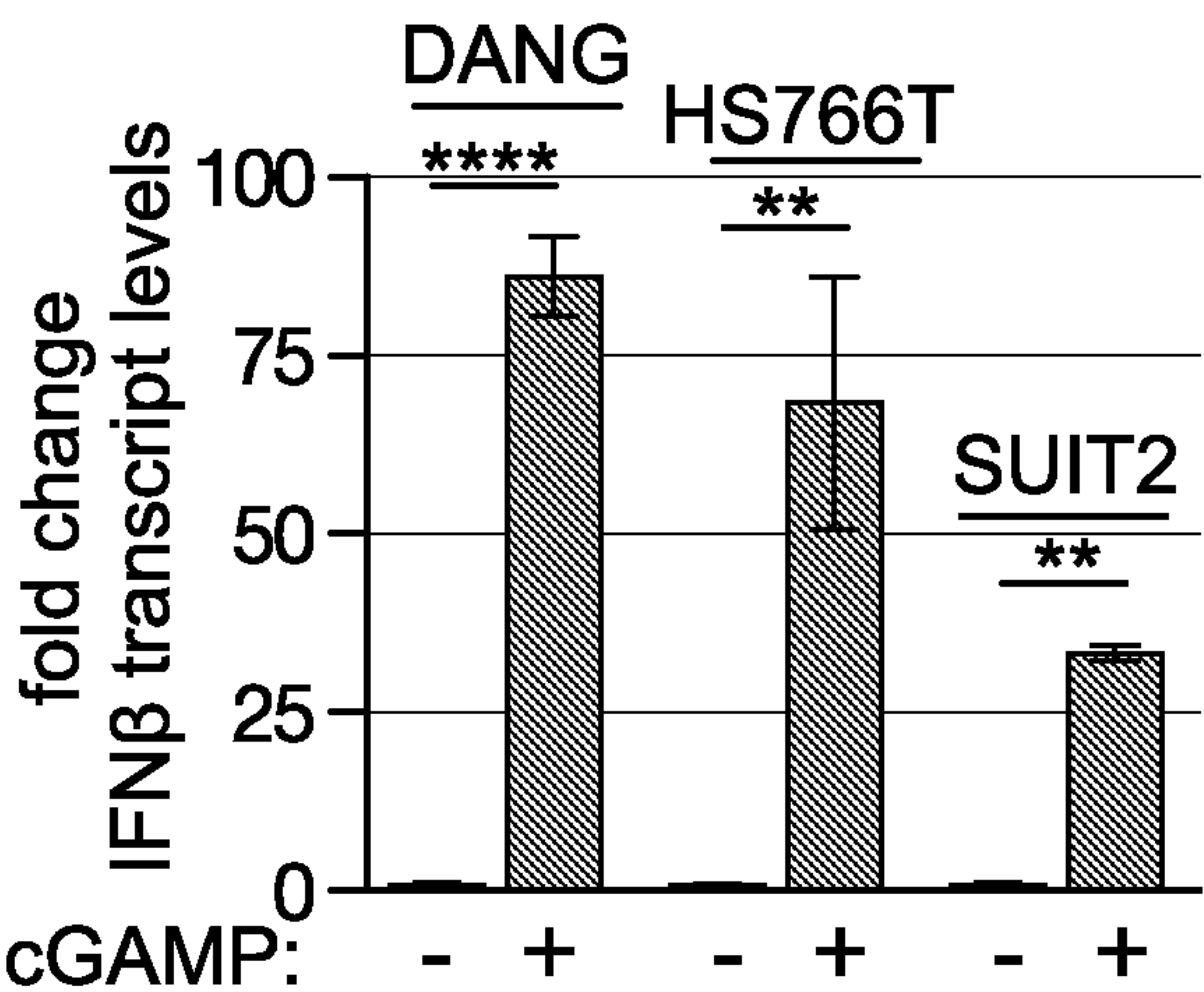


FIG. 14E

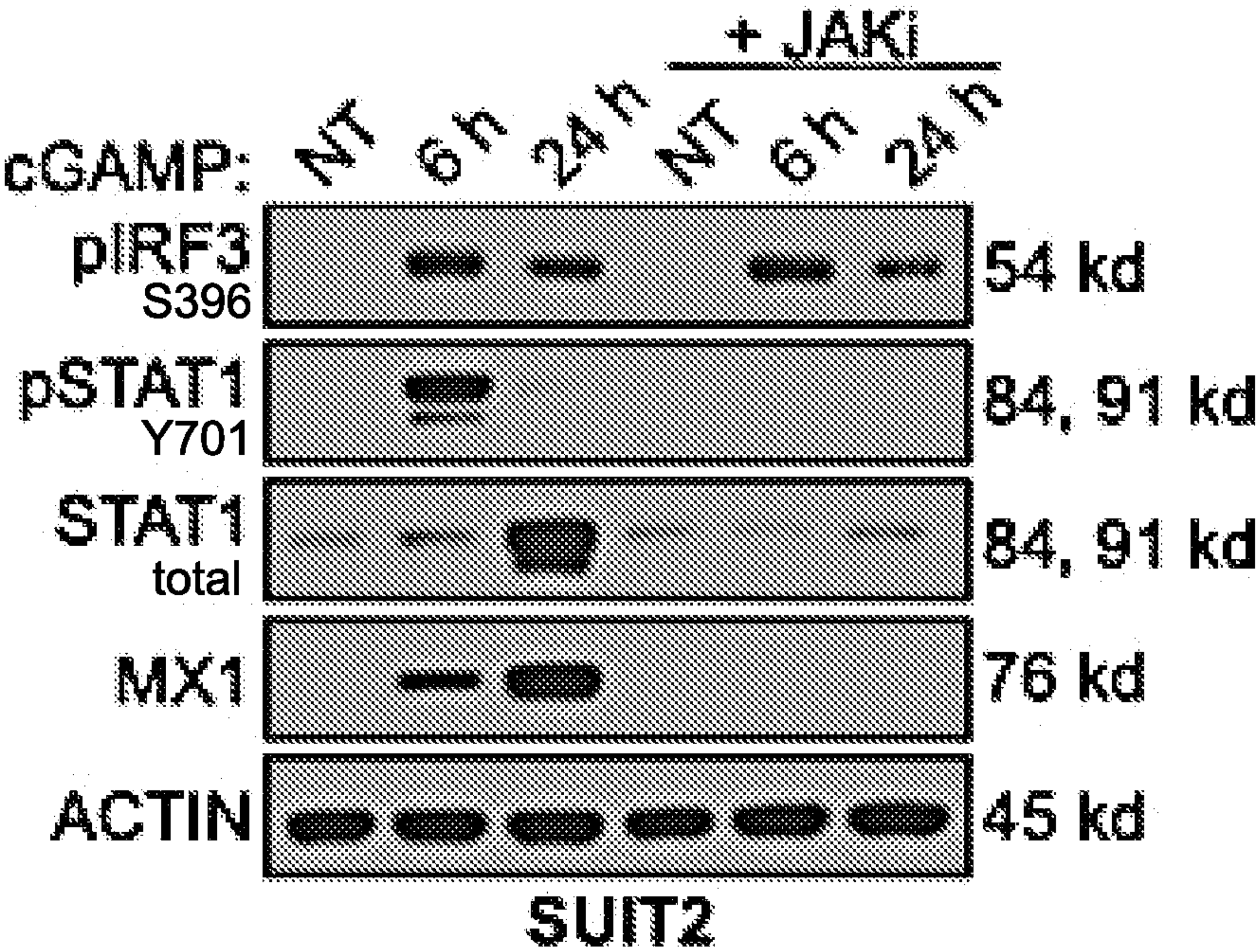


FIG. 14F

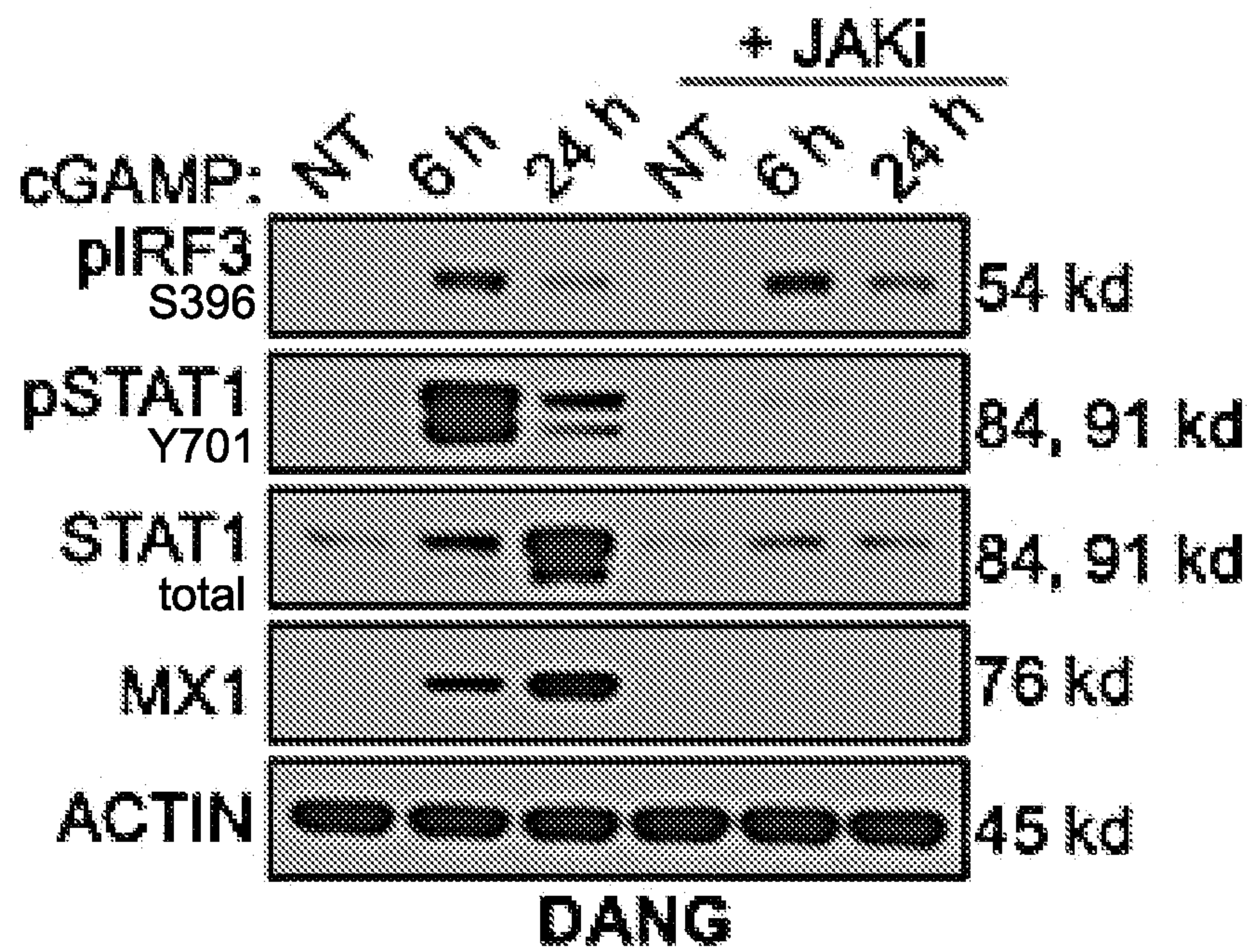


FIG. 14G

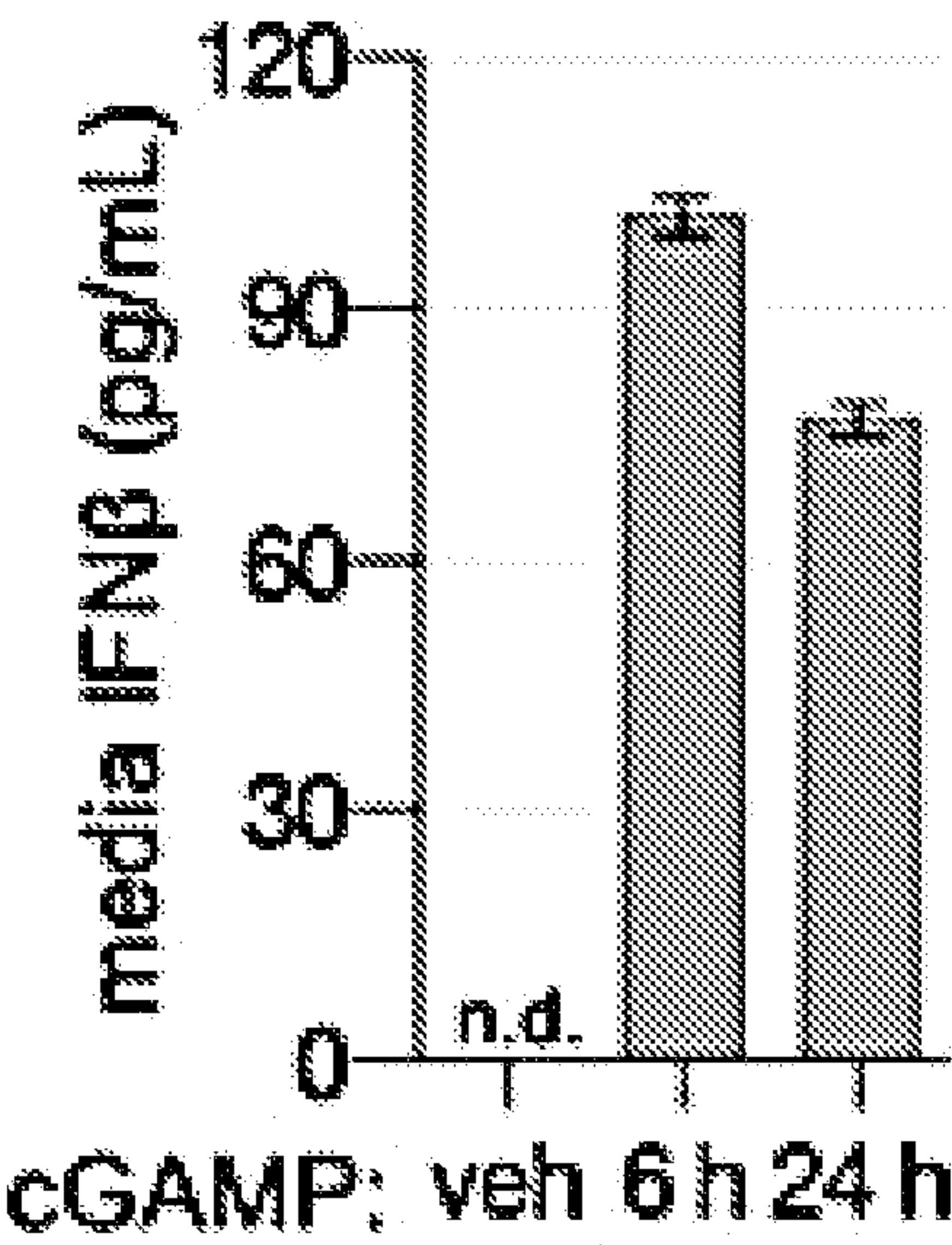


FIG. 14H

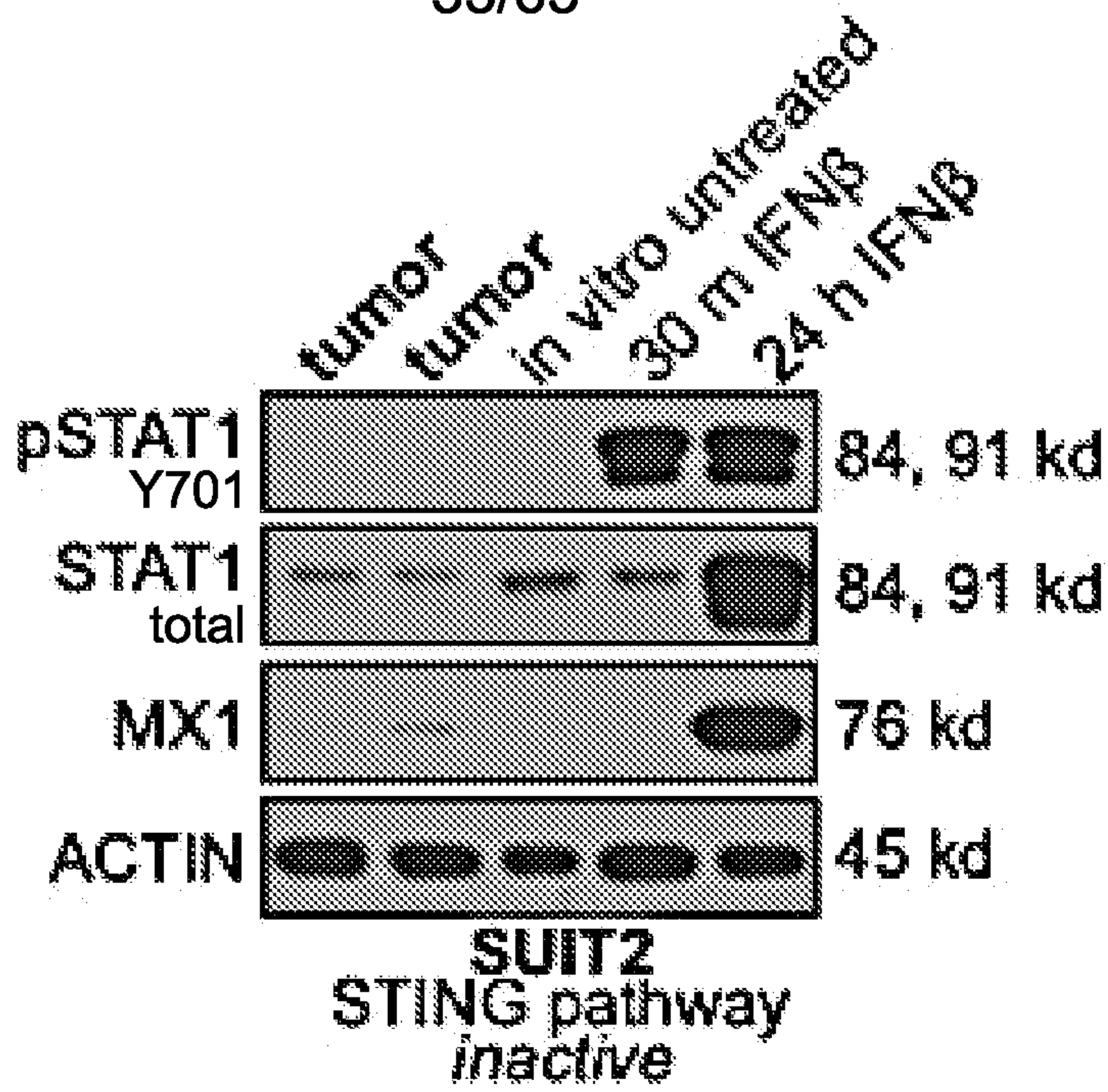


FIG. 15A



FIG. 15B

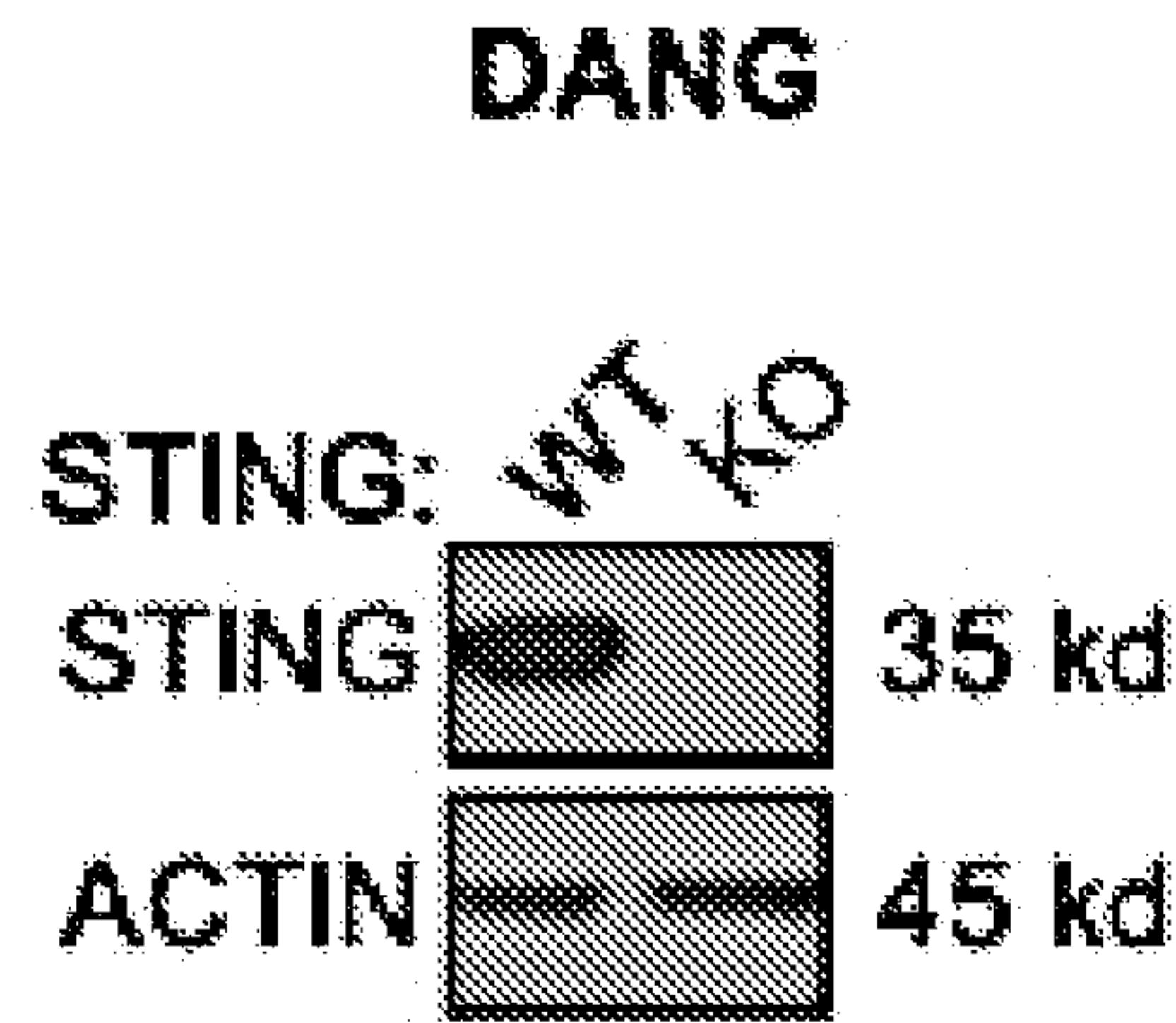


FIG. 15C

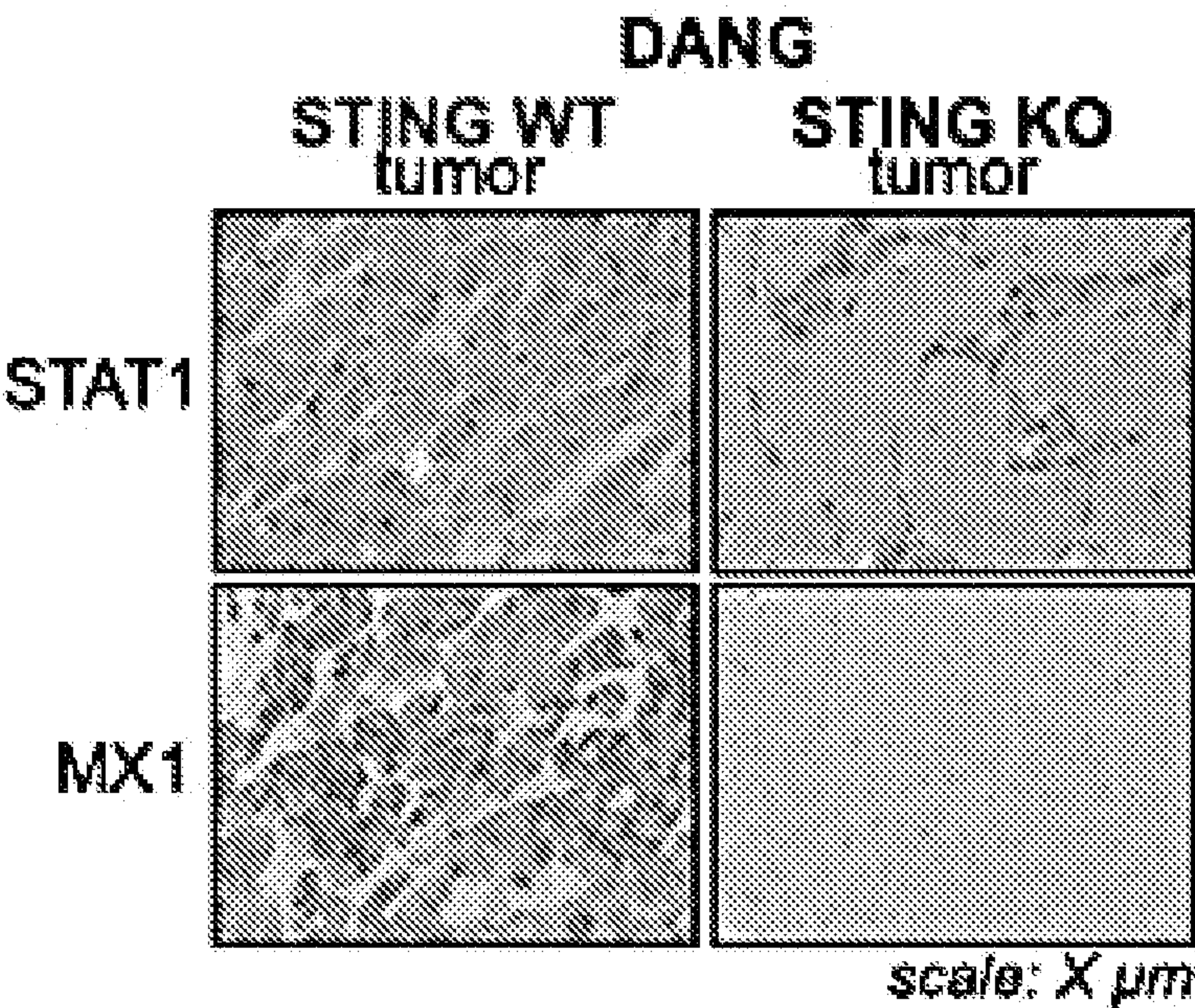


FIG. 15D

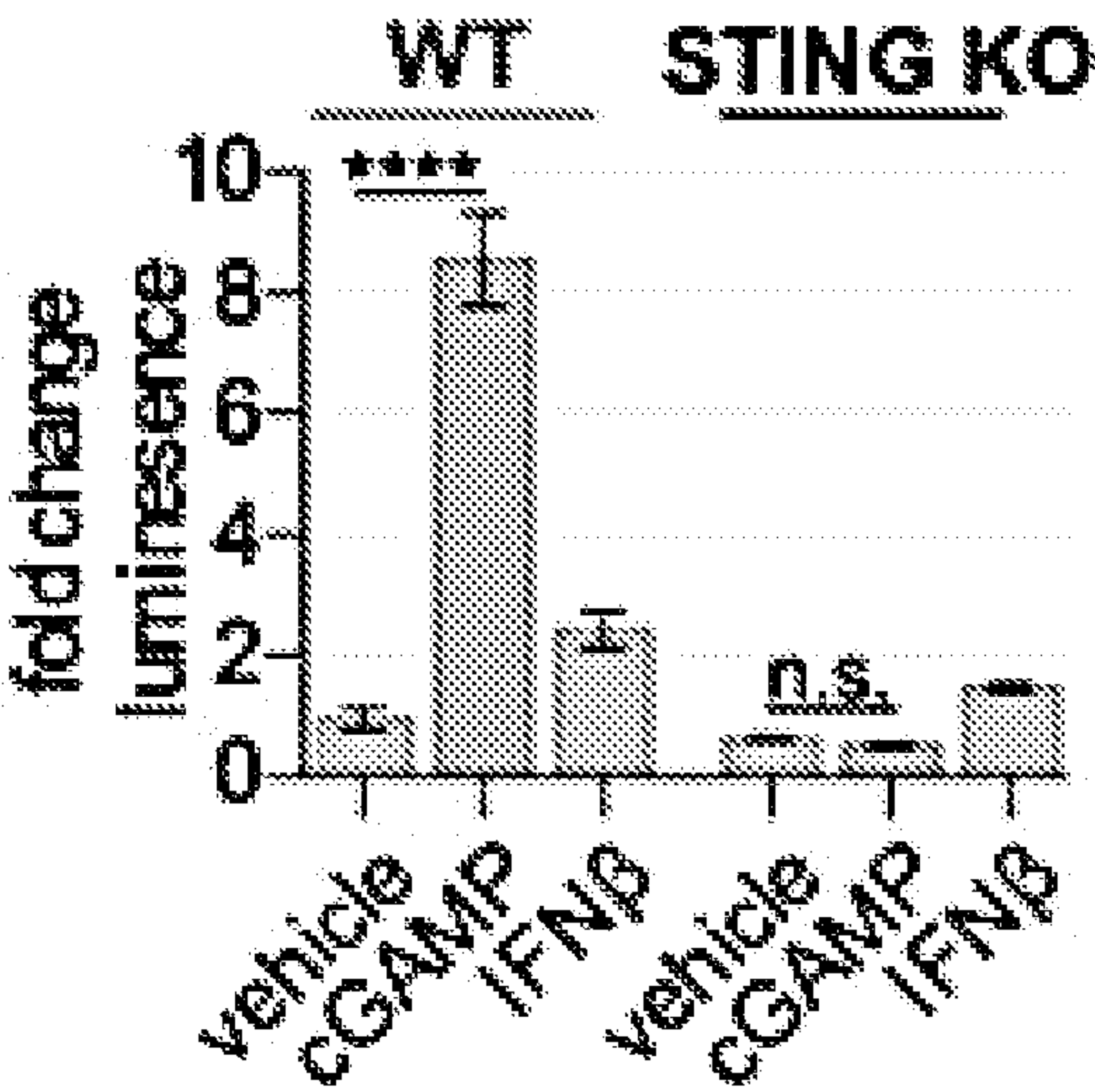


FIG. 15E

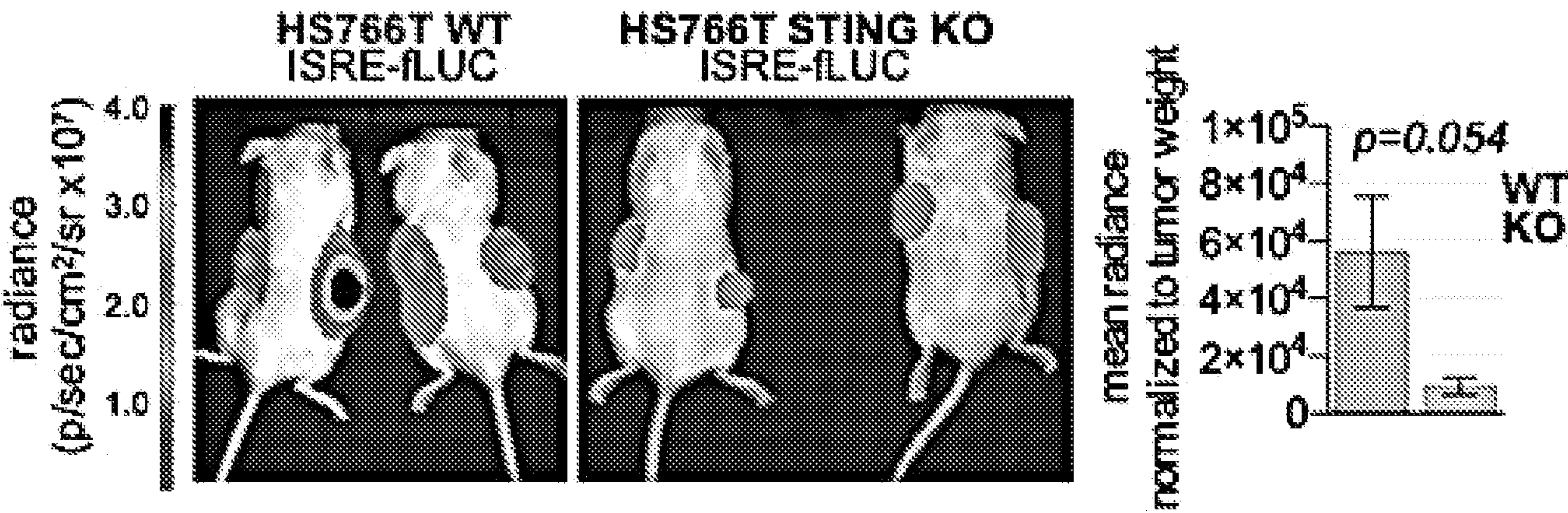


FIG. 15F

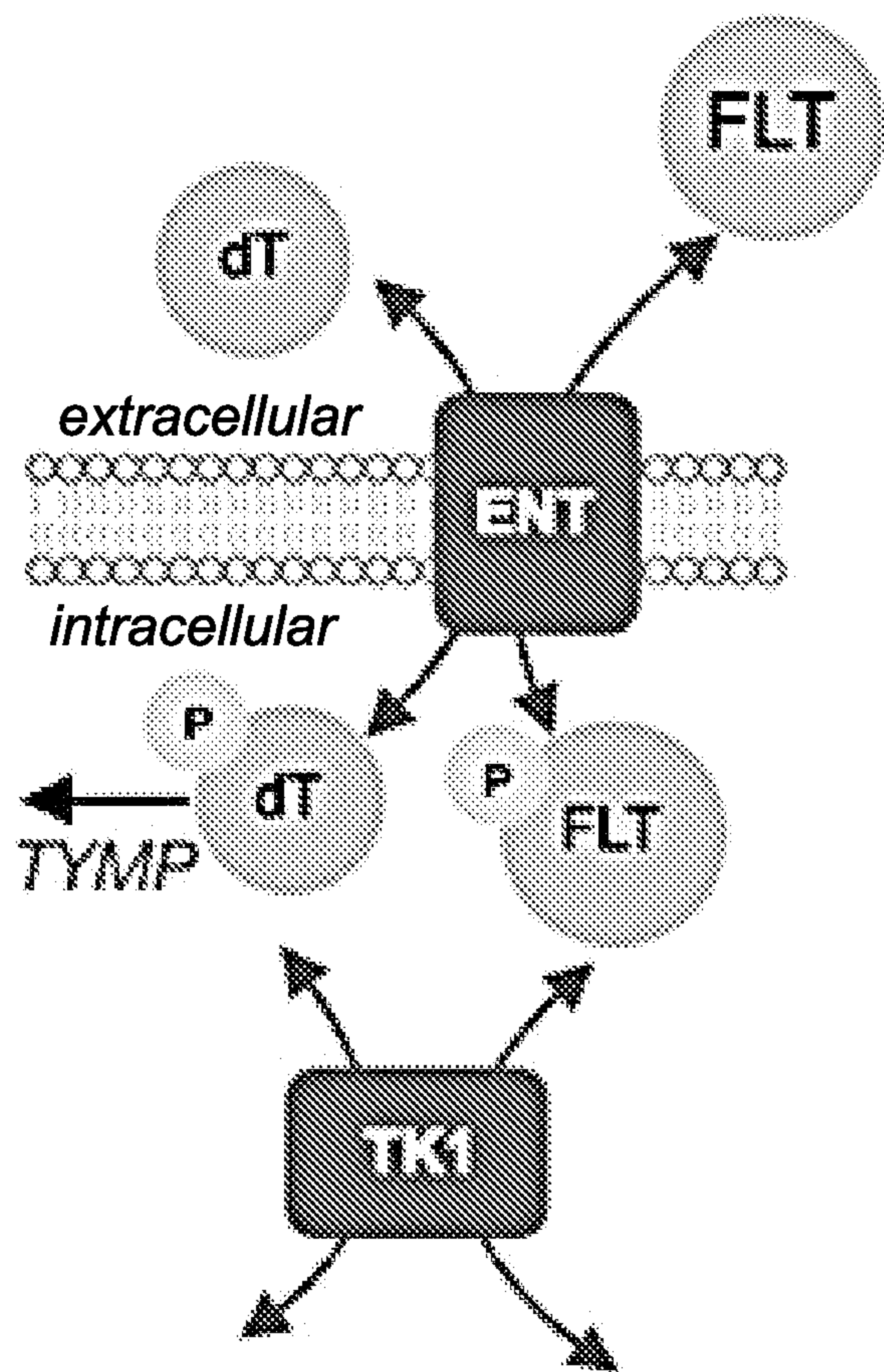


FIG. 15G

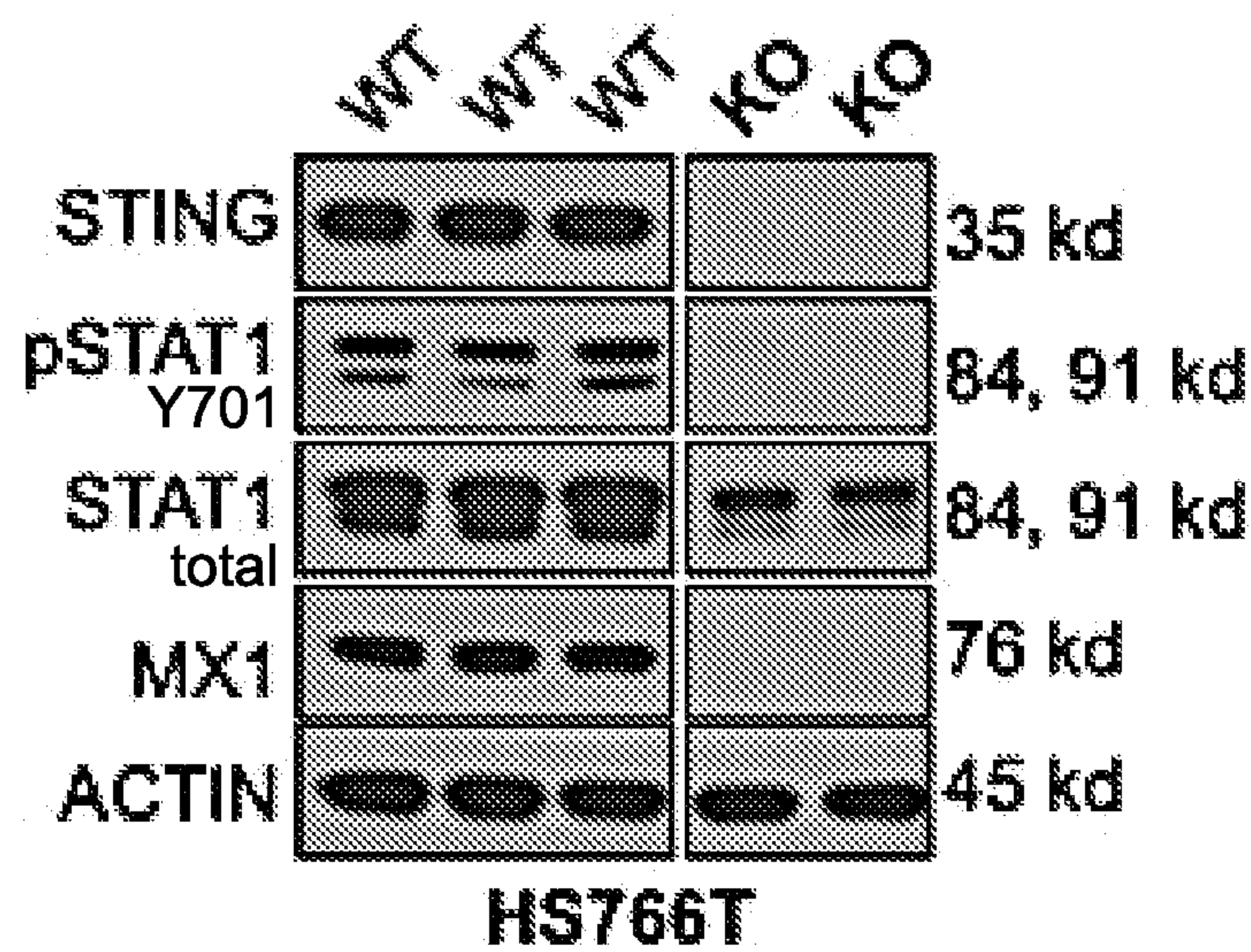


FIG. 16A

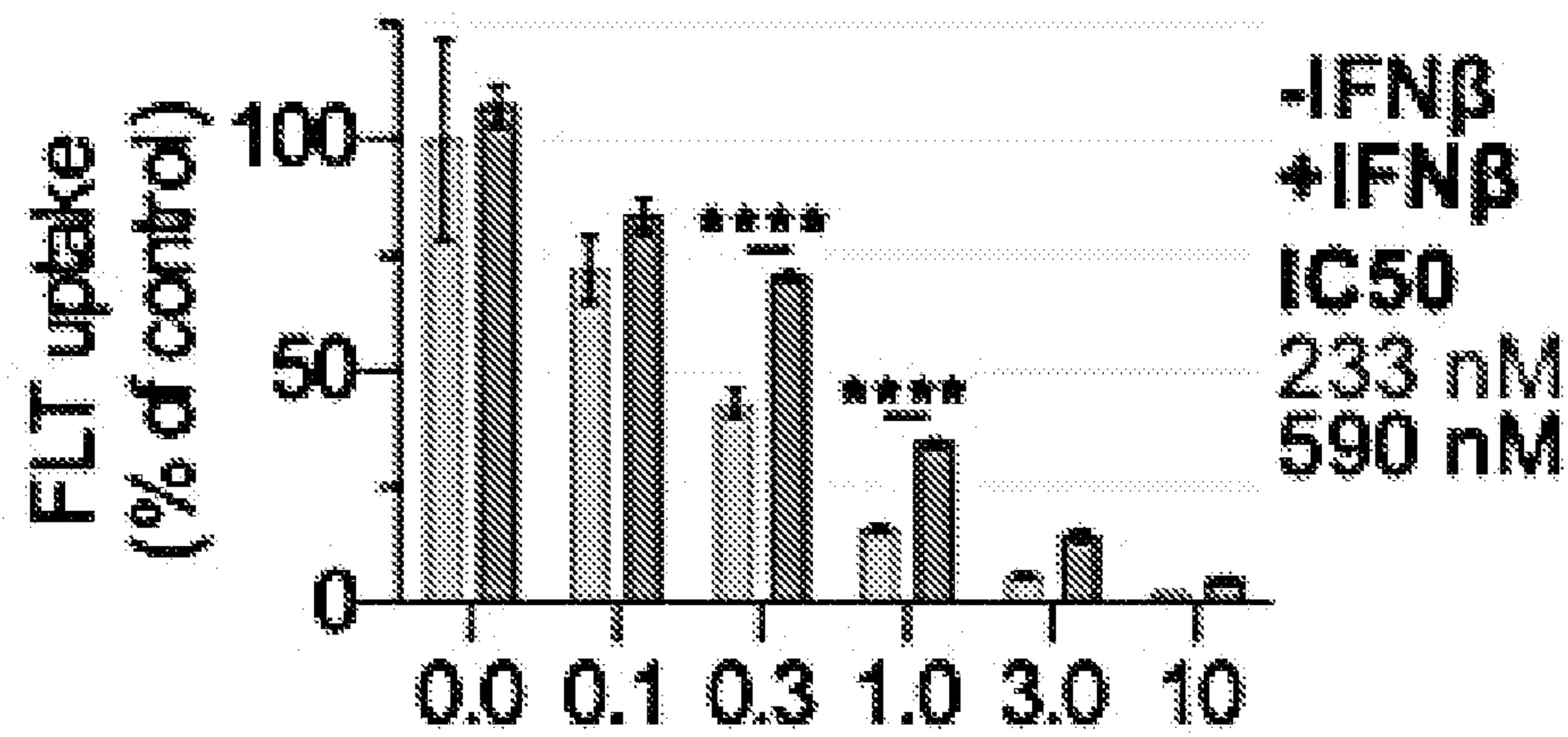


FIG. 16B

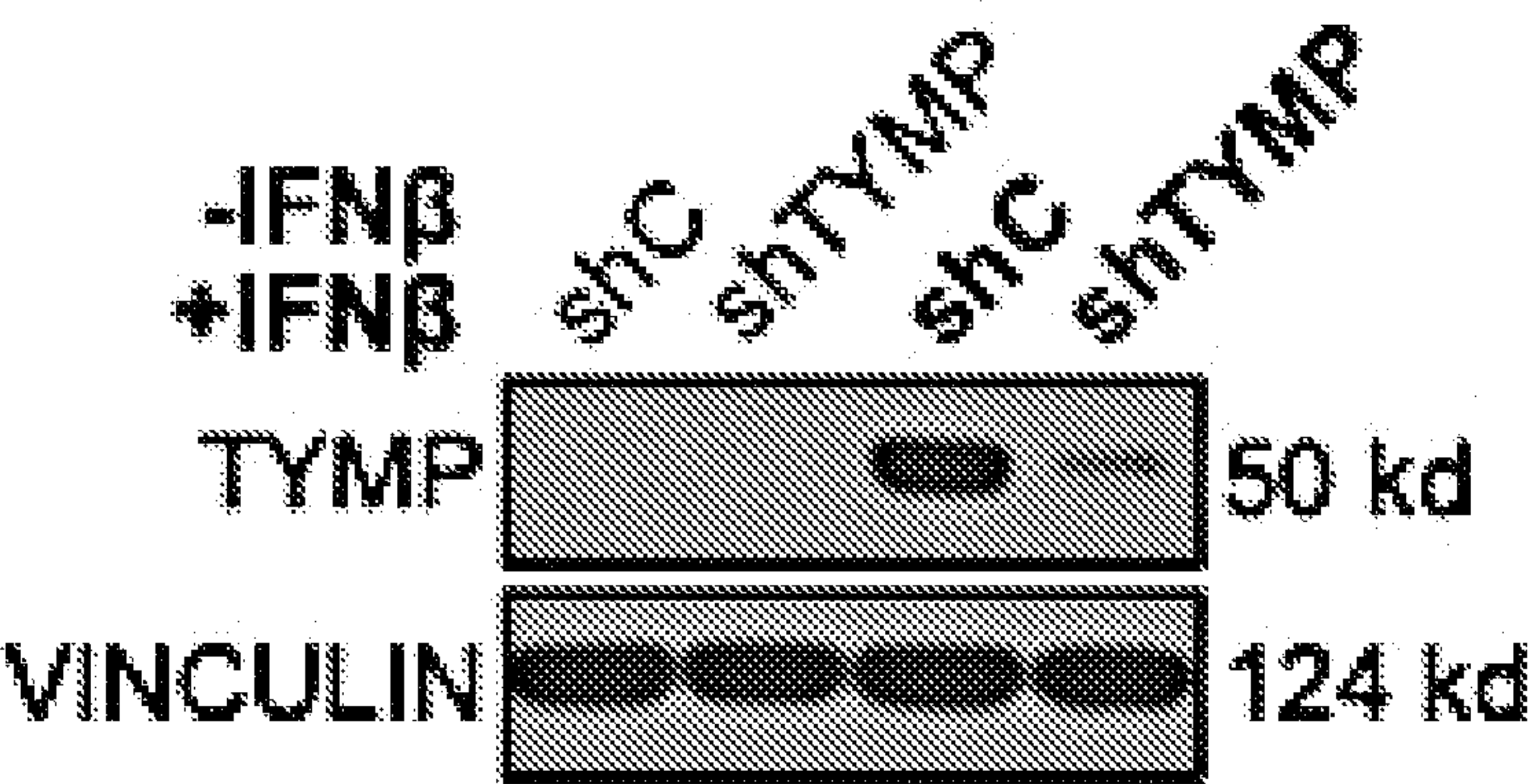


FIG. 16C

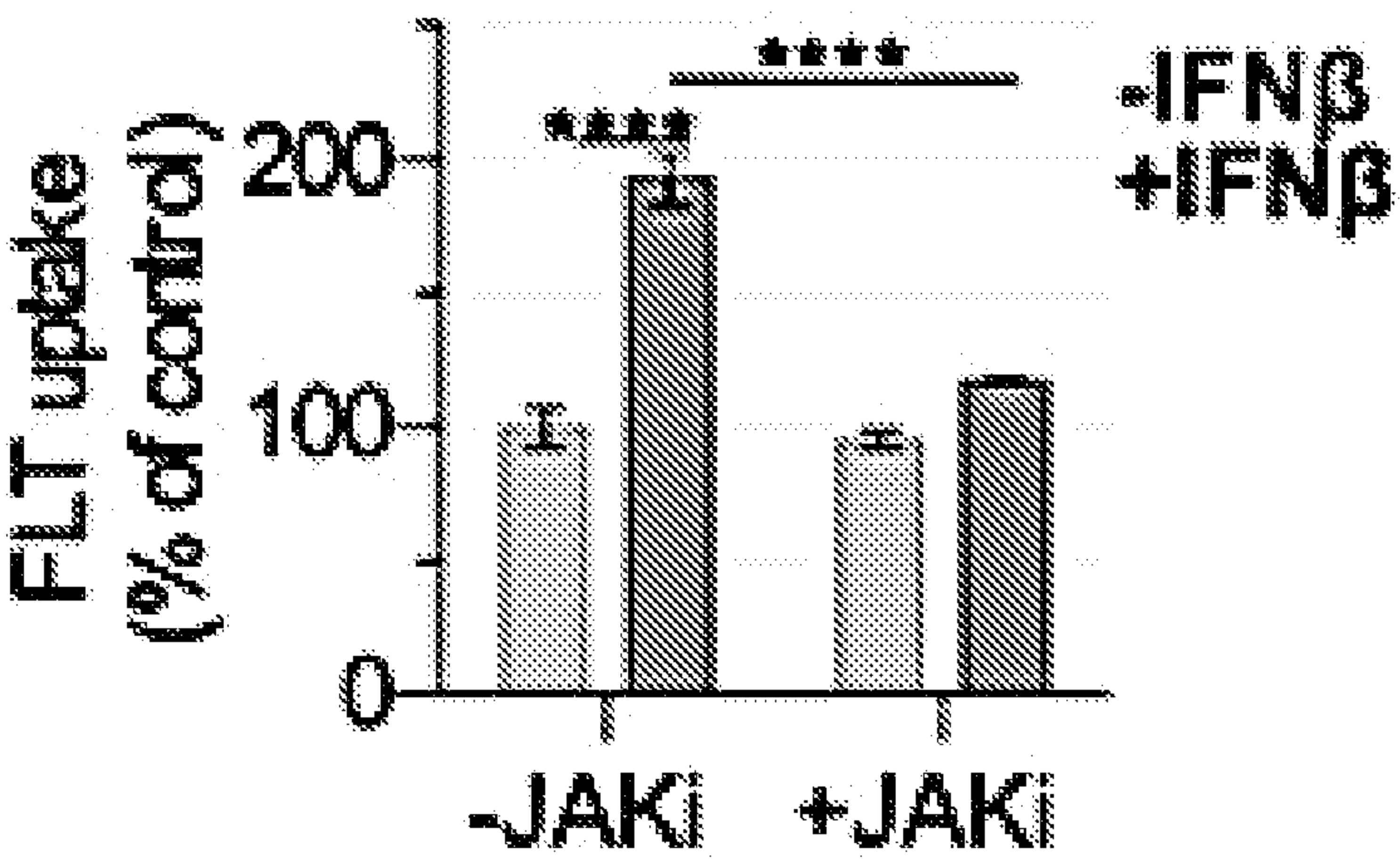


FIG. 16D

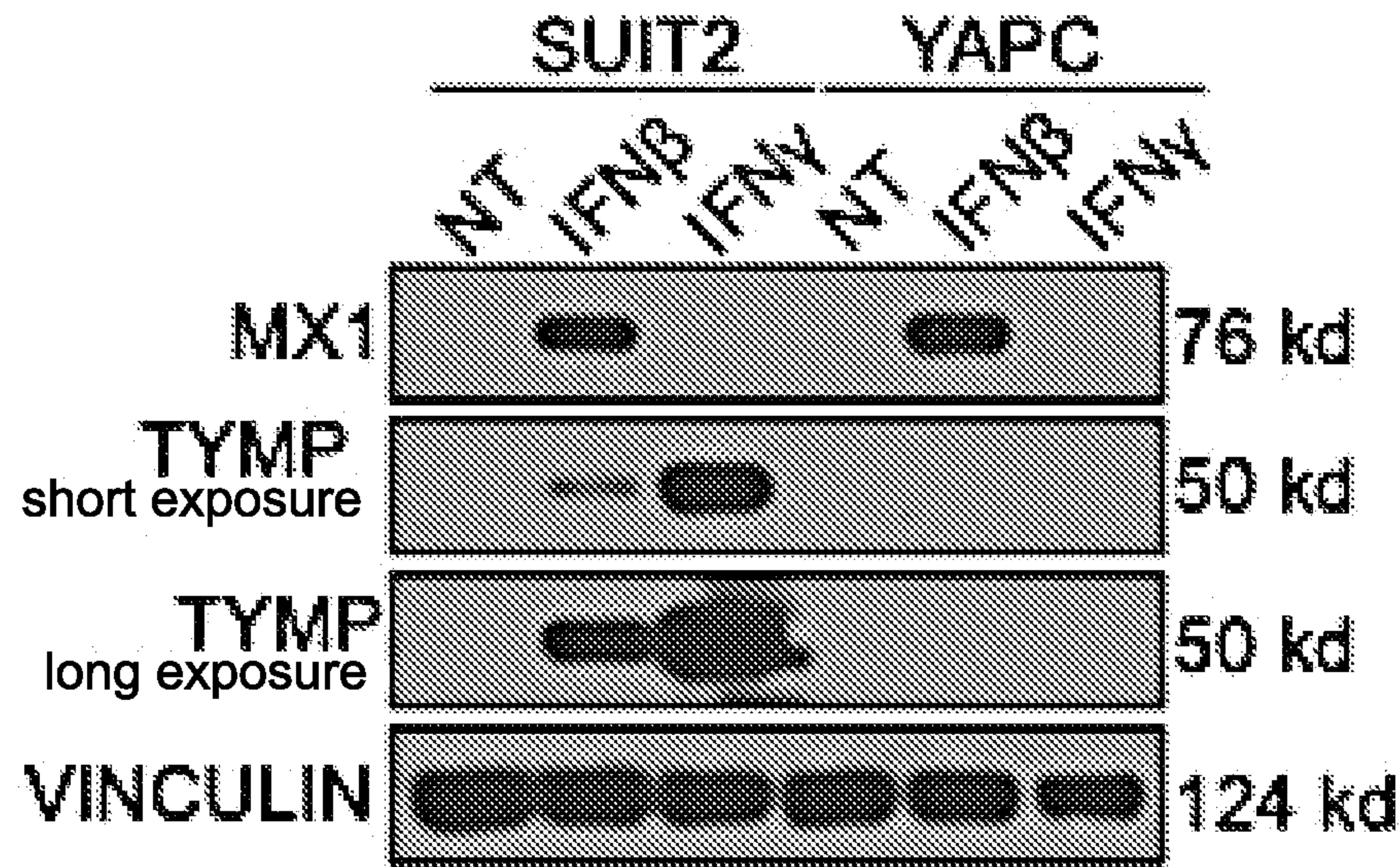


FIG. 16E

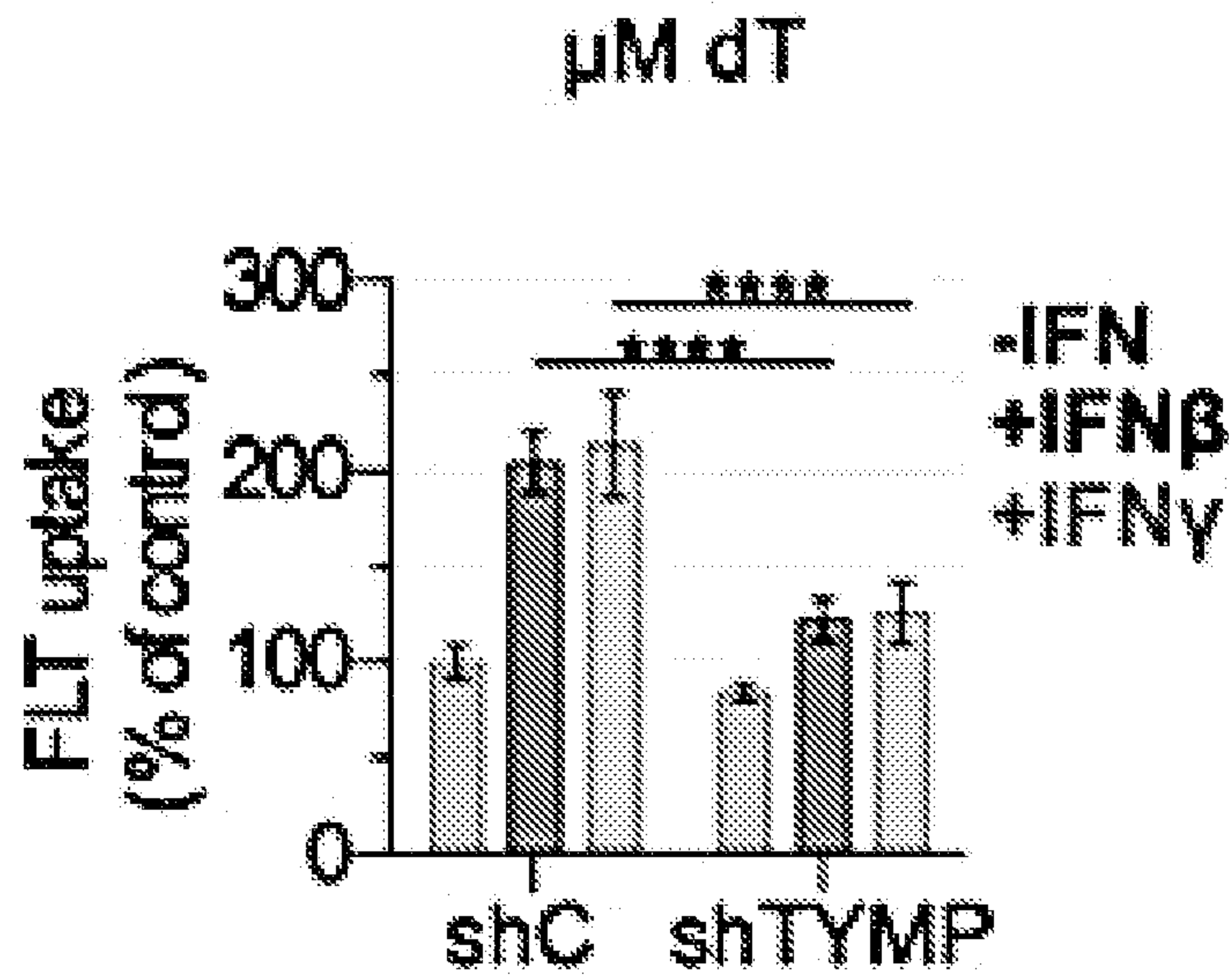


FIG. 16F

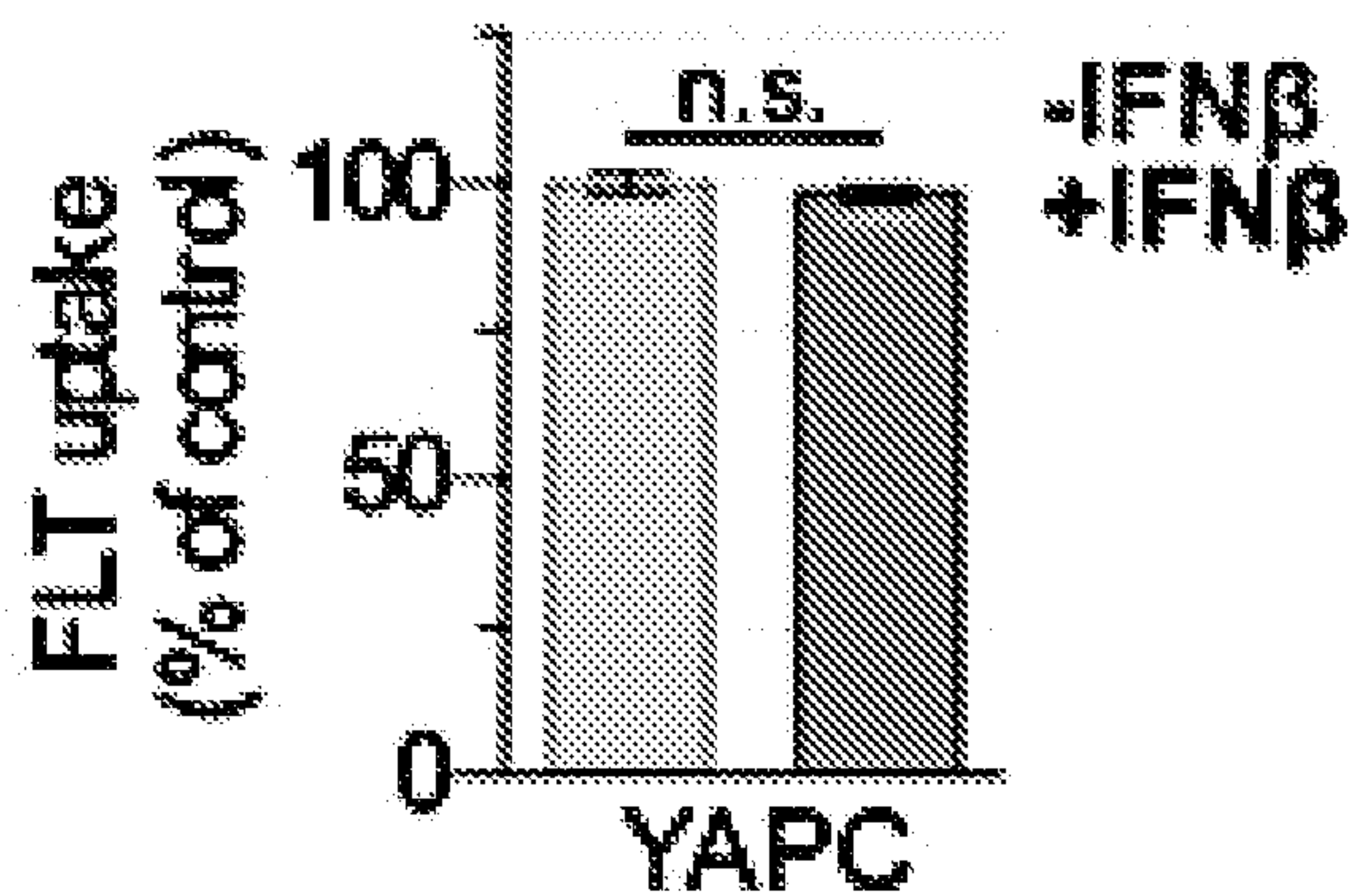


FIG. 16G

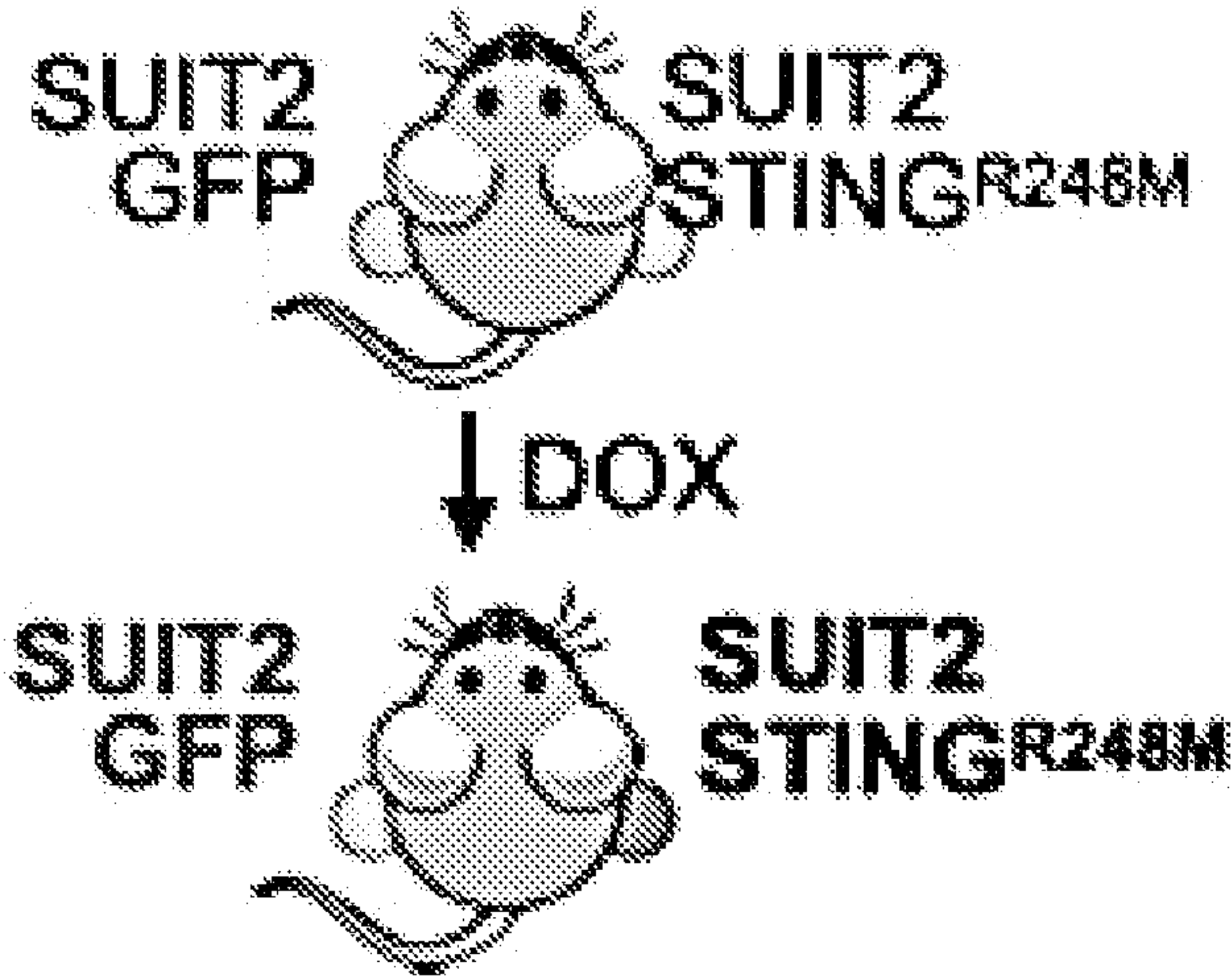


FIG. 16H

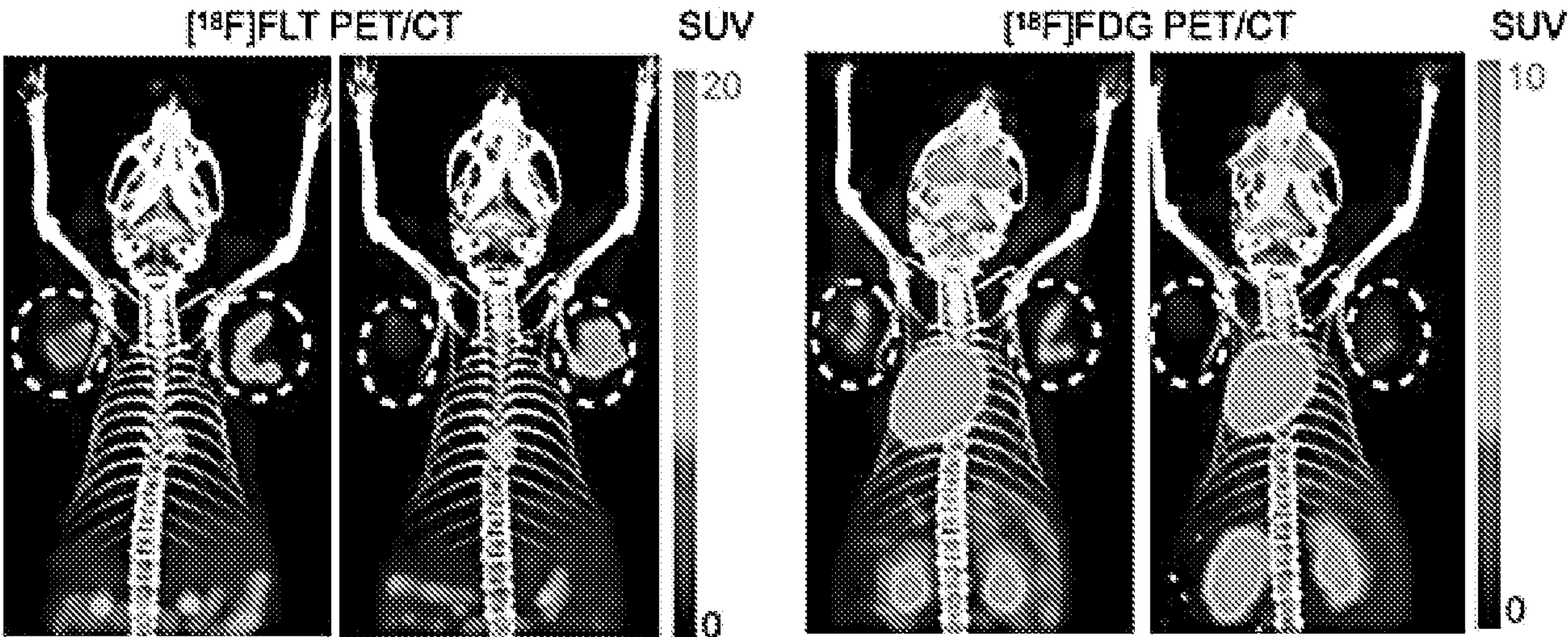
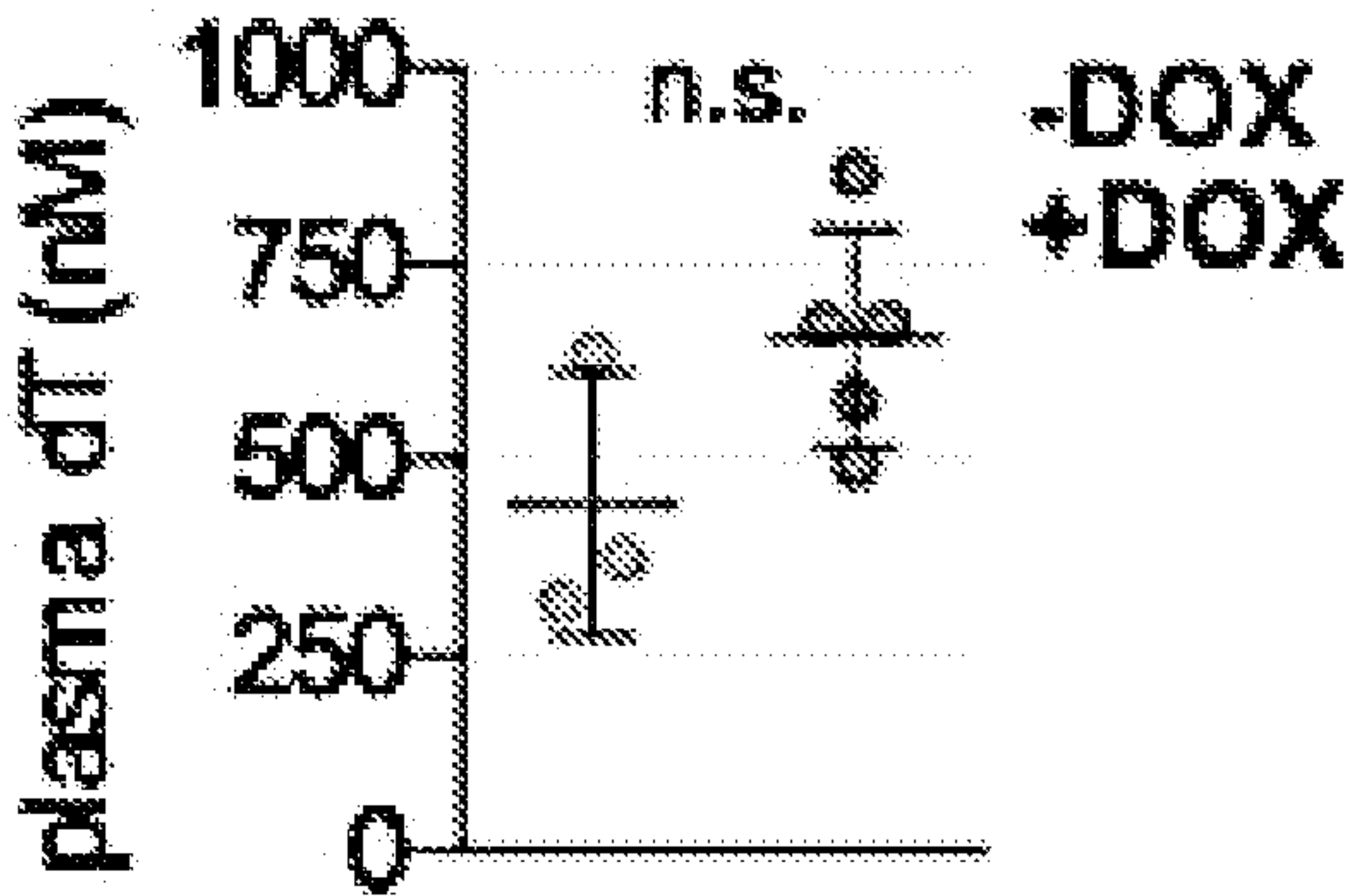


FIG. 16I

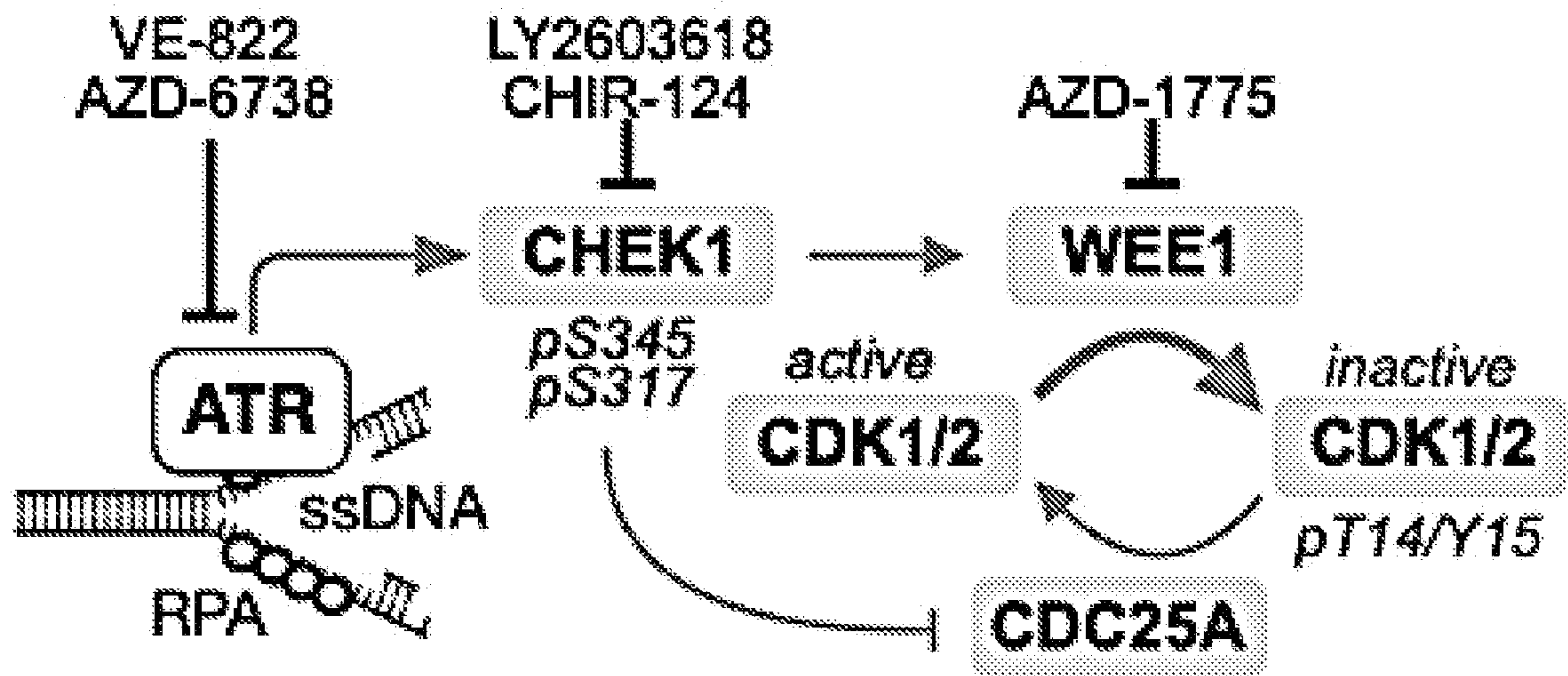


FIG. 17A

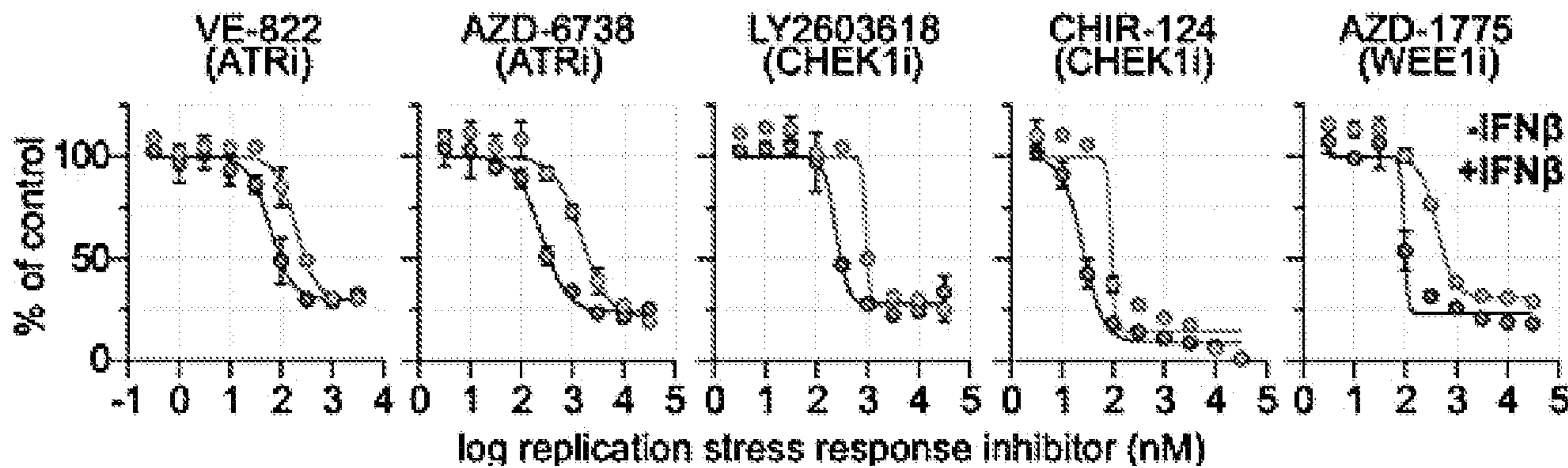


FIG. 17B

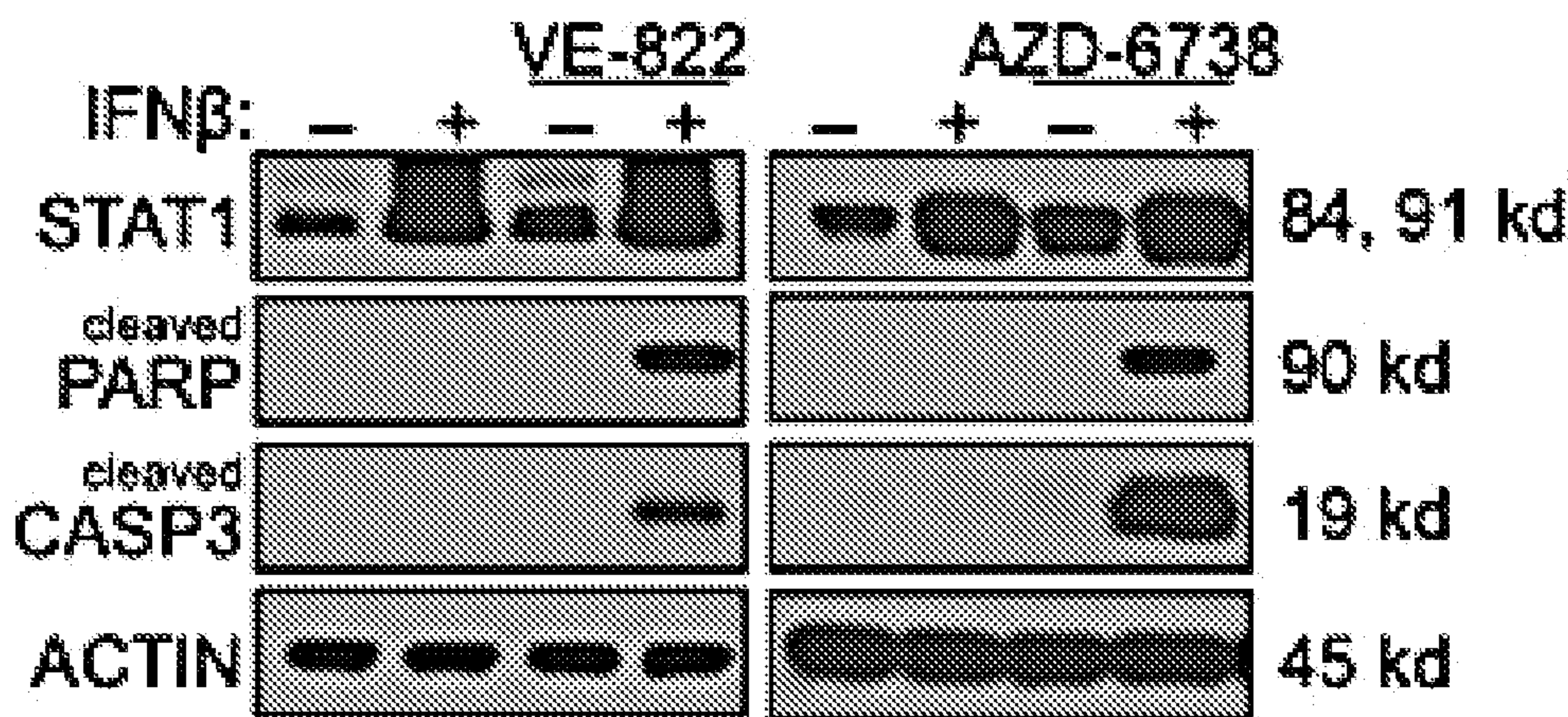


FIG. 17C

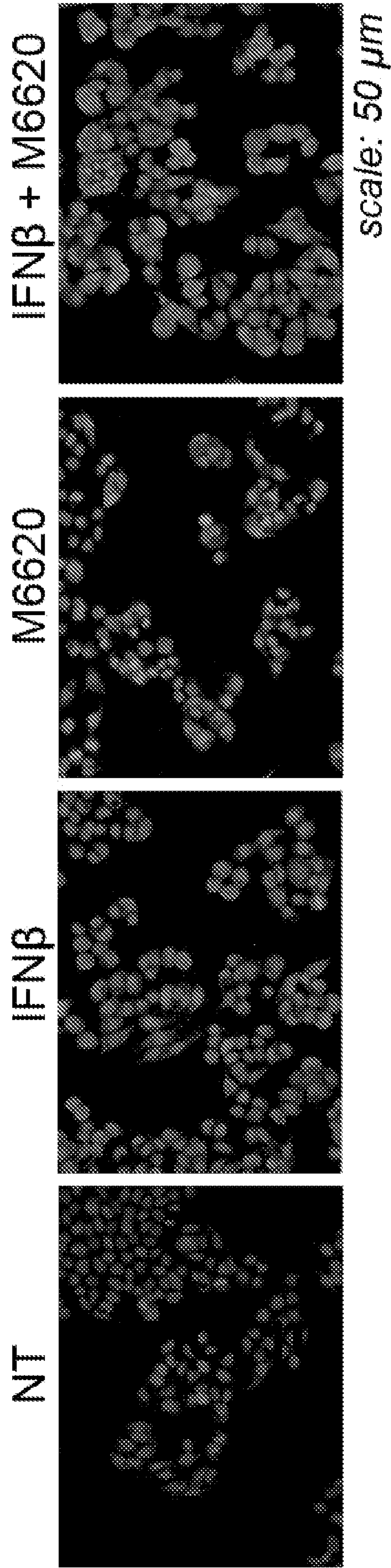
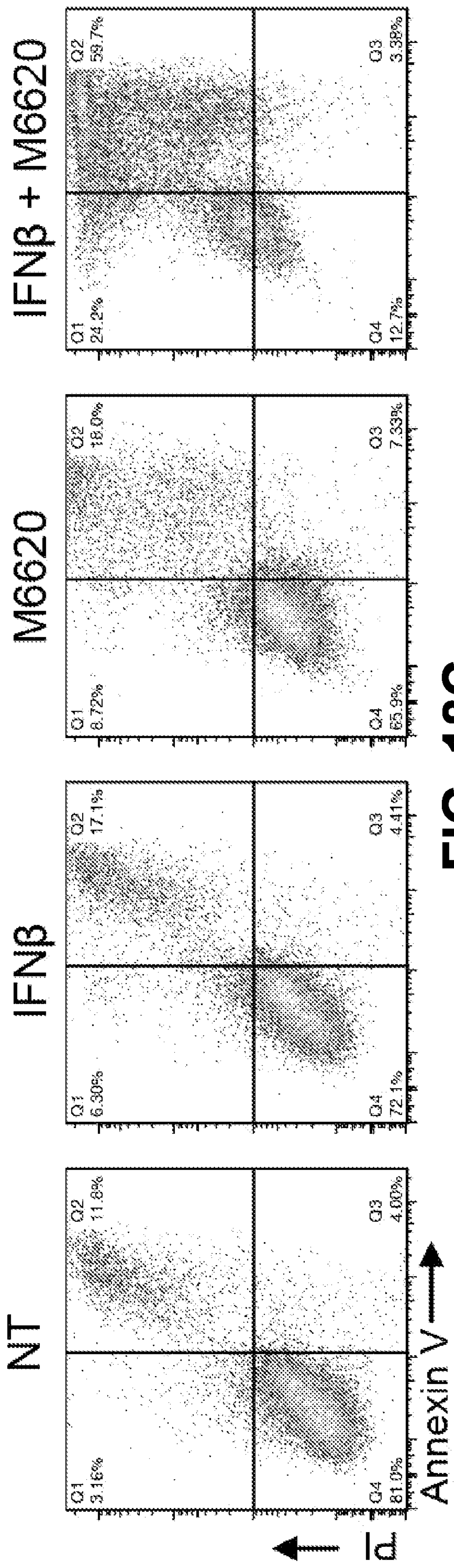
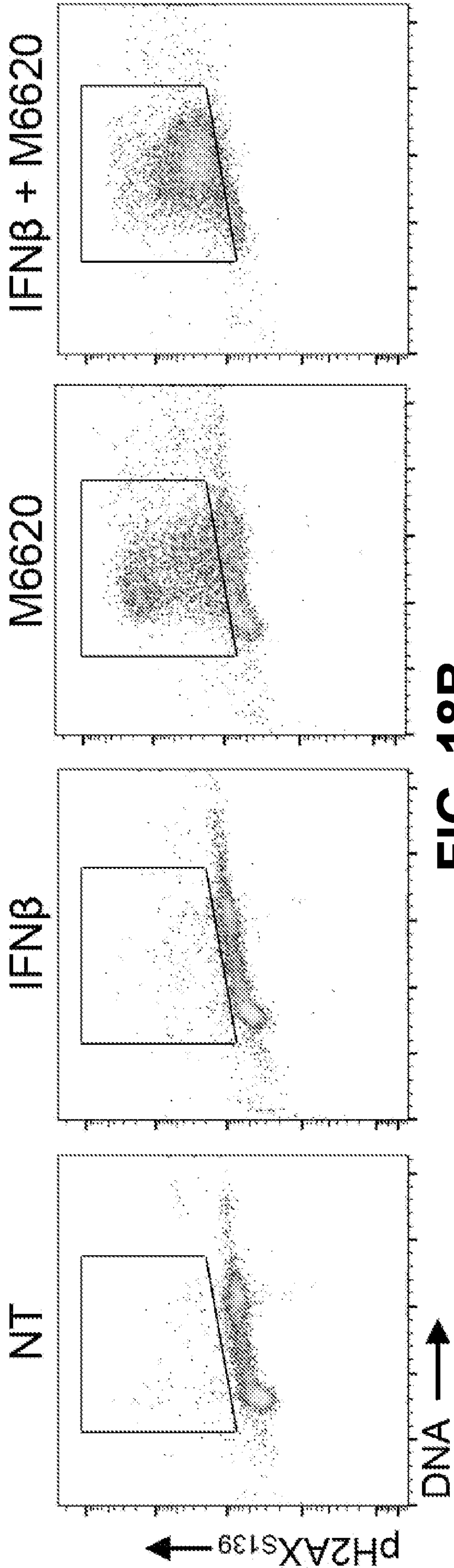


FIG. 18A



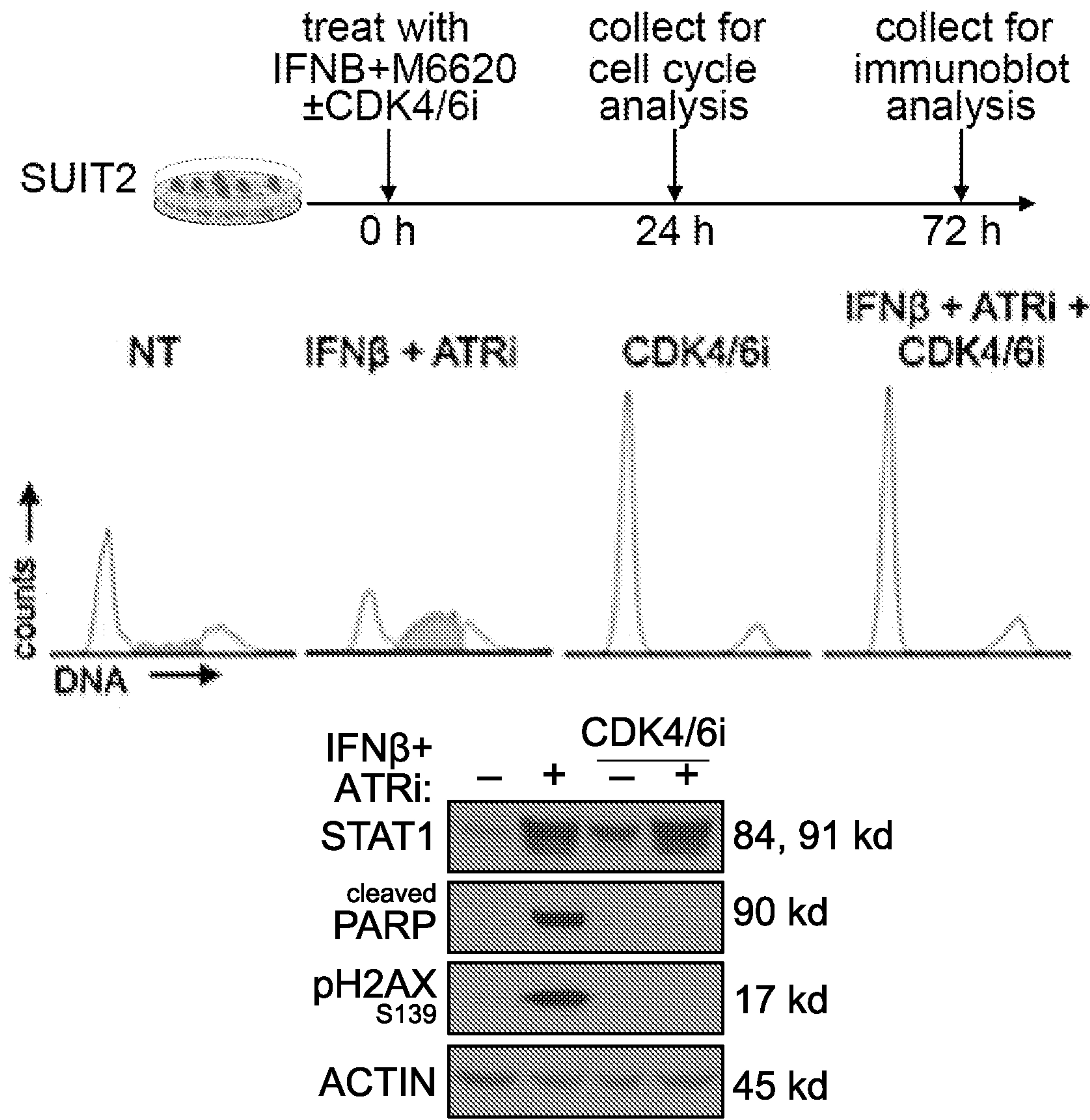


FIG. 18D

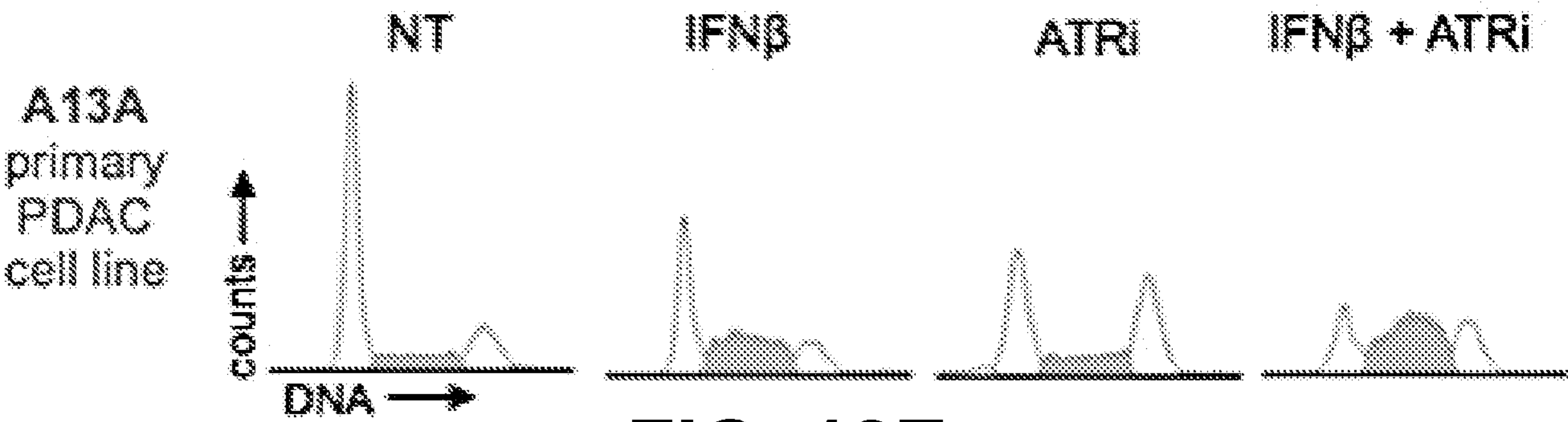


FIG. 18E

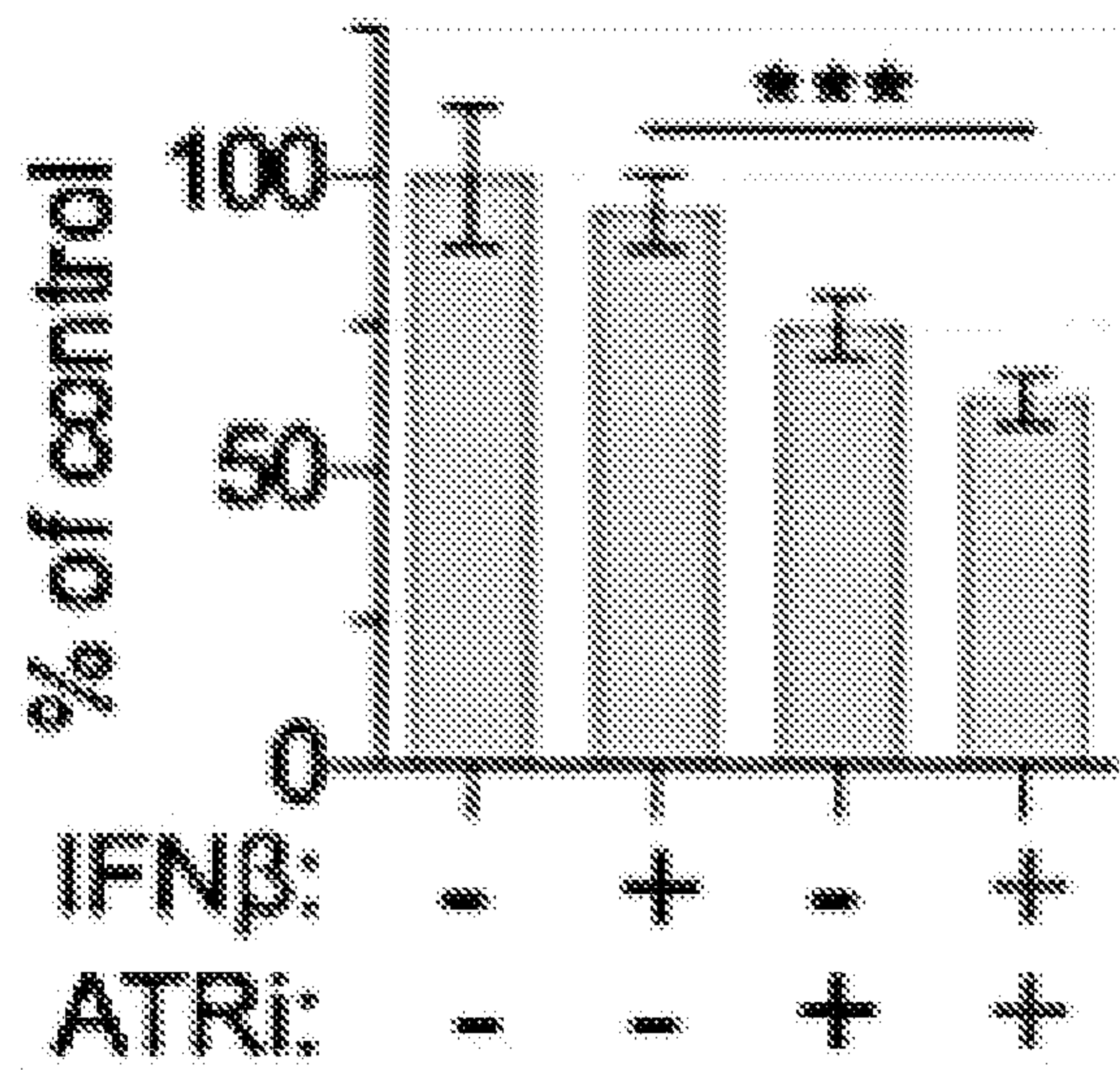


FIG. 18F

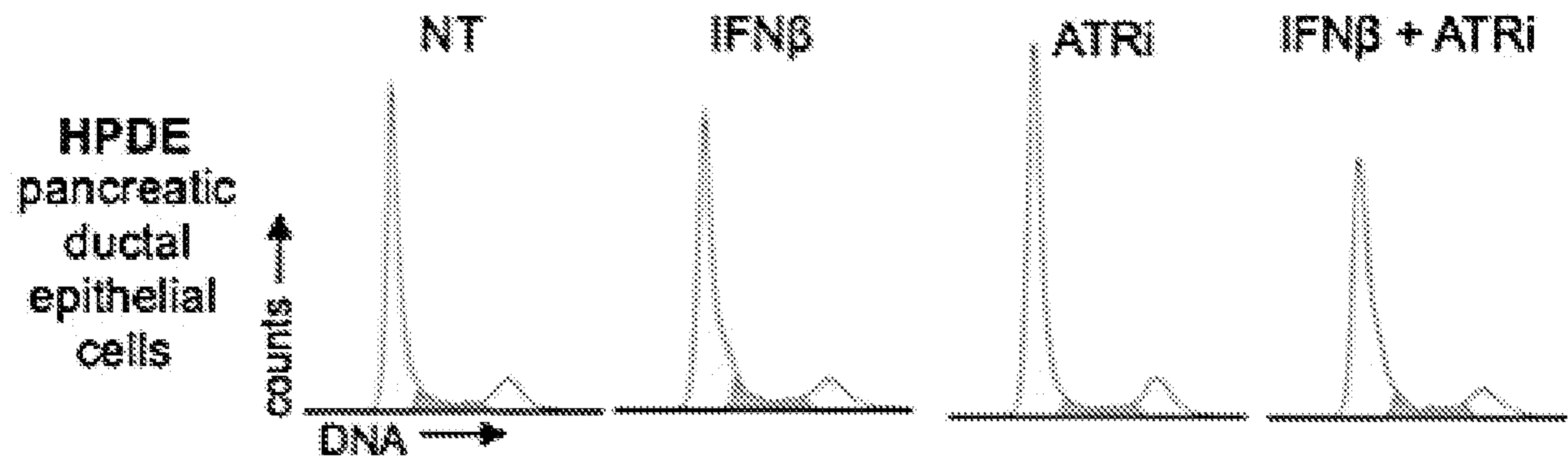


FIG. 18G

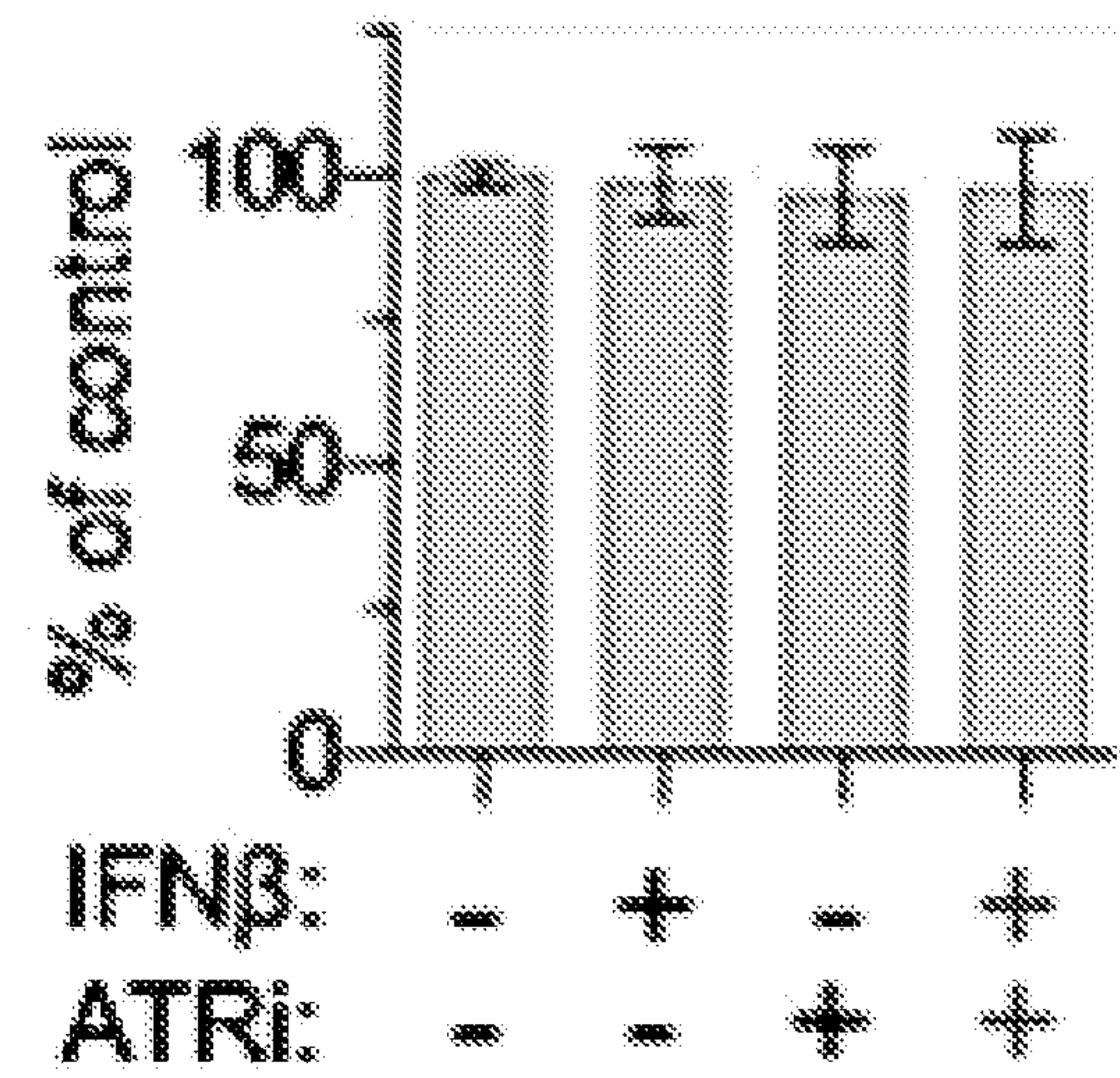


FIG. 18H

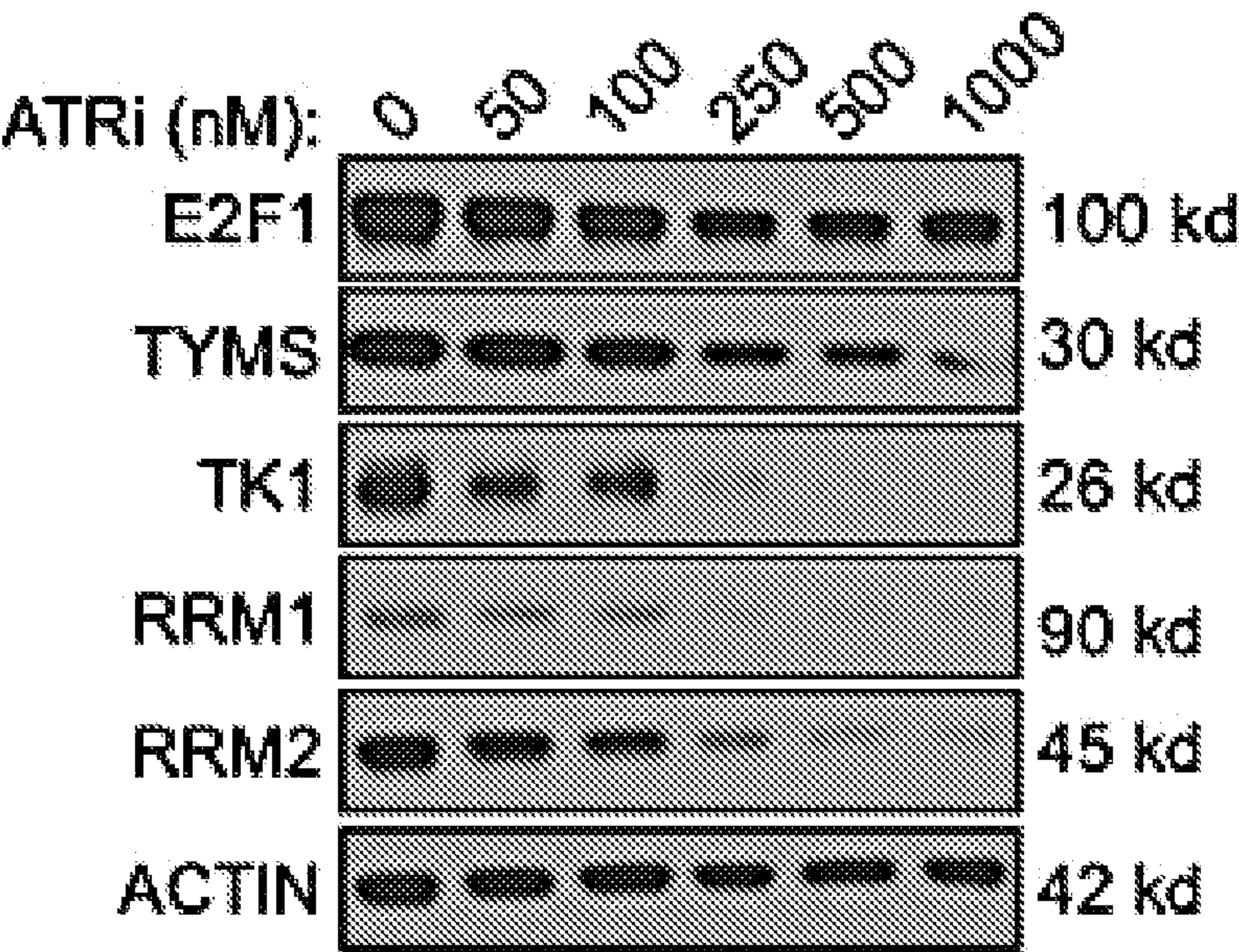


FIG. 19A

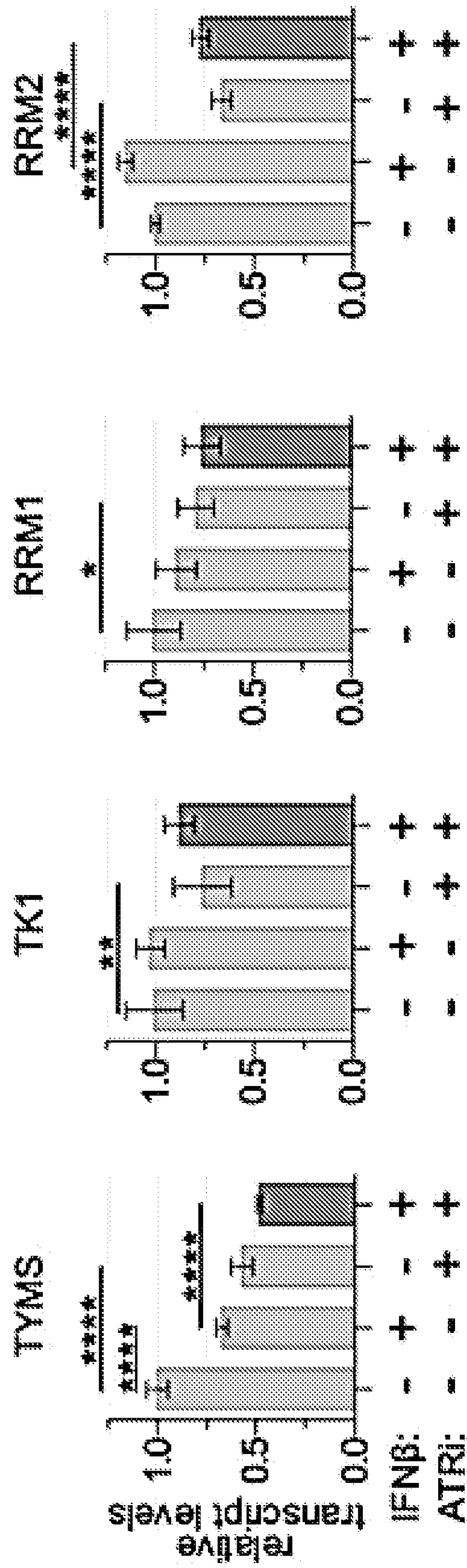


FIG. 19B

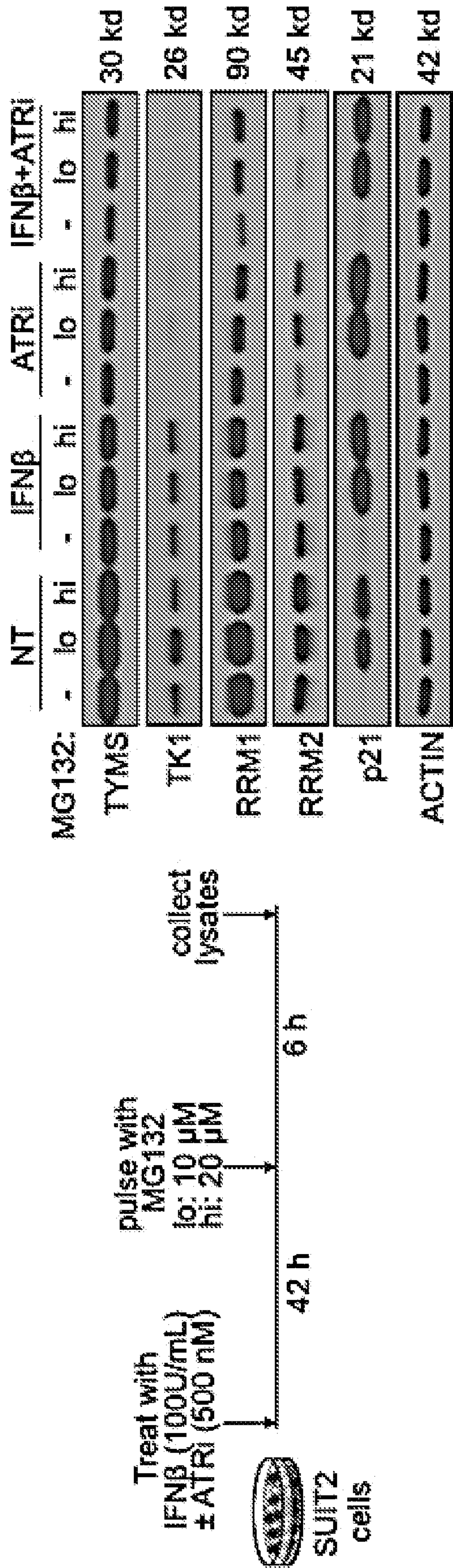


FIG. 19C

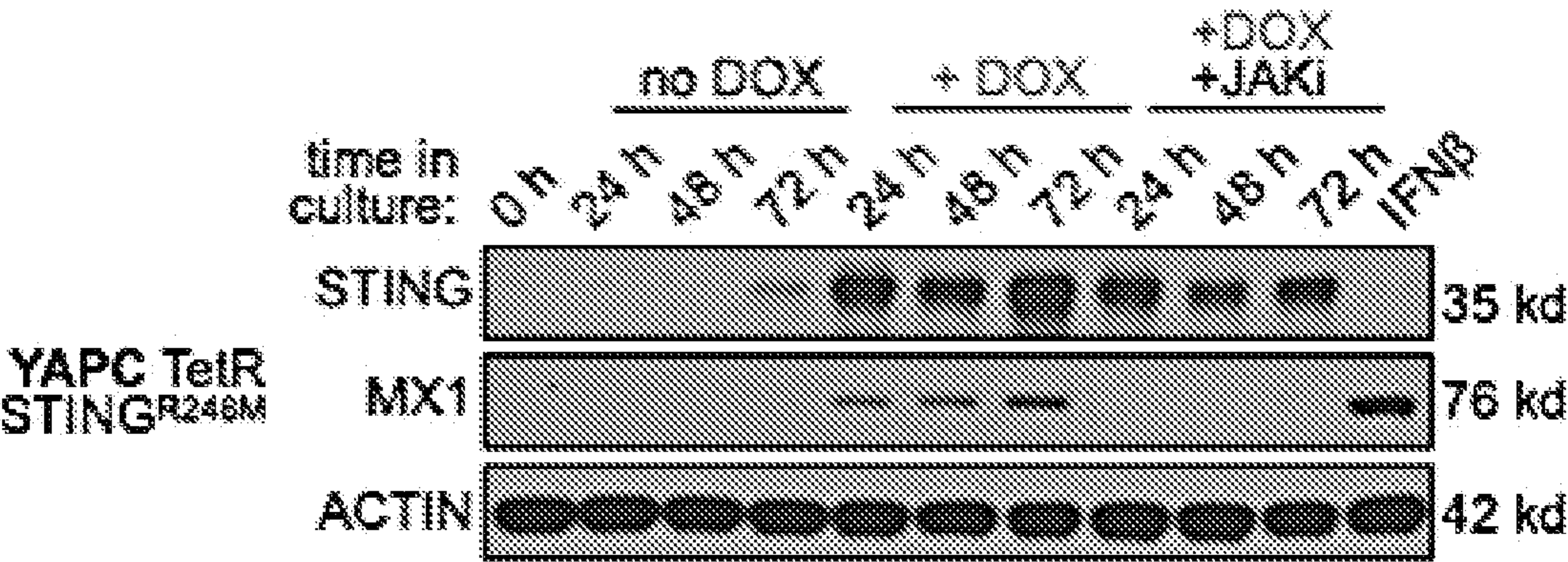


FIG. 20A

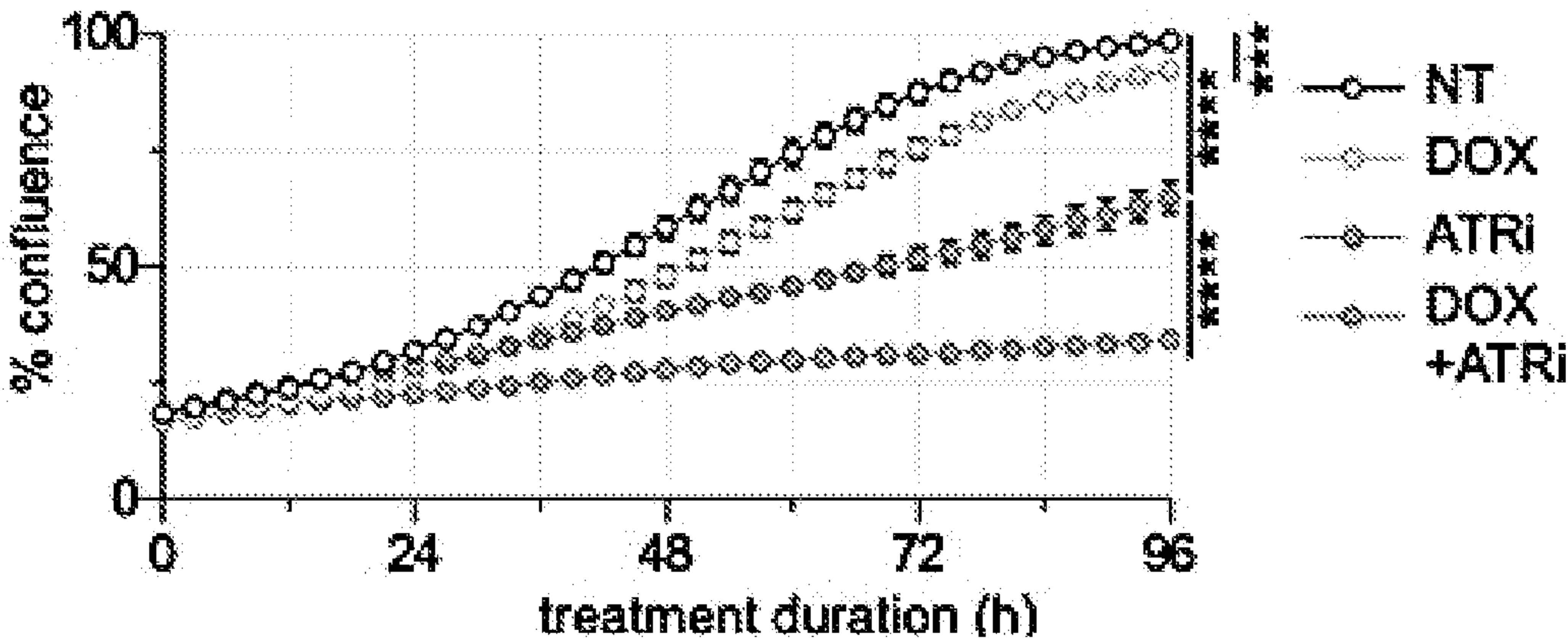


FIG. 20B

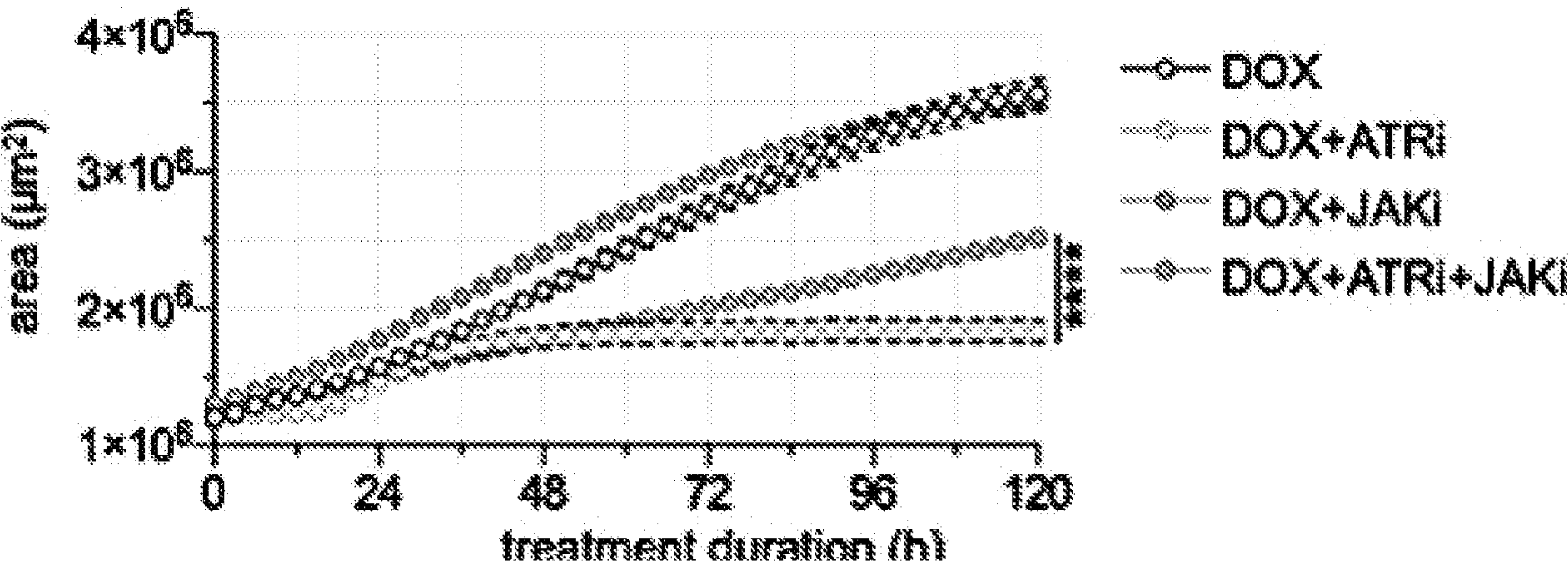


FIG. 20C

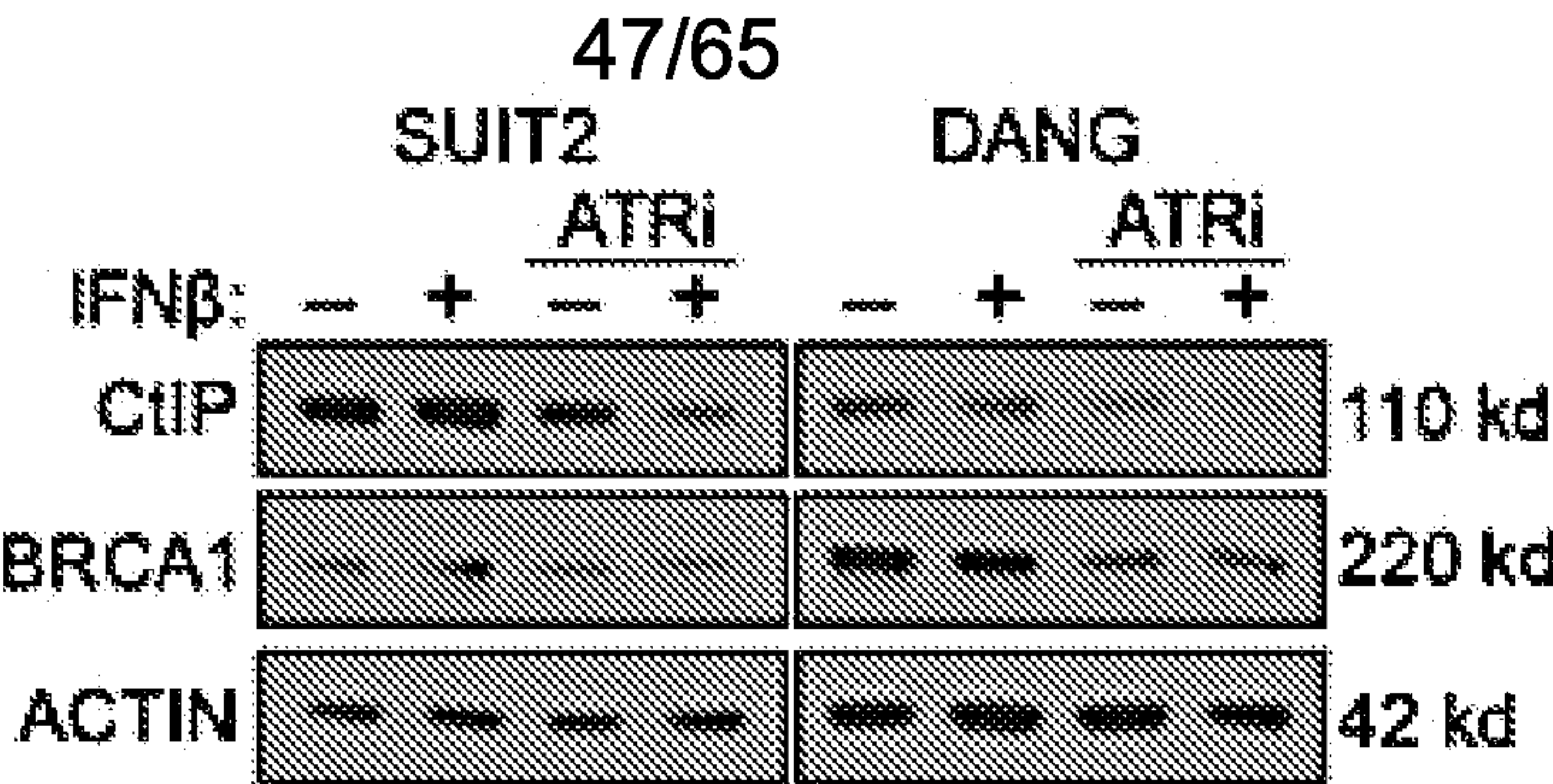


FIG. 21A

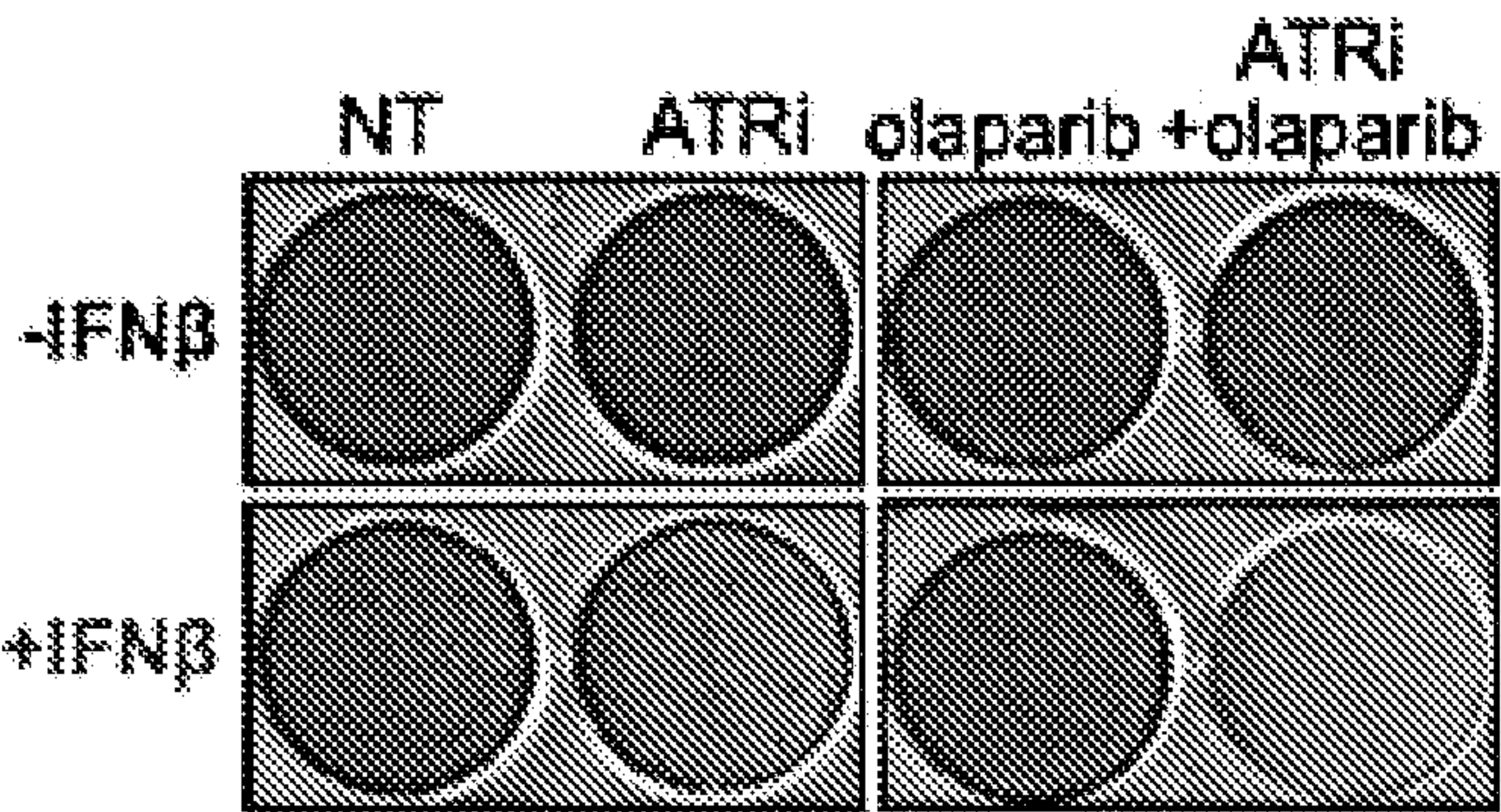


FIG. 21B

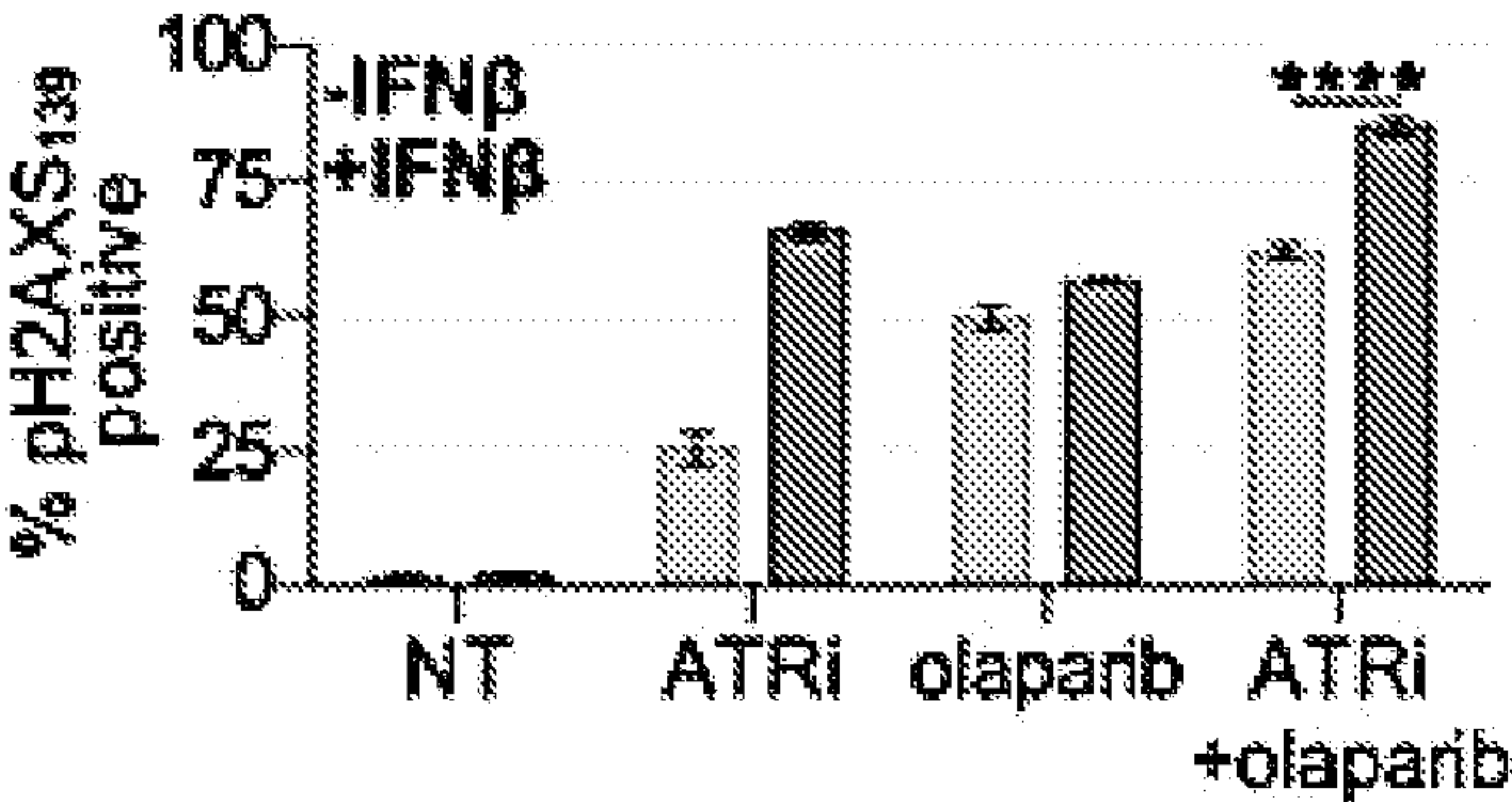


FIG. 21C

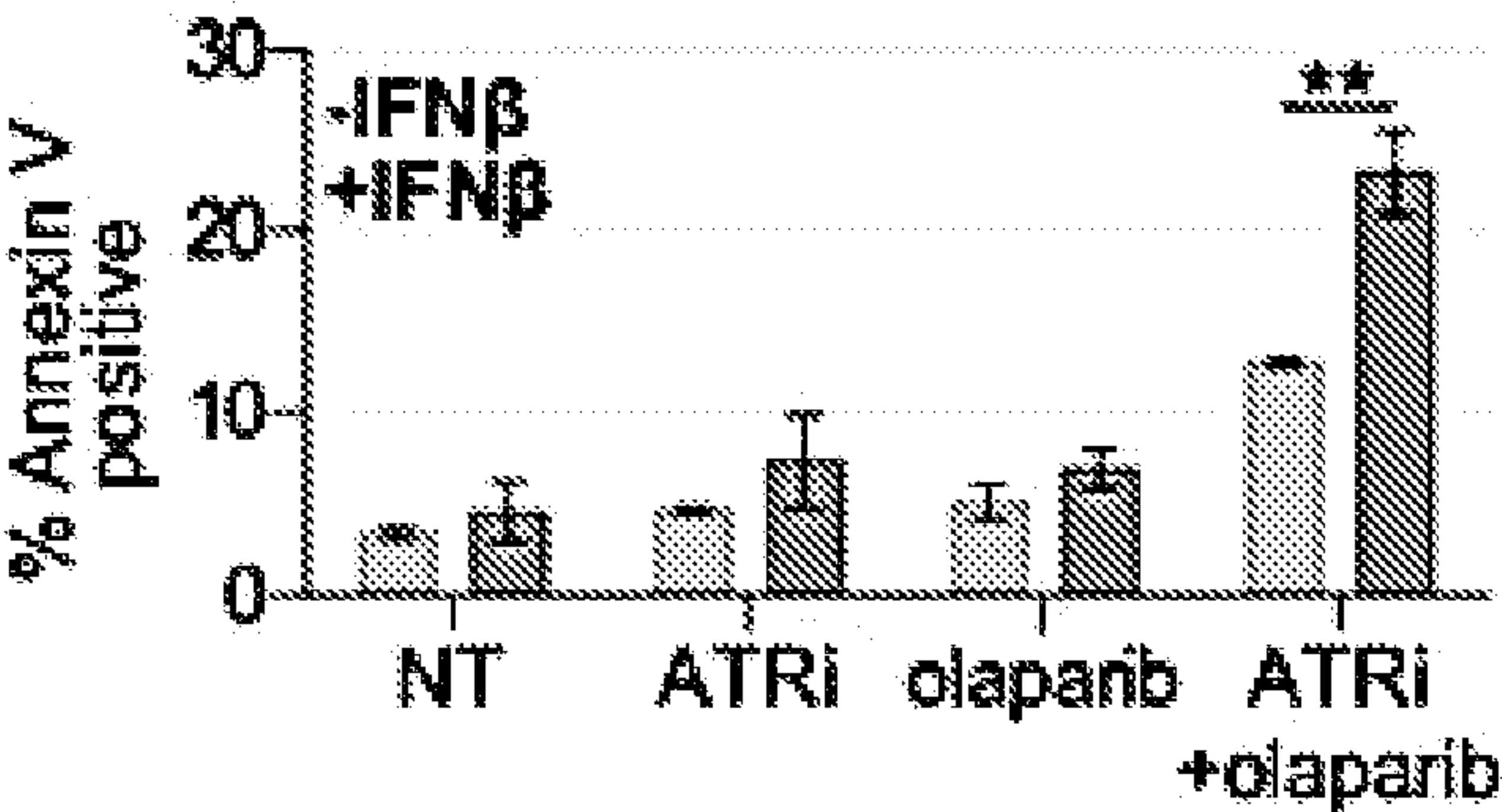


FIG. 21D

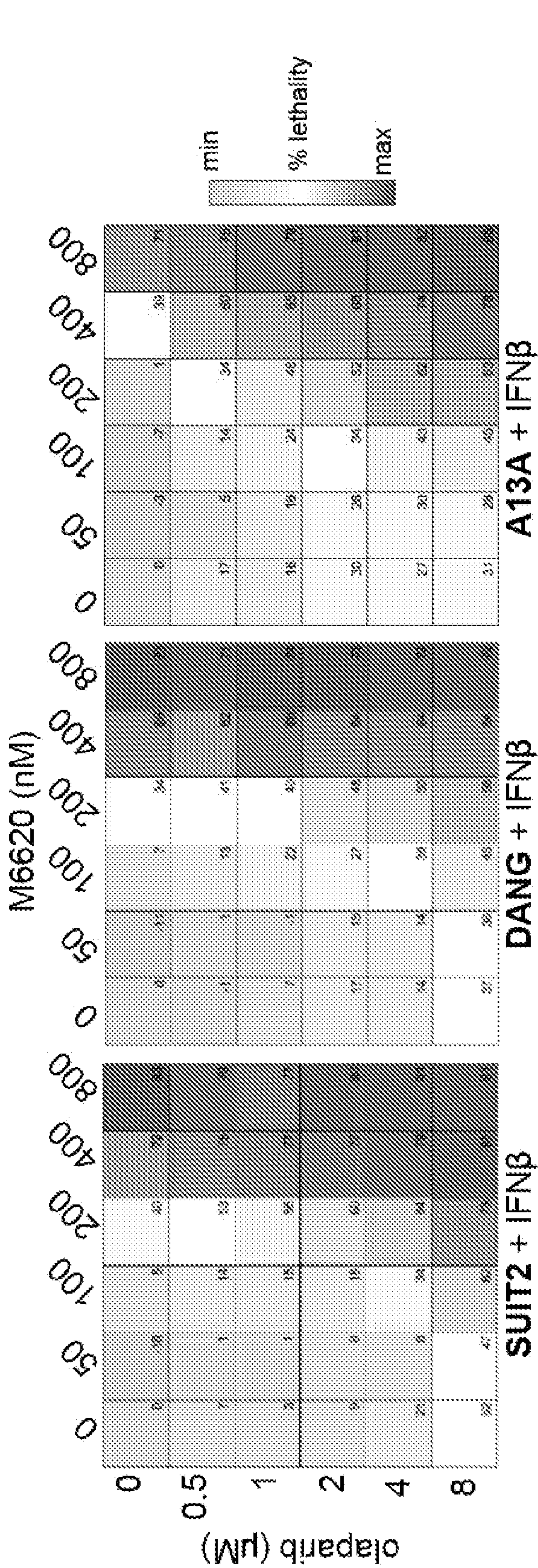


FIG. 21E

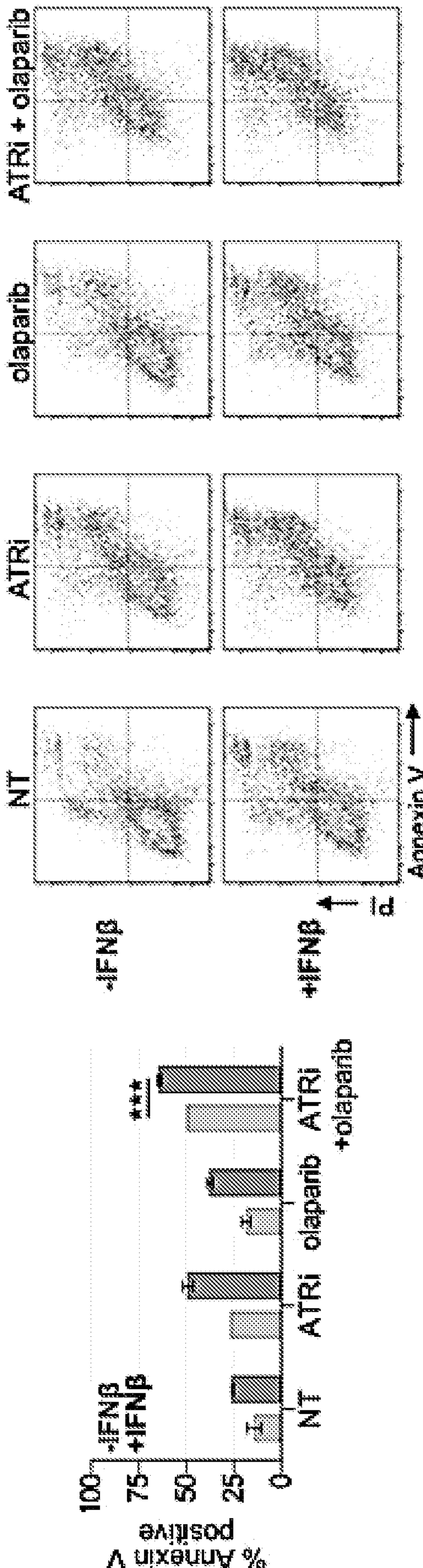


FIG. 21F

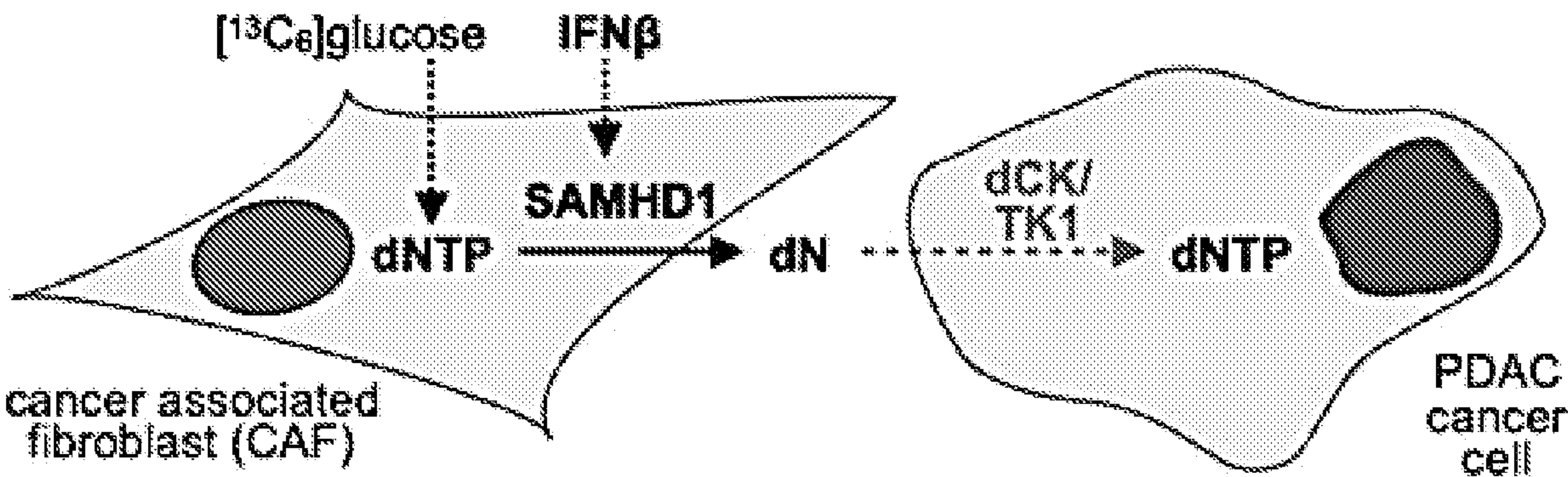


FIG. 22A

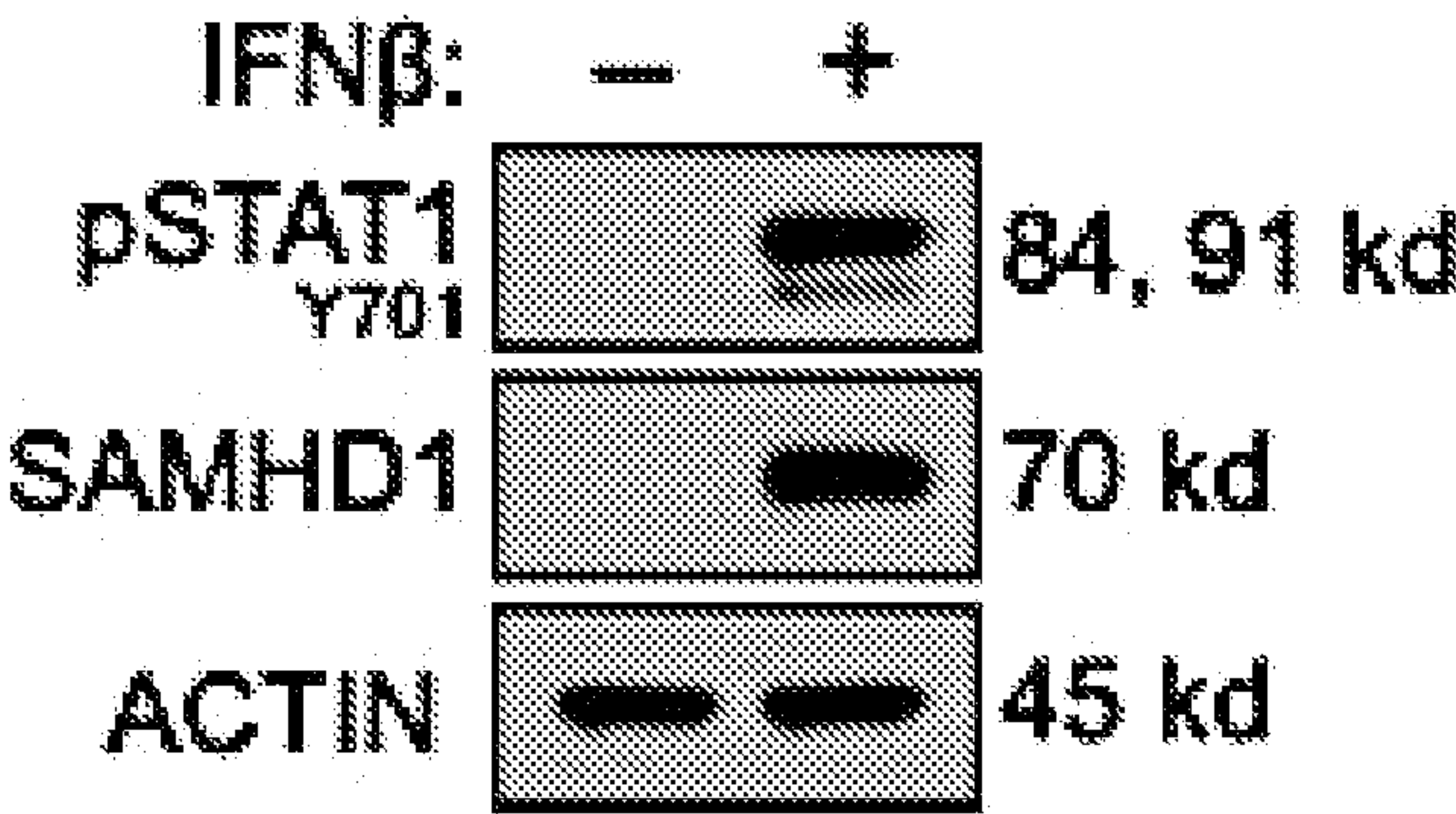


FIG. 22B

$[^{13}\text{C}_6]$ glucose labeled
CAF-secreted dC

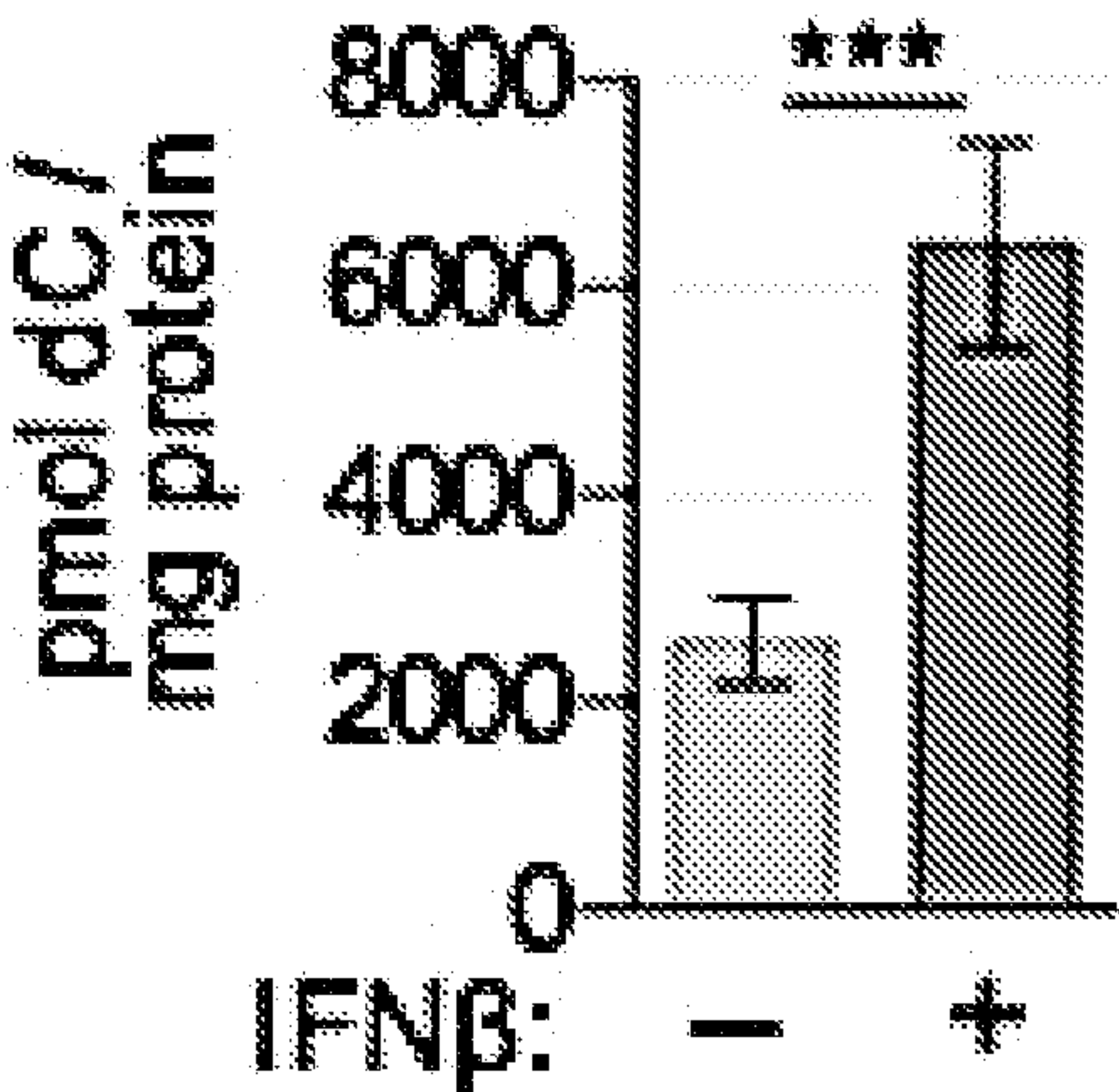


FIG. 22C

Antibodies	Source	Identifier
TOTAL STAT1	Cell Signaling Technology	14994
PHOSPHO STAT1 Y701	Cell Signaling Technology	9167
MX1	Cell Signaling Technology	37849
ACTIN	Cell Signaling Technology	3700
SAMHD1	Cell Signaling Technology	12361
TOTAL CHEK1	Cell Signaling Technology	2360
PHOSPHO CHEK1 S345	Cell Signaling Technology	2348
PHOSPHO H2AX S139	Cell Signaling Technology	9718
dCK	Owen Witte Lab (UCLA)	Clone #9D4
TK1	Cell Signaling Technology	8960
TYMS	Cell Signaling Technology	9045
CLEAVED PARP	Cell Signaling Technology	5625
CLEAVED CASPASE 3	Cell Signaling Technology	9662
RRM1	Cell Signaling Technology	8637
RRM2	Santa Cruz Biotechnology	SC-10846
STING (TMEM173)	Cell Signaling Technology	13647
PHOSPHO IRF3 S396	Cell Signaling Technology	37829
ANTI-RABBIT IgG, HRP-LINKED	Cell Signaling Technology	7074
ANTI-MOUSE IgG, HRP-LINKED	Cell Signaling Technology	7076
pH2AX S139 - FITC	Millipore	05-636
F7.26 ssDNA	Millipore	MAB3299

Vector	Source	Identifier
pMD2G	Addgene	12259
psPAX2	Addgene	12260
Lenticrispr V2	Addgene	52961

Oligonucleotides	Sequence	Vector
SAMHD1 gRNA	GTCATCGCAACGGGGACGCT	LENTICRISPR V2 (addgene #52961)
TK1 gRNA	GCTGCTGTAGCGAGTGTCTT	LENTICRISPR V2 (addgene #52961)
STING (TMEM173) gRNA	AGAGCACACTCTCCGGTACC	LENTICRISPR V2 (addgene #52961)

Software	Source	Identifier
Prism 6	GraphPad Software	N/A
Flowjo 7.6	TreeStar	N/A

Instrument	Manufacturer	Assay
LSRII	BD	Flow Cytometry
Q-Exactive Mass Spectrometer	Thermo	Proteomics/Phosphoproteomics
LTQ OrbitrapXL Mass Spectrometer	Thermo	Non-targeted metabolomics
QQQ Mass Spectrometer	Agilent	Targeted DNA/dNTP metabolites
Microplate reader	BioTek	Luminescence Cell Viability Assays
BeadRuptor Elite	OMNI International	Tissue Homogenization
ECLIPSE Ci-S	Nikon	Fluorescence Microscopy

FIG. 23

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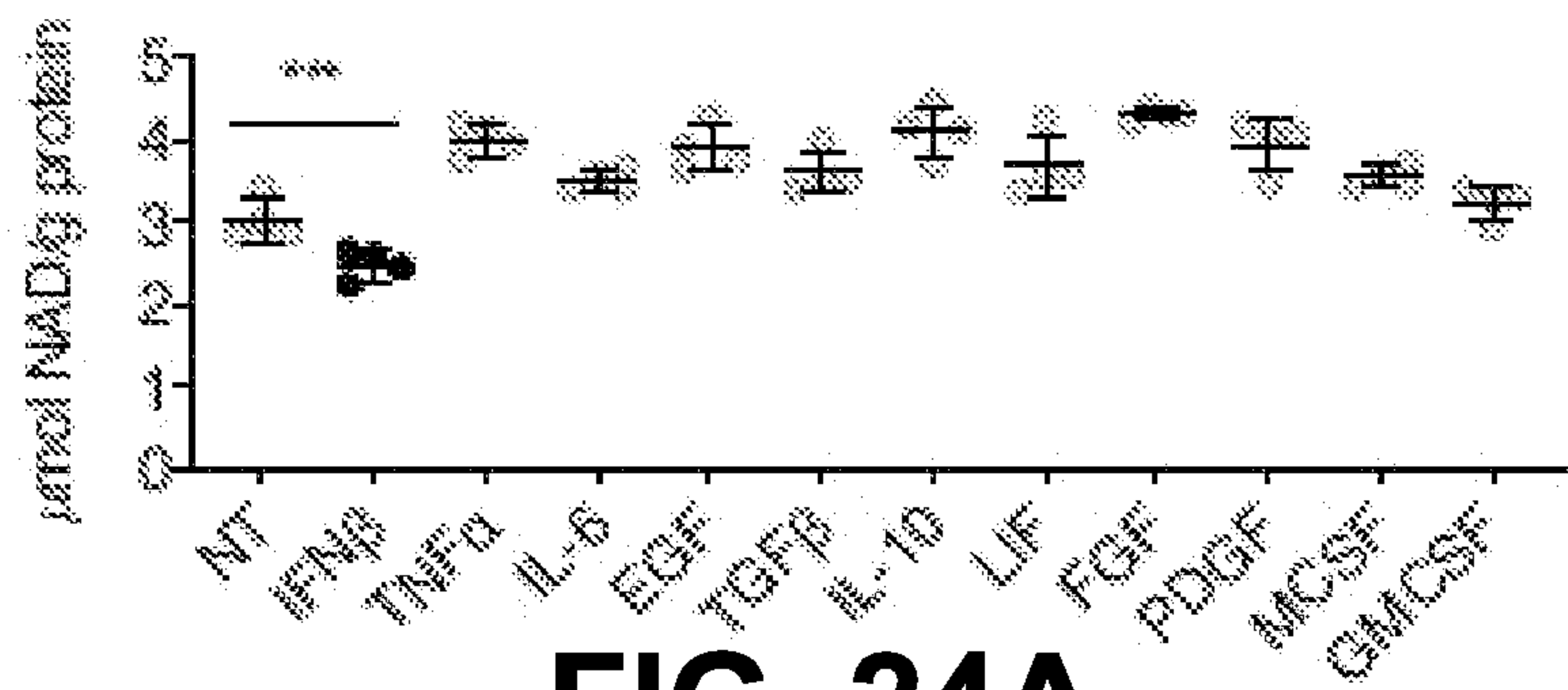


FIG. 24A

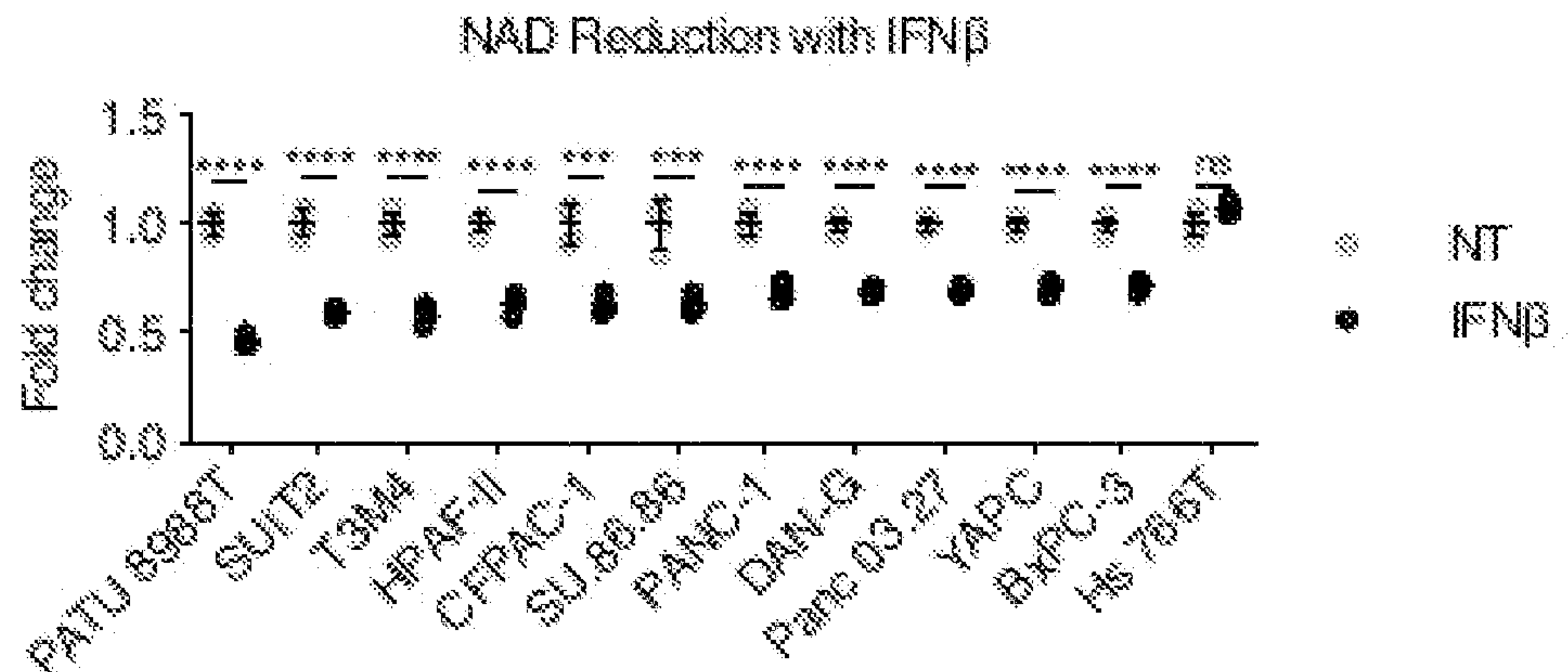


FIG. 24B

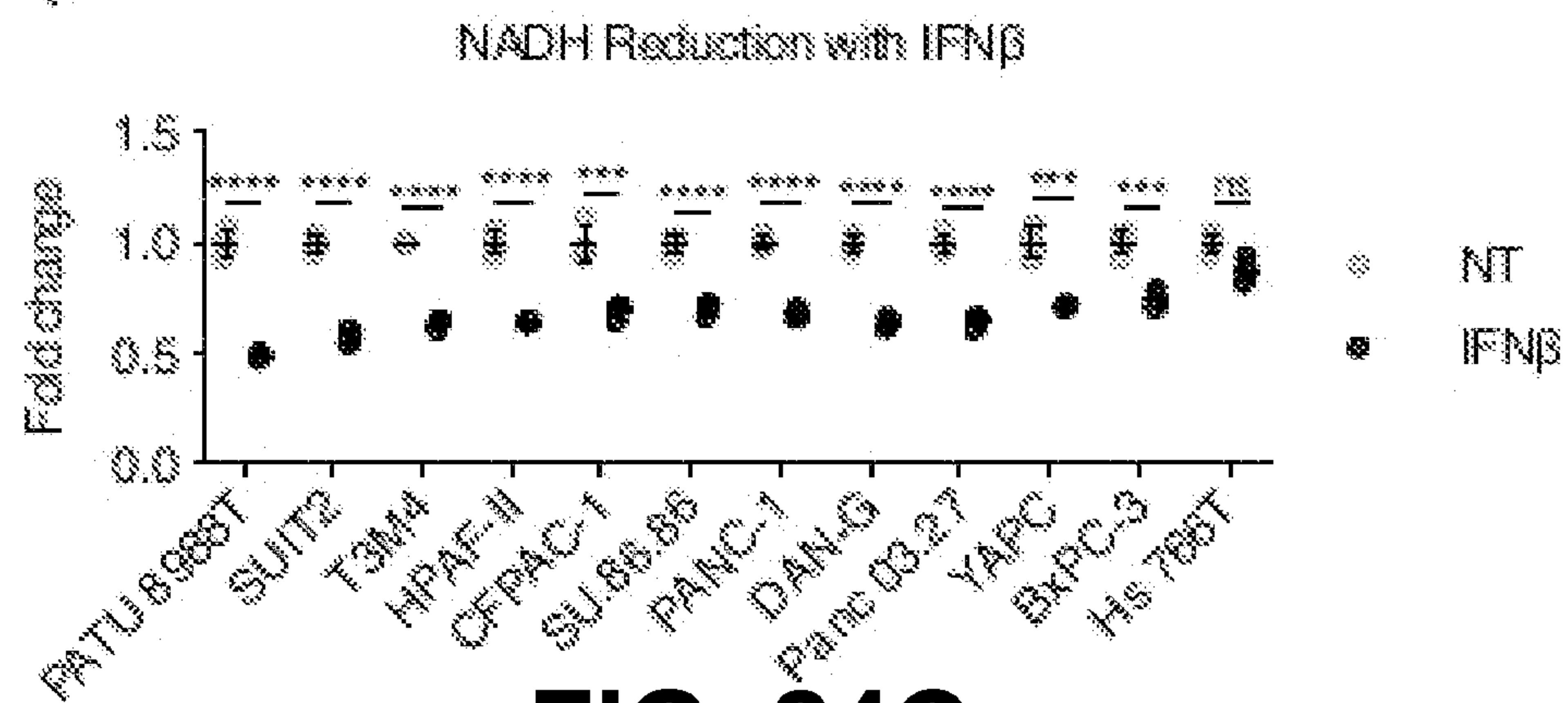


FIG. 24C

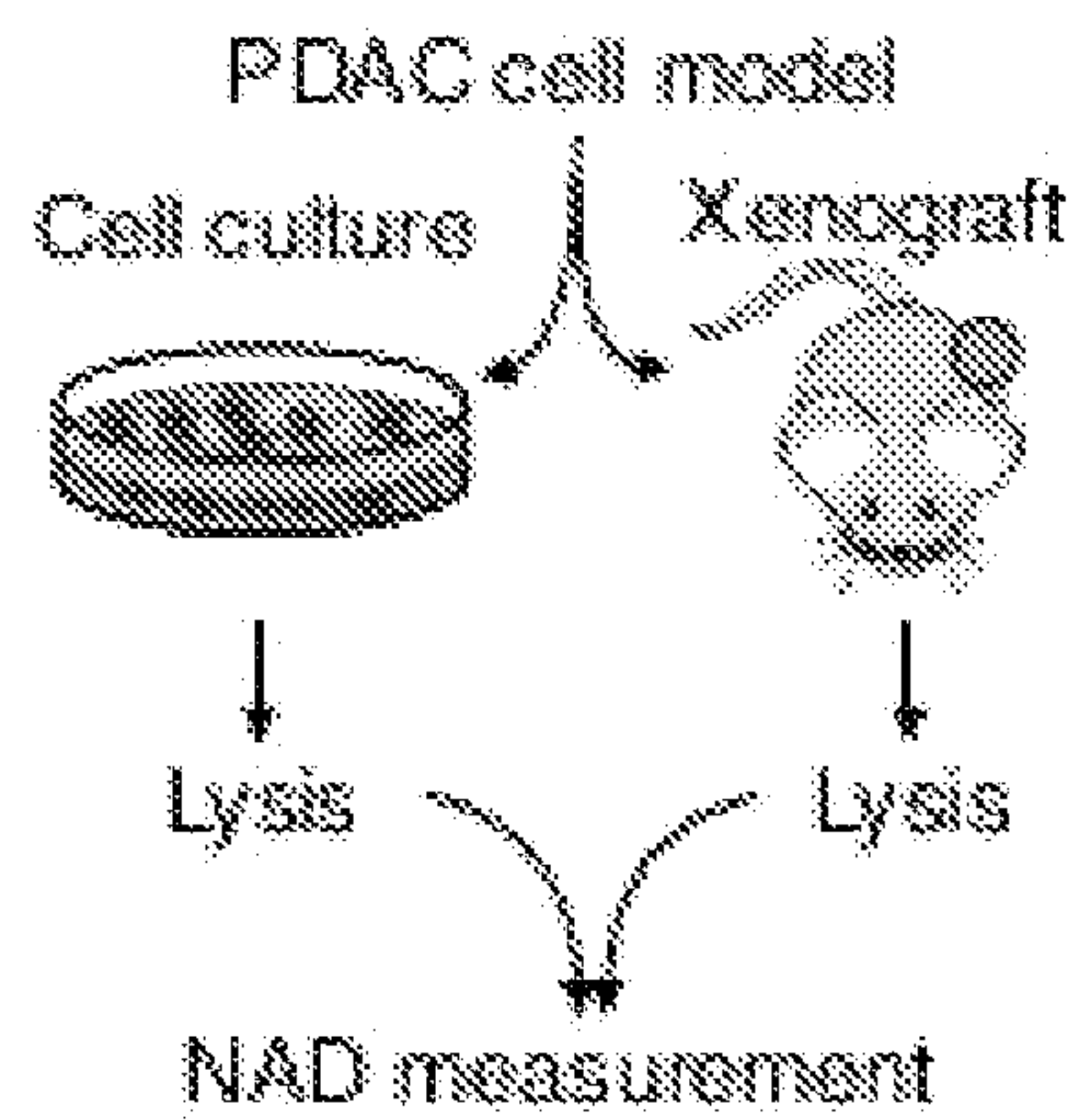


FIG. 24D

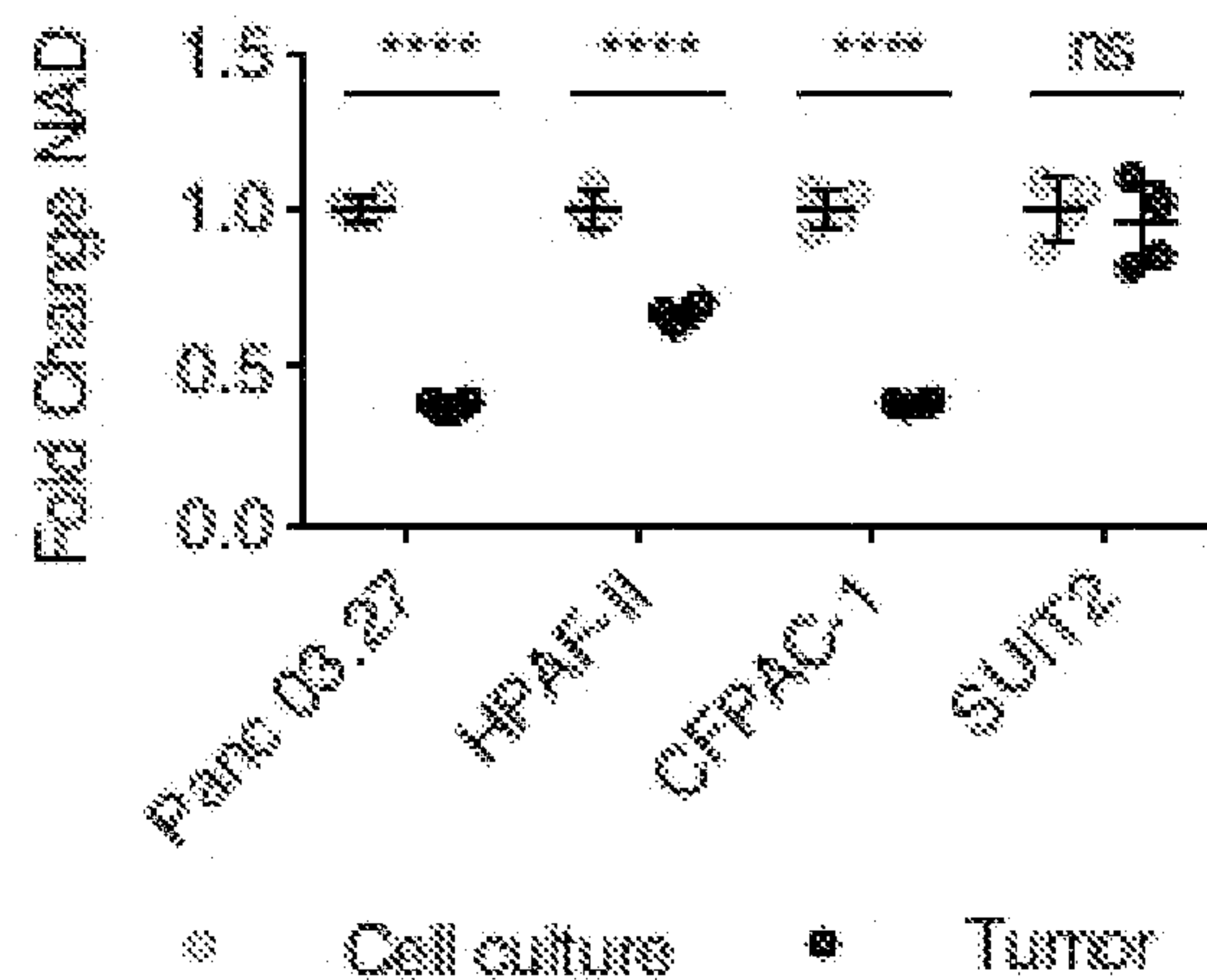


FIG. 24E

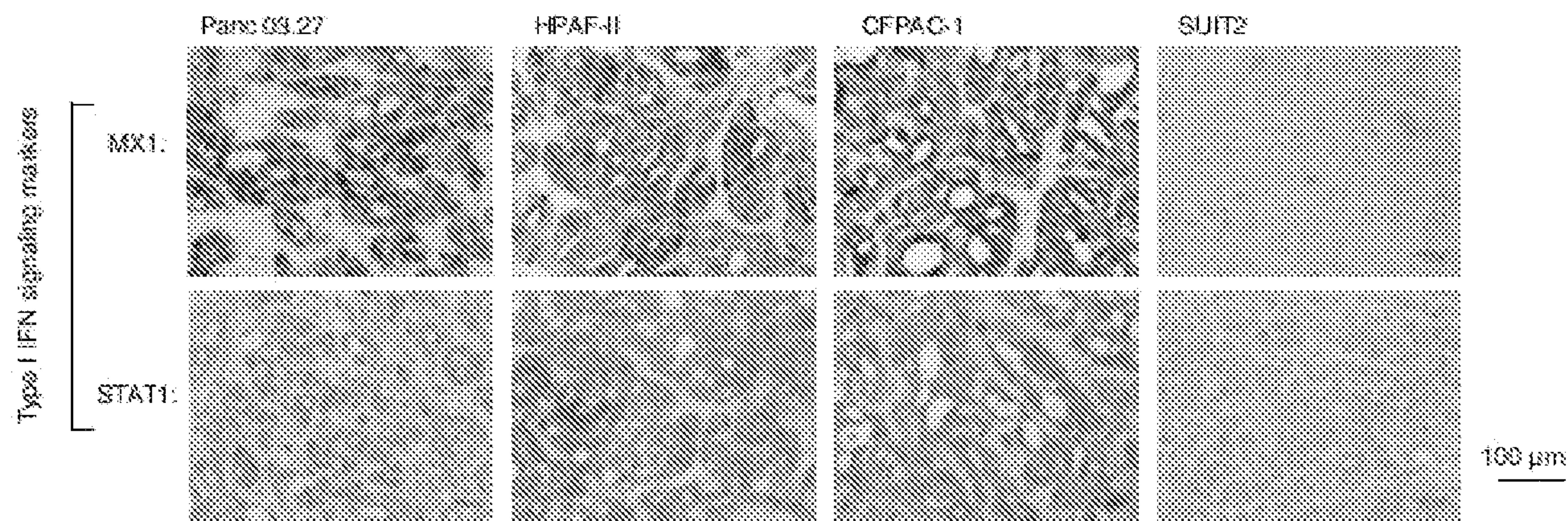


FIG. 24F

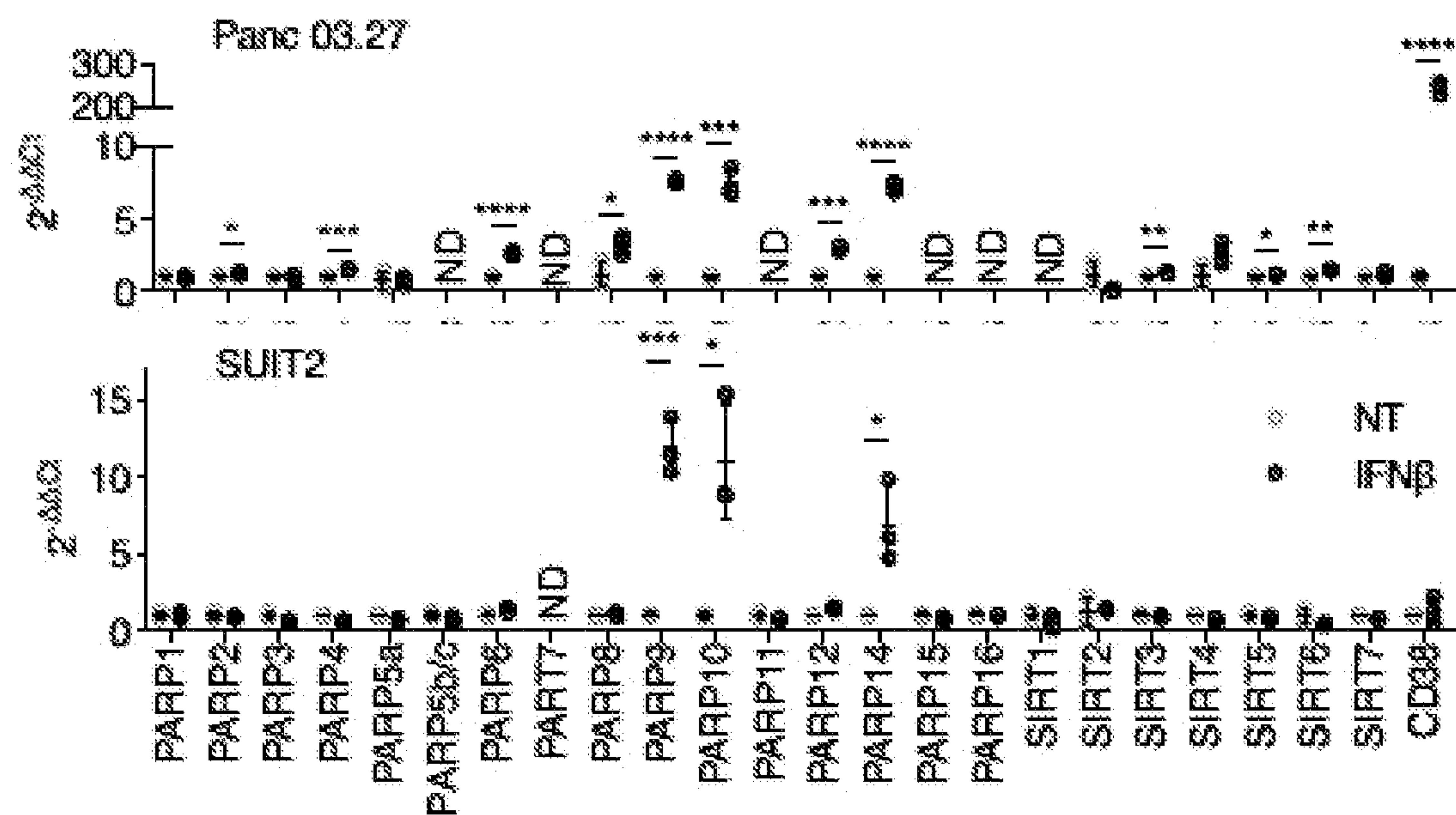


FIG. 25A

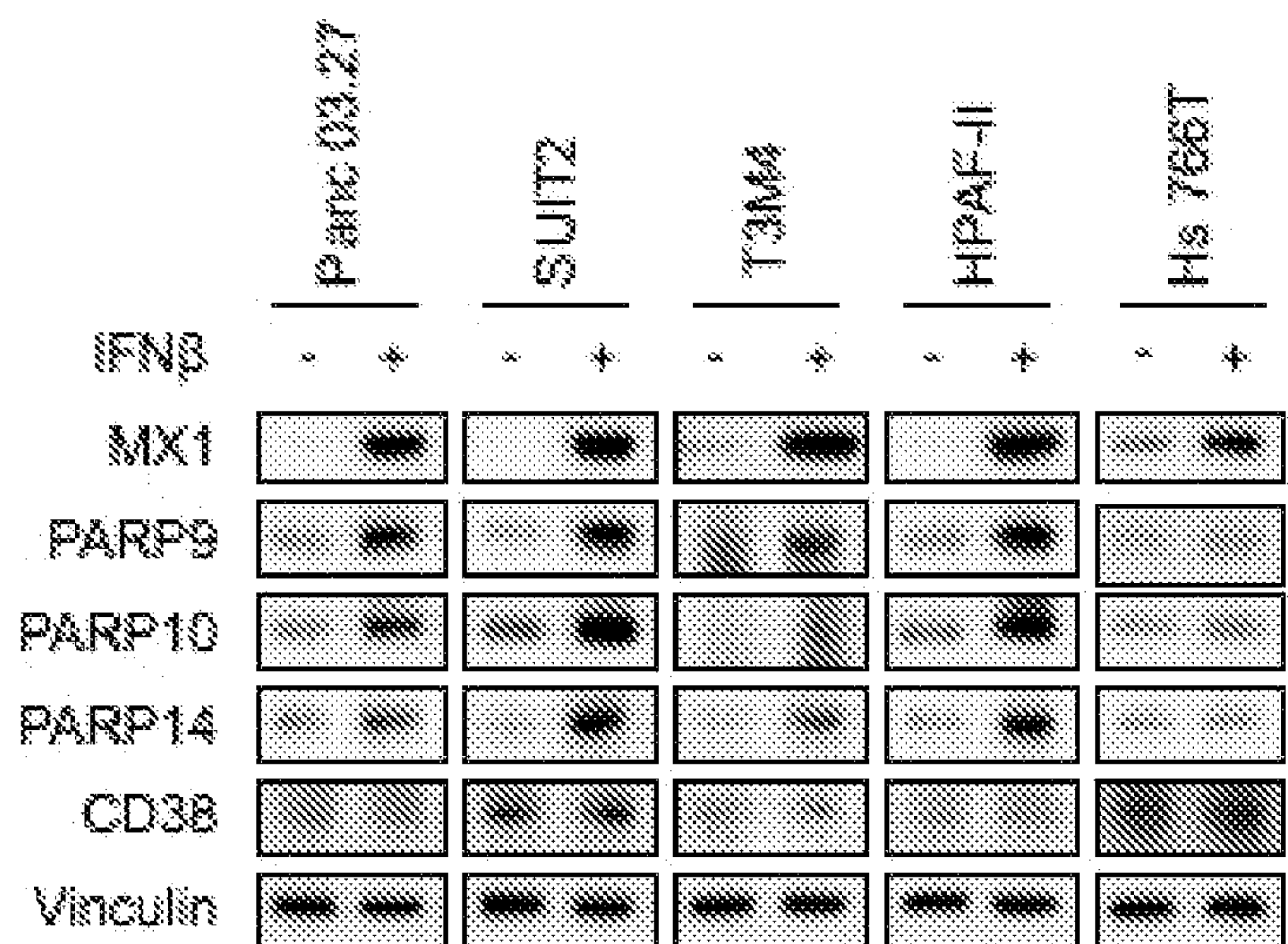


FIG. 25B

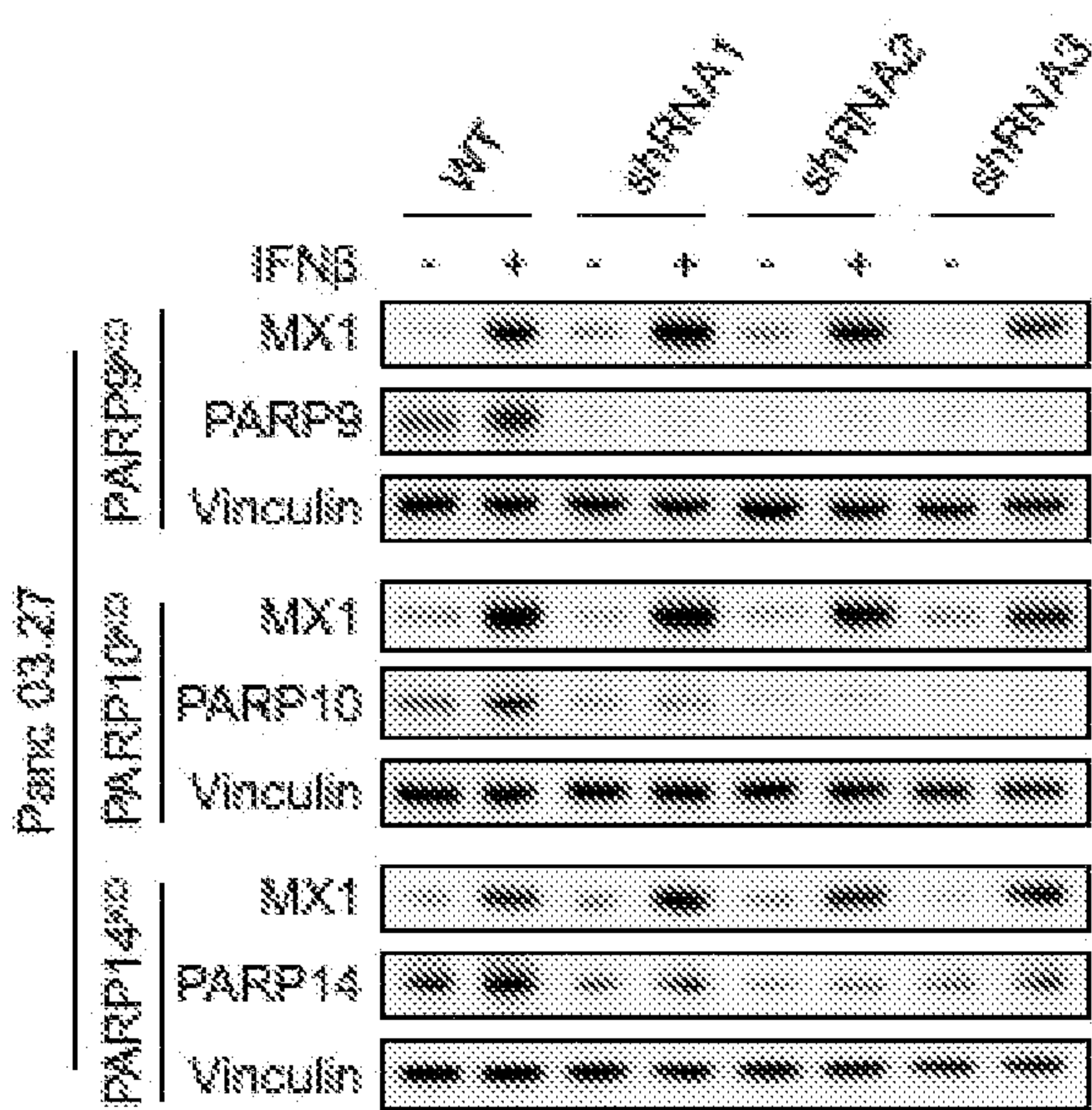


FIG. 26A

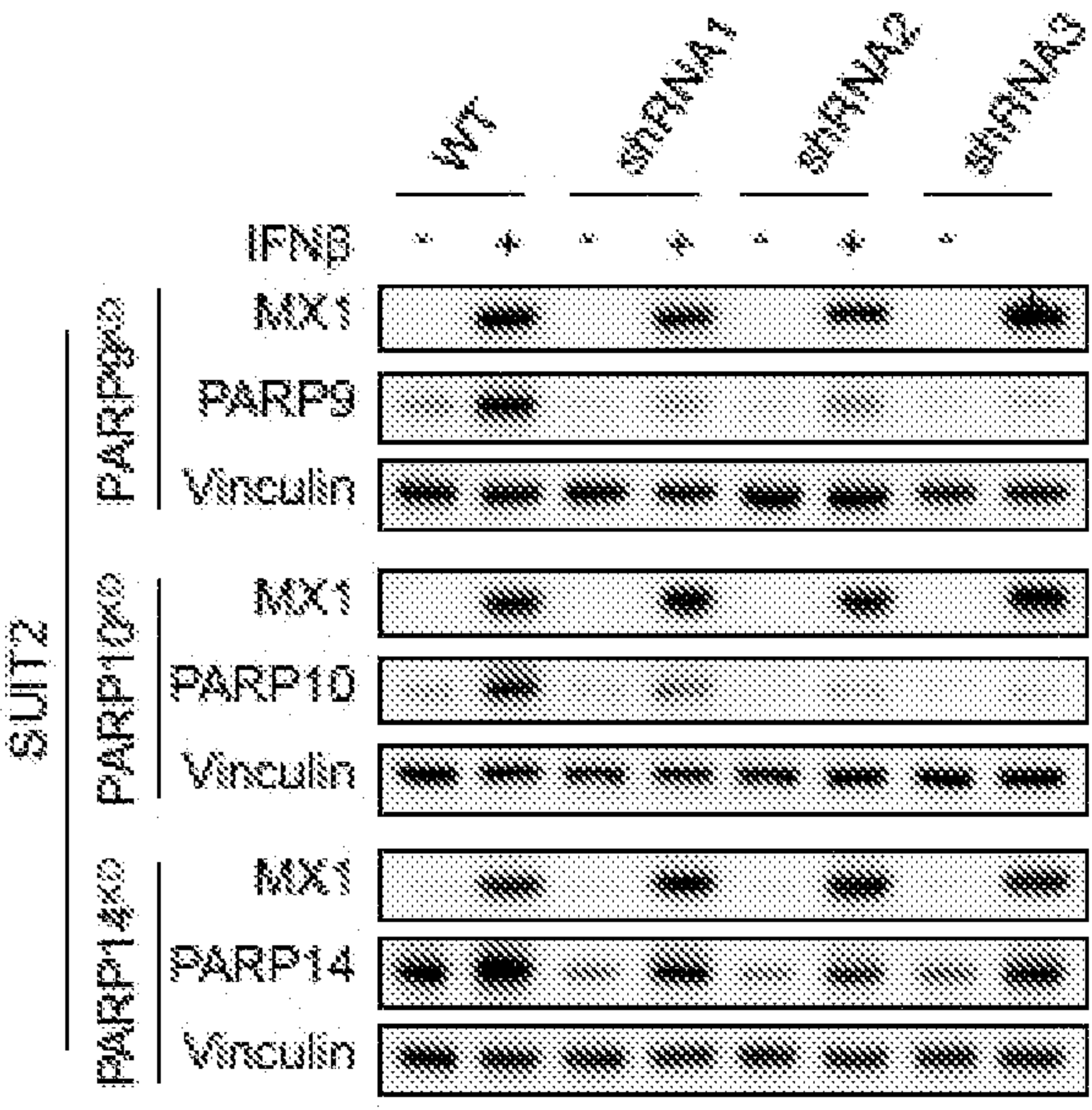


FIG. 26B

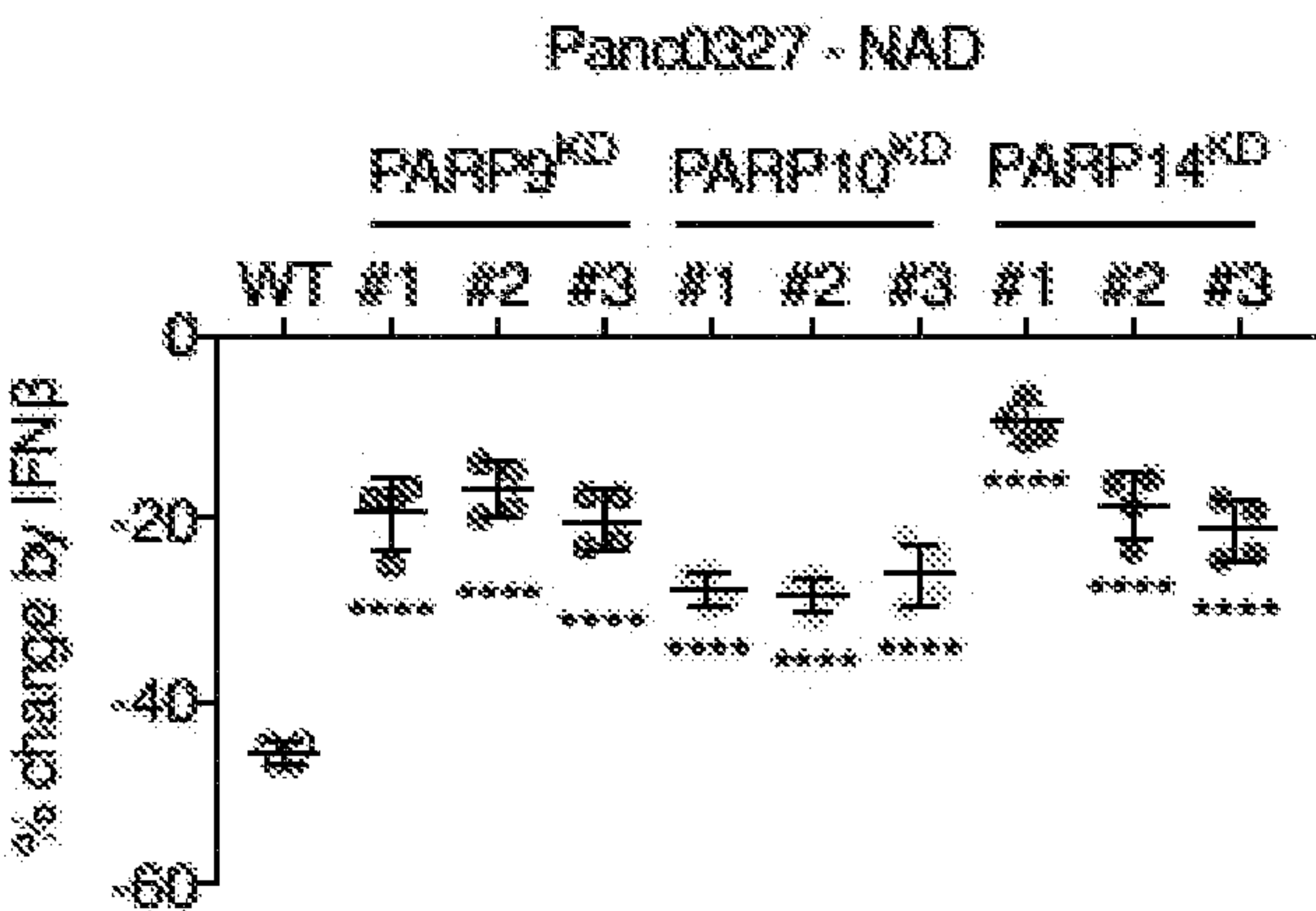


FIG. 26C

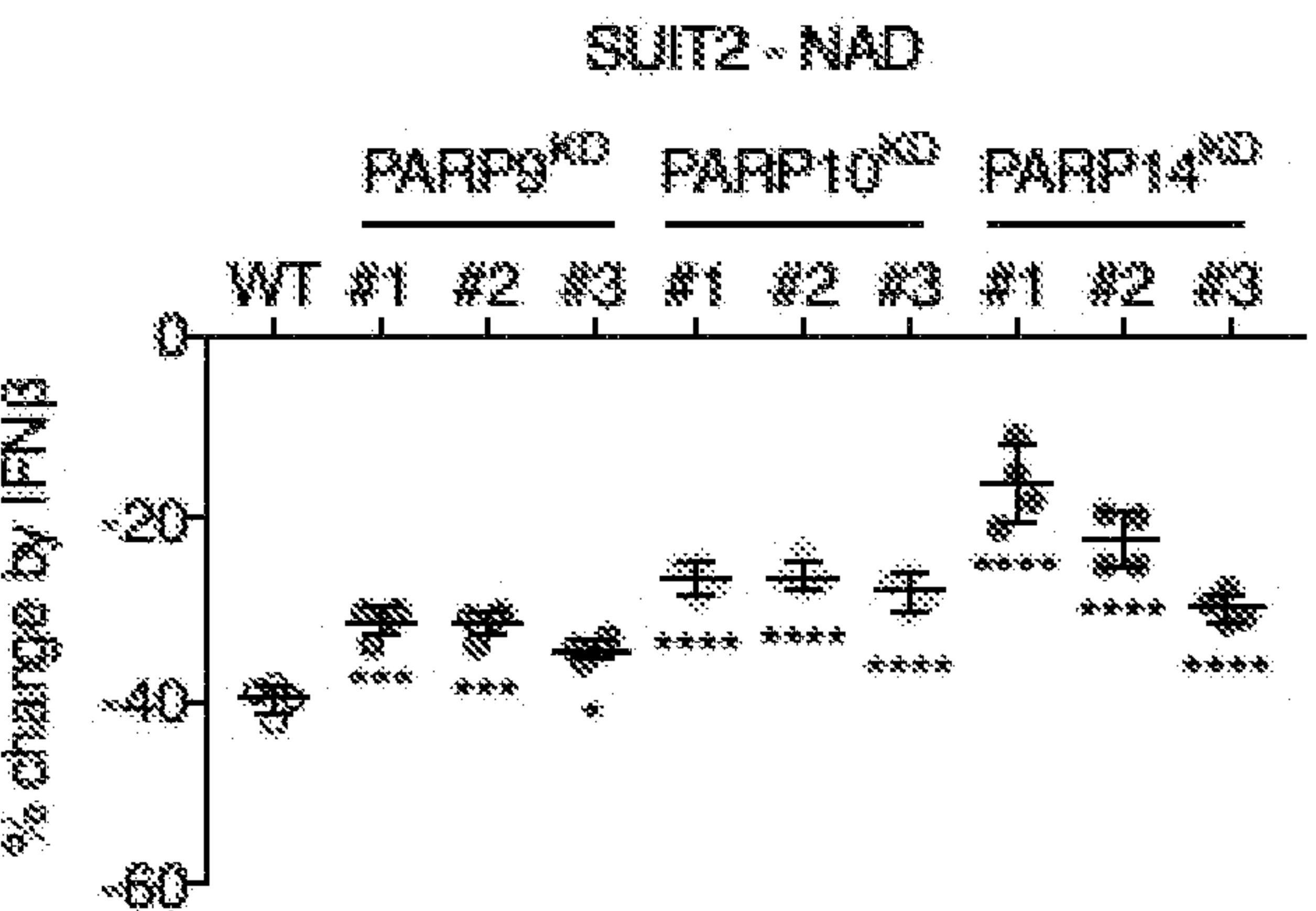


FIG. 26D

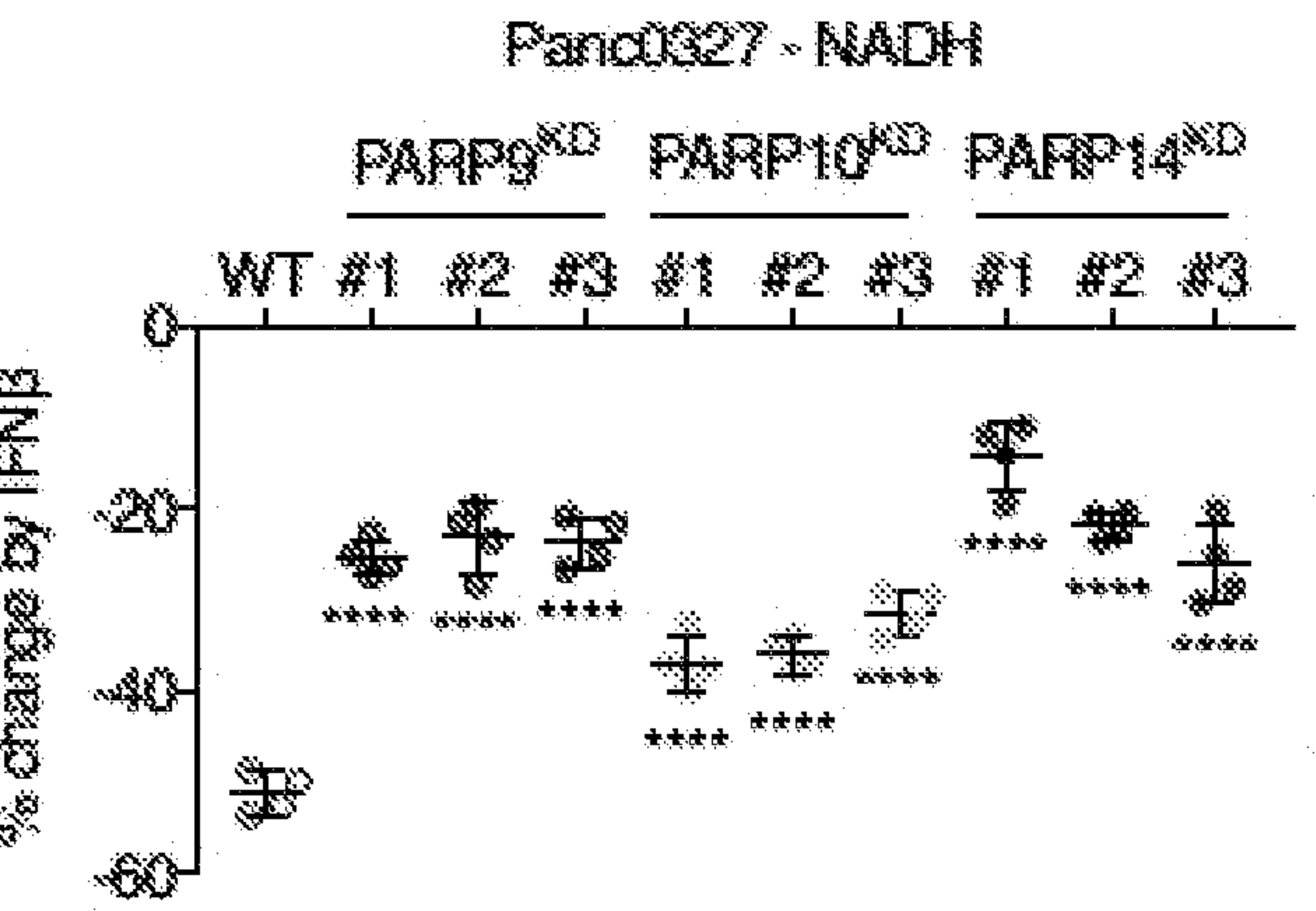


FIG. 26E

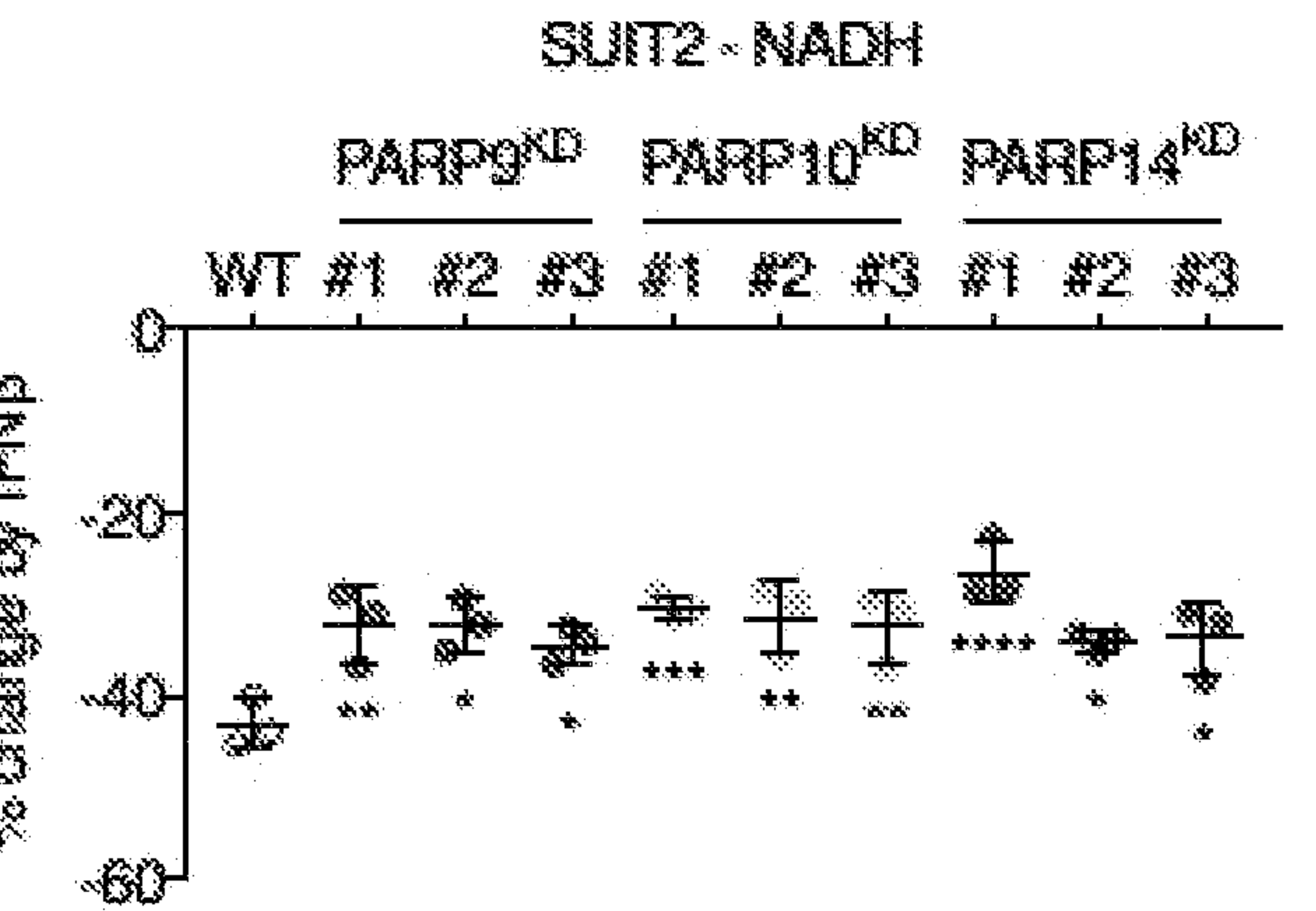


FIG. 26F

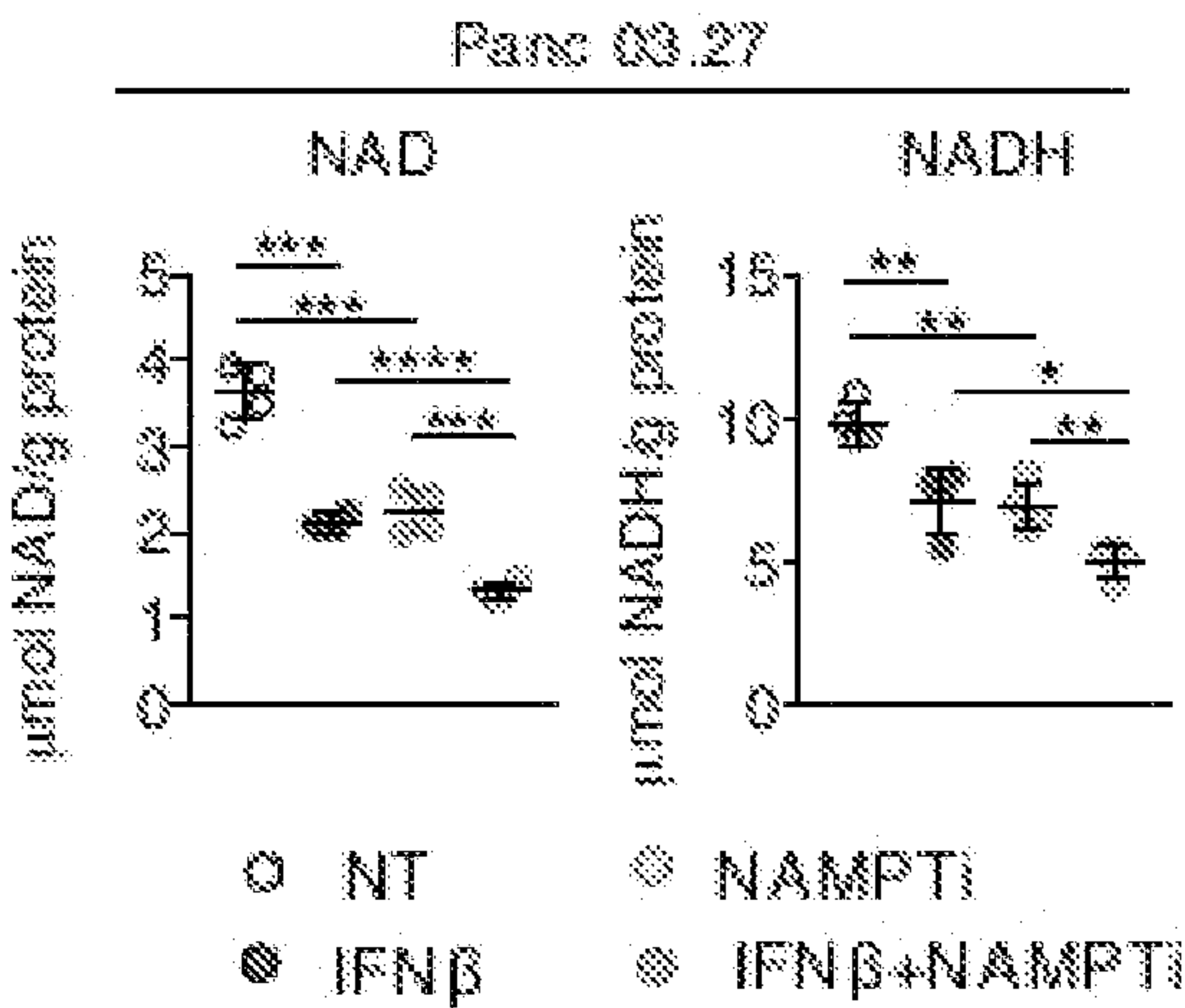
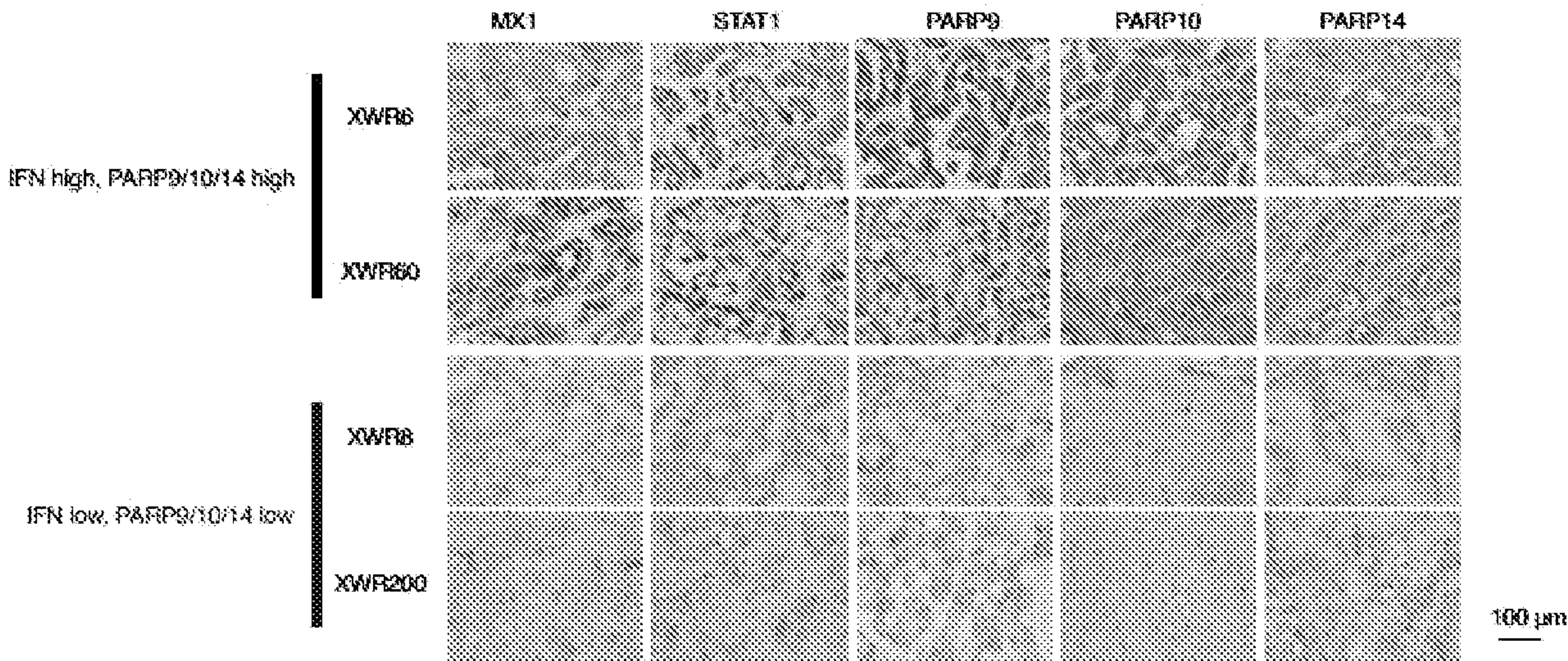
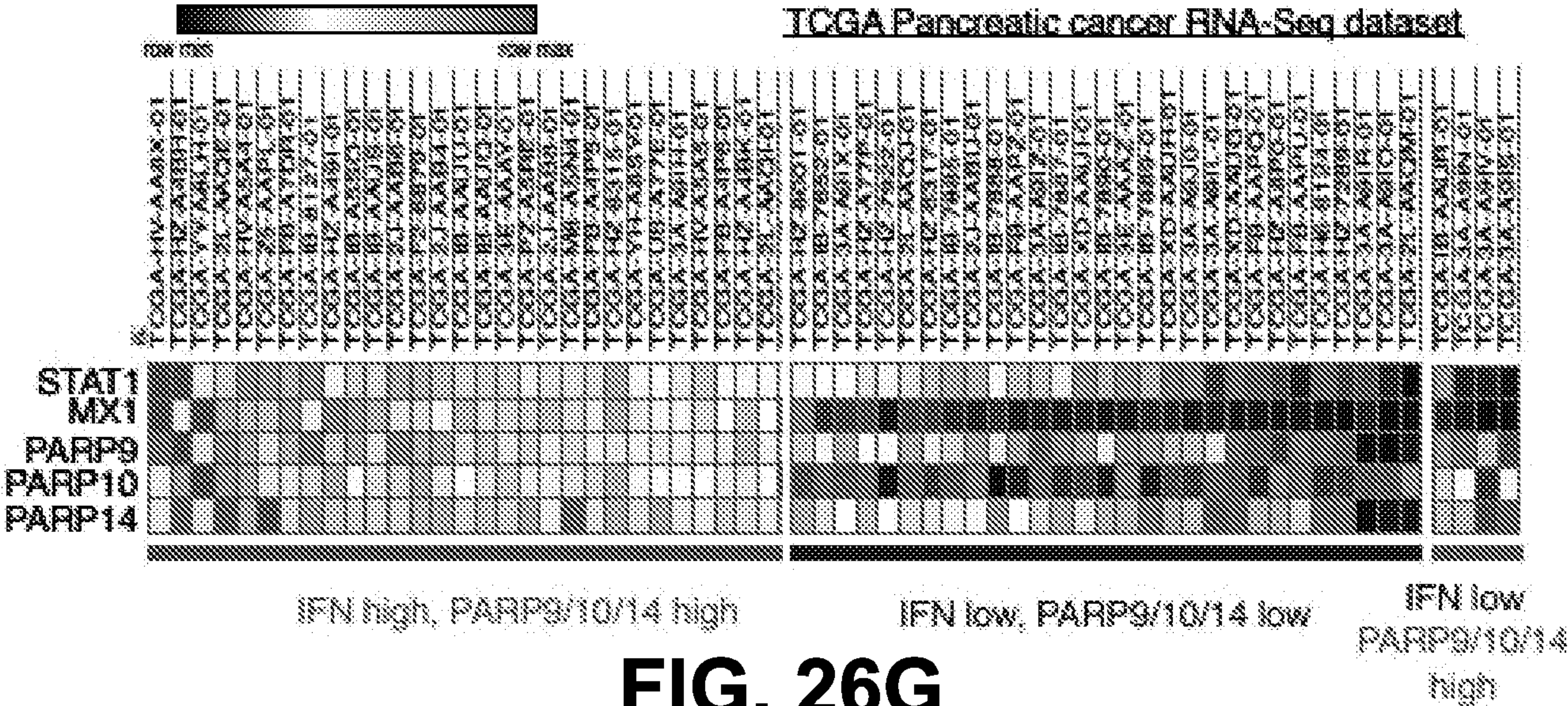


FIG. 27A

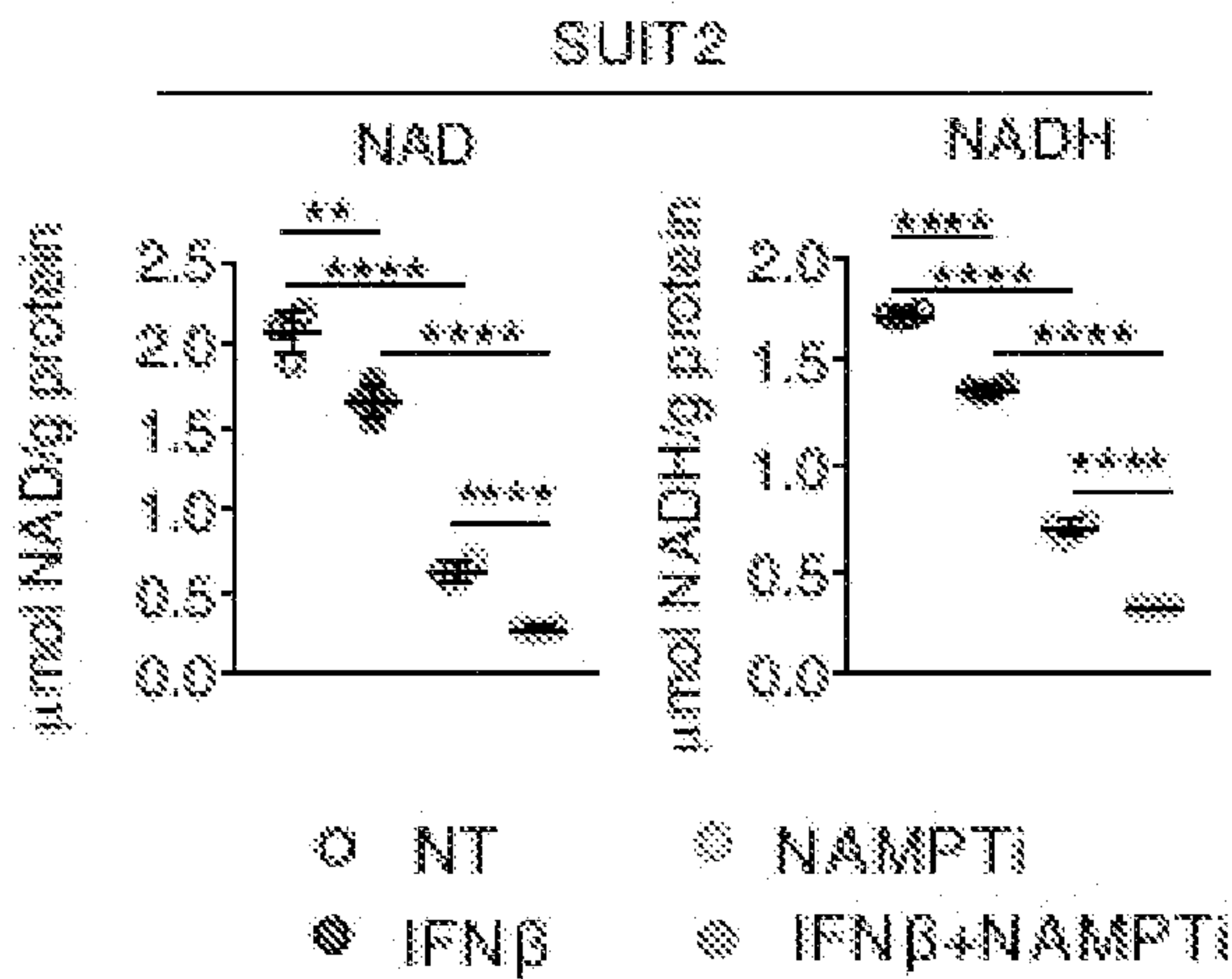


FIG. 27B

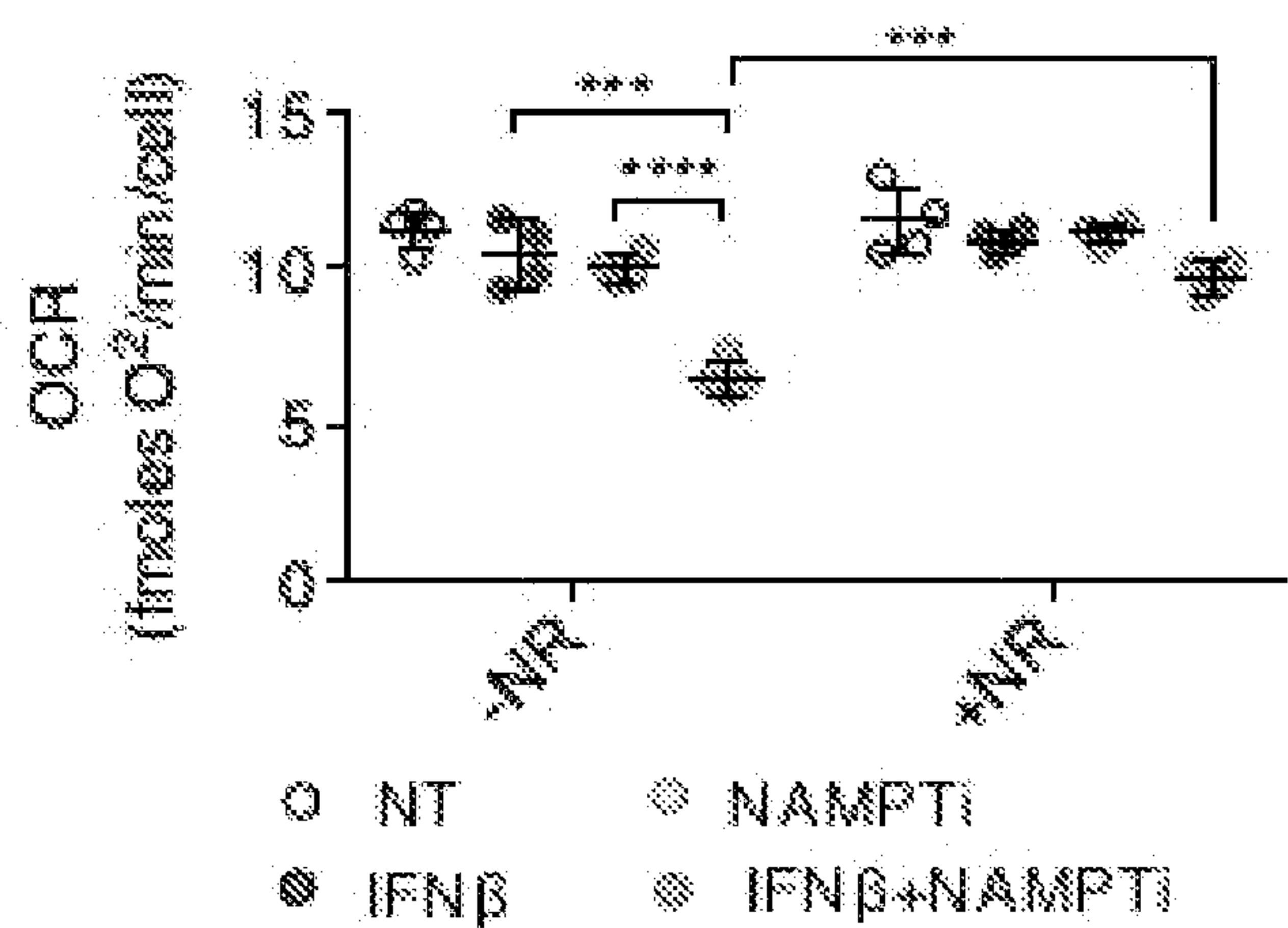


FIG. 27C

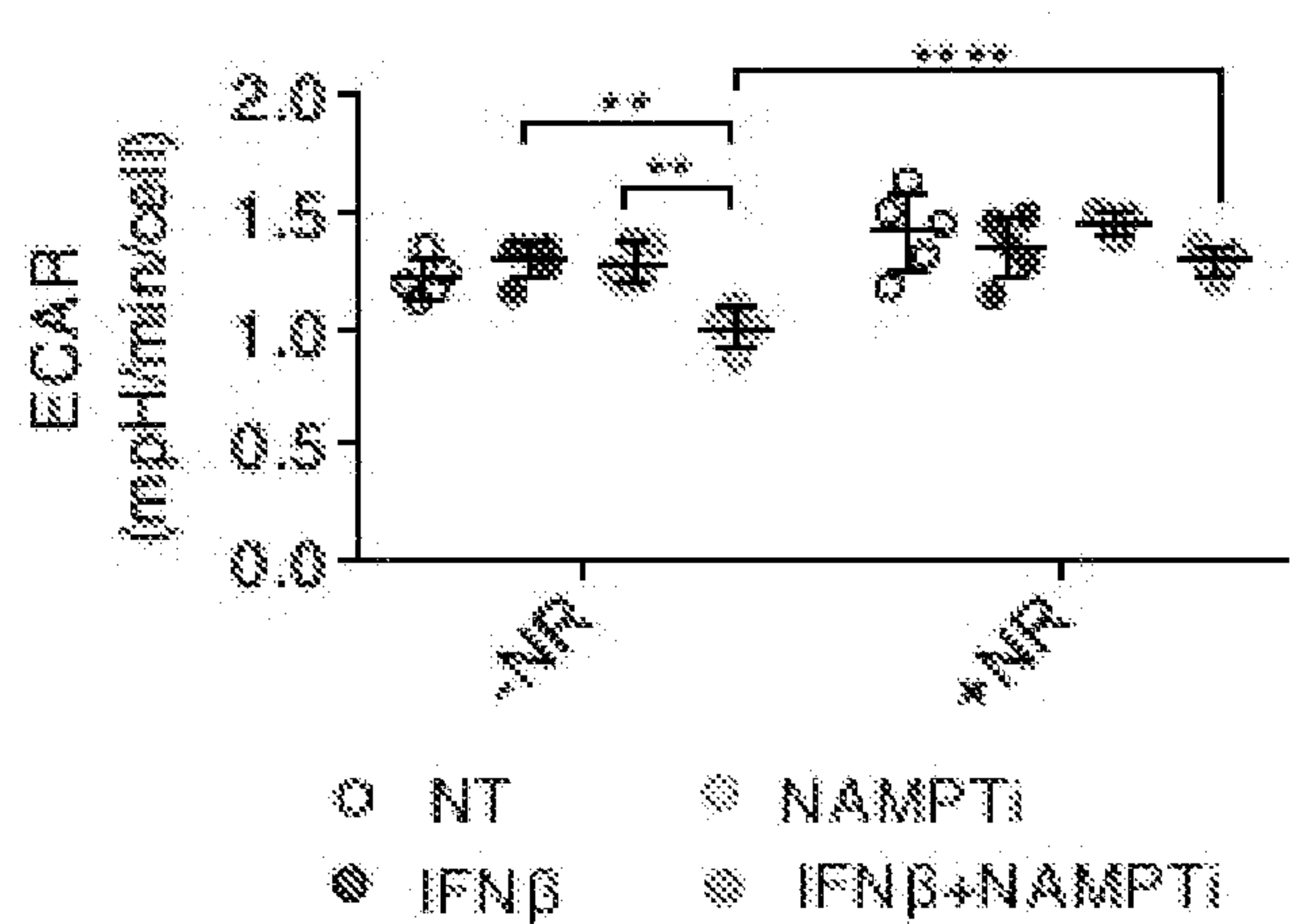


FIG. 27D

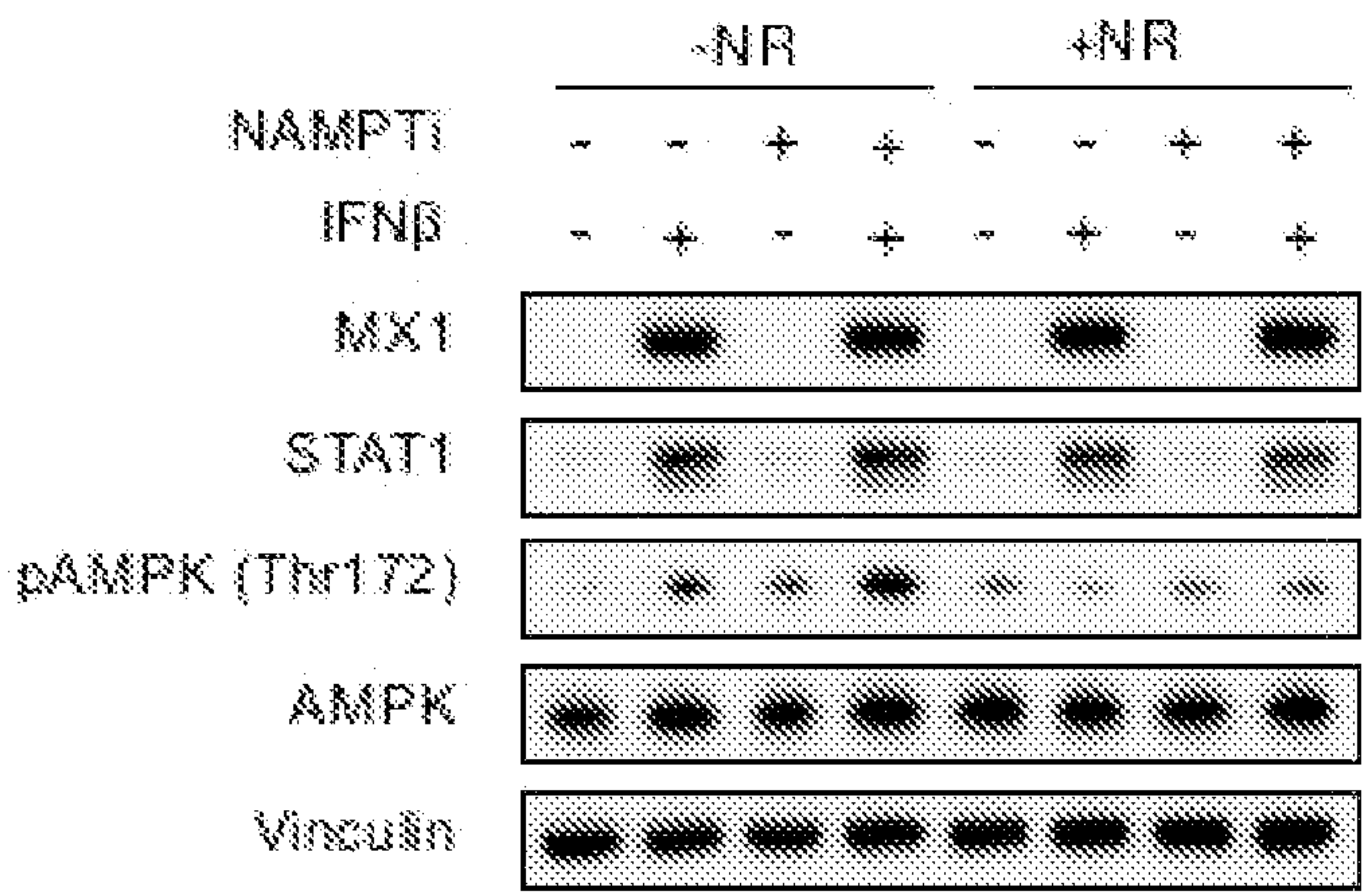


FIG. 27E

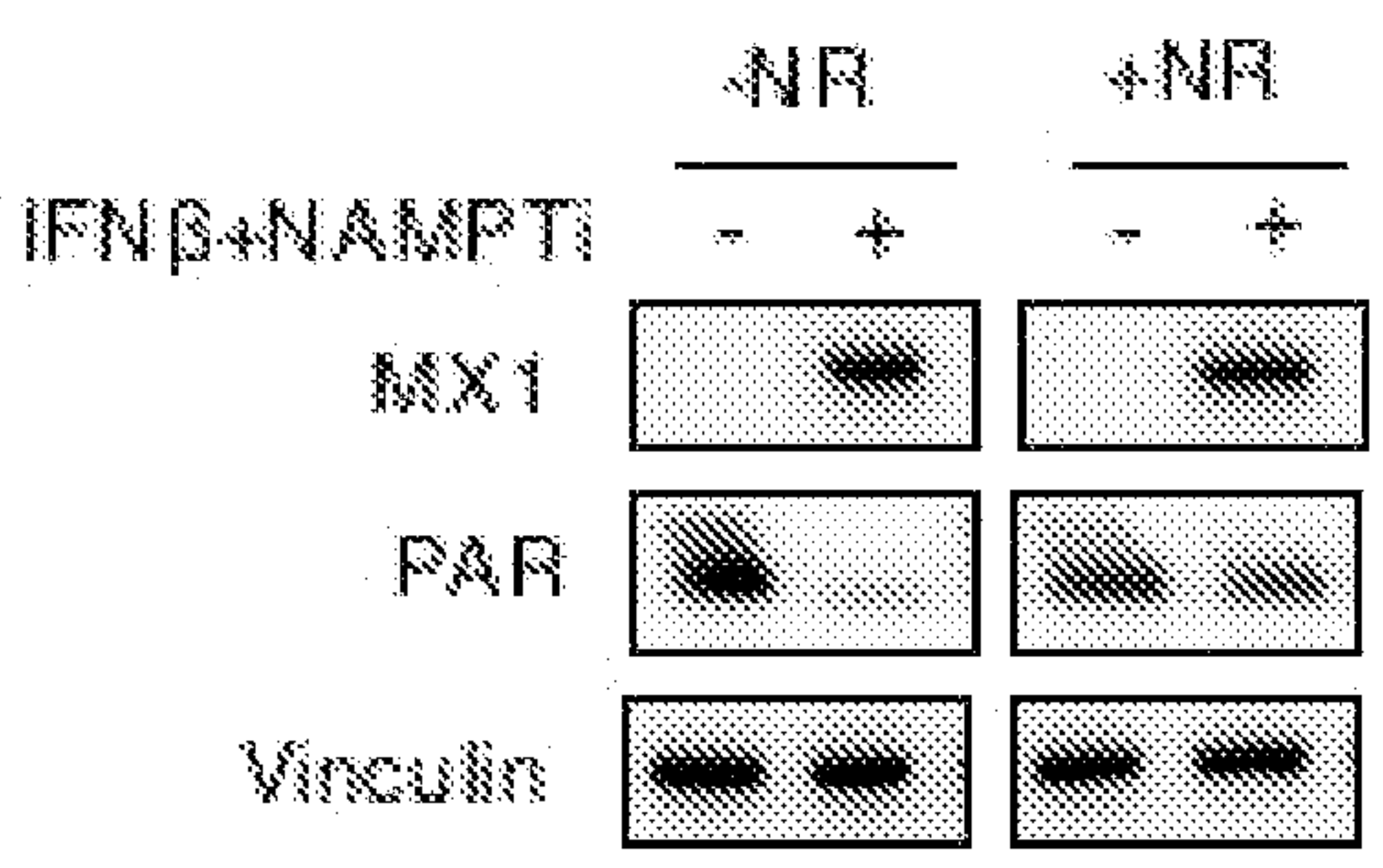


FIG. 27F

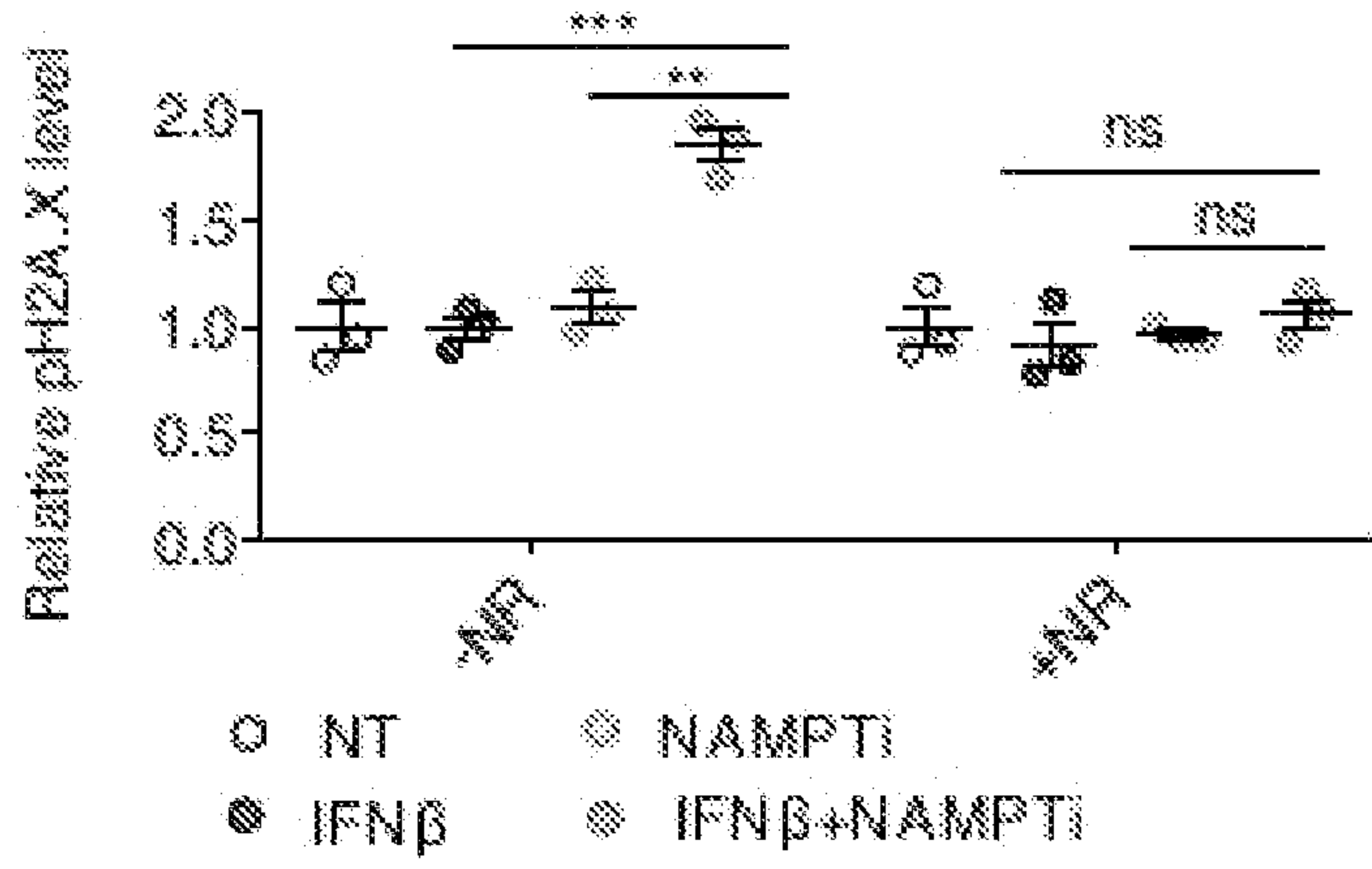


FIG. 27G

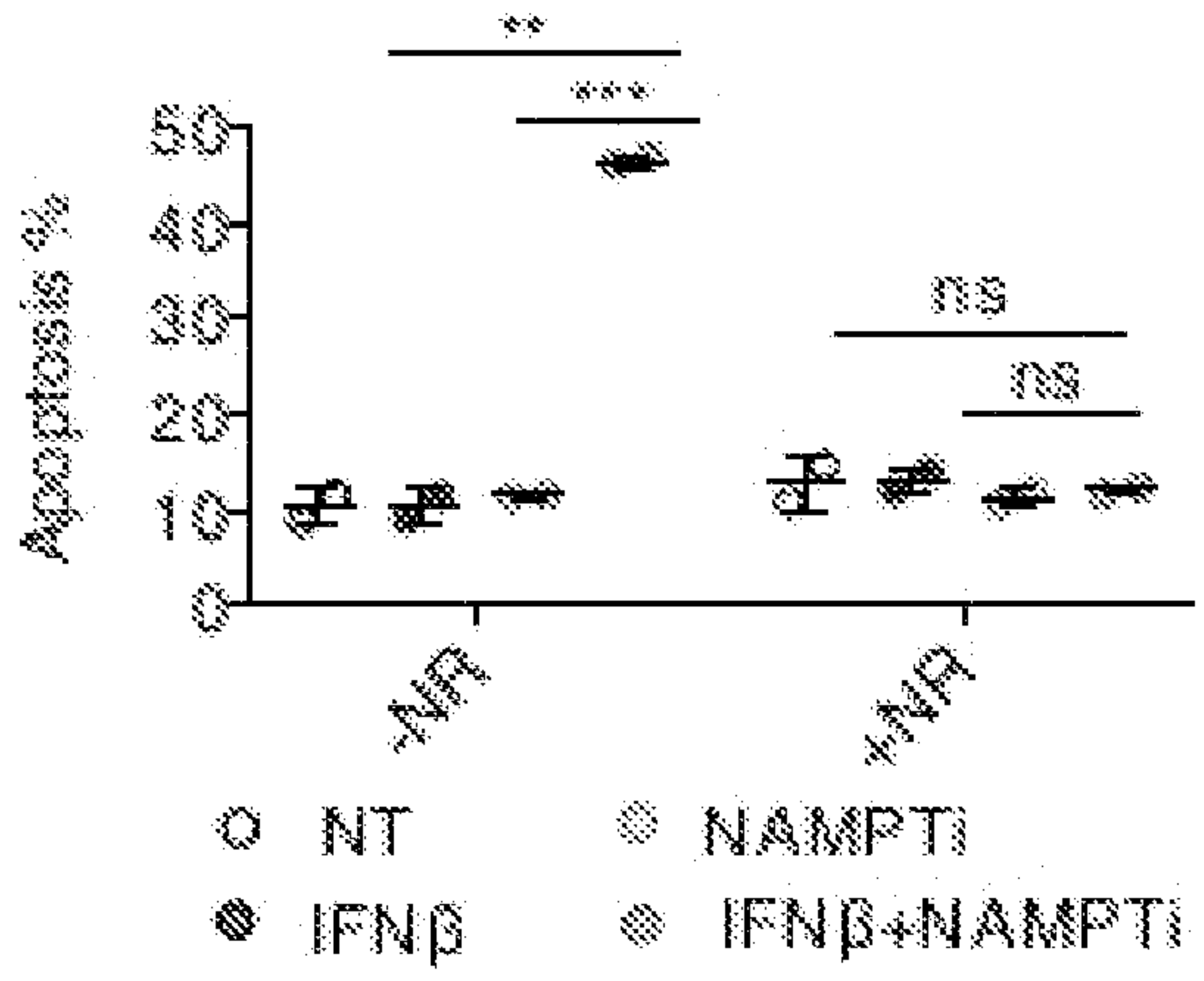


FIG. 27H

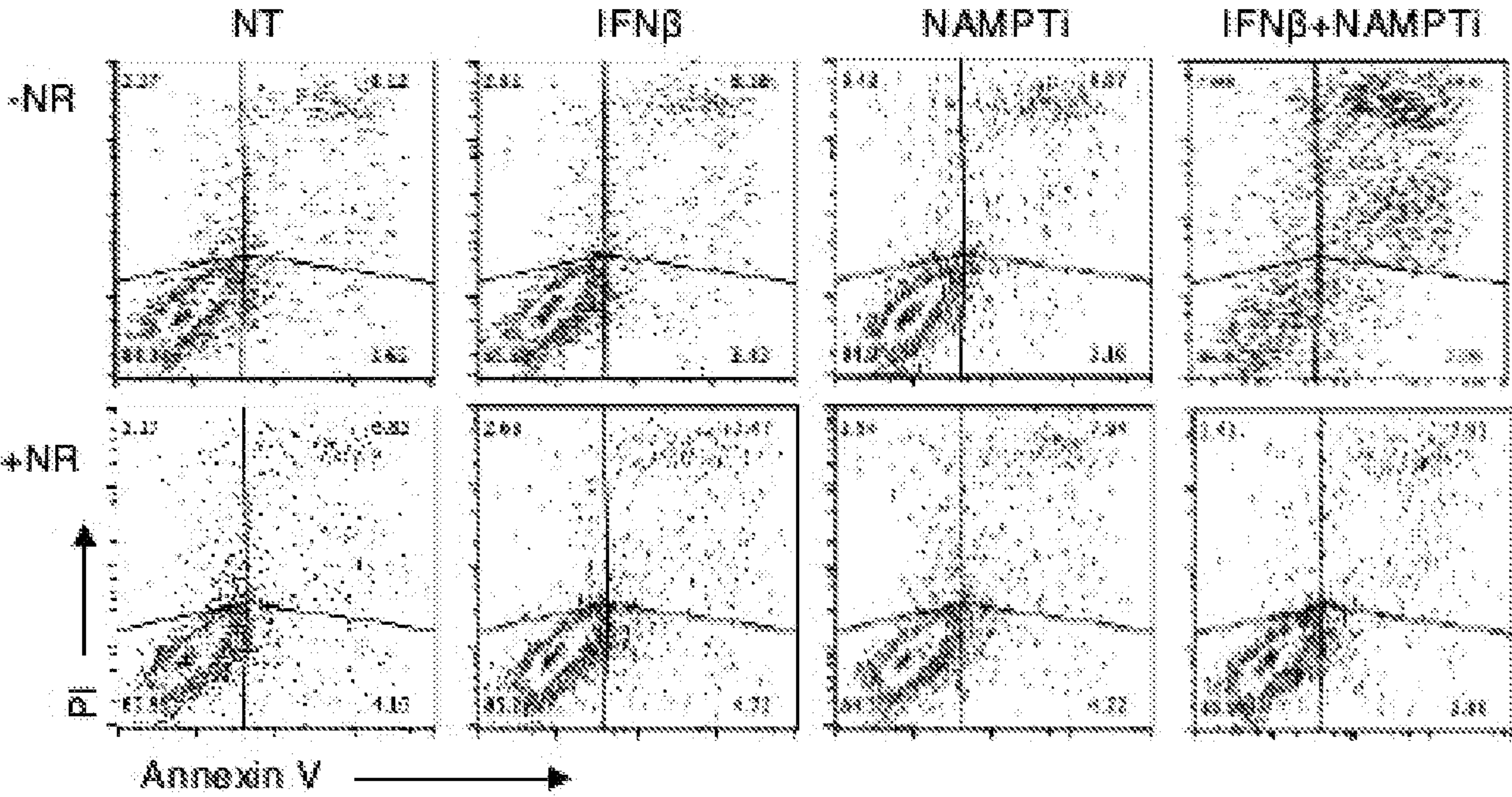


FIG. 27I

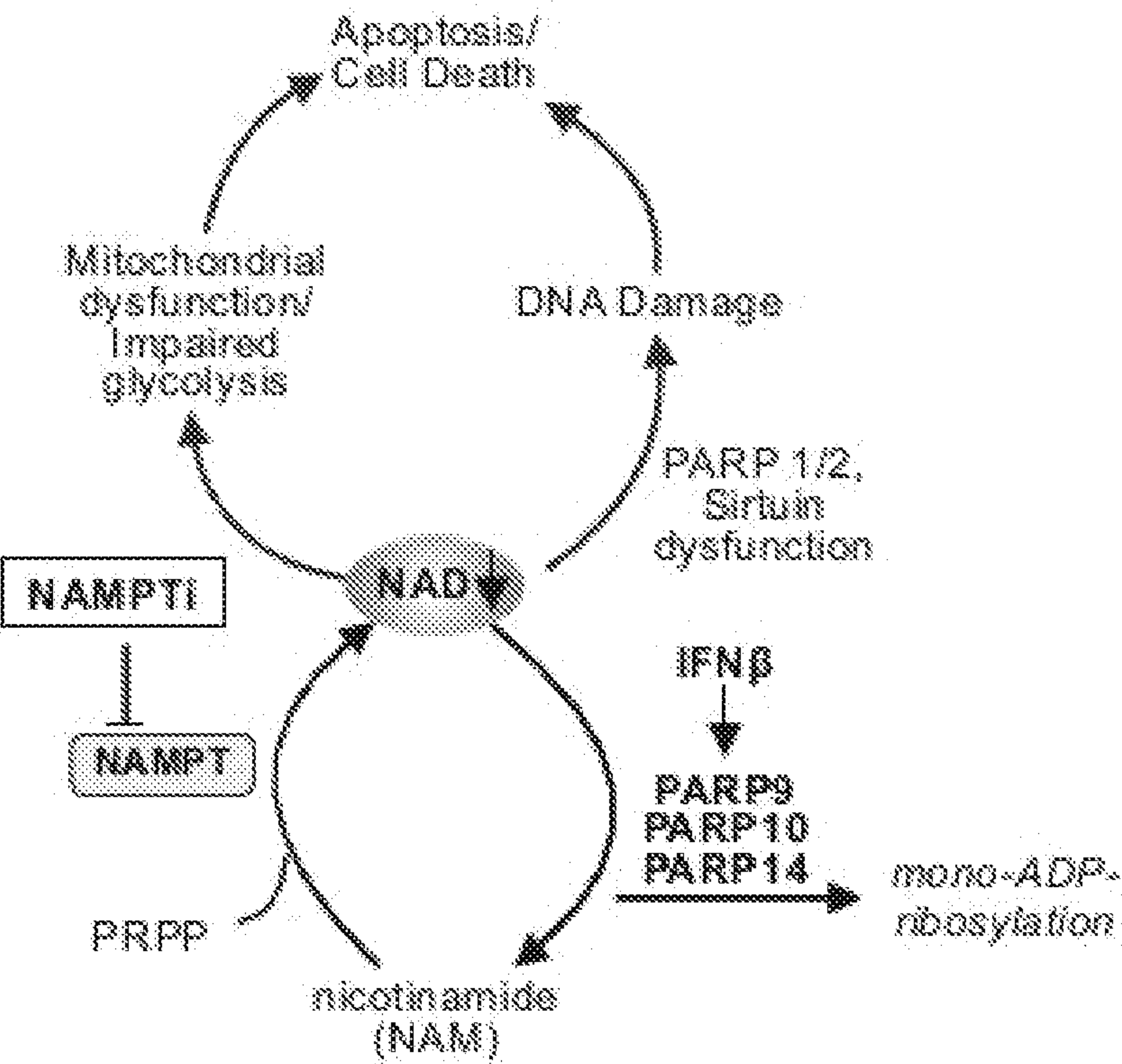


FIG. 27J

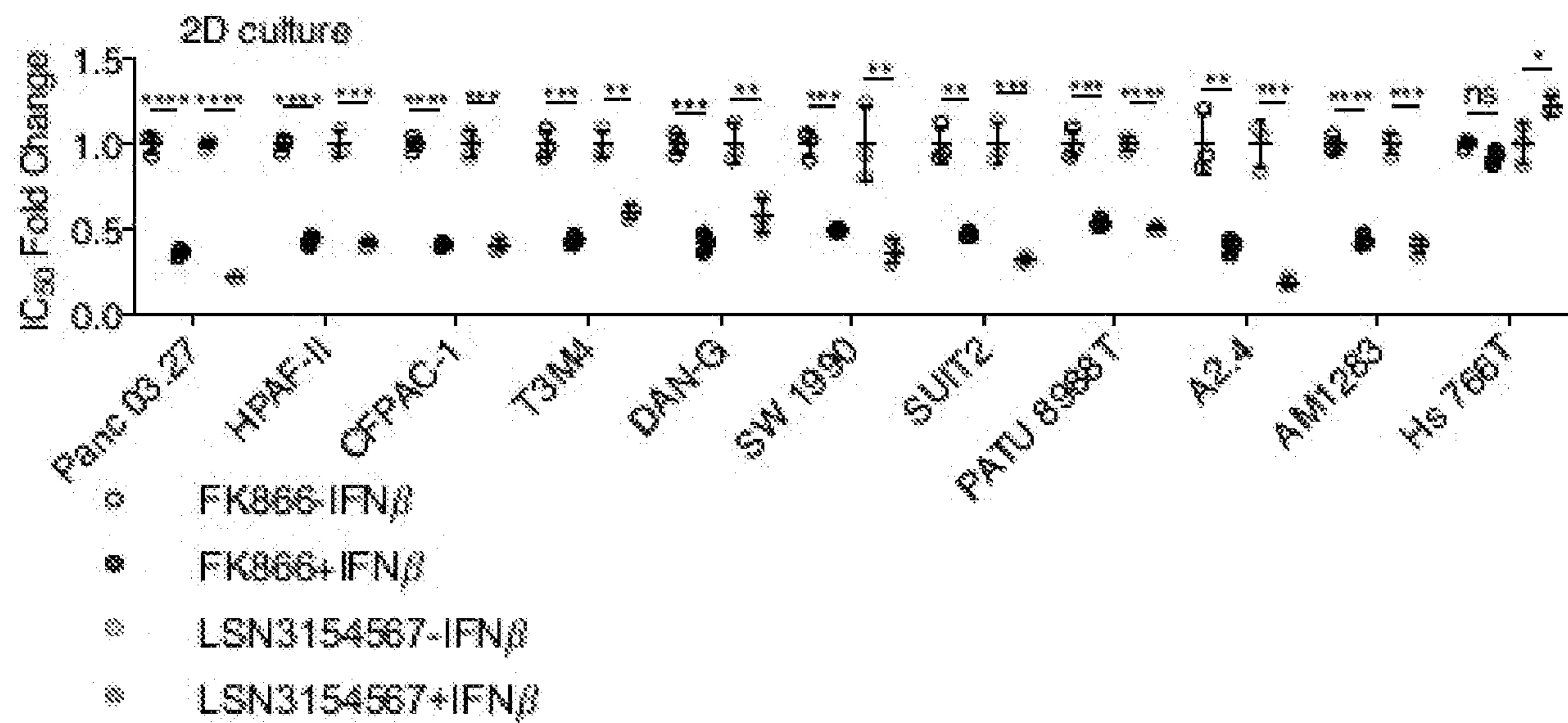


FIG. 28A

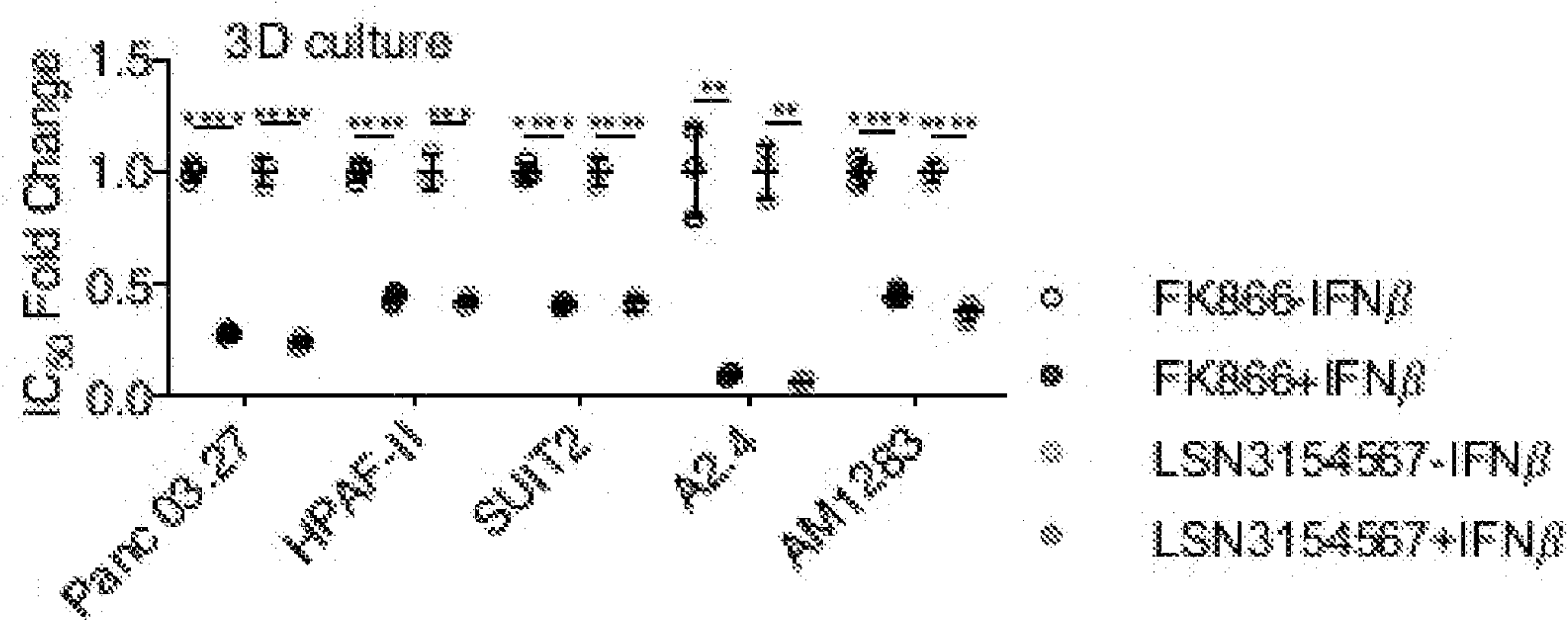


FIG. 28B

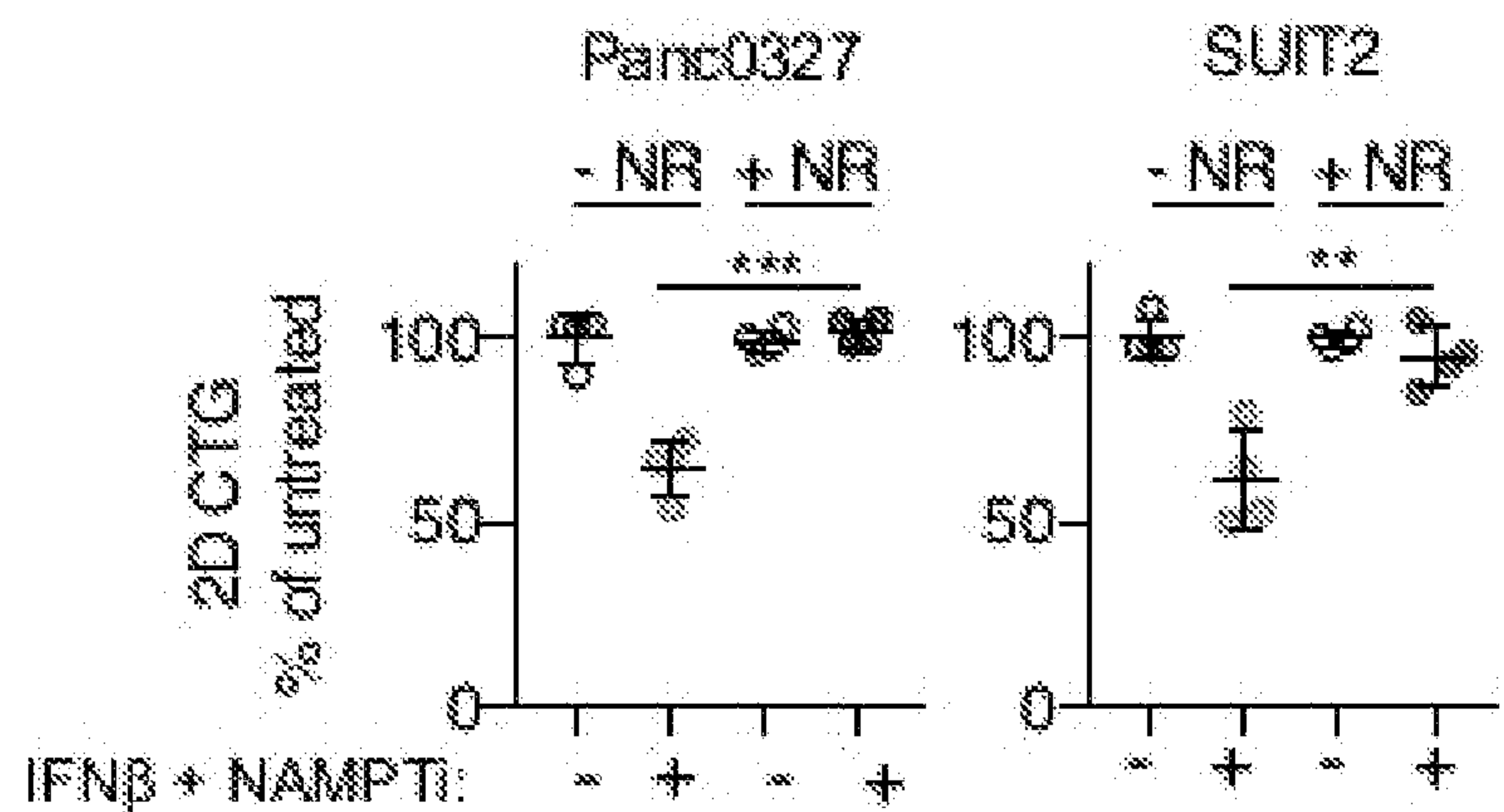


FIG. 28C

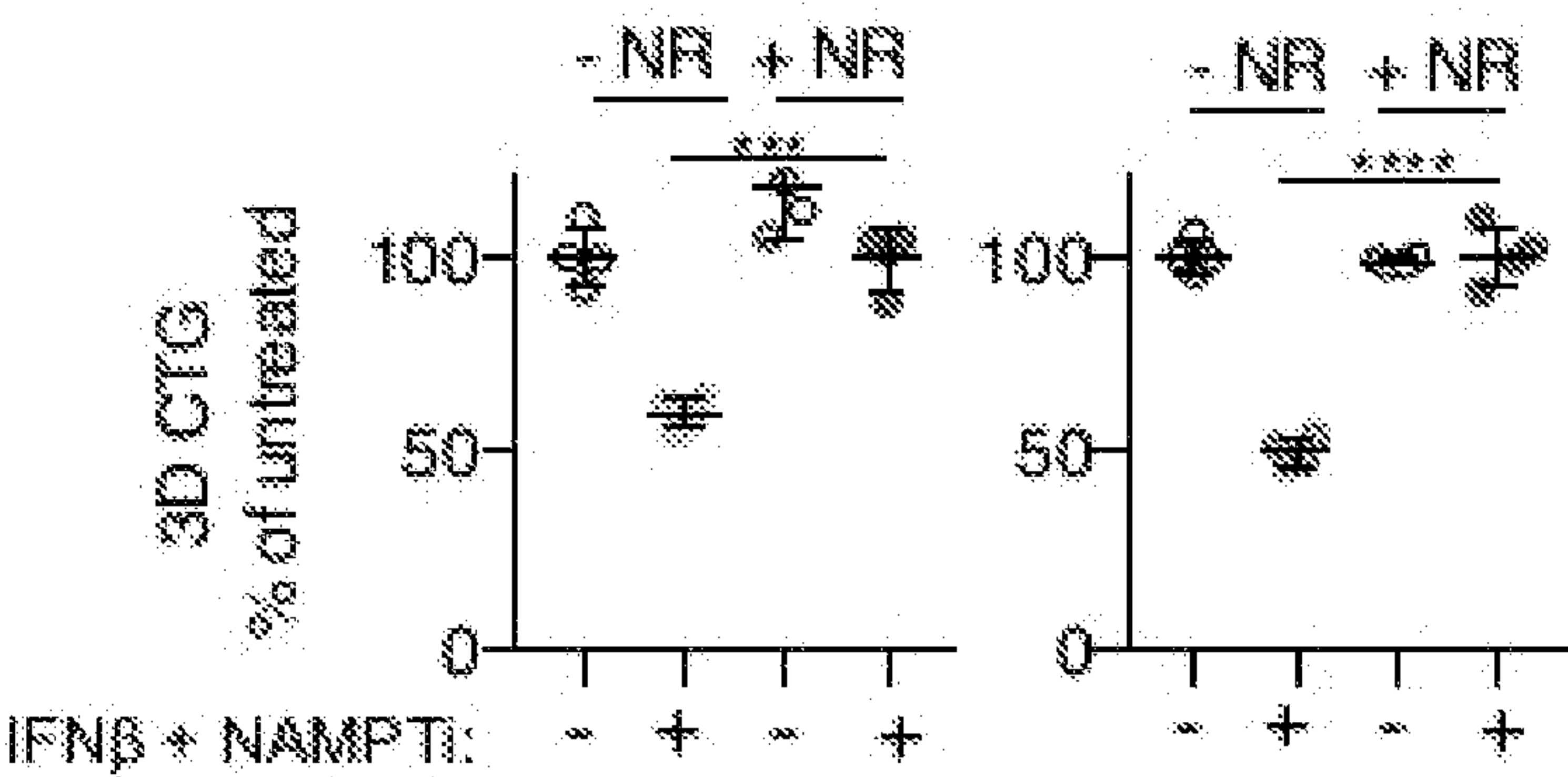


FIG. 28D

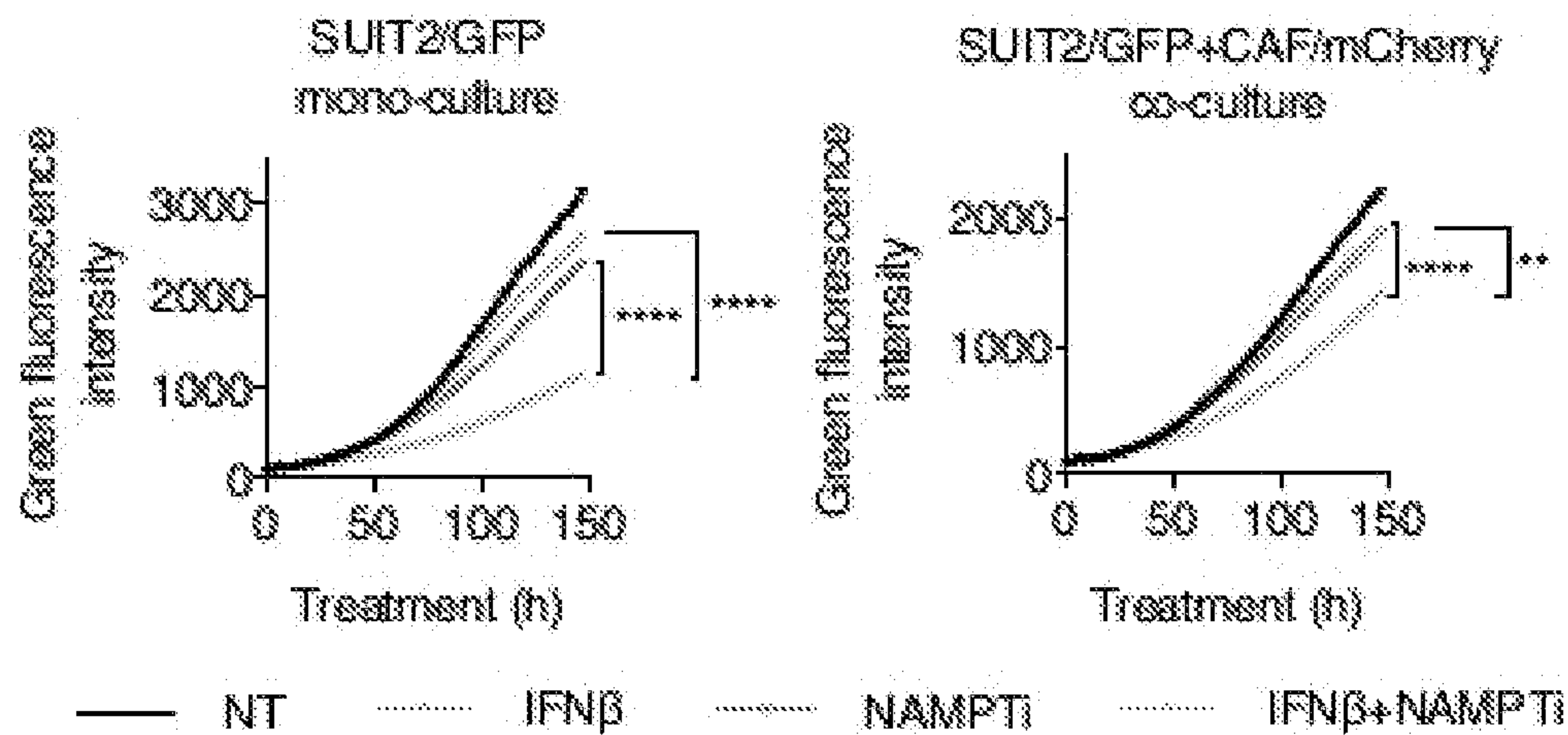


FIG. 28E

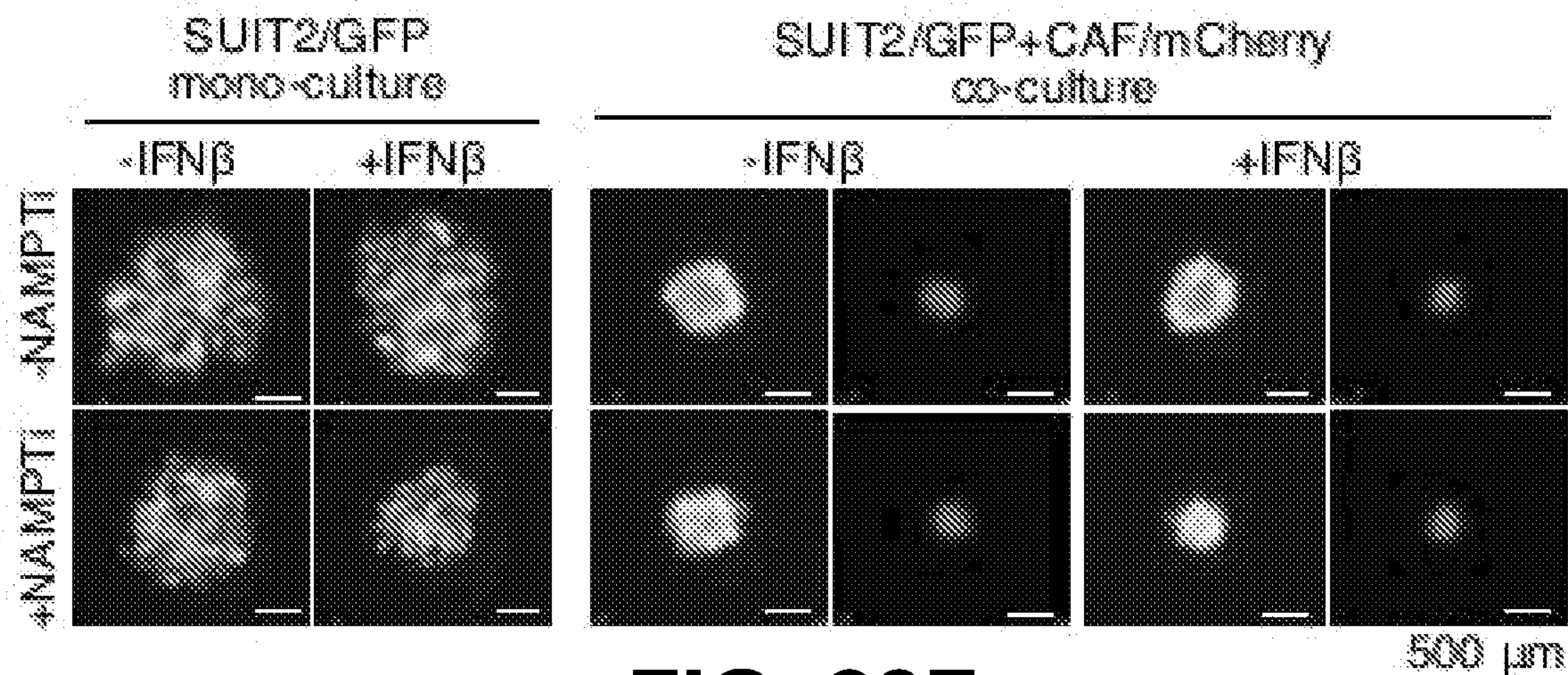


FIG. 28F

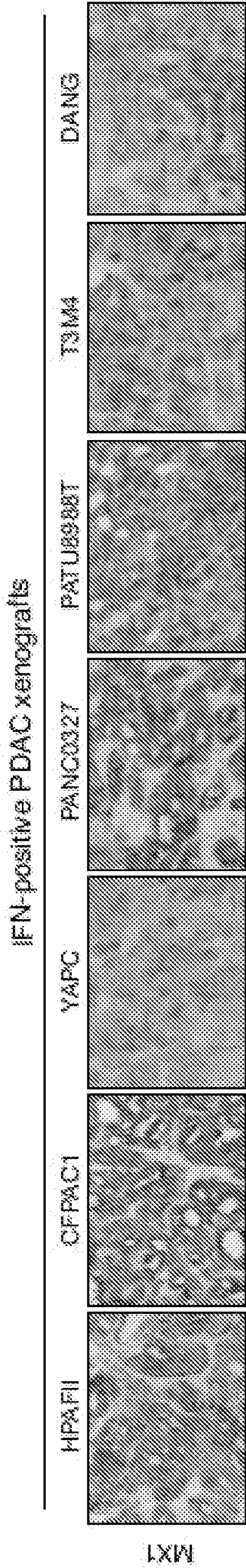


FIG. 29A

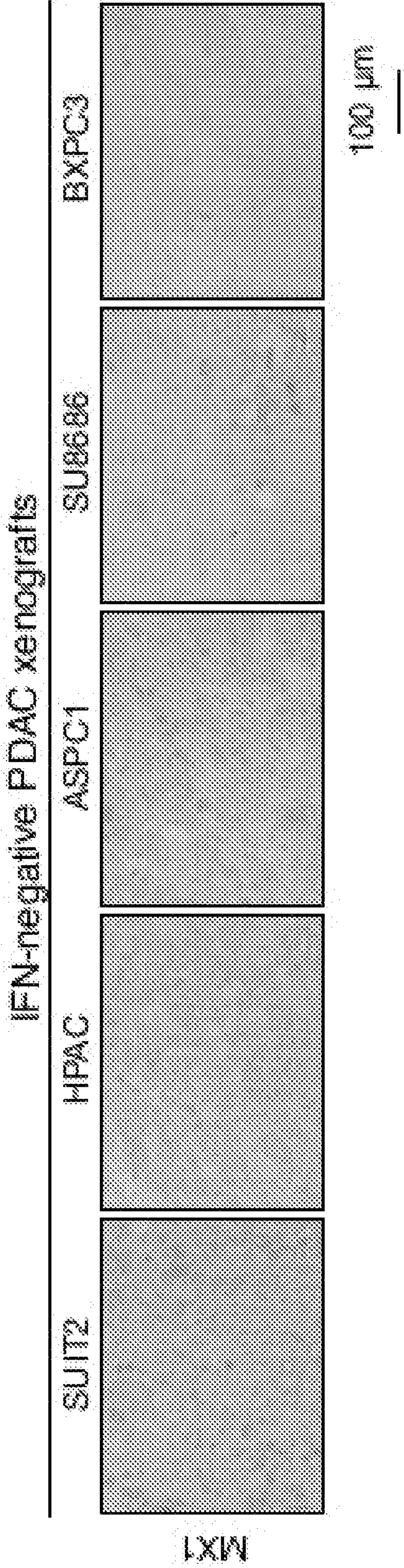


FIG. 29B

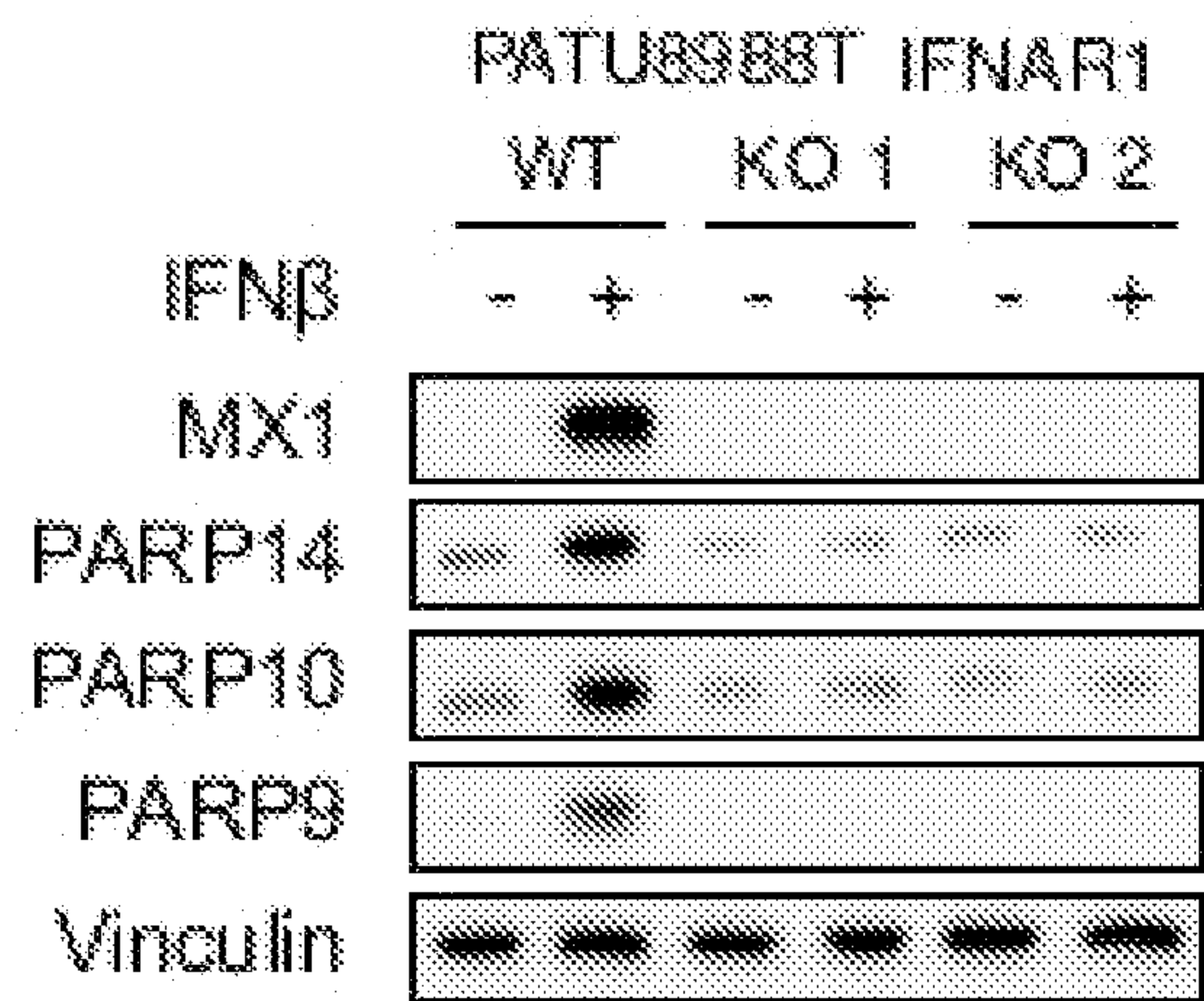


FIG. 29C

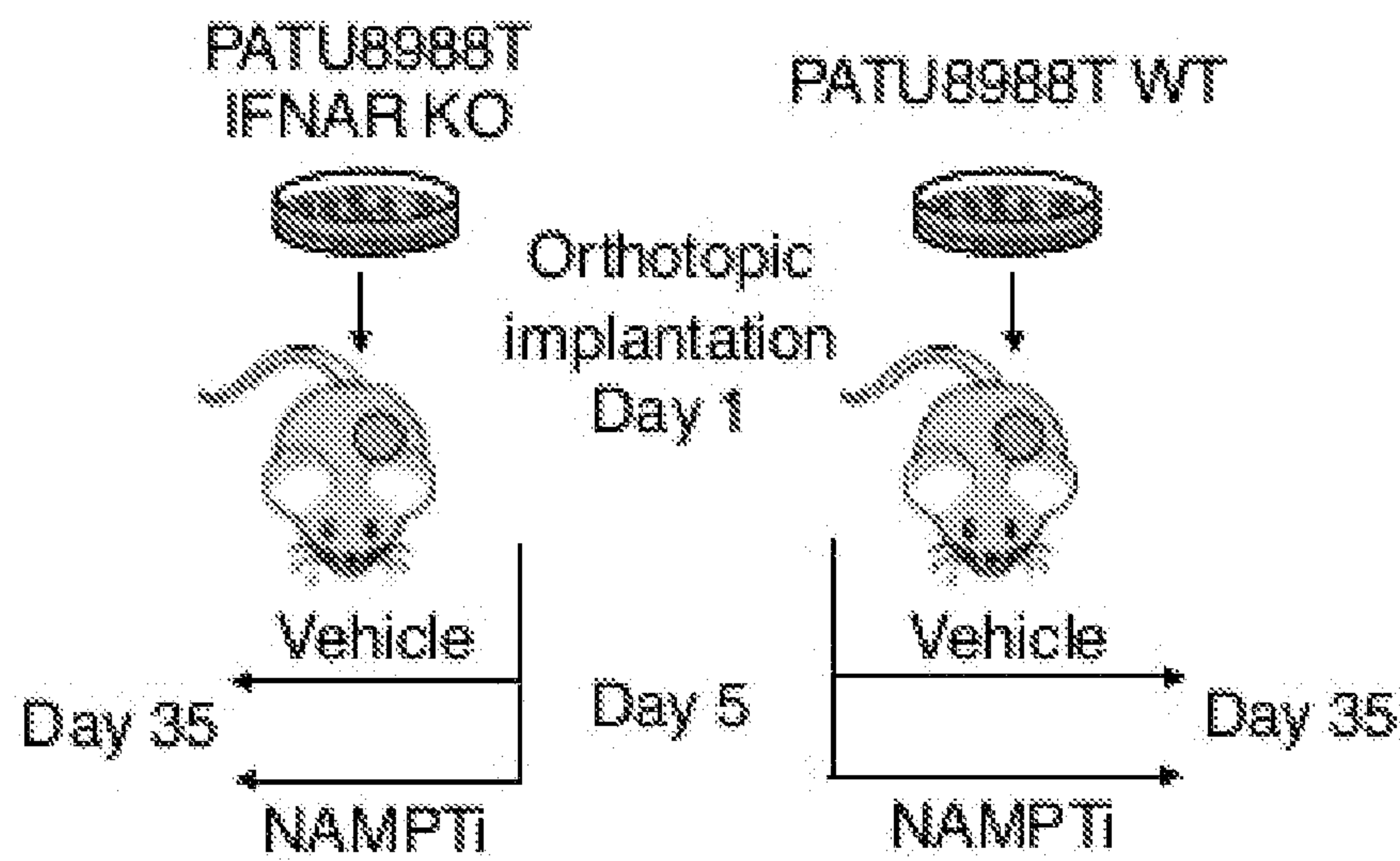


FIG. 29D

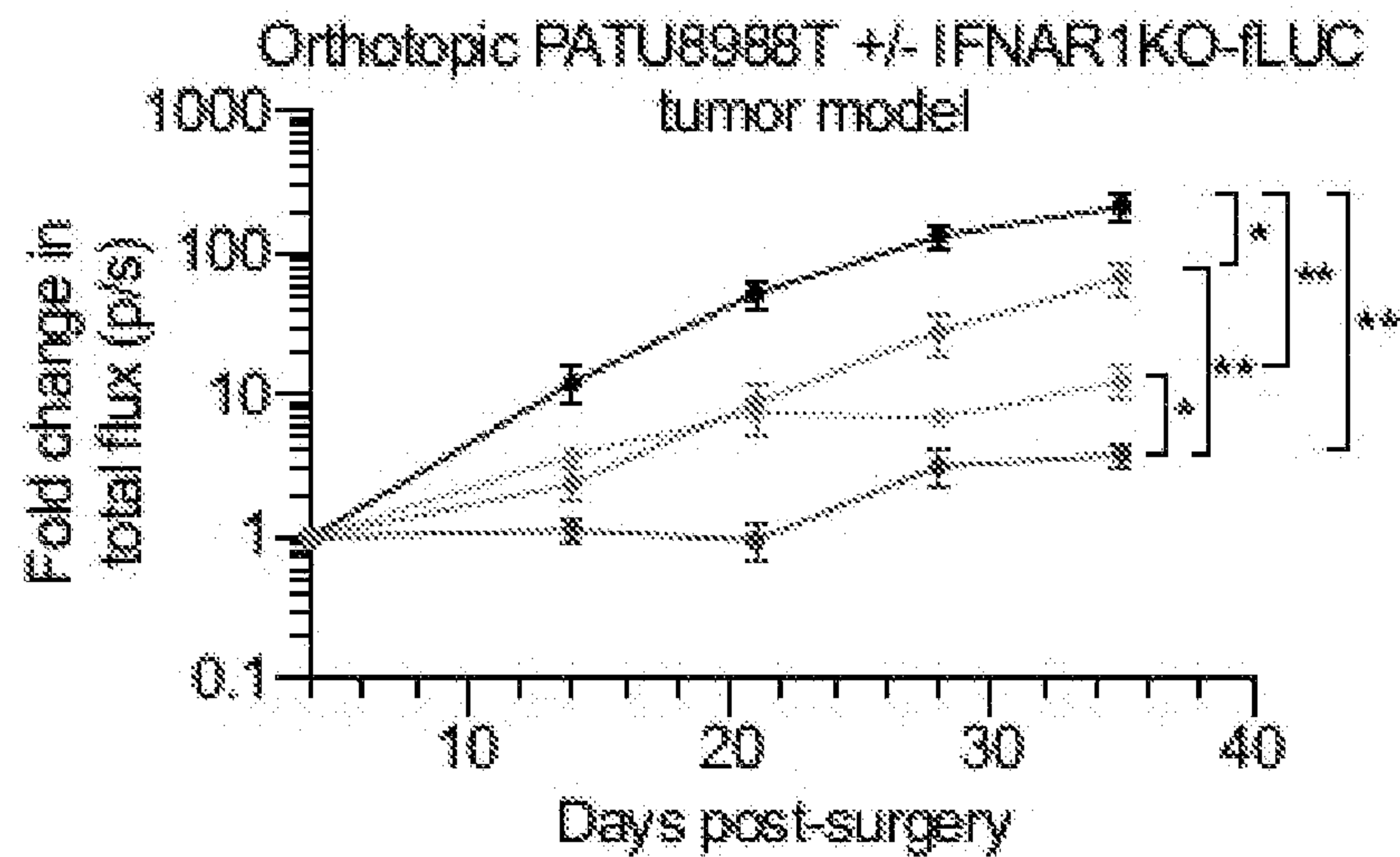


FIG. 29E

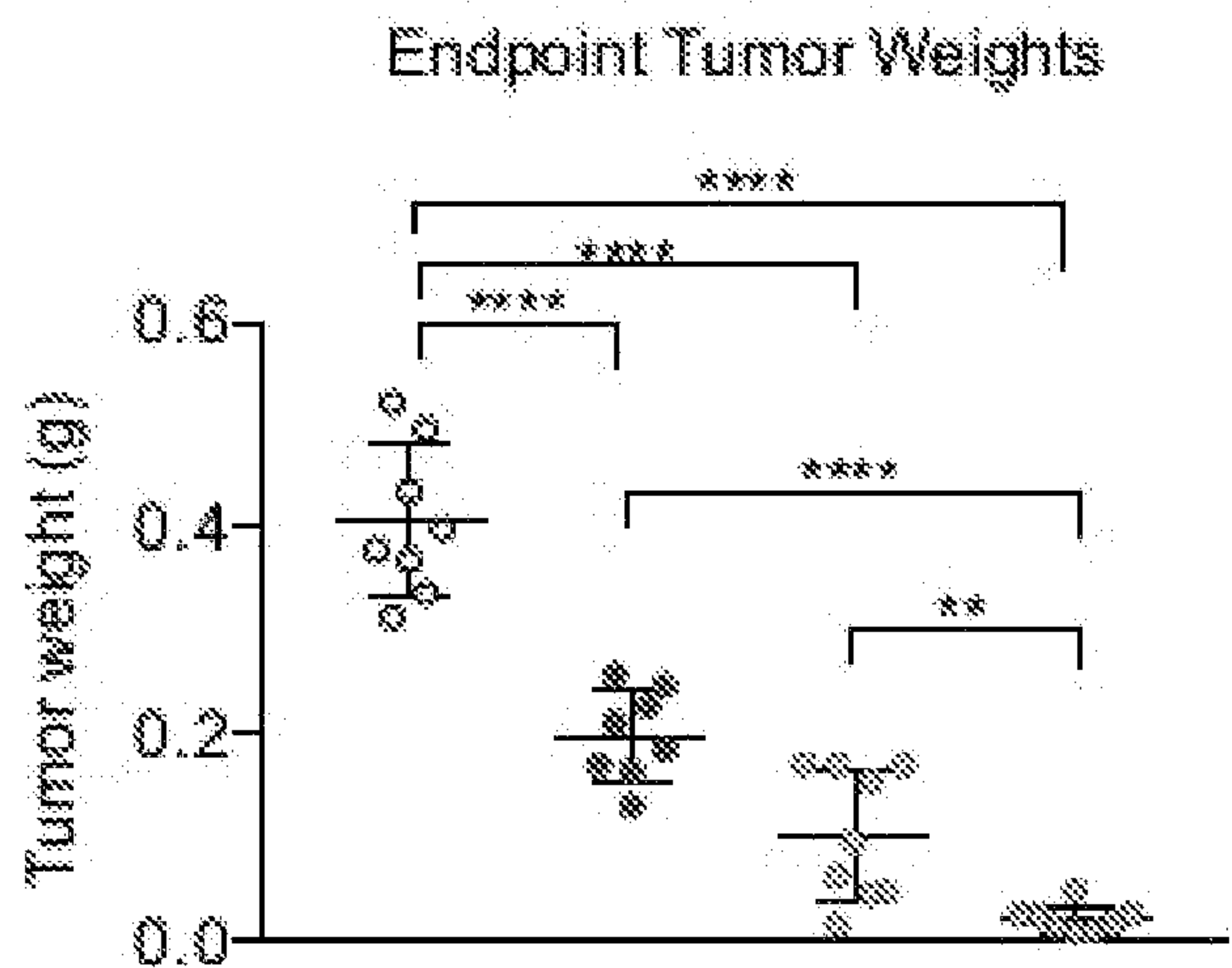


FIG. 29F

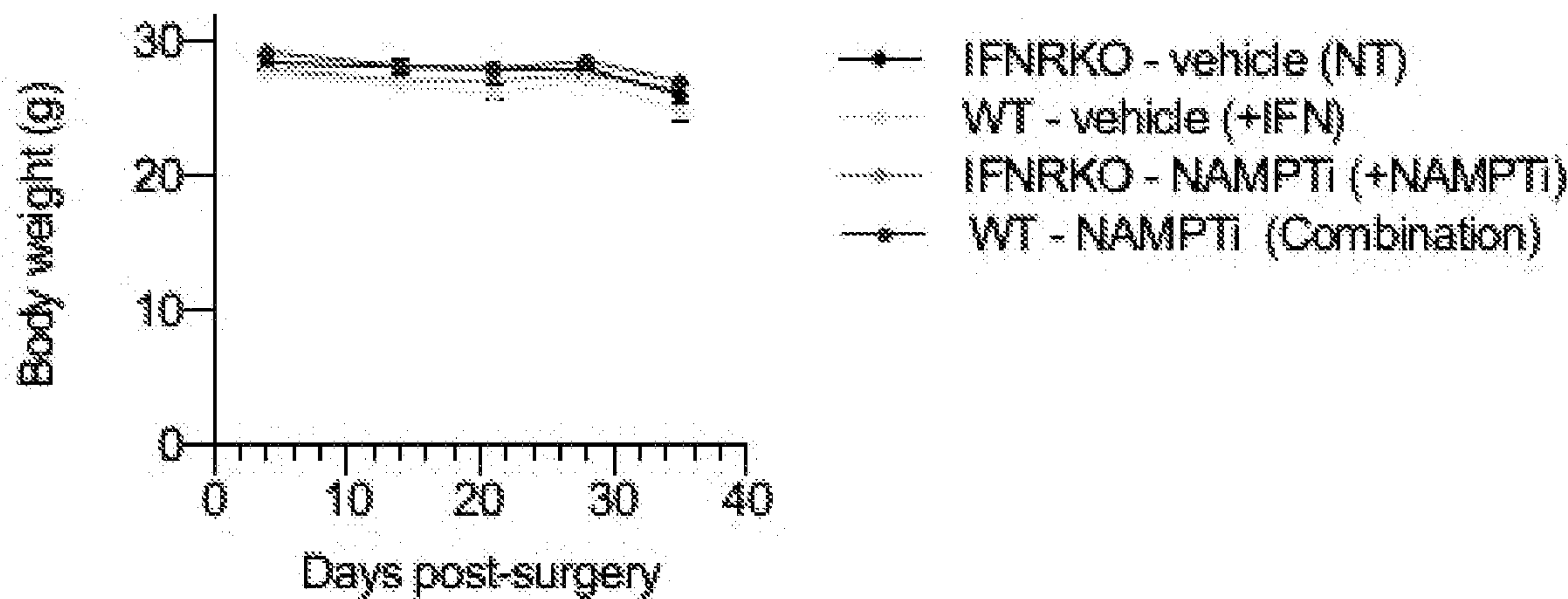


FIG. 29G

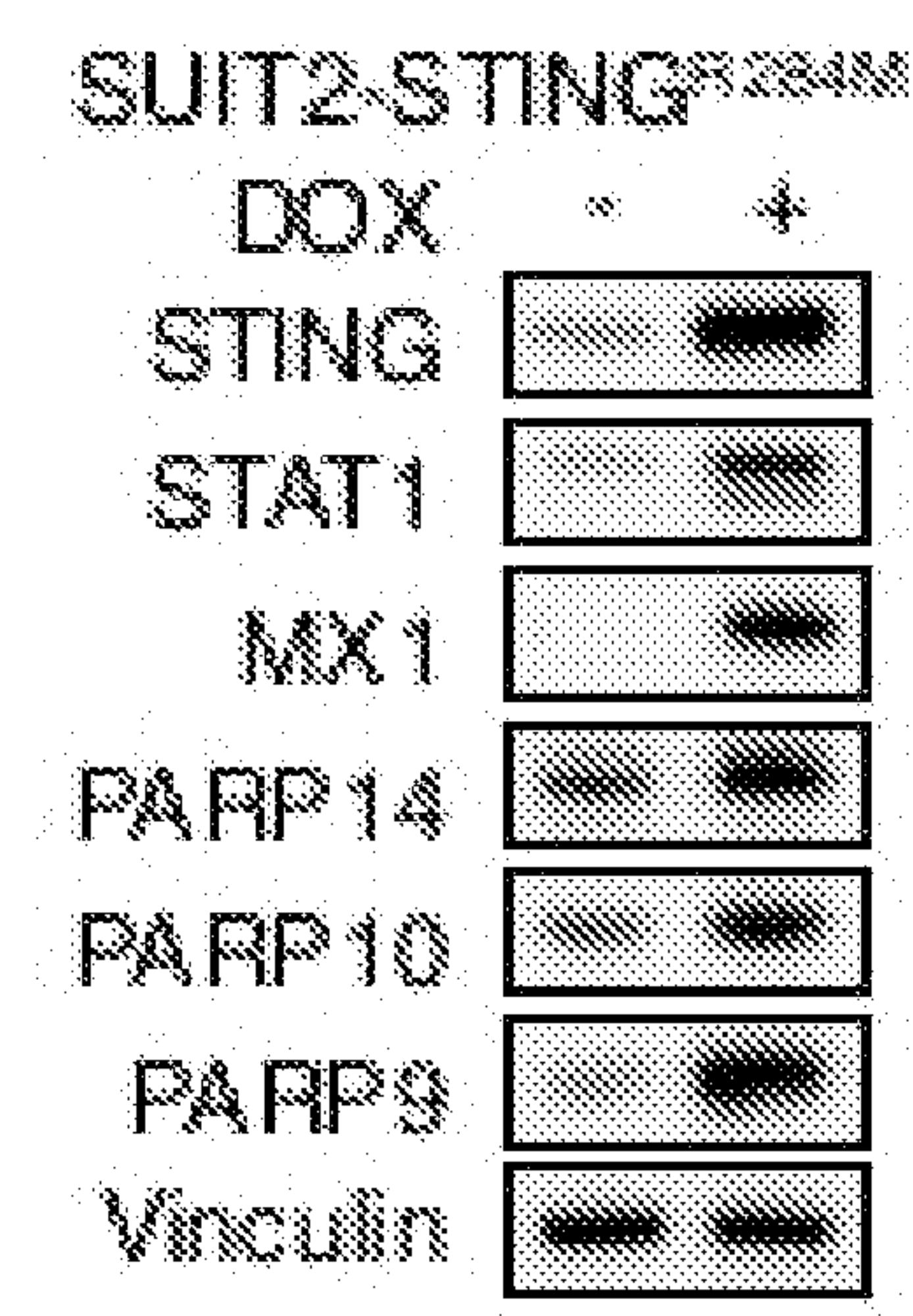


FIG. 30A

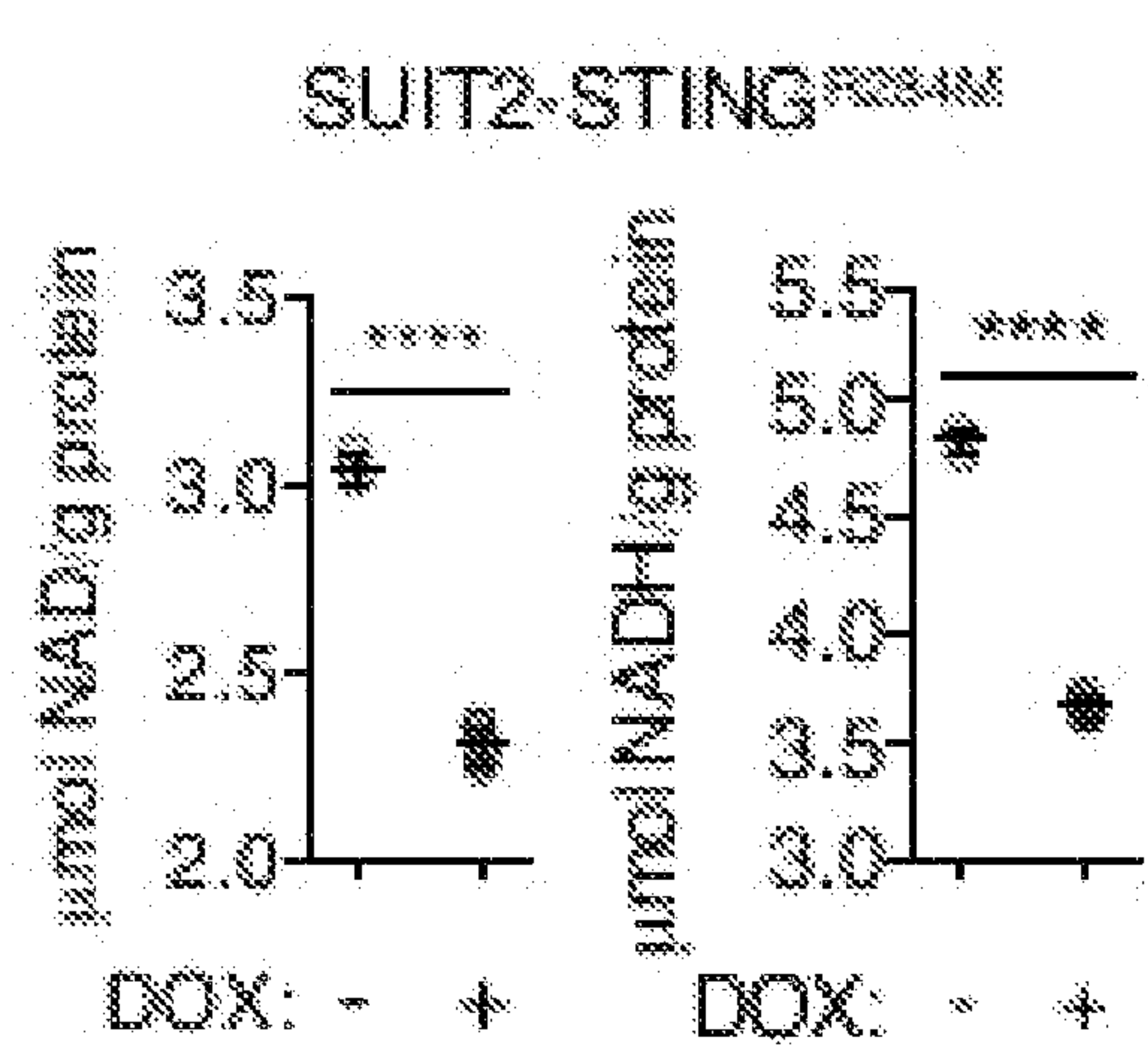


FIG. 30B

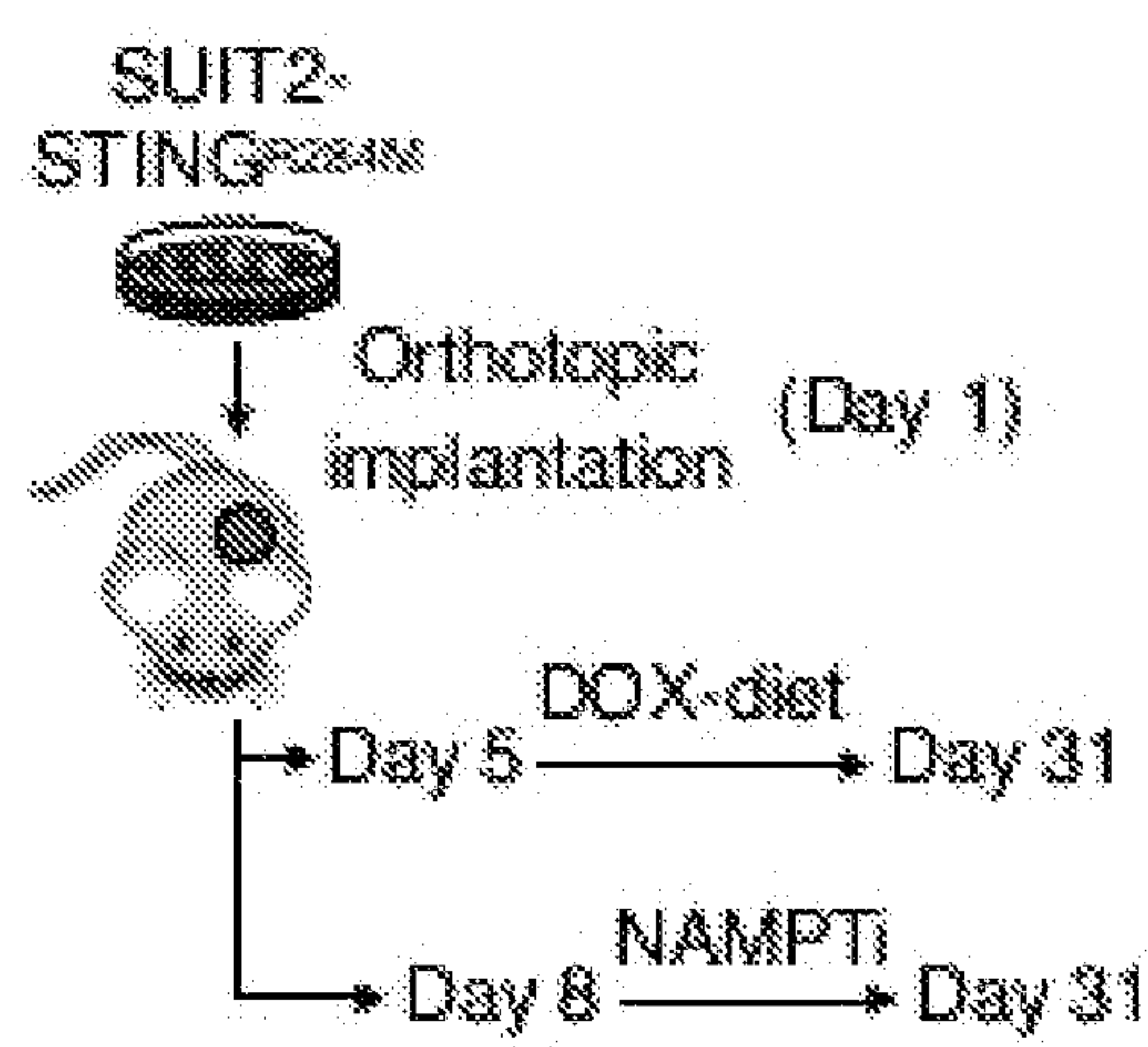


FIG. 30C

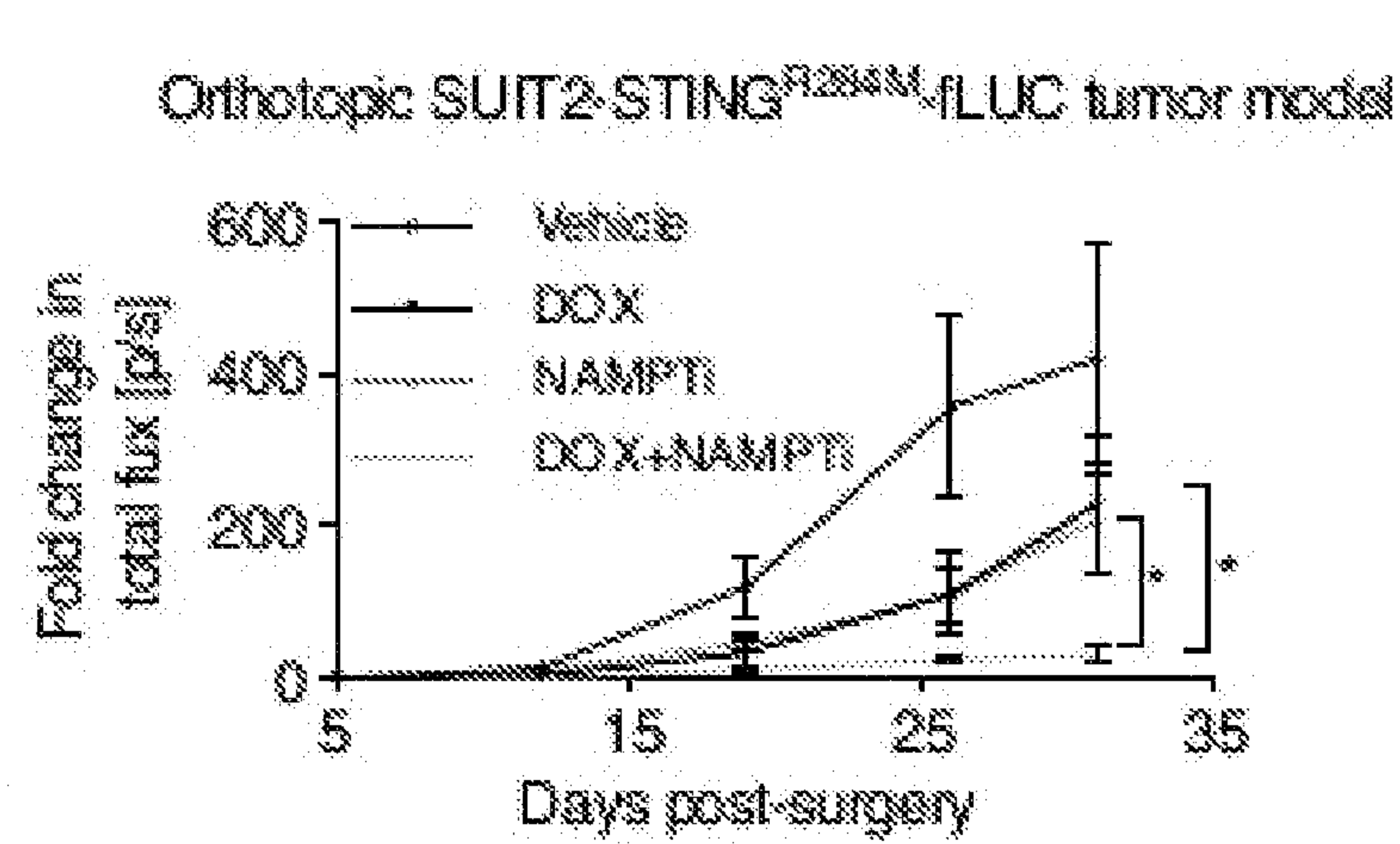


FIG. 30D

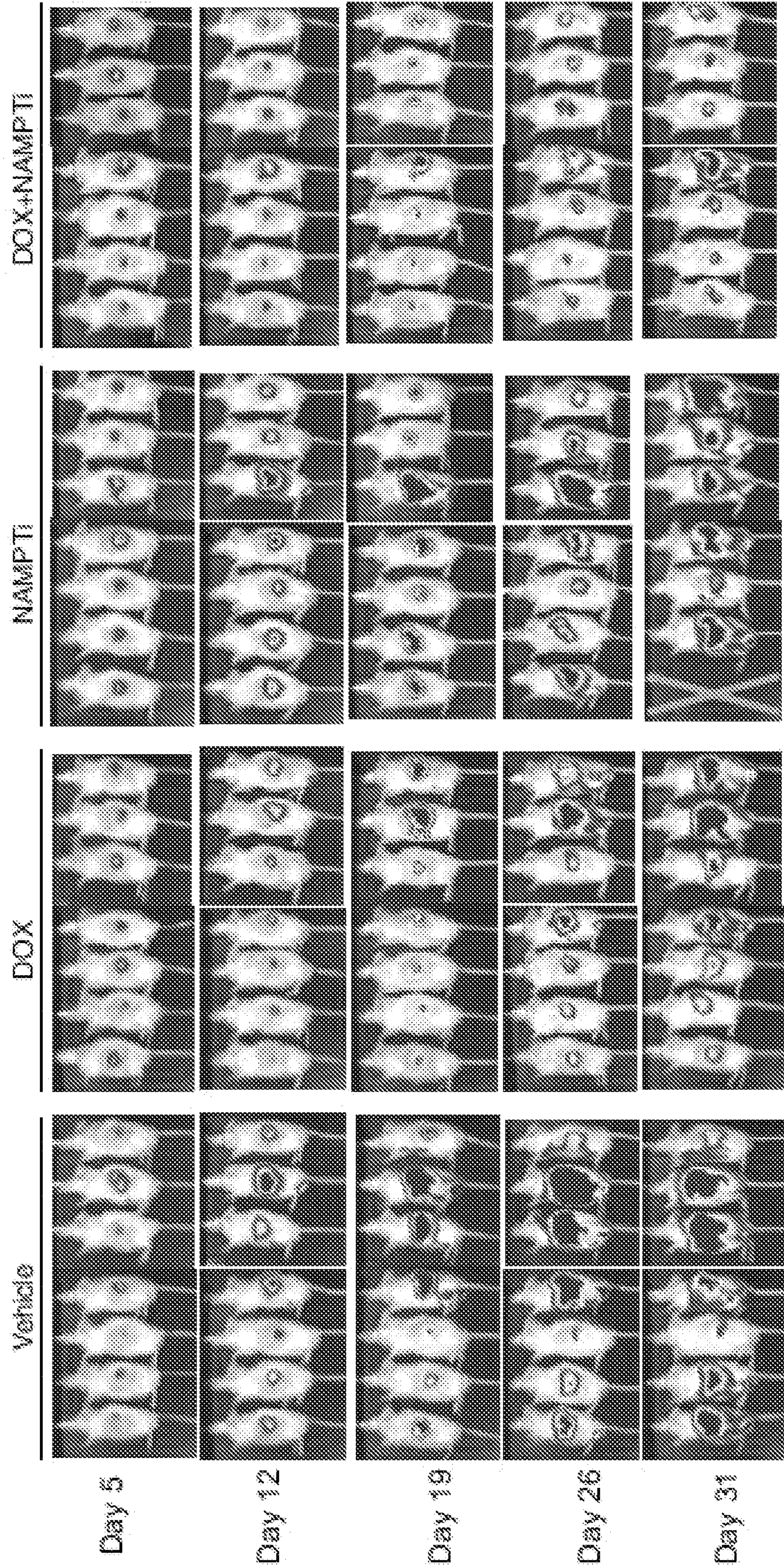


FIG. 30E

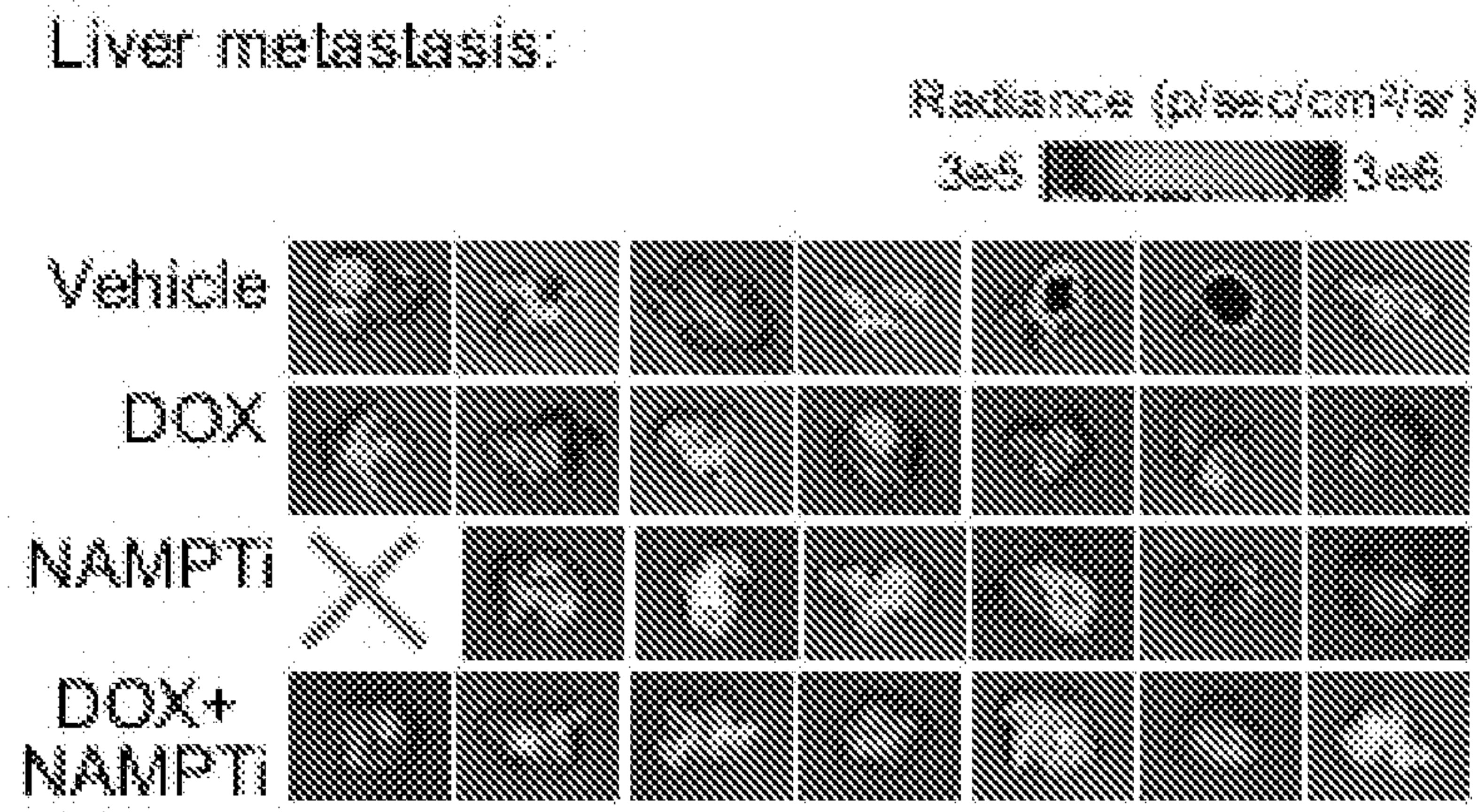


FIG. 30F

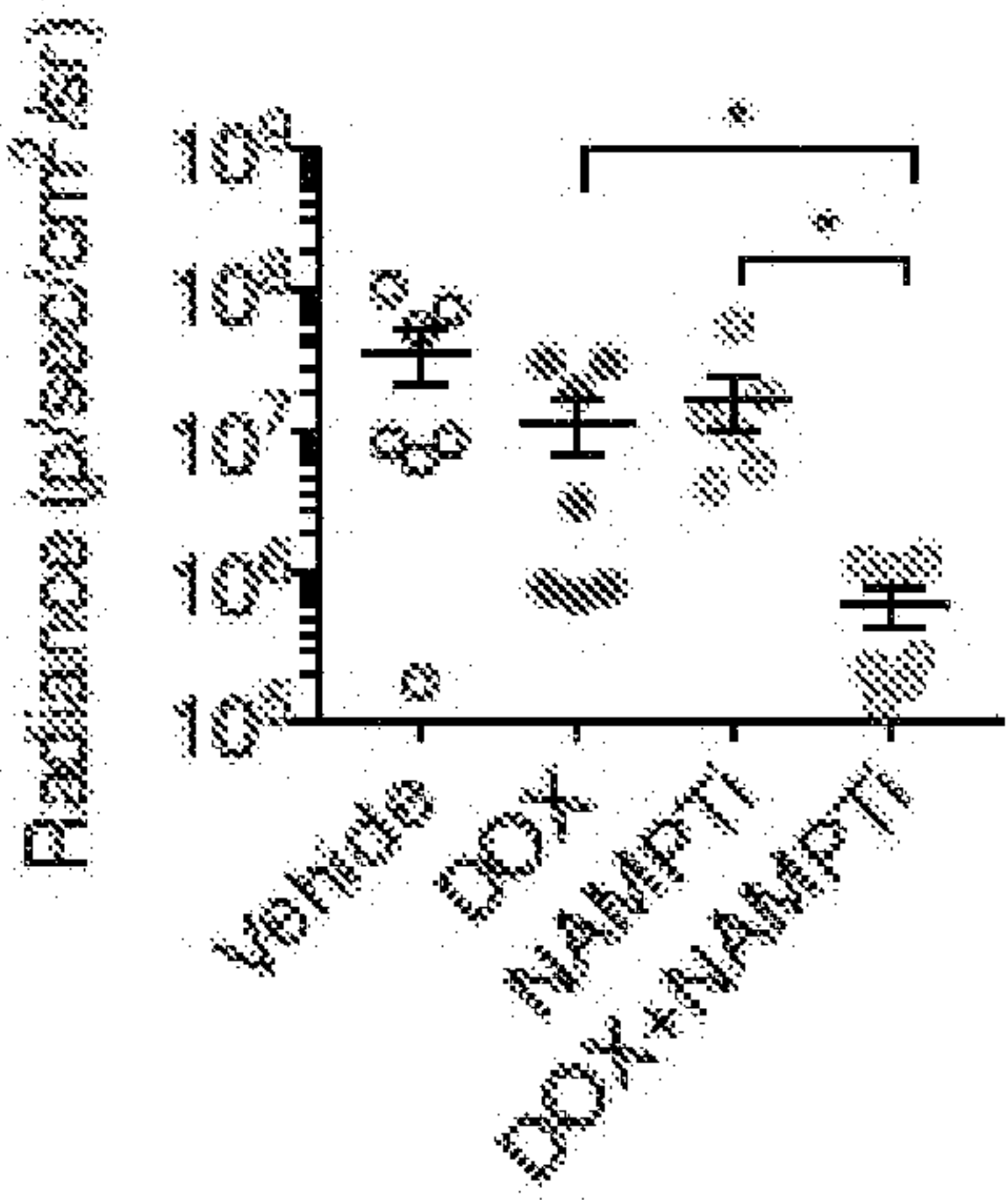


FIG. 30G

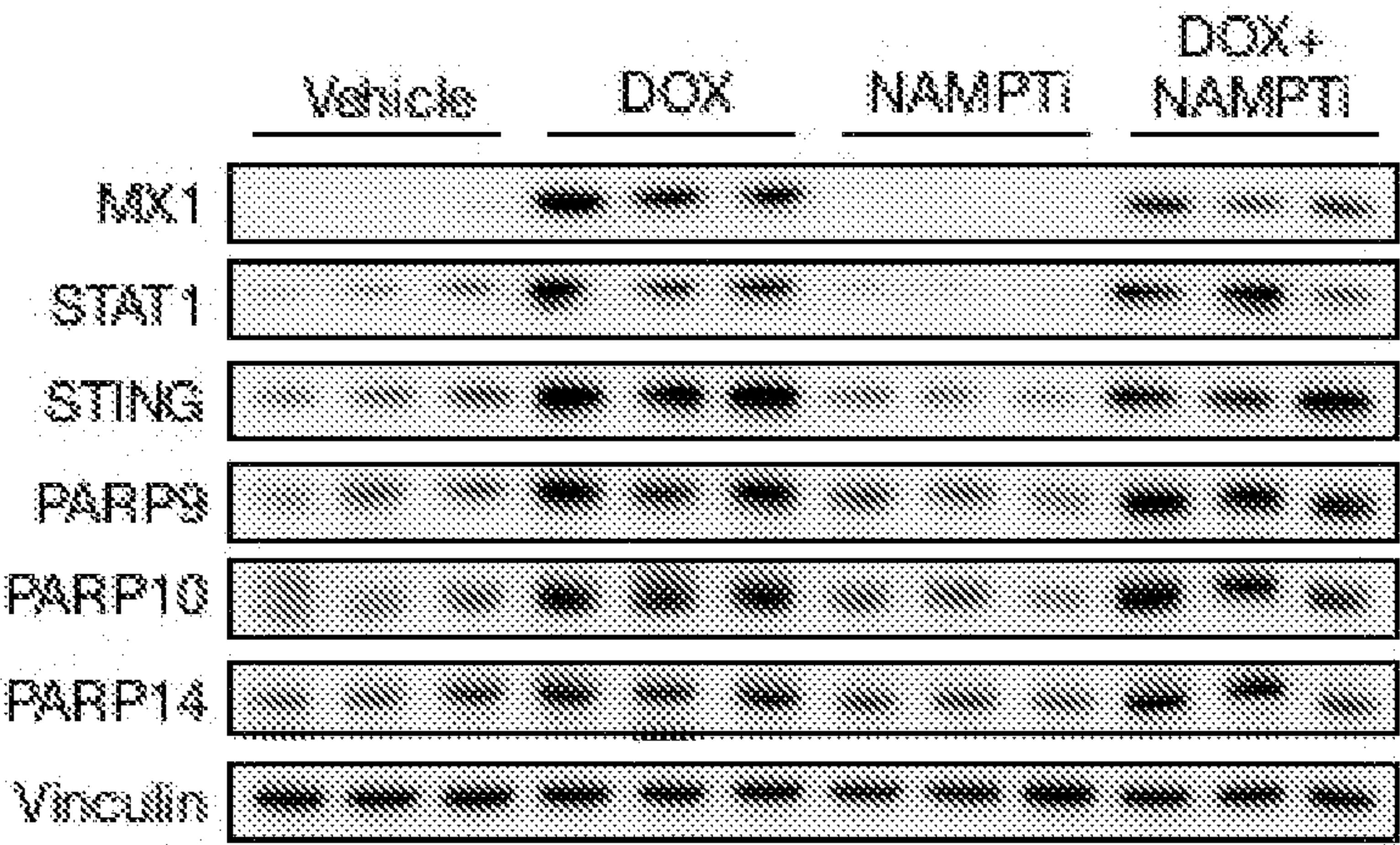


FIG. 30H

	NAMPTi	PDAC model	IC50 (nM)		
			-IFN β	+IFN β	Fold
2D culture	FK866	SW 1990 (cell line)	95.85 $\pm$ 7.71 ¹	47.62 $\pm$ 1.00	2.01
		CFPAC-1 (cell line)	6.78 $\pm$ 0.31	2.80 $\pm$ 0.09	2.43
		Panc 03.27 (cell line)	56.99 $\pm$ 3.45	20.64 $\pm$ 1.23	2.76
		HPAF-II (cell line)	88.47 $\pm$ 3.72	38.83 $\pm$ 2.42	2.28
		PATU 8988T (cell line)	1.66 $\pm$ 0.14	0.89 $\pm$ 0.05	1.85
		DAN-G (cell line)	9.79 $\pm$ 0.63	4.12 $\pm$ 0.54	2.38
		T3M4 (cell line)	96.87 $\pm$ 8.25	42.51 $\pm$ 2.42	2.28
		SUIT2 (cell line)	11.13 $\pm$ 1.22	5.25 $\pm$ 0.19	2.12
		Hs 766T (cell line)	6.32 $\pm$ 0.15	5.86 $\pm$ 0.26	1.08
		A2.4 (primary culture)	6.29 $\pm$ 1.14	2.55 $\pm$ 0.28	2.47
		AM1283 (primary culture)	8.83 $\pm$ 0.42	3.85 $\pm$ 0.29	2.29
	LSN3154567	SW 1990 (cell line)	365.60 $\pm$ 80.61	134.13 $\pm$ 25.11	2.73
		CFPAC-1 (cell line)	152.90 $\pm$ 11.36	61.91 $\pm$ 4.47	2.47
		Panc 03.27 (cell line)	714.97 $\pm$ 18.26	156.23 $\pm$ 1.45	4.58
		HPAF-II (cell line)	1057.67 $\pm$ 81.13	441.20 $\pm$ 21.16	2.40
		PATU 8988T (cell line)	21.71 $\pm$ 0.90	10.99 $\pm$ 0.27	1.97
		DAN-G (cell line)	246.17 $\pm$ 27.94	144.03 $\pm$ 24.56	1.71
		T3M4 (cell line)	632.67 $\pm$ 54.05	380.23 $\pm$ 22.19	1.66
		SUIT2 (cell line)	198.90 $\pm$ 24.04	64.28 $\pm$ 3.92	3.09
		Hs 766T (cell line)	162.30 $\pm$ 18.83	199.37 $\pm$ 9.02	0.81
		A2.4 (primary culture)	163.03 $\pm$ 22.42	31.23 $\pm$ 3.82	5.22
		AM1283 (primary culture)	105.45 $\pm$ 6.97	42.38 $\pm$ 5.10	2.49
3D culture	FK866	Panc 03.27 (cell line)	55.23 $\pm$ 2.05 ¹	15.30 $\pm$ 0.76	3.61
		HPAF-II (cell line)	88.47 $\pm$ 3.72	38.83 $\pm$ 2.42	2.28
		SUIT2 (cell line)	26.89 $\pm$ 1.08	10.88 $\pm$ 0.29	2.47
		A2.4 (primary culture)	50.51 $\pm$ 10.05	4.66 $\pm$ 0.47	10.84
		AM1283 (primary culture)	13.07 $\pm$ 0.74	5.83 $\pm$ 0.30	2.24
	LSN3154567	Panc 03.27 (cell line)	461.47 $\pm$ 25.56	110.30 $\pm$ 9.84	4.18
		HPAF-II (cell line)	1057.67 $\pm$ 81.13	441.20 $\pm$ 21.16	2.40
		SUIT2 (cell line)	254.67 $\pm$ 14.10	104.47 $\pm$ 5.61	2.44
		A2.4 (primary culture)	1886.00 $\pm$ 223.44	117.87 $\pm$ 11.01	16.00
		AM1283 (primary culture)	99.00 $\pm$ 4.18	36.94 $\pm$ 3.55	2.68

FIG. 31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/061827

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 35/00; C12Q 1/6886 (2021.01)
CPC - C12Q 2600/106; C12Q 2600/136; C12Q 2600/142; C12Q 2600/158; G01N 2800/52 (2021.02)

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 data base consulted during the international search (name of data base 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	US 2018/0135134 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 17 May 2018 (17.05.2018) entire document	1, 2, 6-8, 10-12, 17-20, 23, 26, 30, 37-40, 44, 46, 48-50, 52, 55, 59-61, 65, 66
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Y		4, 5, 9, 14-16, 21, 22, 24, 25, 27-29, 31, 34-36, 41-43, 45, 47, 51, 53, 54, 56-58, 62-64, 67-76
X	US 2016/0169901 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 16 June 2016 (16.06.2016) entire document	1, 3, 11, 13, 32, 33
--		
Y		4, 14, 45, 47, 68-70
Y	US 2016/0313300 A1 (CELGENE CORPORATION) 27 October 2016 (27.10.2016) entire document	5, 9, 15, 16, 21, 22, 24, 25, 41-43, 51, 53, 54
Y	WO 2015/104292 A2 (BIOMEDICAL RESEARCH FOUNDATION OF THE ACADEMY OF ATHENS) 16 July 2015 (16.07.2015) entire document	27-29, 62-64
Y	WO 2019/173456 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 12 September 2019 (12.09.2019) entire document	31, 67
Y	WO 2019/165372 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 29 August 2019 (29.08.2019) entire document	34-36, 71-73



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"D" document cited by the applicant in the international application	"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
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"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	

Date of the actual completion of the international search
21 February 2021

Date of mailing of the international search report

MAR 10 2021

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Authorized officer
Blaine R. Copenheaver
Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2020/061827

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2015/0140123 A1 (MERCK PATENT GMBH) 21 May 2015 (21.05.2015) entire document	56-58
Y	US 2019/0153542 A1 (MYRIAD GENETICS, INC.) 23 May 2019 (23.05.2019) entire document	74-76

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2020/061827

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. ☐ forming part of the international application as filed:

☐ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

ISA/225 was mailed on 10 December 2020. The applicant did not, within the prescribed time limit, pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b). Accordingly, ISA/US cannot consider the sequence listing submitted on 05 January 2021.