

Appendix

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Appendix supplementary results

Effects of tazarotene and bexarotene treatment on cell proliferation in MSD and control fibroblasts

MSD fibroblasts (p.Gly247Arg) and control fibroblasts were plated out at day 0 at standard cell quantity (9×10^5 , medium) and additional quantities (4.5×10^5 , low; 13.5×10^5 , high) and grown in presence of 0.1 % DMSO (v/v). Cells were harvested on day 3, 6, and 9, and analysed for cell count, total protein amount and ARSA activity in order to measure effects of cell density on all parameters. In parallel, MSD fibroblasts (p.Gly247Arg) and control fibroblasts were grown under standard conditions (9×10^5 at day 0) treated with 10 μ M tazarotene, 20 μ M bexarotene, and 10/20 μ M tazarotene/bexarotene, respectively. Cells were harvested at the same time points for analysis of the same parameters.

We detected a time dependent significant increase of cell quantity in DMSO only treated MSD fibroblasts compared to day 0 independent of the starting cell quantity. Medium and high cell quantities led to a plateauing increase of cell quantity from day 3 onwards. Cell counts at day 9 were not significantly different in DMSO treated MSD fibroblasts (Appendix Fig. S5A, Appendix Table S3). Control fibroblasts also showed a time dependent significant increase of cell quantity in DMSO only treated independent of the starting cell quantity. The increase plateaued from day 3 onwards for DMSO treated cells plated at medium and high

quantity whereas low quantity cells showed persistent increase of cell number until day 9. Cell counts at day 9 were not significantly different in DMSO treated control fibroblasts (Appendix Fig. S5B, Appendix Table S4) Please note that MSD fibroblasts grew faster than control fibroblasts (Appendix Fig. S5A,B; Appendix Table S3,S4). Treatment with tazarotene, bexarotene and tazarotene/bexarotene, respectively, significantly influenced cell count in both lines with strongest effects in tazarotene/bexarotene treated cells (MSD fibroblasts day 9, DMSO medium: 37.8×10^5 cells, Taz: 24.9×10^5 cells, Bex: 26.3×10^5 cells, Taz/Bex: 20.1×10^5 cells).

Total protein also increased over time in MSD and control fibroblasts under DMSO conditions independent of cell quantity at start. There were no significant differences in total protein amount in DMSO treated MSD fibroblasts at day 6 and 9 and no differences for control fibroblasts from day 3-9 (Appendix Fig. S5C,D; Appendix Table S5). However, under treatment conditions, total protein amounts were significantly reduced in control fibroblasts treated with tazarotene or tazarotene/bexarotene at day 6 and at day 9 compared to DMSO treated cells plated at medium quantity (Appendix Fig. S5D, Appendix Table S6). Interestingly, protein amounts in treated MSD fibroblasts were only significantly reduced at day 6 when treated with tazarotene/bexarotene and compared to DMSO treated cells plated at medium and high quantity. This reduction resolved over time and neither treatment showed significant differences in total protein amount in MSD fibroblasts compared to for DMSO treated cells plated at medium and high quantity (Appendix Fig. S5C, Appendix Table S5).

ARSA activity did not show a time and cell-quantity dependent increase in MSD fibroblasts under DMSO only conditions (Appendix Fig. S5E, Appendix Table S7). However, there was a significant increase of ARSA activity starting at day 3 for tazarotene/bexarotene treated cells compared to DMSO conditions. From day 6 onwards tazarotene treatment led to a significant increase of ARSA activity compared to DMSO conditions. The highest increase

for tazarotene treated cells was 4.5-fold (day 9) and 7.8-fold for tazarotene/bexarotene (day 9), significantly higher than tazarotene treated cells (Appendix Fig. S5E, Appendix Table S7). Interestingly, endogenous ARSA activity was significantly increased at day 6 and 9 between DMSO only treated control fibroblasts plated at low quantity compared to for DMSO treated cells plated at medium and high quantity DMSO medium and high conditions (maximum 1.8-fold increase). Treatment with tazarotene, bexarotene or tazarotene/bexarotene led to no further increase compared to for DMSO treated cells plated at medium quantity conditions (Appendix Fig. S5F, Appendix Table S8).

To validate cell proliferation with a method that does not rely on manual cell counting, we performed XTT assays in control and MSD fibroblasts. Of note, xtt assays are dependent on cellular metabolism, which in turn is influenced by cell count, size and protein amount. 6-day treatment with tazarotene, bexarotene, and tazarotene/bexarotene resulted in reduced cell proliferation of control fibroblasts when compared to cells treated with DMSO only. Changes in treated MSD fibroblasts were not significantly different (Appendix Fig. S6 A,C). Treatment with different concentrations of tazarotene/bexarotene for 6 days showed significantly reduced cell proliferation compared to DMSO treatment starting at 1/2 μ M tazarotene/bexarotene in control fibroblasts (minimal proliferation 65% of DMSO control at 5/10 μ M tazarotene/bexarotene). Again, no significant differences appeared in MSD primary fibroblasts (Appendix Fig. S6 B,D).

Adapalene increases transcription of retinoid target genes via RAR receptors without increasing sulfatase activities in MSD primary fibroblast cell lines

To identify a retinoid that worked on MSD cells but did not increase sulfatase activities we treated primary MSD fibroblasts (p.Gly247Arg) with a selection of retinoids representing generations of pharmacological development (1st generation tretinoin, 2nd generation

acitretin, 3rd generation adapalene) for six days at concentrations of 10 μ M (adapalene 5 μ M) and analysed three different sulfatase activities (ARSA, GALNS, STS). Tazarotene treatment (10 μ M) served as positive control, DMSO treated cells as negative control. Neither retinoid was able to increase ARSA, GALNS, or STS activities (Appendix Fig. S7A). Next, we used the same retinoids and treatment conditions to analyse gene expression of retinoid targets by RT-PCR to prove that the selected retinoids entered treated cells and were effective without increasing sulfatase activities. Tretinoin, acitretin, and adapalene were all able to increase *RARB*, *CYP26B1*, and *RARRES1-3* gene expression compared to untreated controls. Significant differences of gene expression were seen for *CYP26B1* and *RARRES3* that was highest upon tazarotene treatment. *RARB*, *RARRES1* and *RARRES2* showed increased but no significantly different gene expression regardless of the retinoid used (Appendix Fig. S7B). Based on the results we chose to use adapalene, which belongs to the same pharmacological group of retinoid development like tazarotene and bexarotene (3rd generation retinoids), as a control retinoid for further experiments. Next, we wanted to rule out that we have missed the right dose for an effect on sulfatase activities in MSD fibroblasts and treated cells with four different concentrations of adapalene (1, 5, 10, 20 μ M) for six days. Again, tazarotene treatment served as control. Neither ARSA nor GALNS activity increase could be detected at either concentration used (appendix figure S8A). Gene expression analysis of retinoid targets upon treatment with increasing concentrations showed increased expression levels at all four adapalene concentrations compared to DMSO conditions but significantly reduced expression levels at 20 μ M concentration compared to lower concentrations likely because of visual adapalene toxicity on cells. *RARRES3* showed a trend towards differences only (Appendix Fig. S8B). Based on these results we chose a submaximal concentration of adapalene (5 μ M) for further experiments to avoid toxicity. Treatment of eight different MSD fibroblast lines with adapalene showed no ARSA activity increase regardless of the *SUMF1* mutation (Appendix Fig. S8C thereby ruling out mutation specific differences. A refined dose-

concentration analysis with adapalene treatment of MSD fibroblasts with concentrations starting as low as 100 nM and up to 20 μ M for six days still excluded any ARSA activity increase (Appendix Fig. S8D). Finally, we pretreated cells for 24 hours with the pan-RAR antagonist AGN193109 followed by 72 hours of simultaneous treatment with adapalene (control: tazarotene). Incubation with AGN193109 abrogated both adapalene and tazarotene induced retinoid target gene expression in MSD fibroblasts (Appendix Fig. S9) thereby proving that adapalene, like tazarotene, increased retinoid target gene expression in MSD fibroblasts via RAR receptors.

Tazarotene/bexarotene treatment did not change endogenous PDI protein expression but decreased PDI-mediated inhibition of FGE variants residual activity

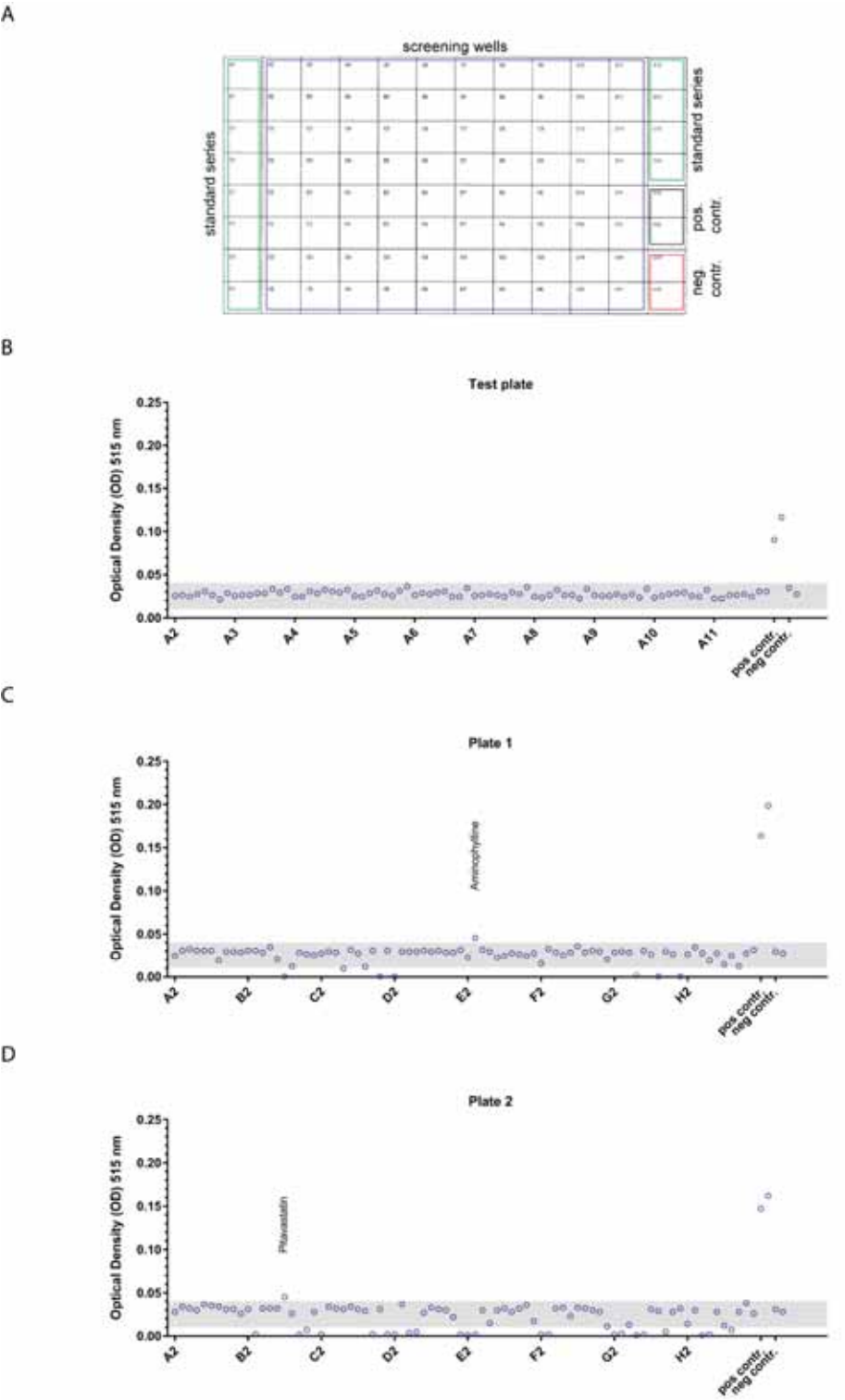
PDI has been described as a pivotal interacting partner of FGE-variants with impact on residual FGE and dependent sulfatase activities by binding to misfolded FGE variants and referring them to early degradation (Schlotawa *et al.*, 2018). In order to see if tazarotene/bexarotene treatment reduces PDI expression resulting in less FGE variant binding and increased FGE activity we analysed three different MSD primary fibroblast lines treated with either DMSO or tazarotene/bexarotene treatment for six days and one control fibroblast line by western blot. No differences could be detected thereby ruling out an effect of tazarotene/bexarotene on PDI expression (Appendix Fig. S12).

To further analyse how PDI interaction with FGE variants changes upon tazarotene/bexarotene treatment we repeated an experiment from our previous publication (Schlotawa *et al.*, 2018). We were aiming to see differences on the activation of steroid sulfatase (STS) by FGE-Ser155Pro variant with and without PDI co-expression and treatment of cells with either DMSO (vehicle control) or tazarotene/bexarotene (Appendix Fig. S13A,B). As compared to DMSO treated cells, tazarotene/bexarotene consistently led to an

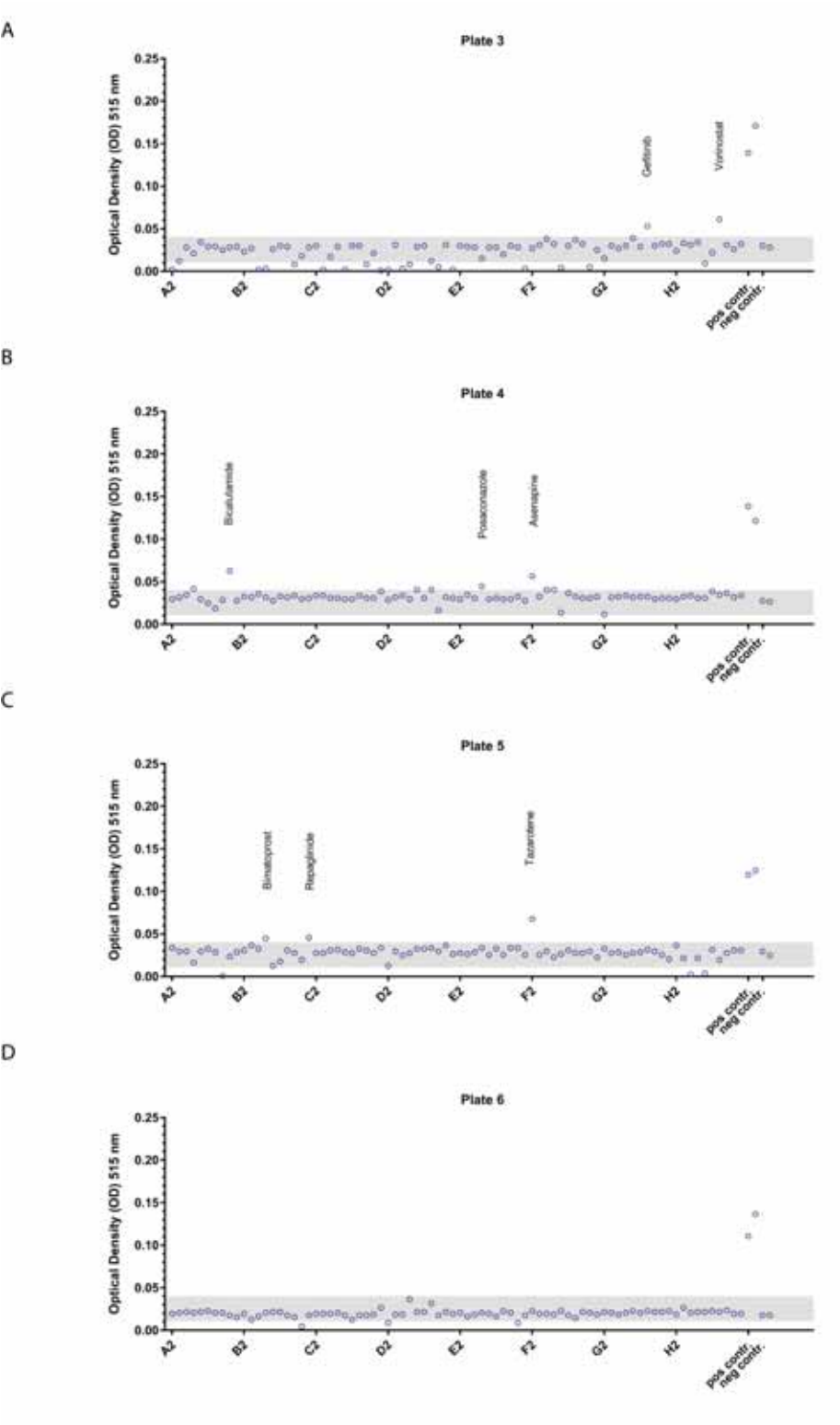
increase in STS activity with and without FGE or FGE-variant co-expression. When compared to respective DMSO controls, in FGE-Ser155Pro alone expressing cells, tazarotene/bexarotene treatment led to an approx. 4.5-fold increase in activity while co-expression of PDI in drug treated cells led to a 7.5-fold increase (Appendix Fig. S13C). However, note that, this apparent increase in activity upon PDI co-expression in drug treated cells is due to the decrease in activity of FGE-Ser155Pro when PDI is co-expressed in DMSO treated cells. In DMSO treated cells, co-expression of PDI and FGE-Ser155Pro led to a 3-fold loss of Ser155Pro variants activity, in agreement to our previous work. Such a loss in activity is also observed in drug treated cells, however, only to 2-fold (Appendix Figure S13D). This indicates that co-expression of PDI has a minor effect on prohibiting FGE-Ser155Pro induced STS activation when cells are treated with tazarotene/bexarotene compared to DMSO treated cells. Supported by our data that tazarotene/bexarotene treatment improves the intracellular stability of FGE variants (Fig. 4), we think that it is plausible that tazarotene/bexarotene treatment reduces the proportion of misfolded FGE variants that bind to PDI and increase the proportion able to escape PDI recognition due to improved folding. This results in increased FGE functionality and the observed increase in sulfatase activities upon tazarotene/bexarotene treatment.

Appendix supplementary figures

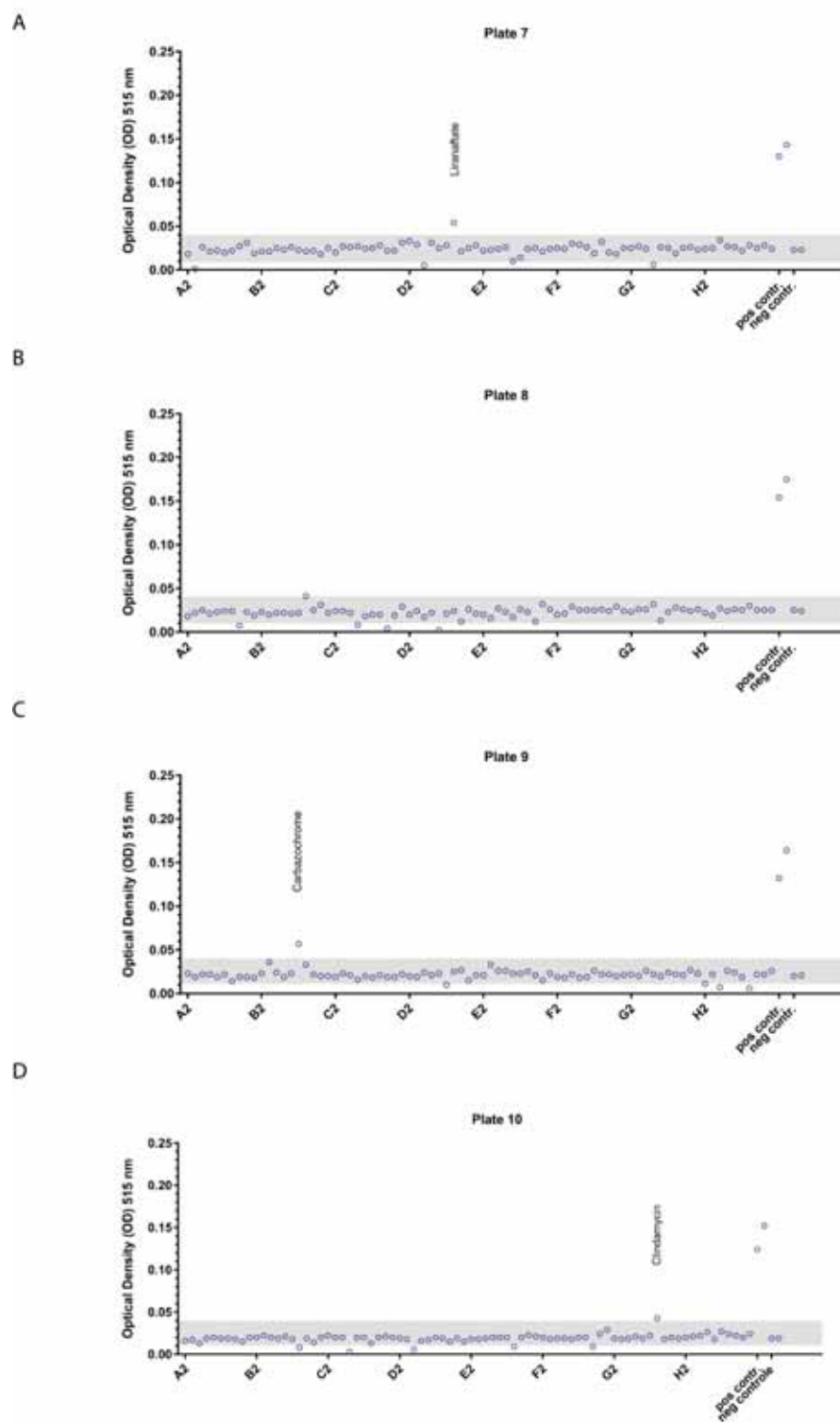
Appendix figure S1



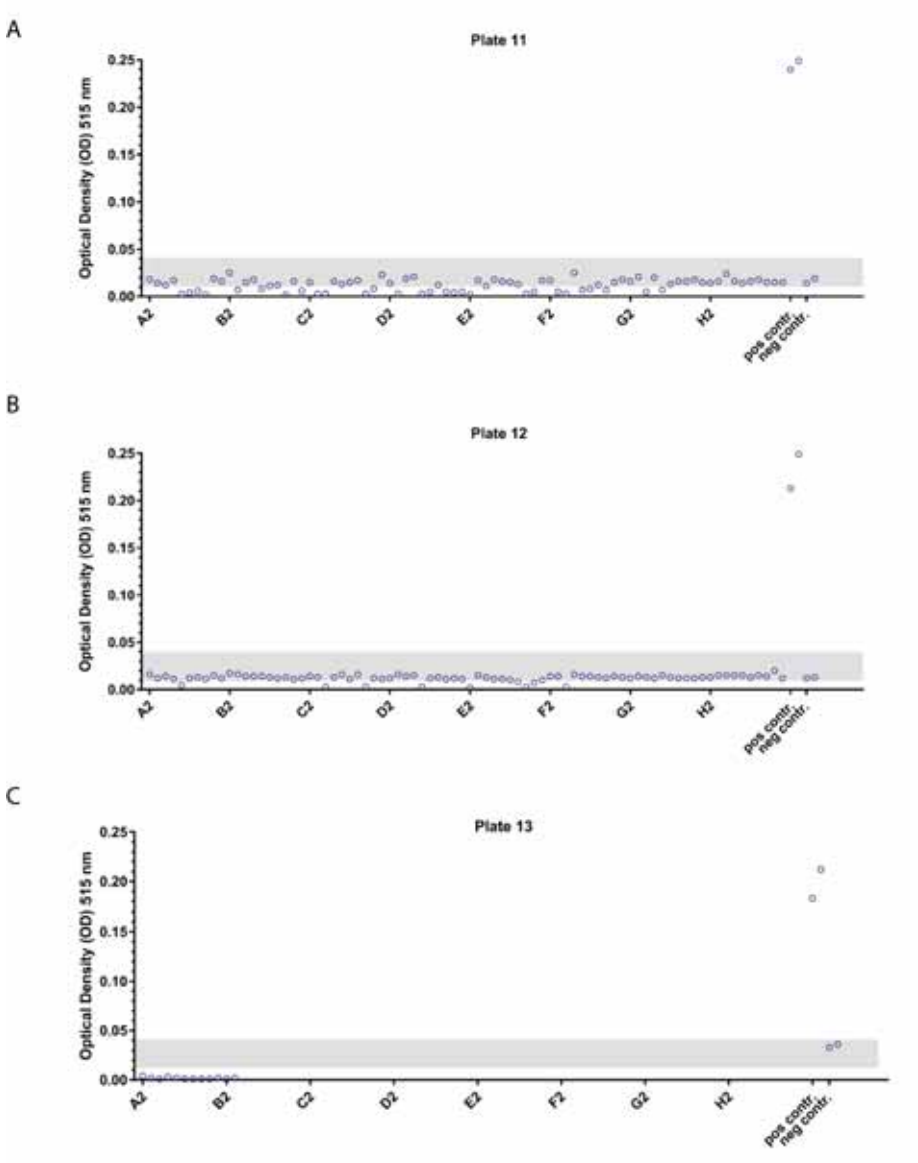
Appendix figure S2



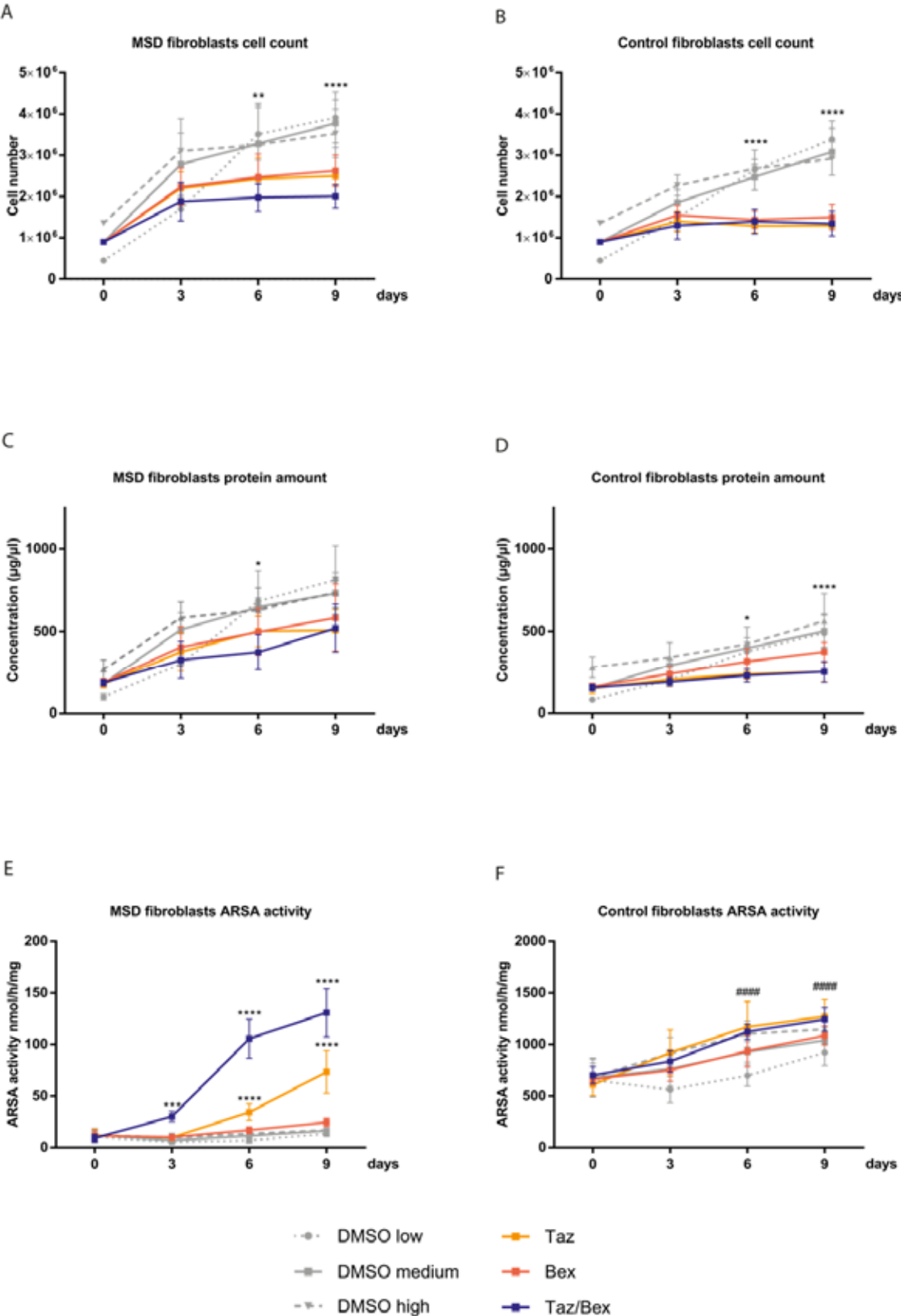
Appendix figure S3



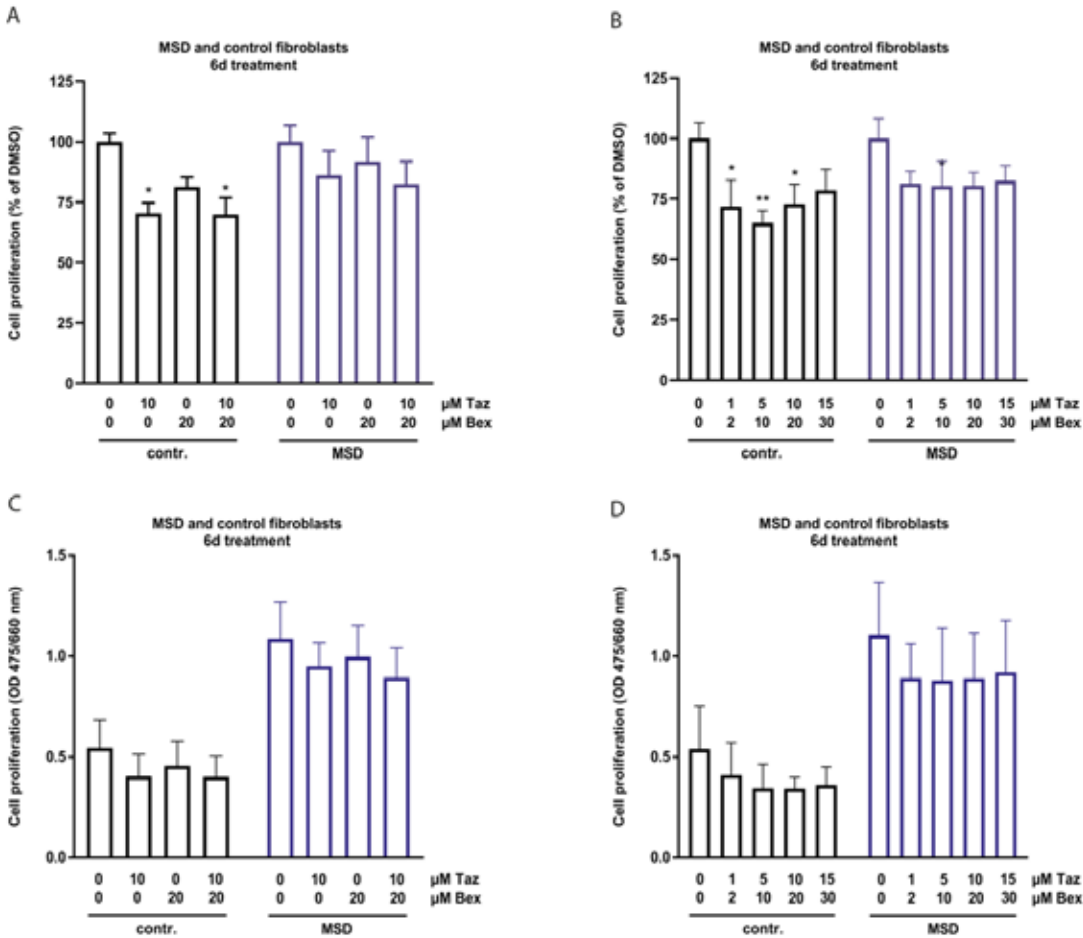
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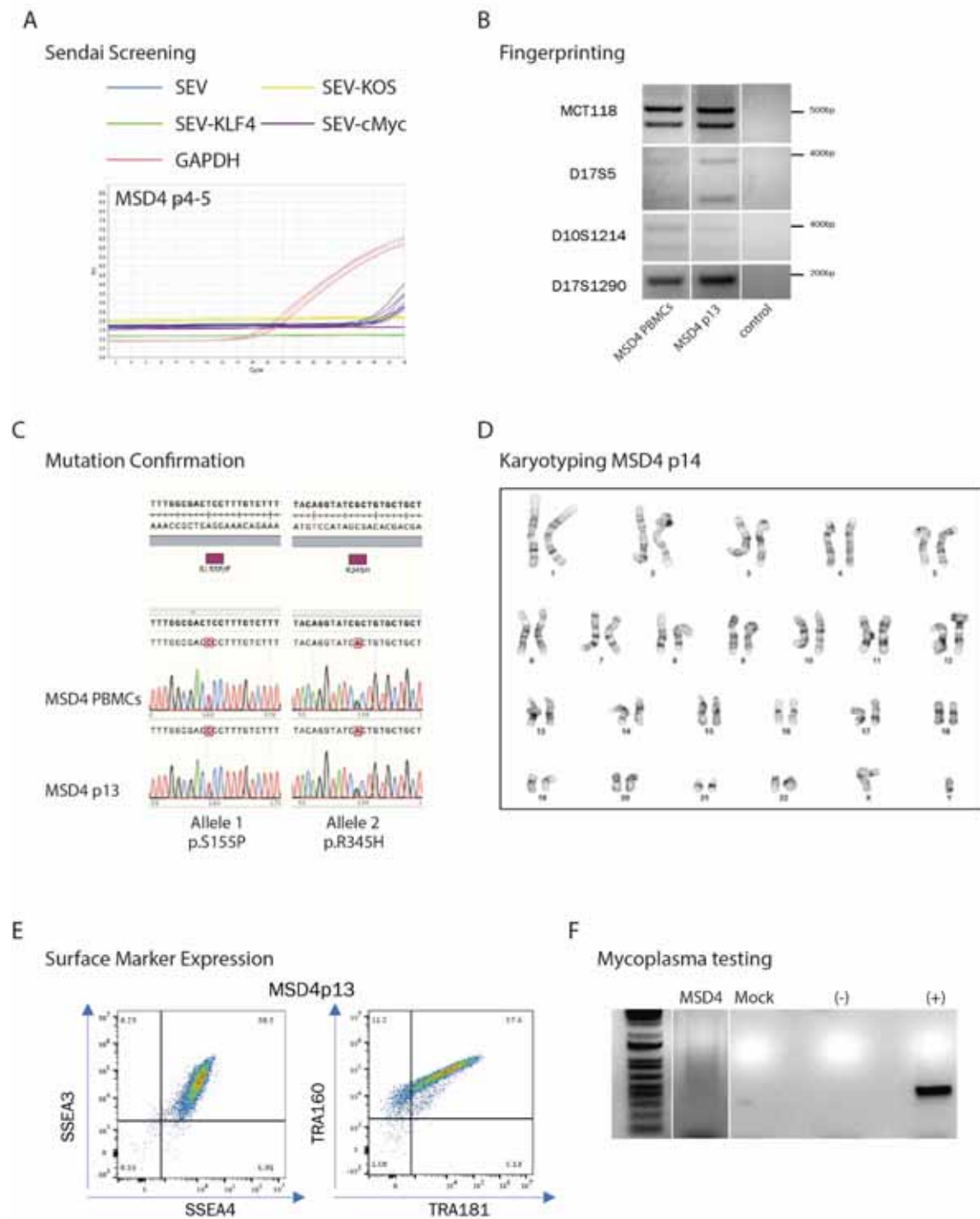
Appendix figure S5



Appendix figure S6

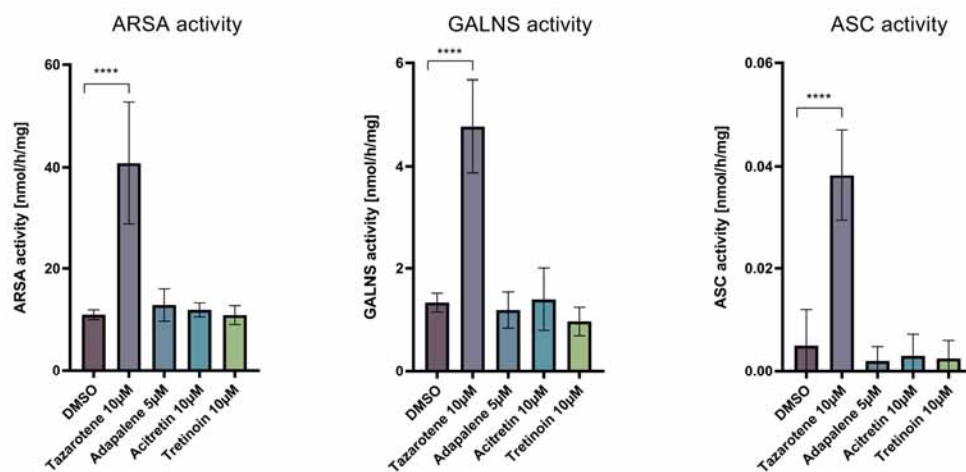


Appendix figure S7

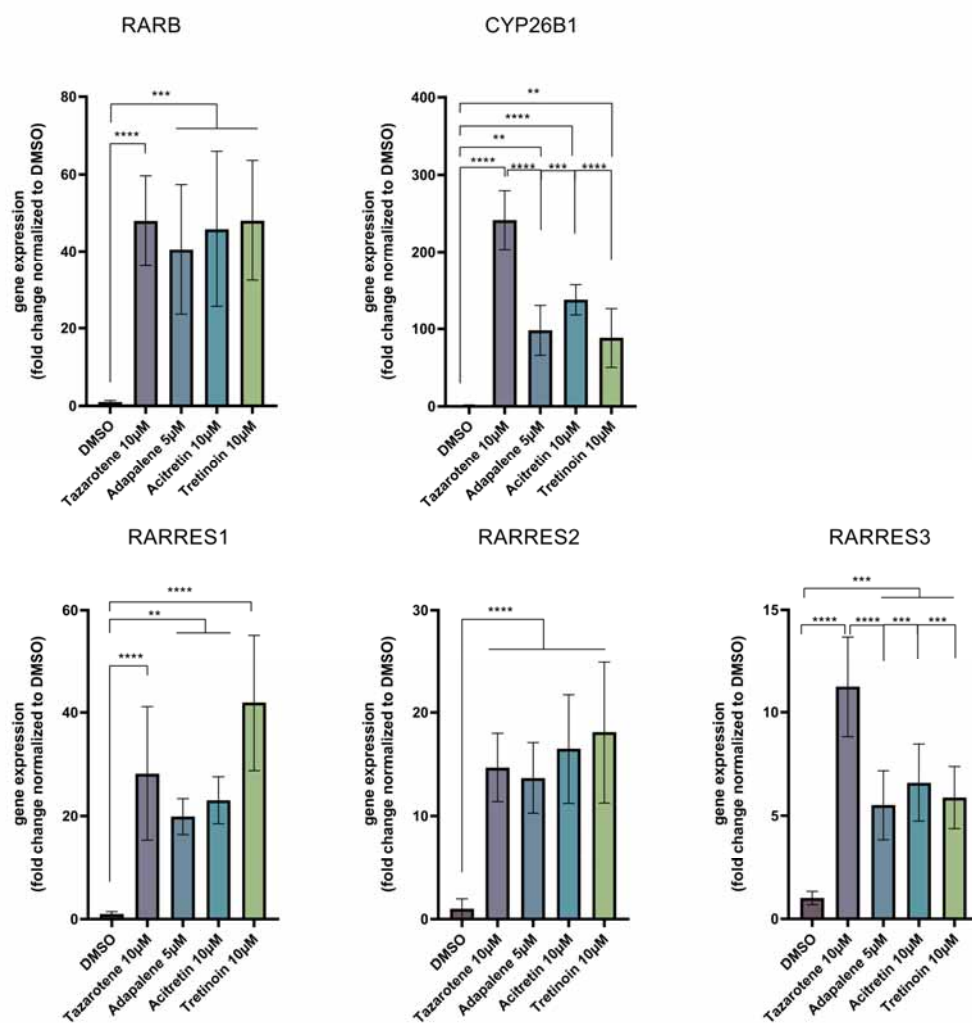


Appendix figure S8

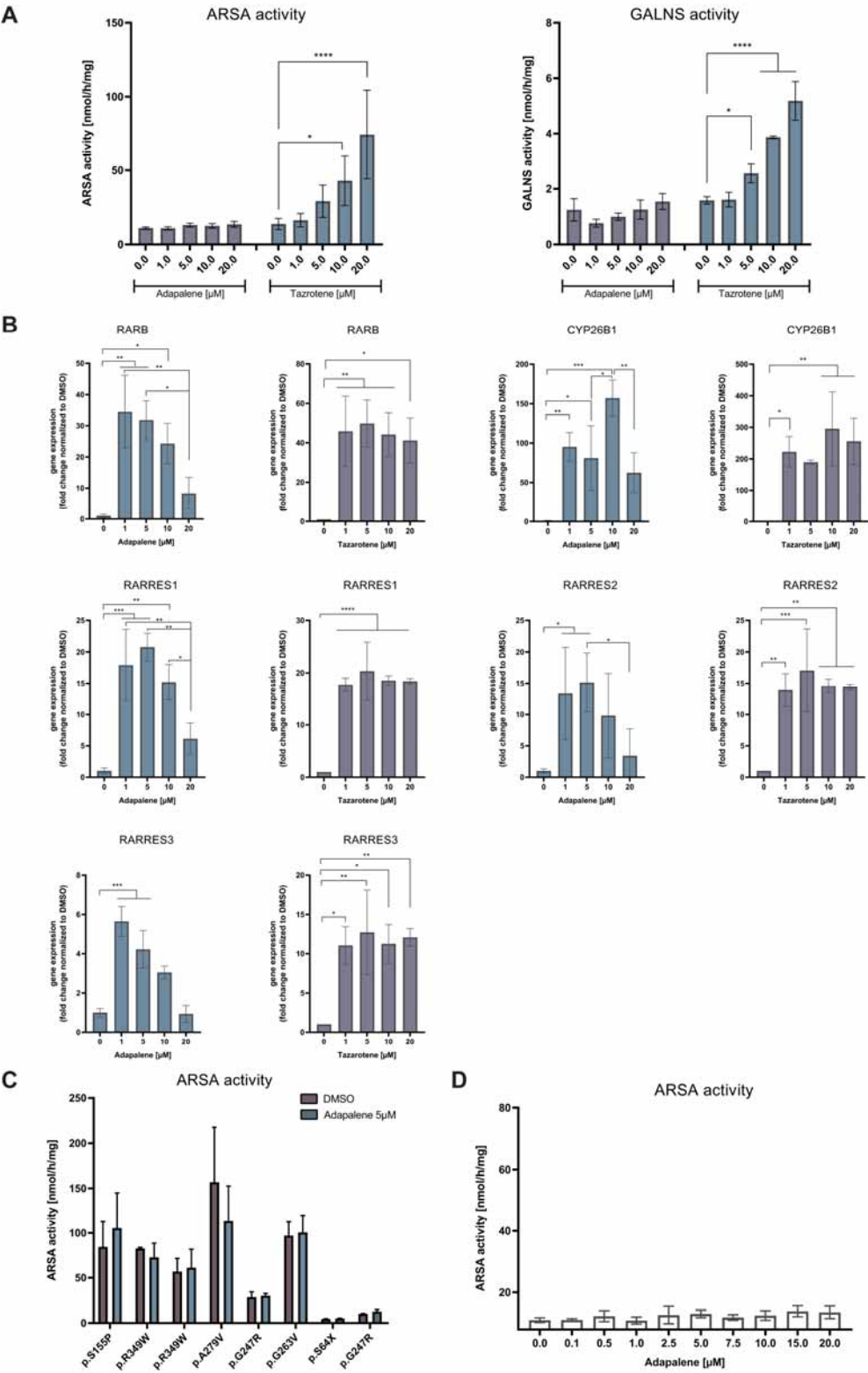
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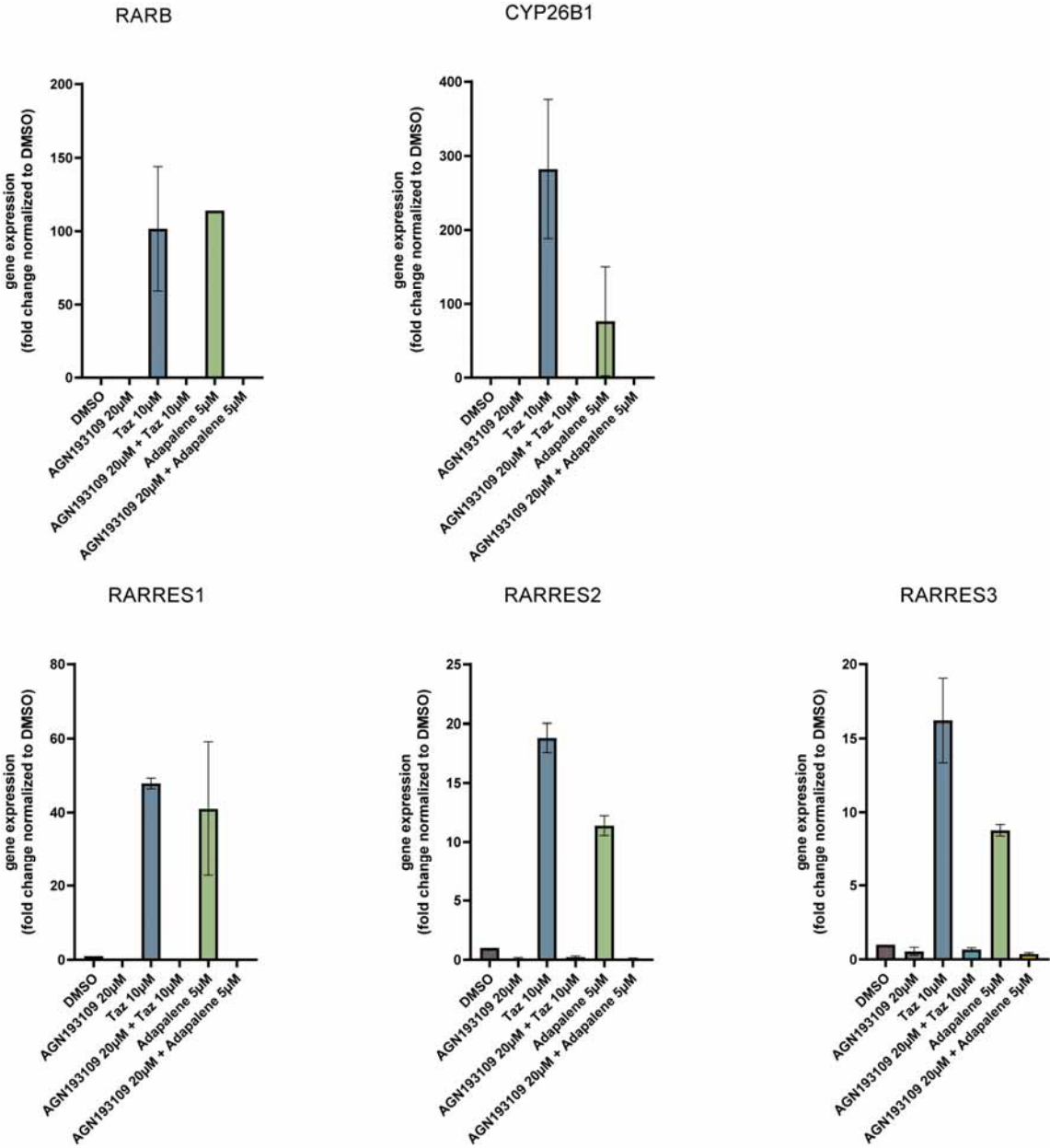
B



Appendix figure S9



Appendix figure S10



A

Heatmaps showing gene expression profiles for TAZ and ADA treatments compared to DMSO. The color scale ranges from -2 (blue) to 2 (red).

B

Bar charts showing FPKM values for RARRES1, CYP26B1, and RARB genes under DMSO, TAZ, and ADA treatments. Statistical significance is indicated by asterisks.

C

Volcano plot titled "Tazarotene vs adapalene" showing $-\log_{10}(\text{padj})$ vs L2FC. 539 genes are upregulated and 508 genes are downregulated. Total analysed genes = 10992.

D

Horizontal bar chart showing pathways induced by tazarotene, including Sterol biosynthetic process, Sterol metabolic process, Cholesterol biosynthetic process, Secondary alcohol biosynthetic process, and Cholesterol metabolic process.

E

Horizontal bar chart showing pathways induced by adapalene, including Extracellular matrix organization, Extracellular structure organization, External encapsulating structure organization, Blood vessel development, and Response to oxygen levels.

F

Venn diagram and bar chart showing gene overlap between DMSO vs TAZ and DMSO vs ADA. 1620 genes are common. Bar chart shows pathways induced by the common genes.

G

Venn diagram and bar chart showing gene overlap between DMSO vs TAZ and DMSO vs ADA. 354 genes are common. Bar chart shows pathways induced by the common genes.

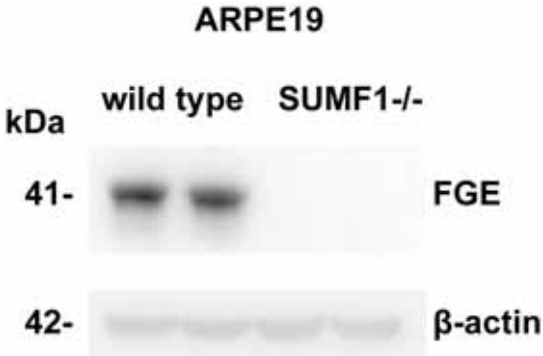
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Bar charts showing FPKM values for SREBF1, SREBF2, and INSIG1 genes under DMSO, TAZ, and ADA treatments.

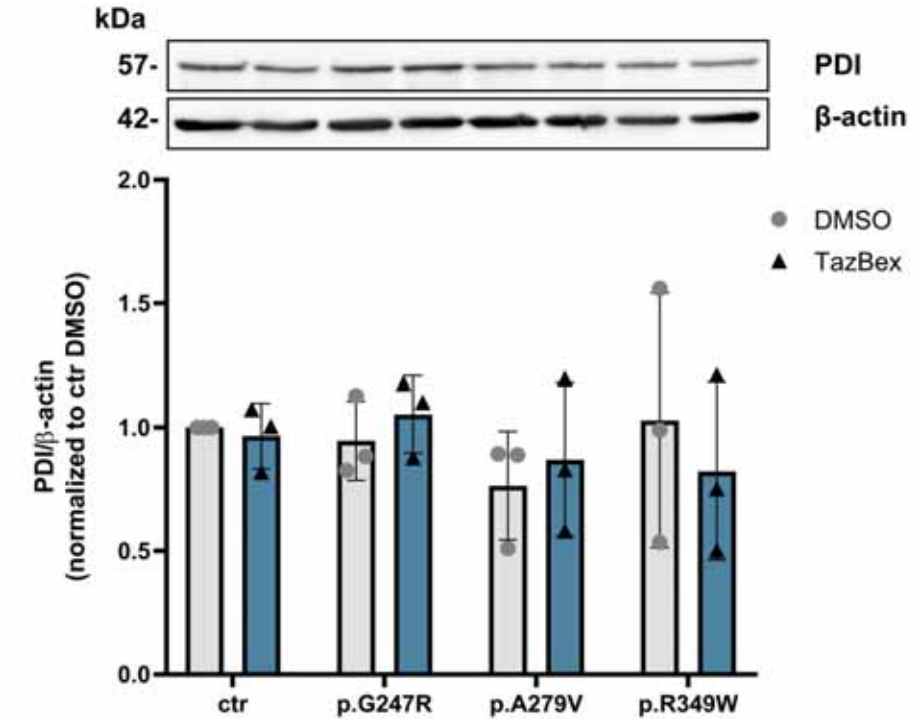
I

Bar chart showing ARSA levels (nmol/h/mg) for MSDi 3d Tazarotene and Fatostatin treatments. Statistical significance is indicated by asterisks.

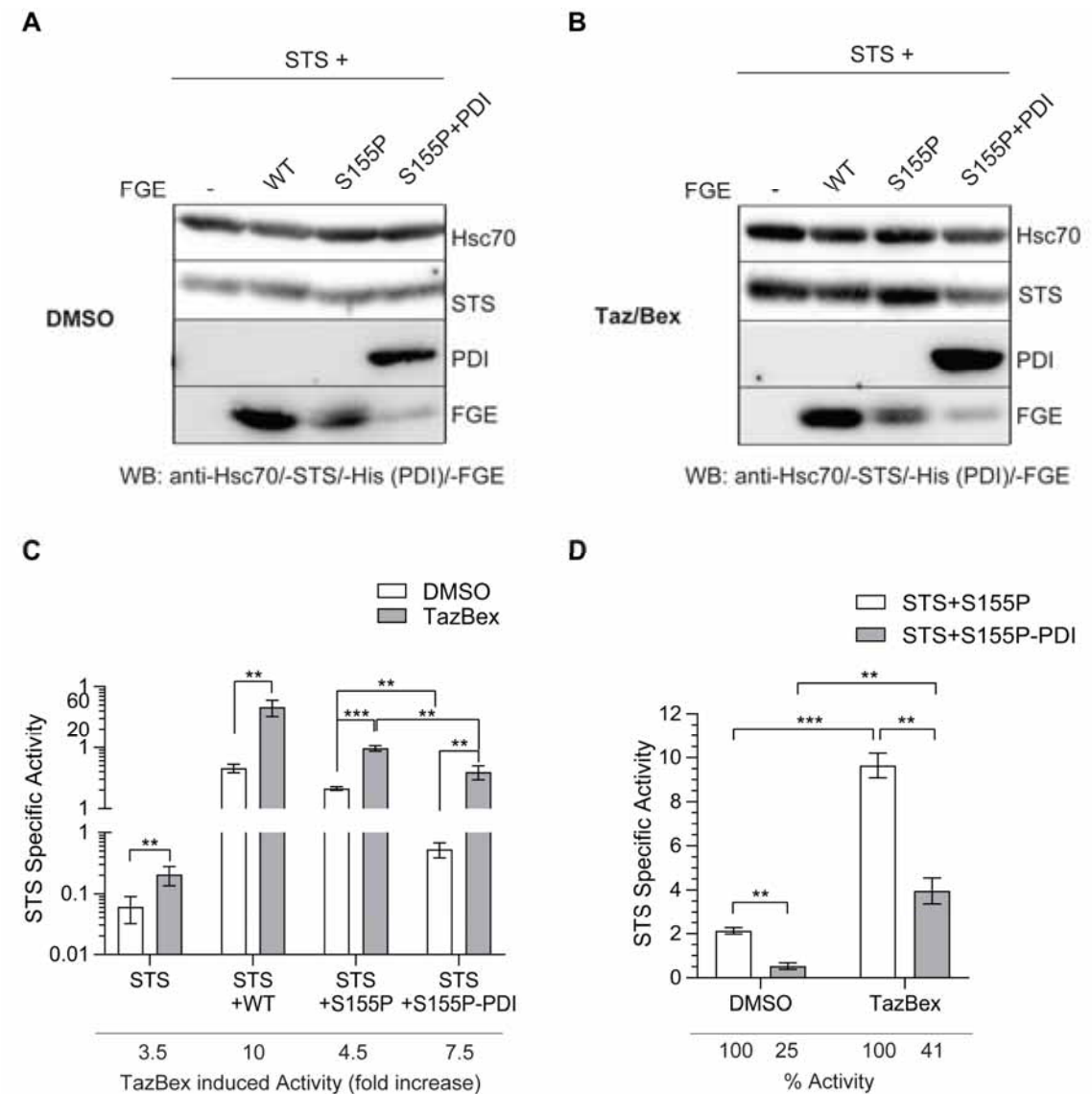
Appendix figure S12



Appendix figure S13



Appendix figure S14



Appendix supplementary figure legends

Appendix figure S1: FDA approved drug library screen on MSD cells – plate layout, test plate and screening results plates 1 and 2.

(A) Plate layout for the 96-well ARSA screening assay. (B) Representative plot of a screening plate with DMSO only treatment. ARSA activity is displayed as OD (y-axis) in every well as circle (x-axis). The grey colored area represents the upper and lower limit of baseline ARSA activity. N = 1 plate with 84 independent ARSA activity assays. (C, D) Original plots from screening a library of 785 licensed drugs with 80 drugs per plate at a final concentration of 10 μ M in DMSO (DMSO concentration 1% per well) and incubation for 48 hours. Drugs that exceeded the upper OD limit of baseline were annotated as hits. N = 1 experiment per well.

Appendix figure S2: FDA approved drug library screen on MSD cells – screening results plates 3-6.

(A-D) Original plots from screening a library of 785 licensed drugs with 80 drugs per plate at a final concentration of 10 μ M in DMSO (DMSO concentration 1% per well) and incubation for 48 hours. Drugs that exceeded the upper OD limit of baseline were annotated as hits. N = 1 experiment per well.

Appendix figure S3: FDA approved drug library screen on MSD cells – screening results plates 7-10.

(A-D) Original plots from screening a library of 785 licensed drugs with 80 drugs per plate at a final concentration of 10 μ M in DMSO (DMSO concentration 1% per well) and incubation

for 48 hours. Drugs that exceeded the upper OD limit of baseline were annotated as hits. N = 1 experiment per well.

Appendix figure S4: FDA approved drug library screen on MSD cells – rescreening and counterscreen plates 11-13

(A) Original plot from rescreening of drugs with ODs below the lower activity range in the initial screen because of toxicity. Cells were incubated at 1 μ M final concentration of each drug for 48 hours. N = 1 experiment per well. (B) Original plot from rescreening of drugs with ODs below the lower activity range in the initial screen because of toxicity. Cells were incubated at 0,1 μ M final concentration of each drug for 48 hours. N = 1 experiment per well. (C) Original plot from counter screening of hit drugs at a concentration of 10 μ M per well (1% DMSO content) for 48 hours devoid of cells. (N= 1 experiment per well).

Appendix figure S5: Comparison of cell count, total protein content, and ARSA activity changes over time in MSD and control fibroblasts under treatment and control conditions

(A) Manual cell count of MSD primary fibroblasts (FGE p.Gly247Arg) plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of 0.1% (v/v) DMSO or at standard treatment conditions (medium cell quantity and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). (B) Manual cell count of control fibroblasts plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of DMSO or at standard treatment conditions (medium cell quantity and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). (C) Total protein amount of MSD primary fibroblasts

(FGE p.Gly247Arg) plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of DMSO or at standard treatment conditions (medium cell quantity and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). **(D)** Total protein amount of control fibroblasts plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of DMSO or at standard treatment conditions (medium cell quantity and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). **(E)** ARSA activity in MSD primary fibroblasts (FGE p.Gly247Arg) plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of DMSO or at standard treatment conditions (medium cell quantity and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). **(F)** ARSA activity in control fibroblasts plated out at day 0 at standard cell quantities (medium) and additional low and high cell quantity. Cells were grown for 3, 6, and 9 days in presence of DMSO or at standard treatment conditions (medium cell quantity middle and 10 μ M tazarotene, 20 μ M bexarotene or 10/20 μ M tazarotene/bexarotene, respectively). All data represent mean \pm SD of 5-6 independent experiments. Two-way ANOVA followed by Tukey's test for multiple comparisons. Panel (A-E): Difference of tazarotene/bexarotene treatment against 0/0 μ M treatment at the same time point, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$. Panel F: Difference of DMSO low at day 9 against DMSO low at day 0. ** $p<0.01$, *** $p<0.001$, ##### $p<0.0001$. Please see Appendix tables S41-S46 for full list of statistics of all comparisons (significant differences only).

Appendix figure S6: Cell proliferation assessed by XTT-assay

(A) Quantification of cell proliferation of MSD primary fibroblasts (variant FGE Gly247Arg homozygous) and control fibroblasts after 6 days of treatment with tazarotene, bexarotene, and tazarotene/bexarotene assessed by XTT assay (see materials and methods). Data represent mean \pm SD of 8-20 independent experiments displayed as percentage of DMSO treated cells (negative control, 100% cell proliferation). One-way ANOVA followed by Tukey's test for multiple comparisons. * $p < 0.05$. (B) Quantification of cell proliferation of MSD primary fibroblasts (variant FGE Gly247Arg homozygous) and control fibroblasts after 6 days of simultaneous treatment with increasing concentrations of tazarotene and bexarotene in a fixed combination of 1:2 assessed by XTT assay (see materials and methods). (C,D) Raw OD data without normalization to DMSO treatment for panel A and B, respectively. Statistical analysis was performed on normalized data only. All data represent mean \pm SD of 8-12 independent experiments displayed as percentage of DMSO treated cells (negative control, 100% cell proliferation). One-way ANOVA followed by Tukey's test for multiple comparisons. * $p < 0.05$, ** $p < 0.01$. (I)

Appendix figure S7: MSD iPSC line characterization.

(A) Representative RT-PCR plot confirming the clearance of Sendai viral vectors in MSD4 iPSC at passages 4-5 by RT-PCR. (B) Representative PCR products using primer sets detecting short tandem repeat (STR) sequences from DNA fingerprinting of MSD patient derived iPSCs in comparison to PBMCs used for reprogramming. (C) Representative pictures of sequence analysis of *SUMF1* mutations in patient PBMCs and iPSC line. (D) Representative picture of G-band analysis for karyotyping MSD patient derived iPSCs (MSD4 p14). Normal karyotype (46,XY). (E) Representative flow cytometry plots of the expression of the stem cell surface markers on MSD4 iPSCs. SSEA3/4 and Tra160/81 were all

>95%. , as shown by flow cytometry. (F) Representative gel of PCR testing for mycoplasma infection in MSD4 cells and mock, positive and negative controls, respectively.

Appendix figure S8: Sulfatase activities and transcriptional response of retinoids targets in MSD fibroblasts

(A) Treatment of MSD primary fibroblasts (FGE p.Gly247Arg) for six days with 10 μ M final concentration of four different retinoids. Only tazarotene significantly increased ARSA, GALNS, and ASC (steroidsulfatase) activities. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against DMSO control: **** $p < 0.0001$. (B) Transcriptional response (gene expression) as determined by RT-PCR of selected targets of retinoids in MSD primary fibroblasts (FGE p.Gly247Arg) for six days with 10 μ M final concentration of four different retinoids. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$,

Appendix figure S9: Sulfatase activities and retinoid target gene expression upon different doses of adapalene and treatment response in different MSD primary fibroblast lines.

(A) Treatment of MSD primary fibroblasts (FGE p.Gly247Arg) for six days with different concentrations of adapalene and tazarotene as control. Adapalene did not increase ARSA and GALNS activities. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against DMSO control: * $p < 0.05$, **** $p < 0.0001$. (B) Retinoid target gene expression in MSD primary fibroblasts (FGE p.Gly247Arg) after six days treatment with increasing concentrations of

adapalene and tazarotene. Adapalene was able to increase retinoid target gene expression. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against DMSO control: * $p < 0.05$, *** $p < 0.01$, *** $p < 0.01$, **** $p < 0.0001$. **(C)** Treatment of eight MSD primary fibroblasts lines for six days with 5 μ M adapalene. Adapalene did not increase ARSA activity in either cell line. Data represent mean \pm SD of 3 independent experiments. Unpaired t-test. **(D)** Refined dose analysis of adapalene treatment in MSD primary fibroblasts (FGE p.Gly247Arg) for six days. Adapalene concentrations between 100 nM and 20 μ M did not increase ARSA activity. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons.

Appendix figure S10: Adapalene increased retinoid target gene expression is mediated via RAR receptors.

24 hours pre-treatment of MSD primary fibroblasts (FGE p.Gly247Arg) with the pan-RAR receptor antagonist AGN193109 followed by treatment with 10 μ M tazarotene and 5 μ M adapalene, respectively, for 72 hours. Retinoid target gene expression was analysed by RT-PCR. AGN193109 treatment abrogated tazarotene and adapalene induced gene expression. Data represent mean \pm SD of 3 independent experiments. RARB and adapalene control $n=1$ experiment.

Appendix figure S11: Total RNAseq and differential gene expression from MSD fibroblast lines treated with tazarotene, adapalene, and DMSO.

(A) Heatmaps illustrating differences in gene expression between seven different MSD fibroblast lines treated with tazarotene, adapalene, and DMSO in triplicates, respectively, and

analysed by total RNA sequencing (RNAseq). Differential gene expression was analysed versus treatment condition and DMSO, respectively. **(B)** Expression levels indicated as fragments per kilobase million (FPKM) of retinoid response markers in all cell lines and treatment conditions. Data represent mean from one total RNAseq analysis in triplicates. Paired t-test. Difference against DMSO control: * $p < 0.05$, *** $p < 0.01$, *** $p < 0.01$, **** $p < 0.0001$. **(C)** Transcriptomic changes of tazarotene and adapalene treated samples displayed as volcano plot and number of up- and down-regulated genes (tazarotene versus adapalene). **(D,E)** GO pathway analysis of genes differentially regulated after comparison of tazarotene and adapalene treatment and \log_{10} value of p-values. **(F,G)** Venn diagram and number of exclusively regulated genes for tazarotene treatment (TAZ) versus DMSO condition (left) and adapalene treatment (ADA) versus DMSO (right) as well as number of overlapping genes identically regulated by both tazarotene and adapalene. **(F)** Subsequent GO pathway analysis and \log_{10} value of p-values for identically regulated genes. **(G)** GO pathway analysis and \log_{10} value of p-values for adapalene only regulated genes. **(H)** Expression levels indicated as fragments per kilobase million (FPKM) of tazarotene only regulated genes in all cell lines. Data represent mean from one total RNAseq analysis in triplicates. Paired t-test. Difference against DMSO control: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.01$. **(I)** Quantification of ARSA activities in ARSA activity quantification after treatment of MSDi cells with increasing concentrations of fatostatin with and without simultaneous treatment of 10 μ M tazarotene for 3 days. Data represent mean \pm SD of 4 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. Displayed are significance levels for significant differences between tazarotene control and adjacent concentrations of combined tazarotene and fatostatin treatment. # $p < 0.05$, ##### $p < 0.0001$. Difference against 0/0 μ M control: **** $p < 0.0001$.

Appendix figure S12: SUMF1 -/- cell line evaluation

Representative western blot pictures of CRISPR/Cas9 generated ARPE19 SUMF1 ^{-/-} cells and ARPE19 wild type control cells. No FGE-expression at 41 kDa in knock-out cells using an anti-FGE antibody. Detection of β -actin served as loading control.

Appendix figure S13: PDI protein expression upon tazarotene/bexarotene treatment in MSD cell lines

Representative western blot pictures and quantification of PDI protein expression in three MSD primary fibroblast cell lines and one control fibroblast line treated with tazarotene 10 μ M and bexarotene 20 μ M for six days compared to DMSO treated cells. Detection of β -actin served as loading control. Data represent mean \pm SD of 3 independent experiments. One-way ANOVA followed by Tukey's test for multiple comparisons. No statistical significant differences were detected.

Appendix figure S14: Expression of PDI mitigates tazarotene/bexarotene-mediated effect of sulfatase activation.

(A,B) MSDi cells were treated with either DMSO or tazarotene 10 μ M and bexarotene 20 μ M for two days and transiently co-transfected with pBI-plasmids that express either steroid sulfatase (STS) alone or together with FGE-WT (wildtype), FGE-Ser155Pro variant or FGE-Ser155Pro and His-tagged PDI from a bi-directional doxycycline inducible promotor. 4h post-transfection, expression was induced with 1 μ g/ml doxycycline for 24 h and cells harvested. Of note, either DMSO or tazarotene/bexarotene were present in all steps till the cells were harvested. STS activity assay was performed in cell lysates and equal amount of total protein from all lysates were resolved in SDS-PAGE and western blot probed with anti-STS, anti-FGE, anti-His and anti-Hsc70 (as loading control). The panels show a representative result from one experiment. (C,D) STS specific activity calculated based on quantification of

western blot signals that correspond to STS (after normalization to that of Hsc70). N=3 independent experiments, error bars represent mean \pm SEM. One-way ANOVA followed by Tukey's test for multiple comparisons. ** $p < 0.01$, *** $p < 0.001$.

Appendix supplementary tables

Appendix table S1: List of drugs, suppliers and catalog numbers

Drug	Supplier	Cat. No.
Vorinostat	Sigma-Aldrich	SML0061
Clindamycine	Sigma-Aldrich	C5269
Asenapine	Sigma-Aldrich	A7861
Tazarotene	Sigma-Aldrich	T7080
Vitamine A	Sigma-Aldrich	7235-407
9-cis retinoic acid	Sigma-Aldrich	R4643
Isotretinoin	Sigma-Aldrich	R3255
Acitretin	Sigma-Aldrich	44707
Etretinate	Toronto Research Chemicals	E938000
Adapalene	Sigma-Aldrich	A7486
Bexarotene	Sigma-Aldrich	SML0282
Tazarotenic acid	Sigma-Aldrich	SML1619
Fatostatin	Sigma-Aldrich	341329
AGN 193109	Tocris	5758
HX 531	Sigma-Aldrich	SML2170
DMSO	Serva	39757

Appendix table S2: RT-PCR primers and primer sequences (5'>3')

beta-actin	Fwd	TGACCCAGATCATGTTTGAG
beta-actin	Rev	ATCACGATGCCAGTGGTA
RARB	Fwd	GTCACCGAGATAAGAACTGTGTTA
RARB	Rev	ACTCAGCTGTCATTTTCATAGCTCTC
CYP26B1	Fwd	TGGACCTCCTCATTGAGAGCA
CYP26B1	Rev	GGCATAGGCCGCAAAGATCA
RARRES1	Fwd	AAACCCCTTGGAATAGTCAGC
RARRES1	Rev	GGAAAGCCAAATCCCAGATGAG
RARRES2	Fwd	AGAAACCCGAGTGCAAAGTCA
RARRES2	Rev	AGAAACCCGAGTGCAAAGTCA
RARRES3	Fwd	AACAGTGCAGAGGTGAAACGG
RARRES3	Rev	GTTGGTACTCATGGTCCAAGC

Appendix table S3: Mean values and significance levels for Figure 1 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
neg. contr. vs. Tazarotene	6,917	14,72	**	0,0016
neg. contr. vs. pos. contr.	6,917	40,27	****	<0,0001
Tazarotene vs. Clindamycin	14,72	7,814	**	0,0064
Tazarotene vs. Vorinostat	14,72	6,957	**	0,0017
Tazarotene vs. pos. contr.	14,72	40,27	****	<0,0001
Clindamycin vs. pos. contr.	7,814	40,27	****	<0,0001
Vorinostat vs. pos. contr.	6,957	40,27	****	<0,0001
Asenapine vs. pos. contr.	9,617	40,27	****	<0,0001

Appendix table S4: Mean values and significance levels for Figure 1 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 2	2,511	5,895	**	0,0076
0 vs. 5	2,511	8,759	****	<0,0001
0 vs. 10	2,511	9,942	****	<0,0001
0 vs. 15	2,511	12,67	****	<0,0001
0 vs. 25	2,511	13,48	****	<0,0001
0 vs. 50	2,511	12,66	****	<0,0001
2 vs. 5	5,895	8,759	*	0,0474
2 vs. 10	5,895	9,942	***	0,001
2 vs. 15	5,895	12,67	****	<0,0001
2 vs. 25	5,895	13,48	****	<0,0001
2 vs. 50	5,895	12,66	****	<0,0001
5 vs. 15	8,759	12,67	**	0,0071
5 vs. 25	8,759	13,48	***	0,0008
5 vs. 50	8,759	12,66	**	0,0074
10 vs. 25	9,942	13,48	*	0,0136

Appendix table S5: Mean values and significance levels for Figure 1 panel D (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value

0 vs. 5	4,121	9,026	**	0,0014
0 vs. 10	4,121	9,185	***	0,0009
0 vs. 15	4,121	9,998	***	0,0002
0 vs. 20	4,121	11,02	****	<0,0001
0 vs. 25	4,121	11,19	****	<0,0001
0 vs. 50	4,121	9,775	***	0,0003

Appendix table S6: Mean values and significance levels for Figure 1 panel E (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
DMSO vs. Isotretinoin	3,303	5,667	**	0,0031
DMSO vs. Tazarotene	3,303	8,72	****	<0,0001
DMSO vs. Bexarotene	3,303	6,2	***	0,0003
DMSO vs. Tazarotenic acid	3,303	5,577	**	0,0046
Vitamin A vs. Etretinate	4,797	2,41	**	0,0028
Vitamin A vs. Tazarotene	4,797	8,72	****	<0,0001
9-cis-retinoic acid vs. Etretinate	4,893	2,41	**	0,0018
9-cis-retinoic acid vs. Tazarotene	4,893	8,72	****	<0,0001
Isotretinoin vs. Etretinate	5,667	2,41	****	<0,0001
Isotretinoin vs. Adapalene 1µM	5,667	3,33	**	0,0035
Isotretinoin vs. Tazarotene	5,667	8,72	***	0,0001
Acitretin vs. Tazarotene	3,963	8,72	****	<0,0001
Acitretin vs. Bexarotene	3,963	6,2	**	0,0054
Etretinate vs. Tazarotene	2,41	8,72	****	<0,0001
Etretinate vs. Bexarotene	2,41	6,2	****	<0,0001
Etretinate vs. Tazarotenic acid	2,41	5,577	****	<0,0001
Adapalene 1µM vs. Tazarotene	3,33	8,72	****	<0,0001
Adapalene 1µM vs. Bexarotene	3,33	6,2	***	0,0003
Adapalene 1µM vs. Tazarotenic acid	3,33	5,577	**	0,0052
Tazarotene vs. Bexarotene	8,72	6,2	**	0,0015
Tazarotene vs. Tazarotenic acid	8,72	5,577	****	<0,0001

Appendix table S7: Mean values and significance levels for Figure 1 panel F (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 5	2,633	5,175	*	0,0253
0 vs. 10	2,633	6,451	****	<0,0001
0 vs. 20	2,633	7,802	****	<0,0001

0 vs. 50	2,633	7,067	***	0,0008
1 vs. 10	3,283	6,451	*	0,0307
1 vs. 20	3,283	7,802	***	0,0006
1 vs. 50	3,283	7,067	*	0,0416
2 vs. 20	3,75	7,802	**	0,0025
5 vs. 20	5,175	7,802	*	0,0189

Appendix table S8: Mean values and significance levels for Figure 1 panel G (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0/0 vs 1/2	4,515	12,56	****	<0,0001
0/0 vs 2/4	4,515	15,88	****	<0,0001
0/0 vs 5/10	4,515	19,9	****	<0,0001
0/0 vs 7.5/15	4,515	20,98	****	<0,0001
0/0 vs 10/20	4,515	19,65	****	<0,0001
0/0 vs 15/30	4,515	14	****	<0,0001
1/2 vs 2/4	12,56	15,88	***	0,0003
1/2 vs 5/10	12,56	19,9	****	<0,0001
1/2 vs 7.5/15	12,56	20,98	****	<0,0001
1/2 vs 10/20	12,56	19,65	****	<0,0001
2/4 vs 5/10	15,88	19,9	****	<0,0001
2/4 vs 7.5/15	15,88	20,98	****	<0,0001
2/4 vs 10/20	15,88	19,65	***	0,0007
5/10 vs 15/30	19,9	14	****	<0,0001
7.5/15 vs 15/30	20,98	14	****	<0,0001
10/20 vs 15/30	19,65	14	****	<0,0001

Appendix table S9: Mean values and significance levels for Figure 1 panel H (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 2	3,415	8,71	*	0,0196
0 vs. 3	3,415	14,29	****	<0,0001
0 vs. 6	3,415	20,06	****	<0,0001
0 vs. 9	3,415	25,76	****	<0,0001
0 vs. 12	3,415	15,18	****	<0,0001
2 vs. 3	8,71	14,29	*	0,0123
2 vs. 6	8,71	20,06	****	<0,0001
2 vs. 9	8,71	25,76	****	<0,0001

2 vs. 12	8,71	15,18	**	0,0081
3 vs. 6	14,29	20,06	***	0,0002
3 vs. 9	14,29	25,76	****	<0,0001
6 vs. 9	20,06	25,76	*	0,0132
6 vs. 12	20,06	15,18	*	0,011
9 vs. 12	25,76	15,18	****	<0,0001

Appendix table S10: Mean values and significance levels for Figure 2 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 5	15,9	30,45	***	0,001
0 vs. 10	15,9	47,89	****	<0,0001
0 vs. 25	15,9	78	****	<0,0001
0 vs. 50	15,9	94,45	****	<0,0001
0 vs. 75	15,9	84,8	****	<0,0001
0 vs. 100	15,9	65,39	****	<0,0001
1 vs. 10	18,91	47,89	****	<0,0001
1 vs. 25	18,91	78	****	<0,0001
1 vs. 50	18,91	94,45	****	<0,0001
1 vs. 75	18,91	84,8	****	<0,0001
1 vs. 100	18,91	65,39	****	<0,0001
2.5 vs. 10	22,34	47,89	****	<0,0001
2.5 vs. 25	22,34	78	****	<0,0001
2.5 vs. 50	22,34	94,45	****	<0,0001
2.5 vs. 75	22,34	84,8	****	<0,0001
2.5 vs. 100	22,34	65,39	****	<0,0001
5 vs. 10	30,45	47,89	****	<0,0001
5 vs. 25	30,45	78	****	<0,0001
5 vs. 50	30,45	94,45	****	<0,0001
5 vs. 75	30,45	84,8	****	<0,0001
5 vs. 100	30,45	65,39	****	<0,0001
10 vs. 25	47,89	78	****	<0,0001
10 vs. 50	47,89	94,45	****	<0,0001
10 vs. 75	47,89	84,8	****	<0,0001
10 vs. 100	47,89	65,39	****	<0,0001
25 vs. 50	78	94,45	***	0,0009
25 vs. 100	78	65,39	*	0,0193
50 vs. 100	94,45	65,39	****	<0,0001
75 vs. 100	84,8	65,39	***	0,0003

Appendix table S11: Mean values and significance levels for Figure 2 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 10	14,84	22,17	*	0,0112
0 vs. 20	14,84	22,48	*	0,0156
0 vs. 25	14,84	26,6	****	<0,0001
0 vs. 50	14,84	30,58	****	<0,0001
2.5 vs. 50	20,2	30,58	**	0,0032
2.5 vs. 75	20,2	7,603	**	0,0017
5 vs. 25	19,37	26,6	**	0,0018
5 vs. 50	19,37	30,58	****	<0,0001
5 vs. 75	19,37	7,603	***	0,0002
10 vs. 50	22,17	30,58	**	0,0061
10 vs. 75	22,17	7,603	****	<0,0001
20 vs. 50	22,48	30,58	*	0,0177
20 vs. 75	22,48	7,603	****	<0,0001
25 vs. 75	26,6	7,603	****	<0,0001
50 vs. 75	30,58	7,603	****	<0,0001

Appendix table S12: Mean values and significance levels for Figure 2 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0/0 vs 2/5	15,59	32,75	**	0,0016
0/0 vs 5/10	15,59	64,17	****	<0,0001
0/0 vs 7/5	15,59	103,1	****	<0,0001
0/0 vs 10/20	15,59	111	****	<0,0001
0/0 vs 15/30	15,59	73,08	****	<0,0001
0.1/0.2 vs 2.5/5	17,28	32,75	*	0,021
0.1/0.2 vs 5/10	17,28	64,17	****	<0,0001
0.1/0.2 vs 7.5/10	17,28	103,1	****	<0,0001
0.1/0.2 vs 10/20	17,28	111	****	<0,0001
0.1/0.2 vs 15/30	17,28	73,08	****	<0,0001
1/2 vs 5/10	22,83	64,17	****	<0,0001
1/2 vs 7/5	22,83	103,1	****	<0,0001
1/2 vs 10/20	22,83	111	****	<0,0001
1/2 vs 15/30	22,83	73,08	****	<0,0001
2.5/5 vs 5/10	32,75	64,17	****	<0,0001
2.5/5 vs 7.5/15	32,75	103,1	****	<0,0001
2.5/5 vs 10/20	32,75	111	****	<0,0001
2.5/5 vs 15/30	32,75	73,08	****	<0,0001
5/10 vs 7/5	64,17	103,1	****	<0,0001

5/10 vs 10/20	64,17	111	****	<0,0001
7.5/15 vs 15/30	103,1	73,08	****	<0,0001
10/20 vs 15/30	111	73,08	****	<0,0001

Appendix table S13: Mean values and significance levels for Figure 2 panel D (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0 vs. 3	16,09	43,1	*	0,0443
0 vs. 6	16,09	109,5	****	<0,0001
0 vs. 9	16,09	175,8	****	<0,0001
0 vs. 14	16,09	181,2	****	<0,0001
0 vs. 21	16,09	168,3	****	<0,0001
3 vs. 6	43,1	109,5	****	<0,0001
3 vs. 9	43,1	175,8	****	<0,0001
3 vs. 14	43,1	181,2	****	<0,0001
3 vs. 21	43,1	168,3	****	<0,0001
6 vs. 9	109,5	175,8	****	<0,0001
6 vs. 14	109,5	181,2	****	<0,0001
6 vs. 21	109,5	168,3	***	0,0001

Appendix table S14: Mean values and significance levels for Figure 2 panel E (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
ARSA - vs. +	17,06	109,5	****	<0,0001
ARSB - vs. +	18,09	46,96	***	0,0001
GALNS - vs. +	3,54	11,67	***	0,0003
STS - vs. +	14,8	113,6	****	<0,0001

Appendix table S15: Mean values and significance levels for Figure 2 panel F (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
p.G247R - vs. +	17,71	98,09	****	<0,0001
p.G263V - vs. +	131,2	324,5	****	<0,0001
p.A279V - vs. +	45	88	***	0,0005

p.R349W - vs. +	27,89	97,87	****	<0,0001
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Appendix table S16: Mean values and significance levels for Figure 2 panel G (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
contr. - vs. +	30,38	35,02	****	<0,0001
MSD - vs. +	10,97	17,57	****	<0,0001

Appendix table S17: Mean values and significance levels for Figure 2 panel H (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
contr. - vs. +	2,287	1,78	*	0,0303
MSD - vs. +	0,219	0,4617	***	0,0002

Appendix table S18: Mean values and significance levels for Figure 3 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
ctr dmso vs. MSD dmso	740085758	3733811299	***	0,0002
MSD dmso vs. ctr tazbex	3733811299	785298854	***	0,0002
MSD dmso vs. msd tazbex	3733811299	1912504979	*	0,0115

Appendix table S19: Mean values and significance levels for Figure 3 panel D (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
ctr dmso vs. MSD dmso	740085758	3733811299	***	0,0002
MSD dmso vs. ctr tazbex	3733811299	785298854	***	0,0002
MSD dmso vs. msd tazbex	3733811299	1912504979	*	0,0115

Appendix table S20: Mean values and significance levels for Figure 4 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0:DMSO vs. 0:Tazarotene 10 µM	3,263	10,38	****	<0,0001
0:DMSO vs. 0:Tazarotene 10 µM Bexarotene 20µM	3,263	13,89	****	<0,0001
0:DMSO vs. 1:Tazarotene 10 µM	3,263	7,273	****	<0,0001
0:DMSO vs. 1:Tazarotene 10 µM Bexarotene 20µM	3,263	11,18	****	<0,0001
0:DMSO vs. 5:Tazarotene 10 µM	3,263	6,725	****	<0,0001
0:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	3,263	10,16	****	<0,0001
0:DMSO vs. 10:Tazarotene 10 µM	3,263	6,546	****	<0,0001
0:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	3,263	9,414	****	<0,0001
0:DMSO vs. 20:Tazarotene 10 µM Bexarotene 20µM	3,263	6,536	**	0,0021
0:Tazarotene 10 µM vs. 0:Bexarotene 20 µM	10,38	4,74	****	<0,0001
0:Tazarotene 10 µM vs. 0:Tazarotene 10 µM Bexarotene 20µM	10,38	13,89	**	0,0011
0:Tazarotene 10 µM vs. 1:DMSO	10,38	3,151	****	<0,0001
0:Tazarotene 10 µM vs. 1:Tazarotene 10 µM	10,38	7,273	***	0,0004
0:Tazarotene 10 µM vs. 1:Bexarotene 20 µM	10,38	4,493	****	<0,0001
0:Tazarotene 10 µM vs. 5:DMSO	10,38	3,326	****	<0,0001
0:Tazarotene 10 µM vs. 5:Tazarotene 10 µM	10,38	6,725	****	<0,0001
0:Tazarotene 10 µM vs. 5:Bexarotene 20 µM	10,38	4,983	****	<0,0001
0:Tazarotene 10 µM vs. 10:DMSO	10,38	3,378	****	<0,0001
0:Tazarotene 10 µM vs. 10:Tazarotene 10 µM	10,38	6,546	****	<0,0001
0:Tazarotene 10 µM vs. 10:Bexarotene 20 µM	10,38	4,517	****	<0,0001
0:Tazarotene 10 µM vs. 20:DMSO	10,38	4,195	****	<0,0001
0:Tazarotene 10 µM vs. 20:Tazarotene 10 µM	10,38	5,021	****	<0,0001
0:Tazarotene 10 µM vs. 20:Bexarotene 20 µM	10,38	4,693	****	<0,0001
0:Tazarotene 10 µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	10,38	6,536	***	0,0002
0:Bexarotene 20 µM vs. 0:Tazarotene 10 µM Bexarotene 20µM	4,74	13,89	****	<0,0001
0:Bexarotene 20 µM vs. 1:Tazarotene 10 µM Bexarotene 20µM	4,74	11,18	****	<0,0001
0:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	4,74	10,16	****	<0,0001
0:Bexarotene 20 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	4,74	9,414	***	0,0008
0:Tazarotene 10 µM Bexarotene 20µM vs. 1:DMSO	13,89	3,151	****	<0,0001

0:Tazarotene 10 µM Bexarotene 20µM vs. 1:Tazarotene 10 µM	13,89	7,273	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 1:Bexarotene 20 µM	13,89	4,493	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:DMSO	13,89	3,326	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:Tazarotene 10 µM	13,89	6,725	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:Bexarotene 20 µM	13,89	4,983	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	13,89	10,16	**	0,0034
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	13,89	3,378	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM	13,89	6,546	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	13,89	4,517	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	13,89	9,414	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	13,89	4,195	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	13,89	5,021	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	13,89	4,693	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	13,89	6,536	****	<0,0001
1:DMSO vs. 1:Tazarotene 10 µM	3,151	7,273	****	<0,0001
1:DMSO vs. 1:Tazarotene 10 µM Bexarotene 20µM	3,151	11,18	****	<0,0001
1:DMSO vs. 5:Tazarotene 10 µM	3,151	6,725	****	<0,0001
1:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	3,151	10,16	****	<0,0001
1:DMSO vs. 10:Tazarotene 10 µM	3,151	6,546	****	<0,0001
1:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	3,151	9,414	****	<0,0001
1:DMSO vs. 20:Tazarotene 10 µM Bexarotene 20µM	3,151	6,536	**	0,0011
1:Tazarotene 10 µM vs. 1:Tazarotene 10 µM Bexarotene 20µM	7,273	11,18	***	0,0001
1:Tazarotene 10 µM vs. 5:DMSO	7,273	3,326	****	<0,0001
1:Tazarotene 10 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	7,273	10,16	*	0,0229
1:Tazarotene 10 µM vs. 10:DMSO	7,273	3,378	****	<0,0001

1:Tazarotene 10 µM vs. 20:DMSO	7,273	4,195	***	0,0002
1:Bexarotene 20 µM vs. 1:Tazarotene 10 µM Bexarotene 20µM	4,493	11,18	****	<0,0001
1:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	4,493	10,16	****	<0,0001
1:Bexarotene 20 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	4,493	9,414	***	0,0003
1:Tazarotene 10 µM Bexarotene 20µM vs. 5:DMSO	11,18	3,326	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 5:Tazarotene 10 µM	11,18	6,725	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 5:Bexarotene 20 µM	11,18	4,983	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	11,18	3,378	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM	11,18	6,546	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	11,18	4,517	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	11,18	4,195	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	11,18	5,021	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	11,18	4,693	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	11,18	6,536	****	<0,0001
5:DMSO vs. 5:Tazarotene 10 µM	3,326	6,725	****	<0,0001
5:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	3,326	10,16	****	<0,0001
5:DMSO vs. 10:Tazarotene 10 µM	3,326	6,546	****	<0,0001
5:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	3,326	9,414	****	<0,0001
5:DMSO vs. 20:Tazarotene 10 µM Bexarotene 20µM	3,326	6,536	**	0,0029
5:Tazarotene 10 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	6,725	10,16	**	0,0016
5:Tazarotene 10 µM vs. 10:DMSO	6,725	3,378	****	<0,0001
5:Tazarotene 10 µM vs. 20:DMSO	6,725	4,195	**	0,007
5:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	4,983	10,16	****	<0,0001
5:Bexarotene 20 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	4,983	9,414	**	0,0021
5:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	10,16	3,378	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM	10,16	6,546	***	0,0006

5:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	10,16	4,517	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	10,16	4,195	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	10,16	5,021	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	10,16	4,693	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	10,16	6,536	**	0,0054
10:DMSO vs. 10:Tazarotene 10 µM	3,378	6,546	***	0,0001
10:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	3,378	9,414	****	<0,0001
10:DMSO vs. 20:Tazarotene 10 µM Bexarotene 20µM	3,378	6,536	**	0,0038
10:Tazarotene 10 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	6,546	9,414	*	0,0244
10:Tazarotene 10 µM vs. 20:DMSO	6,546	4,195	*	0,0197
10:Bexarotene 20 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	4,517	9,414	***	0,0003
10:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	9,414	4,195	****	<0,0001
10:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	9,414	5,021	****	<0,0001
10:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	9,414	4,693	***	0,0006

Appendix table S21: Mean values and significance levels for Figure 4 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0:DMSO vs. 0:Tazarotene 10 µM	2,984	11,07	****	<0,0001
0:DMSO vs. 0:Tazarotene 10 µM Bexarotene 20µM	2,984	16,14	****	<0,0001
0:DMSO vs. 1:Tazarotene 10 µM	2,984	11,93	****	<0,0001
0:DMSO vs. 1:Tazarotene 10 µM Bexarotene 20µM	2,984	14,02	****	<0,0001
0:DMSO vs. 5:Tazarotene 10 µM	2,984	12,7	****	<0,0001
0:DMSO vs. 5:Bexarotene 20 µM	2,984	7,002	*	0,0176
0:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	2,984	11,86	****	<0,0001
0:DMSO vs. 10:Tazarotene 10 µM	2,984	10,11	****	<0,0001

0:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	2,984	7,54	***	0,0005
0:DMSO vs. 20:DMSO	2,984	5,528	*	0,0336
0:DMSO vs. 20:Tazarotene 10 µM Bexarotene 20µM	2,984	6,49	*	0,0337
0:Tazarotene 10 µM vs. 0:Bexarotene 20 µM	11,07	5,085	***	0,0002
0:Tazarotene 10 µM vs. 0:Tazarotene 10 µM Bexarotene 20µM	11,07	16,14	**	0,0013
0:Tazarotene 10 µM vs. 1:DMSO	11,07	4,131	****	<0,0001
0:Tazarotene 10 µM vs. 1:Bexarotene 20 µM	11,07	5,477	***	0,0007
0:Tazarotene 10 µM vs. 5:DMSO	11,07	4,441	****	<0,0001
0:Tazarotene 10 µM vs. 10:DMSO	11,07	5,317	****	<0,0001
0:Tazarotene 10 µM vs. 10:Bexarotene 20 µM	11,07	6,532	*	0,0197
0:Tazarotene 10 µM vs. 20:DMSO	11,07	5,528	****	<0,0001
0:Tazarotene 10 µM vs. 20:Tazarotene 10 µM	11,07	6,067	***	0,0007
0:Tazarotene 10 µM vs. 20:Bexarotene 20 µM	11,07	6,448	*	0,0154
0:Tazarotene 10 µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	11,07	6,49	**	0,007
0:Bexarotene 20 µM vs. 0:Tazarotene 10 µM Bexarotene 20µM	5,085	16,14	****	<0,0001
0:Bexarotene 20 µM vs. 1:Tazarotene 10 µM	5,085	11,93	****	<0,0001
0:Bexarotene 20 µM vs. 1:Tazarotene 10 µM Bexarotene 20µM	5,085	14,02	****	<0,0001
0:Bexarotene 20 µM vs. 5:Tazarotene 10 µM	5,085	12,7	****	<0,0001
0:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	5,085	11,86	****	<0,0001
0:Bexarotene 20 µM vs. 10:Tazarotene 10 µM	5,085	10,11	**	0,0044
0:Tazarotene 10 µM Bexarotene 20µM vs. 1:DMSO	16,14	4,131	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 1:Tazarotene 10 µM	16,14	11,93	*	0,0226
0:Tazarotene 10 µM Bexarotene 20µM vs. 1:Bexarotene 20 µM	16,14	5,477	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:DMSO	16,14	4,441	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	16,14	11,86	*	0,0321
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	16,14	5,317	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM	16,14	10,11	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	16,14	6,532	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	16,14	7,54	****	<0,0001

0:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	16,14	5,528	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	16,14	6,067	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	16,14	6,448	****	<0,0001
0:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	16,14	6,49	****	<0,0001
1:DMSO vs. 1:Tazarotene 10 µM	4,131	11,93	****	<0,0001
1:DMSO vs. 1:Tazarotene 10 µM Bexarotene 20µM	4,131	14,02	****	<0,0001
1:DMSO vs. 5:Tazarotene 10 µM	4,131	12,7	****	<0,0001
1:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	4,131	11,86	****	<0,0001
1:DMSO vs. 10:Tazarotene 10 µM	4,131	10,11	****	<0,0001
1:DMSO vs. 10:Tazarotene 10 µM Bexarotene 20µM	4,131	7,54	*	0,0464
1:Tazarotene 10 µM vs. 1:Bexarotene 20 µM	11,93	5,477	****	<0,0001
1:Tazarotene 10 µM vs. 5:DMSO	11,93	4,441	****	<0,0001
1:Tazarotene 10 µM vs. 5:Bexarotene 20 µM	11,93	7,002	**	0,0061
1:Tazarotene 10 µM vs. 10:DMSO	11,93	5,317	****	<0,0001
1:Tazarotene 10 µM vs. 10:Bexarotene 20 µM	11,93	6,532	**	0,0013
1:Tazarotene 10 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	11,93	7,54	*	0,0131
1:Tazarotene 10 µM vs. 20:DMSO	11,93	5,528	****	<0,0001
1:Tazarotene 10 µM vs. 20:Tazarotene 10 µM	11,93	6,067	****	<0,0001
1:Tazarotene 10 µM vs. 20:Bexarotene 20 µM	11,93	6,448	***	0,001
1:Tazarotene 10 µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	11,93	6,49	***	0,0003
1:Bexarotene 20 µM vs. 1:Tazarotene 10 µM Bexarotene 20µM	5,477	14,02	****	<0,0001
1:Bexarotene 20 µM vs. 5:Tazarotene 10 µM	5,477	12,7	****	<0,0001
1:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	5,477	11,86	****	<0,0001
1:Bexarotene 20 µM vs. 10:Tazarotene 10 µM	5,477	10,11	*	0,0147
1:Tazarotene 10 µM Bexarotene 20µM vs. 5:DMSO	14,02	4,441	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 5:Bexarotene 20 µM	14,02	7,002	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	14,02	5,317	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	14,02	6,532	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	14,02	7,54	****	<0,0001

1:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	14,02	5,528	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	14,02	6,067	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	14,02	6,448	****	<0,0001
1:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	14,02	6,49	****	<0,0001
5:DMSO vs. 5:Tazarotene 10 µM	4,441	12,7	****	<0,0001
5:DMSO vs. 5:Tazarotene 10 µM Bexarotene 20µM	4,441	11,86	****	<0,0001
5:DMSO vs. 10:Tazarotene 10 µM	4,441	10,11	****	<0,0001
5:Tazarotene 10 µM vs. 5:Bexarotene 20 µM	12,7	7,002	***	0,0005
5:Tazarotene 10 µM vs. 10:DMSO	12,7	5,317	****	<0,0001
5:Tazarotene 10 µM vs. 10:Bexarotene 20 µM	12,7	6,532	****	<0,0001
5:Tazarotene 10 µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	12,7	7,54	***	0,0009
5:Tazarotene 10 µM vs. 20:DMSO	12,7	5,528	****	<0,0001
5:Tazarotene 10 µM vs. 20:Tazarotene 10 µM	12,7	6,067	****	<0,0001
5:Tazarotene 10 µM vs. 20:Bexarotene 20 µM	12,7	6,448	****	<0,0001
5:Tazarotene 10 µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	12,7	6,49	****	<0,0001
5:Bexarotene 20 µM vs. 5:Tazarotene 10 µM Bexarotene 20µM	7,002	11,86	*	0,013
5:Tazarotene 10 µM Bexarotene 20µM vs. 10:DMSO	11,86	5,317	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 10:Bexarotene 20 µM	11,86	6,532	**	0,0032
5:Tazarotene 10 µM Bexarotene 20µM vs. 10:Tazarotene 10 µM Bexarotene 20µM	11,86	7,54	*	0,0279
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:DMSO	11,86	5,528	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM	11,86	6,067	****	<0,0001
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Bexarotene 20 µM	11,86	6,448	**	0,0024
5:Tazarotene 10 µM Bexarotene 20µM vs. 20:Tazarotene 10 µM Bexarotene 20µM	11,86	6,49	***	0,001
10:DMSO vs. 10:Tazarotene 10 µM	5,317	10,11	****	<0,0001
10:Tazarotene 10 µM vs. 20:DMSO	10,11	5,528	***	0,0001
10:Tazarotene 10 µM vs. 20:Tazarotene 10 µM	10,11	6,067	*	0,0203

Appendix table S22: Mean values and significance levels for Figure 5 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
control DMSO vs. MSD DMSO	-0,01671	-0,1948	*	0,0411
MSD DMSO vs. control taz/bex	-0,1948	0,2035	**	0,0074
MSD DMSO vs. MSD taz/bex	-0,1948	0,0391	*	0,0404

Appendix table S23: Mean values and significance levels for Figure 5 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
control DMSO vs. MSD taz/bex	0,1004	-0,245	*	0,0107
MSD DMSO vs. MSD taz/bex	0,1558	-0,245	**	0,0045
control taz/bex vs. MSD taz/bex	0,006763	-0,245	*	0,0478

Appendix table S24: Mean values and significance levels for Figure 6 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0/0 vs 10/0	10,13	44	*	0,0402
0/0 vs.10/20	10,13	77,65	***	0,0007
10/0 vs. 10/20	44	77,65	*	0,0414
20/0 vs. 10/20	20,91	77,65	**	0,0022

Appendix table S25: Mean values and significance levels for Figure 6 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
MSDi				
0 vs. 10	4,693	14,64	***	0,0001
0 vs. 25	4,693	21,09	****	<0,0001
0 vs. 50	4,693	19,18	****	<0,0001
10 vs. 25	14,64	21,09	**	0,0048

Appendix table S26: Mean values and significance levels for Figure 6 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
MSD FGE G247R				
0 vs. 6	15,88	113,9	****	<0,0001
0 vs. 14	15,88	181,2	****	<0,0001
0 vs. 21	15,88	168,3	****	<0,0001
6 vs. 14	113,9	181,2	****	<0,0001
6 vs. 21	113,9	168,3	***	0,0003
ARPE 19 SUMF1 +/+				
0 vs. 6	263,5	401,1	****	<0,0001
0 vs. 14	263,5	401,4	****	<0,0001
0 vs. 21	263,5	369,8	****	<0,0001
6 vs. 21	401,1	369,8	*	0,0421
14 vs. 21	401,4	369,8	*	0,0399

Appendix table S27: Mean values and significance levels for Figure 6 panel D (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
p.G247R 0/0 vs. 10/20	15,97	73,76	*	0,0124

Appendix table S28: Mean values and significance levels for Figure 7 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
DMSO0 vs. DMSO1	100	51,07	****	<0,0001
DMSO0 vs. DMSO2	100	24,04	****	<0,0001
DMSO0 vs. DMSO3	100	13,15	****	<0,0001
DMSO0 vs. DMSO4	100	7,216	****	<0,0001
DMSO0 vs. TB1	100	80,88	*	0,0427
DMSO0 vs. TB2	100	50,37	****	<0,0001
DMSO0 vs. TB3	100	27,69	****	<0,0001
DMSO0 vs. TB4	100	16,98	****	<0,0001
DMSO1 vs. DMSO2	51,07	24,04	**	0,0017
DMSO1 vs. DMSO3	51,07	13,15	****	<0,0001

DMSO1 vs. DMSO4	51,07	7,216	****	<0,0001
DMSO1 vs. TB0	51,07	100	****	<0,0001
DMSO1 vs. TB1	51,07	80,88	***	0,0005
DMSO1 vs. TB3	51,07	27,69	**	0,0077
DMSO1 vs. TB4	51,07	16,98	****	<0,0001
DMSO2 vs. TB0	24,04	100	****	<0,0001
DMSO2 vs. TB1	24,04	80,88	****	<0,0001
DMSO2 vs. TB2	24,04	50,37	**	0,0023
DMSO3 vs. TB0	13,15	100	****	<0,0001
DMSO3 vs. TB1	13,15	80,88	****	<0,0001
DMSO3 vs. TB2	13,15	50,37	****	<0,0001
DMSO4 vs. TB0	7,216	100	****	<0,0001
DMSO4 vs. TB1	7,216	80,88	****	<0,0001
DMSO4 vs. TB2	7,216	50,37	****	<0,0001
DMSO4 vs. TB3	7,216	27,69	*	0,0251
TB0 vs. TB1	100	80,88	*	0,0427
TB0 vs. TB2	100	50,37	****	<0,0001
TB0 vs. TB3	100	27,69	****	<0,0001
TB0 vs. TB4	100	16,98	****	<0,0001
TB1 vs. TB2	80,88	50,37	***	0,0004
TB1 vs. TB3	80,88	27,69	****	<0,0001
TB1 vs. TB4	80,88	16,98	****	<0,0001
TB2 vs. TB3	50,37	27,69	*	0,0102
TB2 vs. TB4	50,37	16,98	***	0,0001

Appendix table S29: Mean values and significance levels for Figure 7 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
DMSO0 vs. DMSO1	100	70,59	***	0,0002
DMSO0 vs. Taz/Bex1	100	79,03	**	0,0086
DMSO0 vs. DMSO2	100	43,51	****	<0,0001
DMSO0 vs. Taz/Bex2	100	58,05	****	<0,0001
DMSO0 vs. DMSO3	100	30,77	****	<0,0001
DMSO0 vs. Taz/Bex3	100	46,25	****	<0,0001
DMSO0 vs. DMSO4	100	19,43	****	<0,0001
DMSO0 vs. Taz/Bex4	100	43,13	****	<0,0001
Taz/Bex0 vs. DMSO1	100	70,59	***	0,0002
Taz/Bex0 vs. Taz/Bex1	100	79,03	**	0,0086
Taz/Bex0 vs. DMSO2	100	43,51	****	<0,0001
Taz/Bex0 vs. Taz/Bex2	100	58,05	****	<0,0001
Taz/Bex0 vs. DMSO3	100	30,77	****	<0,0001
Taz/Bex0 vs. Taz/Bex3	100	46,25	****	<0,0001
Taz/Bex0 vs. DMSO4	100	19,43	****	<0,0001

Taz/Bex0 vs. Taz/Bex4	100	43,13	****	<0,0001
DMSO1 vs. DMSO2	70,59	43,51	***	0,0005
DMSO1 vs. DMSO3	70,59	30,77	****	<0,0001
DMSO1 vs. Taz/Bex3	70,59	46,25	**	0,0018
DMSO1 vs. DMSO4	70,59	19,43	****	<0,0001
DMSO1 vs. Taz/Bex4	70,59	43,13	***	0,0004
Taz/Bex1 vs. DMSO2	79,03	43,51	****	<0,0001
Taz/Bex1 vs. Taz/Bex2	79,03	58,05	**	0,0085
Taz/Bex vs. DMSO3	79,03	30,77	****	<0,0001
Taz/Bex1 vs. Taz/Bex3	79,03	46,25	****	<0,0001
Taz/Bex1 vs. DMSO4	79,03	19,43	****	<0,0001
Taz/Bex1 vs. Taz/Bex4	79,03	43,13	****	<0,0001
DMSO2 vs. DMSO4	43,51	19,43	**	0,0021
Taz/Bex2 vs. DMSO3	58,05	30,77	***	0,0005
Taz/Bex2 vs. DMSO4	58,05	19,43	****	<0,0001
Taz/Bex3 vs. DMSO4	46,25	19,43	***	0,0006
DMSO4 vs. Taz/Bex4	19,43	43,13	**	0,0025

Appendix table S30: Mean values and significance levels for Figure 7 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
DMSO0 vs. DMSO1	100	60,06	**	0,0068
DMSO0 vs. DMSO2	100	43,42	***	0,0001
DMSO0 vs. Taz/Bex2	100	59,69	**	0,0062
DMSO0 vs. DMSO3	100	29,36	****	<0,0001
DMSO0 vs. Taz/Bex3	100	43,26	***	0,0001
DMSO0 vs. DMSO4	100	18,16	****	<0,0001
DMSO0 vs. Taz/Bex4	100	33,55	****	<0,0001
Taz/Bex0 vs. DMSO1	100	60,06	**	0,0068
Taz/Bex0 vs. DMSO2	100	43,42	***	0,0001
Taz/Bex0 vs. Taz/Bex2	100	59,69	**	0,0062
Taz/Bex0 vs. DMSO3	100	29,36	****	<0,0001
Taz/Bex0 vs. Taz/Bex3	100	43,26	***	0,0001
Taz/Bex0 vs. DMSO4	100	18,16	****	<0,0001
Taz/Bex0 vs. Taz/Bex4	100	33,55	****	<0,0001
DMSO1 vs. DMSO4	60,06	18,16	**	0,0042
Taz/Bex1 vs. DMSO2	78,12	43,42	*	0,0241
Taz/Bex1 vs. DMSO3	78,12	29,36	***	0,0008
Taz/Bex1 vs. Taz/Bex3	78,12	43,26	*	0,0232
Taz/Bex1 vs. DMSO4	78,12	18,16	****	<0,0001
Taz/Bex1 vs. Taz/Bex4	78,12	33,55	**	0,0022
Taz/Bex2 vs. DMSO4	59,69	18,16	**	0,0046

Appendix table S31: Mean values and significance levels for EV Figure 1 panel A
(significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
neg. contr. vs. Tazarotene	8,696	28,37	****	<0,0001
neg. contr. vs. pos. contr.	8,696	53,63	****	<0,0001
Tazarotene vs. Clindamycin	28,37	10,46	****	<0,0001
Tazarotene vs. Vorinostat	28,37	7,913	****	<0,0001
Tazarotene vs. Asenapine	28,37	9,489	****	<0,0001
Tazarotene vs. pos. contr.	28,37	53,63	****	<0,0001
Clindamycin vs. pos. contr.	10,46	53,63	****	<0,0001
Vorinostat vs. pos. contr.	7,913	53,63	****	<0,0001
Asenapine vs. pos. contr.	9,489	53,63	****	<0,0001

Appendix table S32: Mean values and significance levels for EV Figure 1 panel B
(significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
neg. contr. vs. Tazarotene	1,307	2,782	**	0,0025
Tazarotene vs. Clindamycin	2,782	1,616	*	0,0223
Tazarotene vs. Vorinostat	2,782	1,445	**	0,0068

Appendix table S33: Mean values and significance levels for EV Figure 1 panel C
(significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
neg. contr. vs. Tazarotene	1,517	3,125	**	0,0055
neg. contr. vs. pos. contr.	1,517	2,766	*	0,0446
Tazarotene vs. Vorinostat	3,125	1,315	**	0,0016
Vorinostat vs. pos. contr.	1,315	2,766	*	0,0141

Appendix table S34: Mean values and significance levels for EV Figure 2 panel E
(significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
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0/0 vs 0.25/0.5	13,43	21,47	*	0,0252
0/0 vs 0.5/1	13,43	26,38	***	0,0003
0/0 vs 1/2	13,43	39,13	****	<0,0001
0/0 vs 2.5/5	13,43	74,57	****	<0,0001
0.1/0.2 vs 0.5/1	18,71	26,38	*	0,0352
0.1/0.2 vs 1/2	18,71	39,13	****	<0,0001
0.1/0.2 vs 2.5/5	18,71	74,57	****	<0,0001
0.25/0.5 vs 1/2	21,47	39,13	****	<0,0001
0.25/0.5 vs 2.5/5	21,47	74,57	****	<0,0001
0.5/1 vs 1/2	26,38	39,13	***	0,0003
0.5/1 vs 2.5/5	26,38	74,57	****	<0,0001
1/2 vs 2.5/5	39,13	74,57	****	<0,0001

Appendix table S35: Mean values and significance levels for EV Figure 2 panel F (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
p.G247R - vs. +	17,0	49,2	****	<0,0001
p.G263V - vs. +	130,5	282,4	****	<0,0001
p.A279V - vs. +	132,0	227,8	***	0,0007
p.R349W - vs. +	20,5	39,8	*	0,0152
p.A279V - vs. +	96,0	120,6	**	0,001
p.R349W - vs. +	27,9	67,5	**	0,0015
p.G247R - vs. +	18,1	60,3	*	0,0132

Appendix table S36: Mean values and significance levels for EV Figure 3 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
RARRES1				
ctrl- vs. ctrl+	0,5626	73,99	****	<0,0001
ctrl- vs. MSD+	0,5626	65,22	****	<0,0001
MSD- vs. ctrl+	1,696	73,99	****	<0,0001
MSD- vs. MSD+	1,696	65,22	****	<0,0001
CYP26B1				
ctrl- vs. ctrl+	7,032	406,7	**	0,0033
ctrl- vs. MSD+	7,032	309,4	*	0,0209
MSD- vs. ctrl+	4,105	406,7	**	0,0021

MSD- vs. MSD+	4,105	309,4	*	0,014
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Appendix table S37: Mean values and significance levels for EV Figure 3 panel B (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
SUMF1				
MSD- vs. MSD+	11,21	7,926	*	0,0213

Appendix table S38: Mean values and significance levels for EV Figure 3 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
ARSB				
ctrl- vs. ctrl+	11,16	7,122	*	0,0278
STS				
ctrl- vs. ctrl+	14,12	6,614	*	0,0331
MSD- vs. ctrl+	15,14	6,614	*	0,0101
MSD- vs. MSD+	15,14	7,528	*	0,0165
SULF1				
ctrl- vs. ctrl+	89,04	793,3	****	<0,0001
ctrl- vs. MSD+	89,04	826,2	****	<0,0001
MSD- vs. ctrl+	121,3	793,3	****	<0,0001
MSD- vs. MSD+	121,3	826,2	****	<0,0001

Appendix table S39: Mean values and significance levels for EV Figure 4 panel A (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
control DMSO vs. MSD DMSO	0,2	0,2	ns	0,9972
control DMSO vs. control taz/bex	0,2085	-0,1749	****	<0,0001
control DMSO vs. MSD taz/bex	0,2085	-0,2289	****	<0,0001
MSD DMSO vs. control taz/bex	0,2009	-0,1749	****	<0,0001
MSD DMSO vs. MSD taz/bex	0,2009	-0,2289	****	<0,0001
control taz/bex vs. MSD taz/bex	-0,1749	-0,2289	ns	0,518

Appendix table S40: Mean values and significance levels for EV Figure 4 panel C (significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
control DMSO vs. control taz/bex	-0,1835	0,1222	**	0,0081
control DMSO vs. MSD taz/bex	-0,1835	0,1664	*	0,0147
MSD DMSO vs. control taz/bex	-0,1153	0,1222	*	0,0215
MSD DMSO vs. MSD taz/bex	-0,1153	0,1664	*	0,0275

Appendix table S41: Mean values and significance levels for MSD fibroblast cell count comparison (Appendix fig. S5A, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:MSD DMSO low vs. 3d:MSD DMSO low	450000	1693000	**	0,008
0d:MSD DMSO low vs. 3d:MSD DMSO medium	450000	2787167	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD DMSO high	450000	3110833	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD Taz	450000	2204167	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD Bex	450000	2237500	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD Taz/Bex	450000	1879167	***	0,0007
0d:MSD DMSO low vs. 6d:MSD DMSO low	450000	3514000	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD DMSO medium	450000	3279333	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD DMSO high	450000	3255167	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Taz	450000	2434333	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Bex	450000	2474333	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Taz/Bex	450000	1977167	***	0,0002
0d:MSD DMSO low vs. 9d:MSD DMSO low	450000	3909667	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD DMSO medium	450000	3771250	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD DMSO high	450000	3527833	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz	450000	2496667	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Bex	450000	2628833	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz/Bex	450000	2005917	***	0,0001
0d:MSD DMSO medium vs. 3d:MSD DMSO medium	900000	2787167	****	<0,0001
0d:MSD DMSO medium vs. 3d:MSD DMSO high	900000	3110833	****	<0,0001
0d:MSD DMSO medium vs. 3d:MSD Taz	900000	2204167	**	0,0037
0d:MSD DMSO medium vs. 3d:MSD Bex	900000	2237500	**	0,0024

0d:MSD DMSO medium vs. 6d:MSD DMSO low	900000	3514000	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD DMSO medium	900000	3279333	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD DMSO high	900000	3255167	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD Taz	900000	2434333	***	0,0001
0d:MSD DMSO medium vs. 6d:MSD Bex	900000	2474333	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD DMSO low	900000	3909667	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD DMSO medium	900000	3771250	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD DMSO high	900000	3527833	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz	900000	2496667	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Bex	900000	2628833	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz/Bex	900000	2005917	*	0,0389
0d:MSD DMSO high vs. 3d:MSD DMSO medium	1350000	2787167	***	0,0006
0d:MSD DMSO high vs. 3d:MSD DMSO high	1350000	3110833	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD DMSO low	1350000	3514000	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD DMSO medium	1350000	3279333	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD DMSO high	1350000	3255167	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD Taz	1350000	2434333	*	0,0488
0d:MSD DMSO high vs. 6d:MSD Bex	1350000	2474333	*	0,0318
0d:MSD DMSO high vs. 9d:MSD DMSO low	1350000	3909667	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD DMSO medium	1350000	3771250	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD DMSO high	1350000	3527833	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD Taz	1350000	2496667	*	0,0248
0d:MSD DMSO high vs. 9d:MSD Bex	1350000	2628833	**	0,0051
0d:MSD Taz vs. 3d:MSD DMSO medium	900000	2787167	****	<0,0001
0d:MSD Taz vs. 3d:MSD DMSO high	900000	3110833	****	<0,0001
0d:MSD Taz vs. 3d:MSD Taz	900000	2204167	**	0,0037
0d:MSD Taz vs. 3d:MSD Bex	900000	2237500	**	0,0024
0d:MSD Taz vs. 6d:MSD DMSO low	900000	3514000	****	<0,0001
0d:MSD Taz vs. 6d:MSD DMSO medium	900000	3279333	****	<0,0001
0d:MSD Taz vs. 6d:MSD DMSO high	900000	3255167	****	<0,0001
0d:MSD Taz vs. 6d:MSD Taz	900000	2434333	***	0,0001
0d:MSD Taz vs. 6d:MSD Bex	900000	2474333	****	<0,0001
0d:MSD Taz vs. 9d:MSD DMSO low	900000	3909667	****	<0,0001
0d:MSD Taz vs. 9d:MSD DMSO medium	900000	3771250	****	<0,0001
0d:MSD Taz vs. 9d:MSD DMSO high	900000	3527833	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz	900000	2496667	****	<0,0001
0d:MSD Taz vs. 9d:MSD Bex	900000	2628833	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz/Bex	900000	2005917	*	0,0389
0d:MSD Bex vs. 3d:MSD DMSO medium	900000	2787167	****	<0,0001

0d:MSD Bex vs. 3d:MSD DMSO high	900000	3110833	****	<0,0001
0d:MSD Bex vs. 3d:MSD Taz	900000	2204167	**	0,0037
0d:MSD Bex vs. 3d:MSD Bex	900000	2237500	**	0,0024
0d:MSD Bex vs. 6d:MSD DMSO low	900000	3514000	****	<0,0001
0d:MSD Bex vs. 6d:MSD DMSO medium	900000	3279333	****	<0,0001
0d:MSD Bex vs. 6d:MSD DMSO high	900000	3255167	****	<0,0001
0d:MSD Bex vs. 6d:MSD Taz	900000	2434333	***	0,0001
0d:MSD Bex vs. 6d:MSD Bex	900000	2474333	****	<0,0001
0d:MSD Bex vs. 9d:MSD DMSO low	900000	3909667	****	<0,0001
0d:MSD Bex vs. 9d:MSD DMSO medium	900000	3771250	****	<0,0001
0d:MSD Bex vs. 9d:MSD DMSO high	900000	3527833	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz	900000	2496667	****	<0,0001
0d:MSD Bex vs. 9d:MSD Bex	900000	2628833	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz/Bex	900000	2005917	*	0,0389
0d:MSD Taz/Bex vs. 3d:MSD DMSO medium	900000	2787167	****	<0,0001
0d:MSD Taz/Bex vs. 3d:MSD DMSO high	900000	3110833	****	<0,0001
0d:MSD Taz/Bex vs. 3d:MSD Taz	900000	2204167	**	0,0037
0d:MSD Taz/Bex vs. 3d:MSD Bex	900000	2237500	**	0,0024
0d:MSD Taz/Bex vs. 6d:MSD DMSO low	900000	3514000	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD DMSO medium	900000	3279333	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD DMSO high	900000	3255167	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD Taz	900000	2434333	***	0,0001
0d:MSD Taz/Bex vs. 6d:MSD Bex	900000	2474333	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD DMSO low	900000	3909667	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD DMSO medium	900000	3771250	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD DMSO high	900000	3527833	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Taz	900000	2496667	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Bex	900000	2628833	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Taz/Bex	900000	2005917	*	0,0389
3d:MSD DMSO low vs. 3d:MSD DMSO medium	1693000	2787167	*	0,044
3d:MSD DMSO low vs. 3d:MSD DMSO high	1693000	3110833	***	0,0008
3d:MSD DMSO low vs. 6d:MSD DMSO low	1693000	3514000	****	<0,0001
3d:MSD DMSO low vs. 6d:MSD DMSO medium	1693000	3279333	****	<0,0001
3d:MSD DMSO low vs. 6d:MSD DMSO high	1693000	3255167	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD DMSO low	1693000	3909667	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD DMSO medium	1693000	3771250	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD DMSO high	1693000	3527833	****	<0,0001
3d:MSD DMSO medium vs. 9d:MSD DMSO low	2787167	3909667	*	0,0325
3d:MSD DMSO high vs. 3d:MSD Taz/Bex	3110833	1879167	**	0,0092
3d:MSD DMSO high vs. 6d:MSD Taz/Bex	3110833	1977167	*	0,0287
3d:MSD DMSO high vs. 9d:MSD Taz/Bex	3110833	2005917	*	0,0393
3d:MSD Taz vs. 6d:MSD DMSO low	2204167	3514000	**	0,0034
3d:MSD Taz vs. 9d:MSD DMSO low	2204167	3909667	****	<0,0001
3d:MSD Taz vs. 9d:MSD DMSO medium	2204167	3771250	****	<0,0001

3d:MSD Taz vs. 9d:MSD DMSO high	2204167	3527833	**	0,0028
3d:MSD Bex vs. 6d:MSD DMSO low	2237500	3514000	**	0,0052
3d:MSD Bex vs. 9d:MSD DMSO low	2237500	3909667	****	<0,0001
3d:MSD Bex vs. 9d:MSD DMSO medium	2237500	3771250	***	0,0001
3d:MSD Bex vs. 9d:MSD DMSO high	2237500	3527833	**	0,0044
3d:MSD Taz/Bex vs. 6d:MSD DMSO low	1879167	3514000	****	<0,0001
3d:MSD Taz/Bex vs. 6d:MSD DMSO medium	1879167	3279333	**	0,001
3d:MSD Taz/Bex vs. 6d:MSD DMSO high	1879167	3255167	**	0,0014
3d:MSD Taz/Bex vs. 9d:MSD DMSO low	1879167	3909667	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD DMSO medium	1879167	3771250	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD DMSO high	1879167	3527833	****	<0,0001
6d:MSD DMSO low vs. 6d:MSD Taz/Bex	3514000	1977167	***	0,0001
6d:MSD DMSO low vs. 9d:MSD Taz/Bex	3514000	2005917	***	0,0002
6d:MSD DMSO medium vs. 6d:MSD Taz/Bex	3279333	1977167	**	0,0038
6d:MSD DMSO medium vs. 9d:MSD Taz/Bex	3279333	2005917	**	0,0054
6d:MSD DMSO high vs. 6d:MSD Taz/Bex	3255167	1977167	**	0,0051
6d:MSD DMSO high vs. 9d:MSD Taz/Bex	3255167	2005917	**	0,0074
6d:MSD Taz vs. 9d:MSD DMSO low	2434333	3909667	***	0,0003
6d:MSD Taz vs. 9d:MSD DMSO medium	2434333	3771250	**	0,0024
6d:MSD Taz vs. 9d:MSD DMSO high	2434333	3527833	*	0,0444
6d:MSD Bex vs. 9d:MSD DMSO low	2474333	3909667	***	0,0006
6d:MSD Bex vs. 9d:MSD DMSO medium	2474333	3771250	**	0,004
6d:MSD Taz/Bex vs. 9d:MSD DMSO low	1977167	3909667	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO medium	1977167	3771250	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO high	1977167	3527833	***	0,0001
9d:MSD DMSO low vs. 9d:MSD Taz	3909667	2496667	***	0,0008
9d:MSD DMSO low vs. 9d:MSD Bex	3909667	2628833	**	0,0049
9d:MSD DMSO low vs. 9d:MSD Taz/Bex	3909667	2005917	****	<0,0001
9d:MSD DMSO medium vs. 9d:MSD Taz	3771250	2496667	**	0,0054
9d:MSD DMSO medium vs. 9d:MSD Bex	3771250	2628833	*	0,0261
9d:MSD DMSO medium vs. 9d:MSD Taz/Bex	3771250	2005917	****	<0,0001
9d:MSD DMSO high vs. 9d:MSD Taz/Bex	3527833	2005917	***	0,0002

Appendix table S42: Mean values and significance levels for control fibroblast cell count comparison (Appendix fig. S5B, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:Ctrl. DMSO low vs. 0d:Ctrl. DMSO high	450000	1350000	***	0,0005
0d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO low	450000	1483800	****	<0,0001
0d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO medium	450000	1854200	****	<0,0001
0d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO high	450000	2272200	****	<0,0001
0d:Ctrl. DMSO low vs. 3d:Ctrl. Taz	450000	1394200	***	0,0002
0d:Ctrl. DMSO low vs. 3d:Ctrl. Bex	450000	1548200	****	<0,0001
0d:Ctrl. DMSO low vs. 3d:Ctrl. Taz/Bex	450000	1293200	**	0,0018

0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO low	450000	2646000	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO medium	450000	2476000	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	450000	2682000	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. Taz	450000	1285200	**	0,0021
0d:Ctrl. DMSO low vs. 6d:Ctrl. Bex	450000	1436800	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. Taz/Bex	450000	1393400	***	0,0002
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	450000	3385000	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	450000	3084600	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	450000	2919600	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	450000	1288600	**	0,0019
0d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	450000	1498400	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	450000	1340600	***	0,0006
0d:Ctrl. DMSO medium vs. 3d:Ctrl. DMSO medium	900000	1854200	***	0,0001
0d:Ctrl. DMSO medium vs. 3d:Ctrl. DMSO high	900000	2272200	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO low	900000	2646000	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO medium	900000	2476000	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO high	900000	2682000	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO low	900000	3385000	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO medium	900000	3084600	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	900000	2919600	****	<0,0001
0d:Ctrl. DMSO high vs. 3d:Ctrl. DMSO high	1350000	2272200	***	0,0003
0d:Ctrl. DMSO high vs. 6d:Ctrl. DMSO low	1350000	2646000	****	<0,0001
0d:Ctrl. DMSO high vs. 6d:Ctrl. DMSO medium	1350000	2476000	****	<0,0001
0d:Ctrl. DMSO high vs. 6d:Ctrl. DMSO high	1350000	2682000	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO low	1350000	3385000	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO medium	1350000	3084600	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO high	1350000	2919600	****	<0,0001
0d:Ctrl. Taz vs. 3d:Ctrl. DMSO medium	900000	1854200	***	0,0001
0d:Ctrl. Taz vs. 3d:Ctrl. DMSO high	900000	2272200	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO low	900000	2646000	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO medium	900000	2476000	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO high	900000	2682000	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	900000	3385000	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	900000	3084600	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	900000	2919600	****	<0,0001
0d:Ctrl. Bex vs. 3d:Ctrl. DMSO medium	900000	1854200	***	0,0001
0d:Ctrl. Bex vs. 3d:Ctrl. DMSO high	900000	2272200	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO low	900000	2646000	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO medium	900000	2476000	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	900000	2682000	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	900000	3385000	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	900000	3084600	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	900000	2919600	****	<0,0001
0d:Ctrl. Taz/Bex vs. 3d:Ctrl. DMSO medium	900000	1854200	***	0,0001

0d:Ctrl. Taz/Bex vs. 3d:Ctrl. DMSO high	900000	2272200	****	<0,0001
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO low	900000	2646000	****	<0,0001
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO medium	900000	2476000	****	<0,0001
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO high	900000	2682000	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	900000	3385000	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	900000	3084600	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	900000	2919600	****	<0,0001
3d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO high	1483800	2272200	**	0,0055
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO low	1483800	2646000	****	<0,0001
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO medium	1483800	2476000	****	<0,0001
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	1483800	2682000	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	1483800	3385000	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	1483800	3084600	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	1483800	2919600	****	<0,0001
3d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO low	1854200	2646000	**	0,0051
3d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO high	1854200	2682000	**	0,0024
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO low	1854200	3385000	****	<0,0001
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO medium	1854200	3084600	****	<0,0001
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	1854200	2919600	****	<0,0001
3d:Ctrl. DMSO high vs. 3d:Ctrl. Taz	2272200	1394200	***	0,0008
3d:Ctrl. DMSO high vs. 3d:Ctrl. Bex	2272200	1548200	*	0,0189
3d:Ctrl. DMSO high vs. 3d:Ctrl. Taz/Bex	2272200	1293200	****	<0,0001
3d:Ctrl. DMSO high vs. 6d:Ctrl. Taz	2272200	1285200	****	<0,0001
3d:Ctrl. DMSO high vs. 6d:Ctrl. Bex	2272200	1436800	**	0,0021
3d:Ctrl. DMSO high vs. 6d:Ctrl. Taz/Bex	2272200	1393400	***	0,0008
3d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO low	2272200	3385000	****	<0,0001
3d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO medium	2272200	3084600	**	0,0034
3d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	2272200	1288600	****	<0,0001
3d:Ctrl. DMSO high vs. 9d:Ctrl. Bex	2272200	1498400	**	0,0073
3d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	2272200	1340600	***	0,0003
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO low	1394200	2646000	****	<0,0001
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO medium	1394200	2476000	****	<0,0001
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO high	1394200	2682000	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	1394200	3385000	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	1394200	3084600	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	1394200	2919600	****	<0,0001
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO low	1548200	2646000	****	<0,0001
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO medium	1548200	2476000	***	0,0003
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	1548200	2682000	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	1548200	3385000	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	1548200	3084600	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	1548200	2919600	****	<0,0001
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO low	1293200	2646000	****	<0,0001
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO medium	1293200	2476000	****	<0,0001
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO high	1293200	2682000	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	1293200	3385000	****	<0,0001

3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	1293200	3084600	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	1293200	2919600	****	<0,0001
6d:Ctrl. DMSO low vs. 6d:Ctrl. Taz	2646000	1285200	****	<0,0001
6d:Ctrl. DMSO low vs. 6d:Ctrl. Bex	2646000	1436800	****	<0,0001
6d:Ctrl. DMSO low vs. 6d:Ctrl. Taz/Bex	2646000	1393400	****	<0,0001
6d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	2646000	3385000	*	0,0143
6d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	2646000	1288600	****	<0,0001
6d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	2646000	1498400	****	<0,0001
6d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	2646000	1340600	****	<0,0001
6d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz	2476000	1285200	****	<0,0001
6d:Ctrl. DMSO medium vs. 6d:Ctrl. Bex	2476000	1436800	****	<0,0001
6d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz/Bex	2476000	1393400	****	<0,0001
6d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO low	2476000	3385000	***	0,0004
6d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	2476000	1288600	****	<0,0001
6d:Ctrl. DMSO medium vs. 9d:Ctrl. Bex	2476000	1498400	****	<0,0001
6d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz/Bex	2476000	1340600	****	<0,0001
6d:Ctrl. DMSO high vs. 6d:Ctrl. Taz	2682000	1285200	****	<0,0001
6d:Ctrl. DMSO high vs. 6d:Ctrl. Bex	2682000	1436800	****	<0,0001
6d:Ctrl. DMSO high vs. 6d:Ctrl. Taz/Bex	2682000	1393400	****	<0,0001
6d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO low	2682000	3385000	*	0,0275
6d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	2682000	1288600	****	<0,0001
6d:Ctrl. DMSO high vs. 9d:Ctrl. Bex	2682000	1498400	****	<0,0001
6d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	2682000	1340600	****	<0,0001
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	1285200	3385000	****	<0,0001
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	1285200	3084600	****	<0,0001
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	1285200	2919600	****	<0,0001
6d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	1436800	3385000	****	<0,0001
6d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	1436800	3084600	****	<0,0001
6d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	1436800	2919600	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	1393400	3385000	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	1393400	3084600	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	1393400	2919600	****	<0,0001
9d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	3385000	1288600	****	<0,0001
9d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	3385000	1498400	****	<0,0001
9d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	3385000	1340600	****	<0,0001
9d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	3084600	1288600	****	<0,0001
9d:Ctrl. DMSO medium vs. 9d:Ctrl. Bex	3084600	1498400	****	<0,0001
9d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz/Bex	3084600	1340600	****	<0,0001
9d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	2919600	1288600	****	<0,0001
9d:Ctrl. DMSO high vs. 9d:Ctrl. Bex	2919600	1498400	****	<0,0001
9d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	2919600	1340600	****	<0,0001

Appendix table S43: Mean values and significance levels for MSD fibroblast total protein comparison (Appendix fig. S5C, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:MSD DMSO low vs. 3d:MSD DMSO medium	99,51	512,1	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD DMSO high	99,51	583,4	****	<0,0001
0d:MSD DMSO low vs. 3d:MSD Taz	99,51	375,5	*	0,012
0d:MSD DMSO low vs. 3d:MSD Bex	99,51	405,2	**	0,0023
0d:MSD DMSO low vs. 6d:MSD DMSO low	99,51	683,8	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD DMSO medium	99,51	648	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD DMSO high	99,51	632,2	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Taz	99,51	502,1	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Bex	99,51	497,2	****	<0,0001
0d:MSD DMSO low vs. 6d:MSD Taz/Bex	99,51	373,4	*	0,0134
0d:MSD DMSO low vs. 9d:MSD DMSO low	99,51	811,7	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD DMSO medium	99,51	731,3	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD DMSO high	99,51	737,2	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz	99,51	507,8	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Bex	99,51	582,8	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz/Bex	99,51	520,4	****	<0,0001
0d:MSD DMSO medium vs. 3d:MSD DMSO medium	181,1	512,1	***	0,0005
0d:MSD DMSO medium vs. 3d:MSD DMSO high	181,1	583,4	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD DMSO low	181,1	683,8	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD DMSO medium	181,1	648	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD DMSO high	181,1	632,2	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD Taz	181,1	502,1	**	0,0023
0d:MSD DMSO medium vs. 6d:MSD Bex	181,1	497,2	**	0,0012
0d:MSD DMSO medium vs. 9d:MSD DMSO low	181,1	811,7	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD DMSO medium	181,1	731,3	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD DMSO high	181,1	737,2	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz	181,1	507,8	**	0,0016
0d:MSD DMSO medium vs. 9d:MSD Bex	181,1	582,8	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz/Bex	181,1	520,4	***	0,0003
0d:MSD DMSO high vs. 3d:MSD DMSO high	268,4	583,4	**	0,0013
0d:MSD DMSO high vs. 6d:MSD DMSO low	268,4	683,8	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD DMSO medium	268,4	648	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD DMSO high	268,4	632,2	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD DMSO low	268,4	811,7	****	<0,0001

0d:MSD DMSO high vs. 9d:MSD DMSO medium	268,4	731,3	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD DMSO high	268,4	737,2	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD Bex	268,4	582,8	**	0,0014
0d:MSD DMSO high vs. 9d:MSD Taz/Bex	268,4	520,4	*	0,0396
0d:MSD Taz vs. 3d:MSD DMSO medium	178,4	512,1	***	0,0004
0d:MSD Taz vs. 3d:MSD DMSO high	178,4	583,4	****	<0,0001
0d:MSD Taz vs. 6d:MSD DMSO low	178,4	683,8	****	<0,0001
0d:MSD Taz vs. 6d:MSD DMSO medium	178,4	648	****	<0,0001
0d:MSD Taz vs. 6d:MSD DMSO high	178,4	632,2	****	<0,0001
0d:MSD Taz vs. 6d:MSD Taz	178,4	502,1	**	0,0019
0d:MSD Taz vs. 6d:MSD Bex	178,4	497,2	**	0,0011
0d:MSD Taz vs. 9d:MSD DMSO low	178,4	811,7	****	<0,0001
0d:MSD Taz vs. 9d:MSD DMSO medium	178,4	731,3	****	<0,0001
0d:MSD Taz vs. 9d:MSD DMSO high	178,4	737,2	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz	178,4	507,8	**	0,0014
0d:MSD Taz vs. 9d:MSD Bex	178,4	582,8	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz/Bex	178,4	520,4	***	0,0002
0d:MSD Bex vs. 3d:MSD DMSO medium	187,7	512,1	***	0,0008
0d:MSD Bex vs. 3d:MSD DMSO high	187,7	583,4	****	<0,0001
0d:MSD Bex vs. 6d:MSD DMSO low	187,7	683,8	****	<0,0001
0d:MSD Bex vs. 6d:MSD DMSO medium	187,7	648	****	<0,0001
0d:MSD Bex vs. 6d:MSD DMSO high	187,7	632,2	****	<0,0001
0d:MSD Bex vs. 6d:MSD Taz	187,7	502,1	**	0,0032
0d:MSD Bex vs. 6d:MSD Bex	187,7	497,2	**	0,0018
0d:MSD Bex vs. 9d:MSD DMSO low	187,7	811,7	****	<0,0001
0d:MSD Bex vs. 9d:MSD DMSO medium	187,7	731,3	****	<0,0001
0d:MSD Bex vs. 9d:MSD DMSO high	187,7	737,2	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz	187,7	507,8	**	0,0024
0d:MSD Bex vs. 9d:MSD Bex	187,7	582,8	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz/Bex	187,7	520,4	***	0,0005
0d:MSD Taz/Bex vs. 3d:MSD DMSO medium	185,9	512,1	***	0,0007
0d:MSD Taz/Bex vs. 3d:MSD DMSO high	185,9	583,4	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD DMSO low	185,9	683,8	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD DMSO medium	185,9	648	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD DMSO high	185,9	632,2	****	<0,0001
0d:MSD Taz/Bex vs. 6d:MSD Taz	185,9	502,1	**	0,0029
0d:MSD Taz/Bex vs. 6d:MSD Bex	185,9	497,2	**	0,0017
0d:MSD Taz/Bex vs. 9d:MSD DMSO low	185,9	811,7	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD DMSO medium	185,9	731,3	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD DMSO high	185,9	737,2	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Taz	185,9	507,8	**	0,0022
0d:MSD Taz/Bex vs. 9d:MSD Bex	185,9	582,8	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Taz/Bex	185,9	520,4	***	0,0004
3d:MSD DMSO low vs. 3d:MSD DMSO high	300,4	583,4	**	0,0082
3d:MSD DMSO low vs. 6d:MSD DMSO low	300,4	683,8	****	<0,0001
3d:MSD DMSO low vs. 6d:MSD DMSO	300,4	648	***	0,0002

medium				
3d:MSD DMSO low vs. 6d:MSD DMSO high	300,4	632,2	***	0,0005
3d:MSD DMSO low vs. 9d:MSD DMSO low	300,4	811,7	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD DMSO medium	300,4	731,3	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD DMSO high	300,4	737,2	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD Bex	300,4	582,8	**	0,0085
3d:MSD DMSO medium vs. 9d:MSD DMSO low	512,1	811,7	**	0,0033
3d:MSD DMSO high vs. 3d:MSD Taz/Bex	583,4	326,5	*	0,0313
3d:MSD Taz vs. 6d:MSD DMSO low	375,5	683,8	**	0,002
3d:MSD Taz vs. 6d:MSD DMSO medium	375,5	648	*	0,0144
3d:MSD Taz vs. 6d:MSD DMSO high	375,5	632,2	*	0,0317
3d:MSD Taz vs. 9d:MSD DMSO low	375,5	811,7	****	<0,0001
3d:MSD Taz vs. 9d:MSD DMSO medium	375,5	731,3	***	0,0001
3d:MSD Taz vs. 9d:MSD DMSO high	375,5	737,2	****	<0,0001
3d:MSD Bex vs. 6d:MSD DMSO low	405,2	683,8	*	0,0104
3d:MSD Bex vs. 9d:MSD DMSO low	405,2	811,7	****	<0,0001
3d:MSD Bex vs. 9d:MSD DMSO medium	405,2	731,3	***	0,0007
3d:MSD Bex vs. 9d:MSD DMSO high	405,2	737,2	***	0,0005
3d:MSD Taz/Bex vs. 6d:MSD DMSO low	326,5	683,8	****	<0,0001
3d:MSD Taz/Bex vs. 6d:MSD DMSO medium	326,5	648	***	0,0009
3d:MSD Taz/Bex vs. 6d:MSD DMSO high	326,5	632,2	**	0,0023
3d:MSD Taz/Bex vs. 9d:MSD DMSO low	326,5	811,7	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD DMSO medium	326,5	731,3	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD DMSO high	326,5	737,2	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD Bex	326,5	582,8	*	0,0322
6d:MSD DMSO low vs. 6d:MSD Taz/Bex	683,8	373,4	**	0,0017
6d:MSD DMSO medium vs. 6d:MSD Taz/Bex	648	373,4	*	0,0129
6d:MSD DMSO high vs. 6d:MSD Taz/Bex	632,2	373,4	*	0,0286
6d:MSD Taz vs. 9d:MSD DMSO low	502,1	811,7	**	0,0042
6d:MSD Bex vs. 9d:MSD DMSO low	497,2	811,7	**	0,0014
6d:MSD Taz/Bex vs. 9d:MSD DMSO low	373,4	811,7	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO medium	373,4	731,3	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO high	373,4	737,2	****	<0,0001
9d:MSD DMSO low vs. 9d:MSD Taz	811,7	507,8	**	0,0057
9d:MSD DMSO low vs. 9d:MSD Taz/Bex	811,7	520,4	**	0,0052

Appendix table S44: Mean values and significance levels for control fibroblast total protein comparison (Appendix fig. S5D, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:Ctrl. DMSO low vs. 0d:Ctrl. DMSO high	81,28	279,2	***	0,0009
0d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO medium	81,28	291,5	***	0,0002

0d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO high	81,28	340,4	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO low	81,28	376,2	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO medium	81,28	397,2	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	81,28	422,7	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. Bex	81,28	316,4	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	81,28	488,7	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	81,28	501,3	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	81,28	563,2	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	81,28	251,4	*	0,0215
0d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	81,28	373,4	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	81,28	251,7	*	0,0209
0d:Ctrl. DMSO medium vs. 3d:Ctrl. DMSO high	150,9	340,4	**	0,0019
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO low	150,9	376,2	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO medium	150,9	397,2	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO high	150,9	422,7	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. Bex	150,9	316,4	*	0,0303
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO low	150,9	488,7	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO medium	150,9	501,3	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	150,9	563,2	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. Bex	150,9	373,4	***	0,0002
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO low	279,2	488,7	***	0,0003
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO medium	279,2	501,3	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO high	279,2	563,2	****	<0,0001
0d:Ctrl. Taz vs. 3d:Ctrl. DMSO high	149,4	340,4	**	0,0038
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO low	149,4	376,2	***	0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO medium	149,4	397,2	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO high	149,4	422,7	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. Bex	149,4	316,4	*	0,0457
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	149,4	488,7	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	149,4	501,3	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	149,4	563,2	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. Bex	149,4	373,4	***	0,0004
0d:Ctrl. Bex vs. 3d:Ctrl. DMSO high	159,6	340,4	**	0,0091
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO low	159,6	376,2	***	0,0004
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO medium	159,6	397,2	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	159,6	422,7	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	159,6	488,7	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	159,6	501,3	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	159,6	563,2	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. Bex	159,6	373,4	**	0,0011
0d:Ctrl. Taz/Bex vs. 3d:Ctrl. DMSO high	154,4	340,4	**	0,0059
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO low	154,4	376,2	***	0,0002
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO medium	154,4	397,2	****	<0,0001
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO high	154,4	422,7	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	154,4	488,7	****	<0,0001

0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	154,4	501,3	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	154,4	563,2	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. Bex	154,4	373,4	***	0,0007
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO low	200,4	376,2	**	0,0068
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO medium	200,4	397,2	***	0,001
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	200,4	422,7	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	200,4	488,7	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	200,4	501,3	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	200,4	563,2	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	200,4	373,4	*	0,0172
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO low	291,5	488,7	***	0,0009
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO medium	291,5	501,3	***	0,0003
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	291,5	563,2	****	<0,0001
3d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO medium	340,4	501,3	*	0,024
3d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO high	340,4	563,2	****	<0,0001
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO low	205,3	376,2	*	0,0201
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO medium	205,3	397,2	**	0,0036
3d:Ctrl. Taz vs. 6d:Ctrl. DMSO high	205,3	422,7	***	0,0003
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	205,3	488,7	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	205,3	501,3	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	205,3	563,2	****	<0,0001
3d:Ctrl. Taz vs. 9d:Ctrl. Bex	205,3	373,4	*	0,0424
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO medium	238,1	397,2	*	0,0488
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	238,1	422,7	**	0,0067
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	238,1	488,7	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	238,1	501,3	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	238,1	563,2	****	<0,0001
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO low	190,1	376,2	**	0,0058
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO medium	190,1	397,2	***	0,0009
3d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO high	190,1	422,7	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	190,1	488,7	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	190,1	501,3	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	190,1	563,2	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. Bex	190,1	373,4	*	0,0141
6d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	376,2	563,2	**	0,0025
6d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz	397,2	236,8	*	0,0444
6d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz/Bex	397,2	228,3	*	0,0236
6d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	397,2	563,2	*	0,0157
6d:Ctrl. DMSO high vs. 6d:Ctrl. Taz	422,7	236,8	**	0,006
6d:Ctrl. DMSO high vs. 6d:Ctrl. Taz/Bex	422,7	228,3	**	0,0029
6d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	422,7	251,4	*	0,0196
6d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	422,7	251,7	*	0,0202
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	236,8	488,7	****	<0,0001
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	236,8	501,3	****	<0,0001
6d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	236,8	563,2	****	<0,0001
6d:Ctrl. Bex vs. 9d:Ctrl. DMSO low	316,4	488,7	*	0,0181

6d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	316,4	501,3	**	0,0065
6d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	316,4	563,2	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO low	228,3	488,7	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	228,3	501,3	****	<0,0001
6d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	228,3	563,2	****	<0,0001
9d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	488,7	251,4	****	<0,0001
9d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	488,7	251,7	****	<0,0001
9d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	501,3	251,4	****	<0,0001
9d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz/Bex	501,3	251,7	****	<0,0001
9d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	563,2	251,4	****	<0,0001
9d:Ctrl. DMSO high vs. 9d:Ctrl. Bex	563,2	373,4	**	0,0043
9d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	563,2	251,7	****	<0,0001

Appendix table S45: Mean values and significance levels for MSD fibroblast ARSA activity comparison (Appendix fig. S5E, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:MSD DMSO low vs. 3d:MSD Taz/Bex	10,36	30,16	*	0,0159
0d:MSD DMSO low vs. 6d:MSD Taz	10,36	34,32	***	0,0006
0d:MSD DMSO low vs. 6d:MSD Taz/Bex	10,36	105,6	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz	10,36	73,39	****	<0,0001
0d:MSD DMSO low vs. 9d:MSD Taz/Bex	10,36	130,8	****	<0,0001
0d:MSD DMSO medium vs. 6d:MSD Taz	12,1	34,32	**	0,0026
0d:MSD DMSO medium vs. 6d:MSD Taz/Bex	12,1	105,6	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz	12,1	73,39	****	<0,0001
0d:MSD DMSO medium vs. 9d:MSD Taz/Bex	12,1	130,8	****	<0,0001
0d:MSD DMSO high vs. 6d:MSD Taz	12,28	34,32	**	0,003
0d:MSD DMSO high vs. 6d:MSD Taz/Bex	12,28	105,6	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD Taz	12,28	73,39	****	<0,0001
0d:MSD DMSO high vs. 9d:MSD Taz/Bex	12,28	130,8	****	<0,0001
0d:MSD Taz vs. 3d:MSD Taz/Bex	11,59	30,16	*	0,0363
0d:MSD Taz vs. 6d:MSD Taz	11,59	34,32	**	0,0017
0d:MSD Taz vs. 6d:MSD Taz/Bex	11,59	105,6	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz	11,59	73,39	****	<0,0001
0d:MSD Taz vs. 9d:MSD Taz/Bex	11,59	130,8	****	<0,0001
0d:MSD Bex vs. 3d:MSD Taz/Bex	11,23	30,16	*	0,0287
0d:MSD Bex vs. 6d:MSD Taz	11,23	34,32	**	0,0013
0d:MSD Bex vs. 6d:MSD Taz/Bex	11,23	105,6	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz	11,23	73,39	****	<0,0001
0d:MSD Bex vs. 9d:MSD Taz/Bex	11,23	130,8	****	<0,0001
0d:MSD Taz/Bex vs. 3d:MSD Taz/Bex	9,065	30,16	**	0,0062
0d:MSD Taz/Bex vs. 6d:MSD Taz	9,065	34,32	***	0,0002
0d:MSD Taz/Bex vs. 6d:MSD Taz/Bex	9,065	105,6	****	<0,0001
0d:MSD Taz/Bex vs. 9d:MSD Taz	9,065	73,39	****	<0,0001

0d:MSD Taz/Bex vs. 9d:MSD Taz/Bex	9,065	130,8	****	<0,0001
3d:MSD DMSO low vs. 3d:MSD Taz/Bex	5,343	30,16	***	0,0003
3d:MSD DMSO low vs. 6d:MSD Taz	5,343	34,32	****	<0,0001
3d:MSD DMSO low vs. 6d:MSD Taz/Bex	5,343	105,6	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD Taz	5,343	73,39	****	<0,0001
3d:MSD DMSO low vs. 9d:MSD Bex	5,343	24,37	*	0,027
3d:MSD DMSO low vs. 9d:MSD Taz/Bex	5,343	130,8	****	<0,0001
3d:MSD DMSO medium vs. 3d:MSD Taz/Bex	7,02	30,16	**	0,0012
3d:MSD DMSO medium vs. 6d:MSD Taz	7,02	34,32	****	<0,0001
3d:MSD DMSO medium vs. 6d:MSD Taz/Bex	7,02	105,6	****	<0,0001
3d:MSD DMSO medium vs. 9d:MSD Taz	7,02	73,39	****	<0,0001
3d:MSD DMSO medium vs. 9d:MSD Taz/Bex	7,02	130,8	****	<0,0001
3d:MSD DMSO high vs. 3d:MSD Taz/Bex	9,503	30,16	**	0,0086
3d:MSD DMSO high vs. 6d:MSD Taz	9,503	34,32	***	0,0003
3d:MSD DMSO high vs. 6d:MSD Taz/Bex	9,503	105,6	****	<0,0001
3d:MSD DMSO high vs. 9d:MSD Taz	9,503	73,39	****	<0,0001
3d:MSD DMSO high vs. 9d:MSD Taz/Bex	9,503	130,8	****	<0,0001
3d:MSD Taz vs. 3d:MSD Taz/Bex	9,762	30,16	*	0,0103
3d:MSD Taz vs. 6d:MSD Taz	9,762	34,32	***	0,0004
3d:MSD Taz vs. 6d:MSD Taz/Bex	9,762	105,6	****	<0,0001
3d:MSD Taz vs. 9d:MSD Taz	9,762	73,39	****	<0,0001
3d:MSD Taz vs. 9d:MSD Taz/Bex	9,762	130,8	****	<0,0001
3d:MSD Bex vs. 3d:MSD Taz/Bex	10,12	30,16	*	0,0134
3d:MSD Bex vs. 6d:MSD Taz	10,12	34,32	***	0,0005
3d:MSD Bex vs. 6d:MSD Taz/Bex	10,12	105,6	****	<0,0001
3d:MSD Bex vs. 9d:MSD Taz	10,12	73,39	****	<0,0001
3d:MSD Bex vs. 9d:MSD Taz/Bex	10,12	130,8	****	<0,0001
3d:MSD Taz/Bex vs. 6d:MSD DMSO low	30,16	7,14	**	0,0014
3d:MSD Taz/Bex vs. 6d:MSD DMSO medium	30,16	11,21	*	0,0284
3d:MSD Taz/Bex vs. 6d:MSD Taz/Bex	30,16	105,6	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD Taz	30,16	73,39	****	<0,0001
3d:MSD Taz/Bex vs. 9d:MSD Taz/Bex	30,16	130,8	****	<0,0001
6d:MSD DMSO low vs. 6d:MSD Taz	7,14	34,32	****	<0,0001
6d:MSD DMSO low vs. 6d:MSD Taz/Bex	7,14	105,6	****	<0,0001
6d:MSD DMSO low vs. 9d:MSD Taz	7,14	73,39	****	<0,0001
6d:MSD DMSO low vs. 9d:MSD Taz/Bex	7,14	130,8	****	<0,0001
6d:MSD DMSO medium vs. 6d:MSD Taz	11,21	34,32	**	0,0013
6d:MSD DMSO medium vs. 6d:MSD Taz/Bex	11,21	105,6	****	<0,0001
6d:MSD DMSO medium vs. 9d:MSD Taz	11,21	73,39	****	<0,0001
6d:MSD DMSO medium vs. 9d:MSD Taz/Bex	11,21	130,8	****	<0,0001
6d:MSD DMSO high vs. 6d:MSD Taz	13,55	34,32	**	0,0079
6d:MSD DMSO high vs. 6d:MSD Taz/Bex	13,55	105,6	****	<0,0001
6d:MSD DMSO high vs. 9d:MSD Taz	13,55	73,39	****	<0,0001
6d:MSD DMSO high vs. 9d:MSD Taz/Bex	13,55	130,8	****	<0,0001
6d:MSD Taz vs. 6d:MSD Taz/Bex	34,32	105,6	****	<0,0001
6d:MSD Taz vs. 9d:MSD DMSO low	34,32	13,27	**	0,0064
6d:MSD Taz vs. 9d:MSD DMSO medium	34,32	16,23	*	0,0493

6d:MSD Taz vs. 9d:MSD Taz	34,32	73,39	****	<0,0001
6d:MSD Taz vs. 9d:MSD Taz/Bex	34,32	130,8	****	<0,0001
6d:MSD Bex vs. 6d:MSD Taz/Bex	16,87	105,6	****	<0,0001
6d:MSD Bex vs. 9d:MSD Taz	16,87	73,39	****	<0,0001
6d:MSD Bex vs. 9d:MSD Taz/Bex	16,87	130,8	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO low	105,6	13,27	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO medium	105,6	16,23	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD DMSO high	105,6	16,67	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD Taz	105,6	73,39	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD Bex	105,6	24,37	****	<0,0001
6d:MSD Taz/Bex vs. 9d:MSD Taz/Bex	105,6	130,8	***	0,0002
9d:MSD DMSO low vs. 9d:MSD Taz	13,27	73,39	****	<0,0001
9d:MSD DMSO low vs. 9d:MSD Taz/Bex	13,27	130,8	****	<0,0001
9d:MSD DMSO medium vs. 9d:MSD Taz	16,23	73,39	****	<0,0001
9d:MSD DMSO medium vs. 9d:MSD Taz/Bex	16,23	130,8	****	<0,0001
9d:MSD DMSO high vs. 9d:MSD Taz	16,67	73,39	****	<0,0001
9d:MSD DMSO high vs. 9d:MSD Taz/Bex	16,67	130,8	****	<0,0001
9d:MSD Taz vs. 9d:MSD Bex	73,39	24,37	****	<0,0001
9d:MSD Taz vs. 9d:MSD Taz/Bex	73,39	130,8	****	<0,0001
9d:MSD Bex vs. 9d:MSD Taz/Bex	24,37	130,8	****	<0,0001

Appendix table S46: Mean values and significance levels for control fibroblast ARSA activity comparison (Appendix fig. S5F, significant differences only)

Comparison	Mean 1	Mean 2	Summary	Adjusted P Value
0d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	654,9	1102	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. Taz	654,9	1171	****	<0,0001
0d:Ctrl. DMSO low vs. 6d:Ctrl. Taz/Bex	654,9	1124	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	654,9	1040	**	0,0019
0d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	654,9	1147	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	654,9	1271	****	<0,0001
0d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	654,9	1087	***	0,0005
0d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	654,9	1244	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO high	679,3	1102	***	0,0003
0d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz	679,3	1171	****	<0,0001
0d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz/Bex	679,3	1124	***	0,0003
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO medium	679,3	1040	**	0,0059
0d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	679,3	1147	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	679,3	1271	****	<0,0001
0d:Ctrl. DMSO medium vs. 9d:Ctrl. Bex	679,3	1087	**	0,0017
0d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz/Bex	679,3	1244	****	<0,0001
0d:Ctrl. DMSO high vs. 6d:Ctrl. DMSO high	680,6	1102	***	0,0003
0d:Ctrl. DMSO high vs. 6d:Ctrl. Taz	680,6	1171	****	<0,0001
0d:Ctrl. DMSO high vs. 6d:Ctrl. Taz/Bex	680,6	1124	***	0,0003

0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO medium	680,6	1040	**	0,0063
0d:Ctrl. DMSO high vs. 9d:Ctrl. DMSO high	680,6	1147	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	680,6	1271	****	<0,0001
0d:Ctrl. DMSO high vs. 9d:Ctrl. Bex	680,6	1087	**	0,0018
0d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	680,6	1244	****	<0,0001
0d:Ctrl. Taz vs. 3d:Ctrl. Taz	609,6	921	*	0,0437
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO medium	609,6	927,9	*	0,0338
0d:Ctrl. Taz vs. 6d:Ctrl. DMSO high	609,6	1102	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. Taz	609,6	1171	****	<0,0001
0d:Ctrl. Taz vs. 6d:Ctrl. Bex	609,6	935,8	*	0,0444
0d:Ctrl. Taz vs. 6d:Ctrl. Taz/Bex	609,6	1124	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO low	609,6	922,1	*	0,042
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO medium	609,6	1040	***	0,0002
0d:Ctrl. Taz vs. 9d:Ctrl. DMSO high	609,6	1147	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. Taz	609,6	1271	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. Bex	609,6	1087	****	<0,0001
0d:Ctrl. Taz vs. 9d:Ctrl. Taz/Bex	609,6	1244	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	664,4	1102	***	0,0004
0d:Ctrl. Bex vs. 6d:Ctrl. Taz	664,4	1171	****	<0,0001
0d:Ctrl. Bex vs. 6d:Ctrl. Taz/Bex	664,4	1124	***	0,0004
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO medium	664,4	1040	**	0,0066
0d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	664,4	1147	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. Taz	664,4	1271	****	<0,0001
0d:Ctrl. Bex vs. 9d:Ctrl. Bex	664,4	1087	**	0,0019
0d:Ctrl. Bex vs. 9d:Ctrl. Taz/Bex	664,4	1244	****	<0,0001
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. DMSO high	702,5	1102	**	0,0024
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. Taz	702,5	1171	***	0,0002
0d:Ctrl. Taz/Bex vs. 6d:Ctrl. Taz/Bex	702,5	1124	**	0,002
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO medium	702,5	1040	*	0,0294
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. DMSO high	702,5	1147	***	0,0003
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. Taz	702,5	1271	****	<0,0001
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. Bex	702,5	1087	**	0,0091
0d:Ctrl. Taz/Bex vs. 9d:Ctrl. Taz/Bex	702,5	1244	****	<0,0001
3d:Ctrl. DMSO low vs. 3d:Ctrl. DMSO high	562,8	913,5	**	0,0091
3d:Ctrl. DMSO low vs. 3d:Ctrl. Taz	562,8	921	**	0,0066
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO medium	562,8	927,9	**	0,0049
3d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	562,8	1102	****	<0,0001
3d:Ctrl. DMSO low vs. 6d:Ctrl. Taz	562,8	1171	****	<0,0001
3d:Ctrl. DMSO low vs. 6d:Ctrl. Bex	562,8	935,8	**	0,0074
3d:Ctrl. DMSO low vs. 6d:Ctrl. Taz/Bex	562,8	1124	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO low	562,8	922,1	**	0,0063
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	562,8	1040	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	562,8	1147	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	562,8	1271	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	562,8	1087	****	<0,0001
3d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	562,8	1244	****	<0,0001
3d:Ctrl. DMSO medium vs. 6d:Ctrl. DMSO high	762,2	1102	*	0,0143

3d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz	762,2	1171	**	0,0016
3d:Ctrl. DMSO medium vs. 6d:Ctrl. Taz/Bex	762,2	1124	*	0,0116
3d:Ctrl. DMSO medium vs. 9d:Ctrl. DMSO high	762,2	1147	**	0,002
3d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	762,2	1271	****	<0,0001
3d:Ctrl. DMSO medium vs. 9d:Ctrl. Bex	762,2	1087	*	0,0472
3d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz/Bex	762,2	1244	****	<0,0001
3d:Ctrl. DMSO high vs. 9d:Ctrl. Taz	913,5	1271	*	0,0138
3d:Ctrl. DMSO high vs. 9d:Ctrl. Taz/Bex	913,5	1244	*	0,038
3d:Ctrl. Taz vs. 9d:Ctrl. Taz	921	1271	*	0,0185
3d:Ctrl. Taz vs. 9d:Ctrl. Taz/Bex	921	1244	*	0,0495
3d:Ctrl. Bex vs. 6d:Ctrl. DMSO high	751,4	1102	*	0,0179
3d:Ctrl. Bex vs. 6d:Ctrl. Taz	751,4	1171	**	0,0022
3d:Ctrl. Bex vs. 6d:Ctrl. Taz/Bex	751,4	1124	*	0,0142
3d:Ctrl. Bex vs. 9d:Ctrl. DMSO high	751,4	1147	**	0,0028
3d:Ctrl. Bex vs. 9d:Ctrl. Taz	751,4	1271	****	<0,0001
3d:Ctrl. Bex vs. 9d:Ctrl. Taz/Bex	751,4	1244	****	<0,0001
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. Taz	836,1	1271	**	0,0011
3d:Ctrl. Taz/Bex vs. 9d:Ctrl. Taz/Bex	836,1	1244	**	0,0035
6d:Ctrl. DMSO low vs. 6d:Ctrl. DMSO high	699	1102	***	0,0008
6d:Ctrl. DMSO low vs. 6d:Ctrl. Taz	699	1171	****	<0,0001
6d:Ctrl. DMSO low vs. 6d:Ctrl. Taz/Bex	699	1124	***	0,0007
6d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO medium	699	1040	*	0,0137
6d:Ctrl. DMSO low vs. 9d:Ctrl. DMSO high	699	1147	****	<0,0001
6d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	699	1271	****	<0,0001
6d:Ctrl. DMSO low vs. 9d:Ctrl. Bex	699	1087	**	0,004
6d:Ctrl. DMSO low vs. 9d:Ctrl. Taz/Bex	699	1244	****	<0,0001
6d:Ctrl. DMSO medium vs. 9d:Ctrl. Taz	927,9	1271	*	0,0241
9d:Ctrl. DMSO low vs. 9d:Ctrl. Taz	922,1	1271	*	0,0193

Expanded View Figures

Figure EV1. Hit drug evaluation on immortalized MSD fibroblasts.

- A ARSA activity quantification (nmol/h/mg) after treatment of MSDi cells in 25 cm² cell culture flasks with a selection of four positive hit drugs at a final concentration of 10 μ M for 6 days. Data represent mean \pm SD of seven independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against negative control: **** P < 0.0001. See details on P -values in Appendix Table S31.
- B GALNS activity quantification (nmol/h/mg) after treatment of MSDi cells with a selection of four positive hit drugs at a final concentration of 10 μ M for 3 days. Data represent mean \pm SD of five independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against negative control: ** P < 0.001. See details on P -values in Appendix Table S32.
- C GALNS activity quantification (nmol/h/mg) after treatment of MSDi cells with a selection of four positive hit drugs at a final concentration of 10 μ M for 6 days. Data represent mean \pm SD of five independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons. Difference against negative control: * P < 0.05, ** P < 0.001. See details on P -values in Appendix Table S33.
- D β -galactosidase (betaGAL) activity quantification (nmol/h/mg) after treatment of MSDi cells with a selection of four positive hit drugs at a final concentration of 10 μ M for 3 days. Data represent mean \pm SD of five independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons.
- E β -hexosaminidase A and B (betaHEXAB) activity quantification (nmol/h/mg) after treatment of MSDi cells with a selection of four positive hit drugs at a final concentration of 10 μ M for 3 days. Data represent mean \pm SD of five independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons.
- F Dose-response curve of ARSA activity calculated from data displayed in Fig 1C (MSDi cells, tazarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log₁₀ values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- G Dose-response curve of GALNS activity calculated from data displayed in Fig 1D (MSDi cells, tazarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log₁₀ values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- H Dose-response curve of ARSA activity calculated from data displayed in Fig 1F (MSDi cells, bexarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log₁₀ values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- I Dose-response curve of ARSA activity calculated from data displayed in Fig 1G (MSDi cells, tazarotene/bexarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log₁₀ values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.

Source data are available online for this figure.

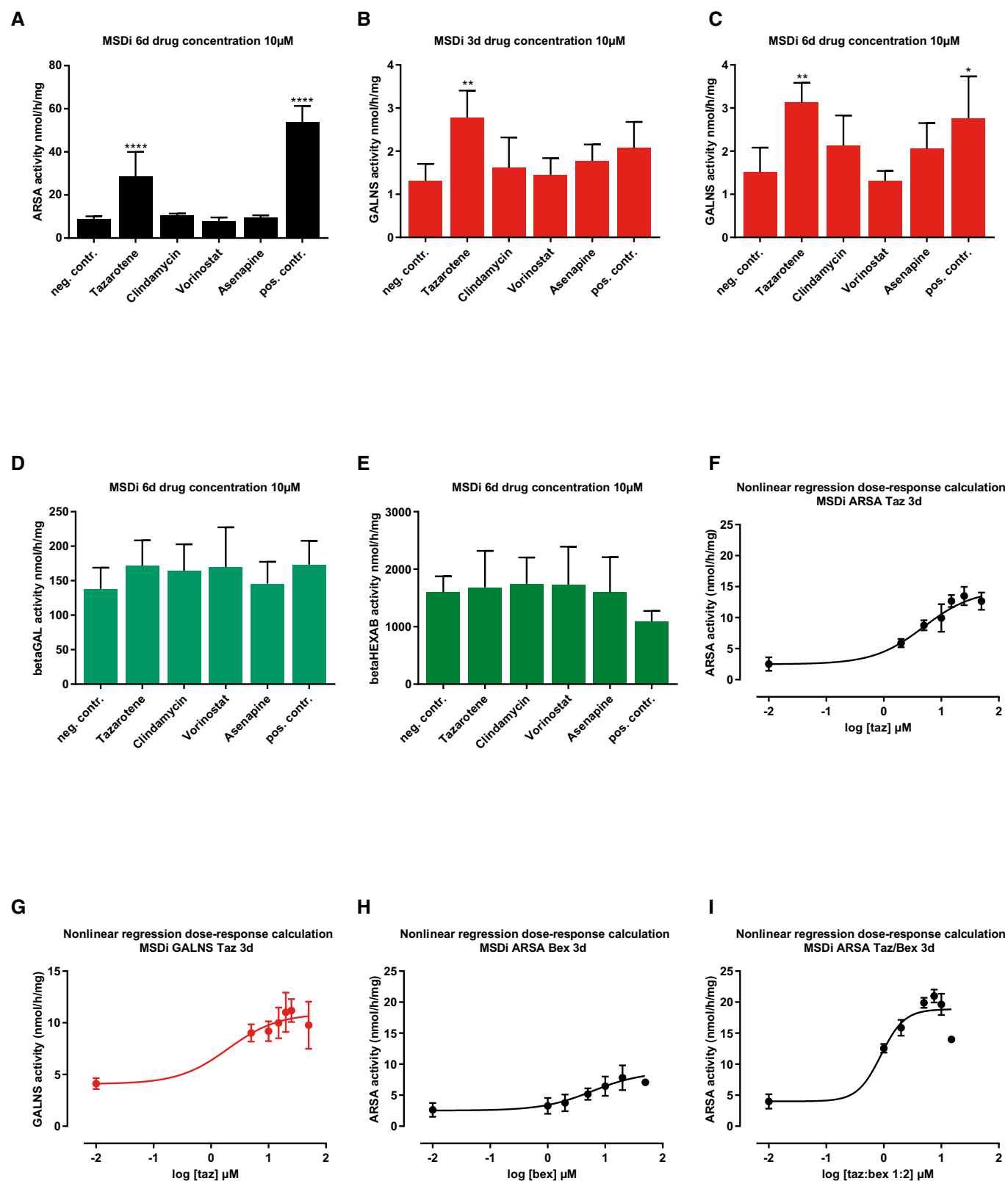


Figure EV1.

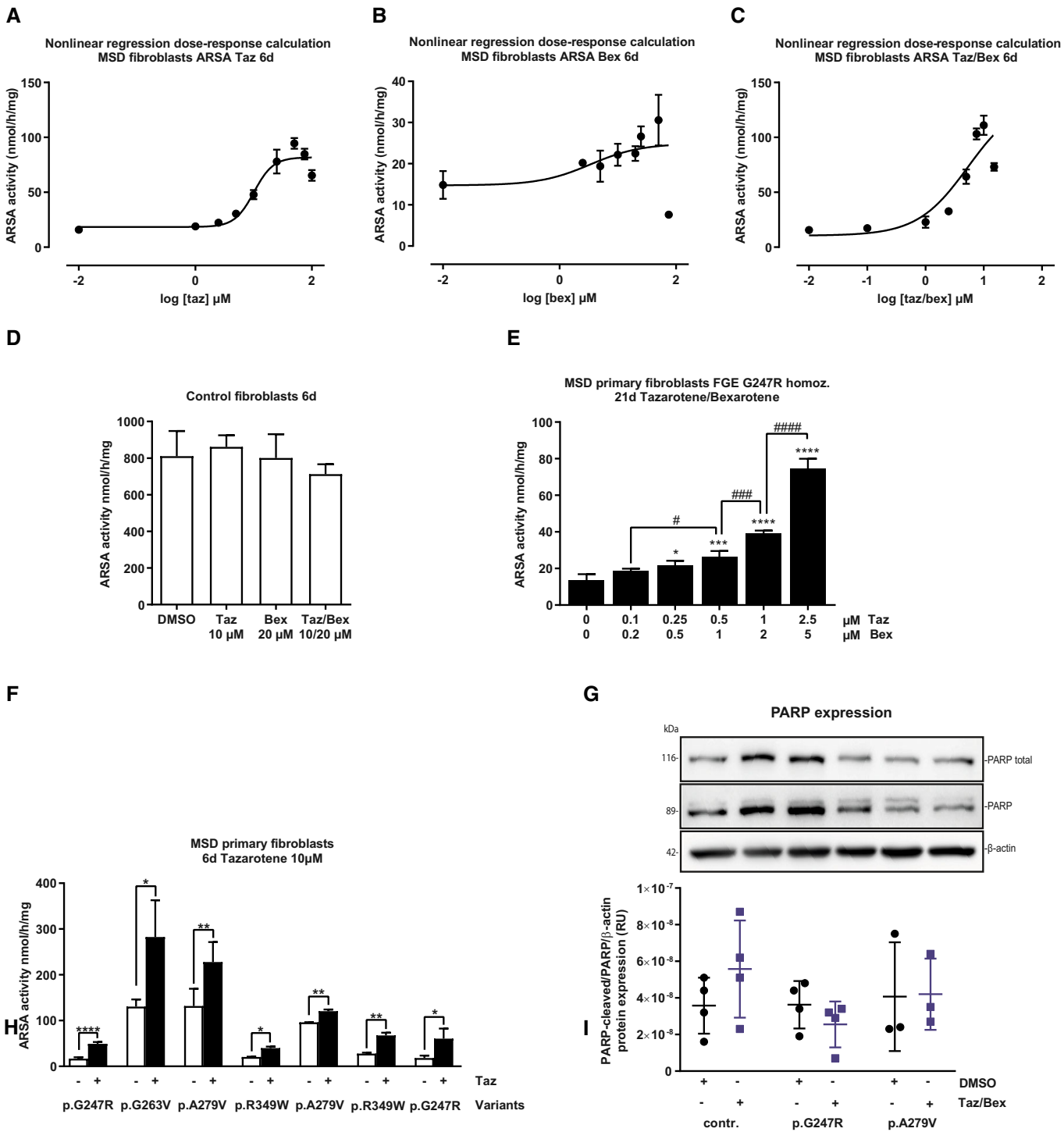


Figure EV2.

Figure EV2. Treatment response and toxicity assessment.

- A Dose-response curve of ARSA activity calculated from data displayed in Fig 2A (variant FGE Gly247Arg homozygous, tazarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log10 values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- B Dose-response curve of ARSA activity calculated from data displayed in Fig 2B (variant FGE Gly247Arg homozygous, bexarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log10 values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- C Dose-response curve of ARSA activity calculated from data displayed in Fig 2C (variant FGE Gly247Arg homozygous, tazarotene/bexarotene treatment) by nonlinear regression analysis. Drug concentrations are displayed after transformation into log10 values and baseline activity (negative control, DMSO-only treatment) was manually referred to log-2. Dots and error bars represent mean \pm SD.
- D ARSA activity quantification after treatment of five different control, non-MSD, fibroblast lines with tazarotene, bexarotene, and tazarotene/bexarotene in combination for 6 days referred to β -actin amounts and calculation of ARSA activity based on ARSA protein amount (specific ARSA activity). Data represent mean \pm SD of five independent experiments (biological replicates) in duplicates to determine the range of normal ARSA activities and treatment response as the basis for the calculation of residual activities in MSD fibroblasts.
- E ARSA activity quantification after simultaneous treatment of MSD primary fibroblasts (variant FGE Gly247Arg homozygous) with increasing concentrations of tazarotene and bexarotene in a fixed combination of 1:2 for 21 days. Data represent mean \pm SD of four independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons. Displayed are significance levels for the next significant difference between adjacent concentrations/conditions. # $P < 0.05$, ### $P < 0.001$, #### $P < 0.0001$. Difference against 0/0 μ M control: * $P < 0.05$, *** $P < 0.001$, **** $P < 0.0001$. See details on P -values in Appendix Table S34.
- F Quantification of ARSA activities in MSD primary fibroblasts with different homozygous *SUMF1* mutations (FGE Gly247Arg, FGE Gly263Val, FGE Ala279Val, FGE Arg349Trp) after 6 days of treatment with tazarotene 10 μ M. Data represent mean \pm SD of 2–5 independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$. See details on P -values in Appendix Table S35.
- G Upper panel: Representative pictures of Western Blot analysis of (PARP) and cleaved PARP in tazarotene/bexarotene-treated MSD primary fibroblasts (variant FGE Gly247Arg, FGE Ala279Val, homozygous) and control fibroblasts. β -actin expression served as loading control. Lower panel: Quantification of protein amounts from western blots displayed as ratio cleaved PARP to total PARP expression normalized to β -actin. Data represent mean \pm SD of 3–4 independent experiments (biological replicates). Unpaired t-tests. No statistical differences. RU, relative units.

Source data are available online for this figure.

Figure EV3. Transcriptional response of MSD and retinoic acid gene targets upon tazarotene/bexarotene treatment.

- A Gene expression analysis of genes in relation to retinoic acid receptor signaling of six different MSD primary fibroblast lines and five different control fibroblast lines after 6 days of treatment with tazarotene/bexarotene (10/20 μ M) and DMSO, respectively. Changes in RPKM (reads per kilobase million) are displayed as mean \pm SD of three independent experiments (biological replicates). One-way ANOVA test followed by Tukey's test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.001$, **** $P < 0.0001$. See details on P -values in Appendix Table S36.
- B Gene expression analysis of *SUMF1*- and FGE-interacting partners (nonsulfatases) of six different MSD primary fibroblast lines and five different control fibroblast lines after 6 days of treatment with tazarotene/bexarotene (10/20 μ M) and DMSO, respectively. Changes in RPKM (reads per kilobase million) are displayed as mean \pm SD of three independent experiments (biological replicates). One-way ANOVA test followed by Tukey's test for multiple comparisons. * $P < 0.05$. See details on P -values in Appendix Table S37.
- C Gene expression analysis of sulfatases of six different MSD primary fibroblast lines and five different control fibroblast lines after 6 days of treatment with tazarotene/bexarotene (10/20 μ M) and DMSO, respectively. Changes in RPKM (reads per kilobase million) are displayed as mean \pm SD of three independent experiments (biological replicates). One-way ANOVA test followed by Tukey's test for multiple comparisons. * $P < 0.05$, **** $P < 0.0001$. See details on P -values in Appendix Table S38.

Source data are available online for this figure.

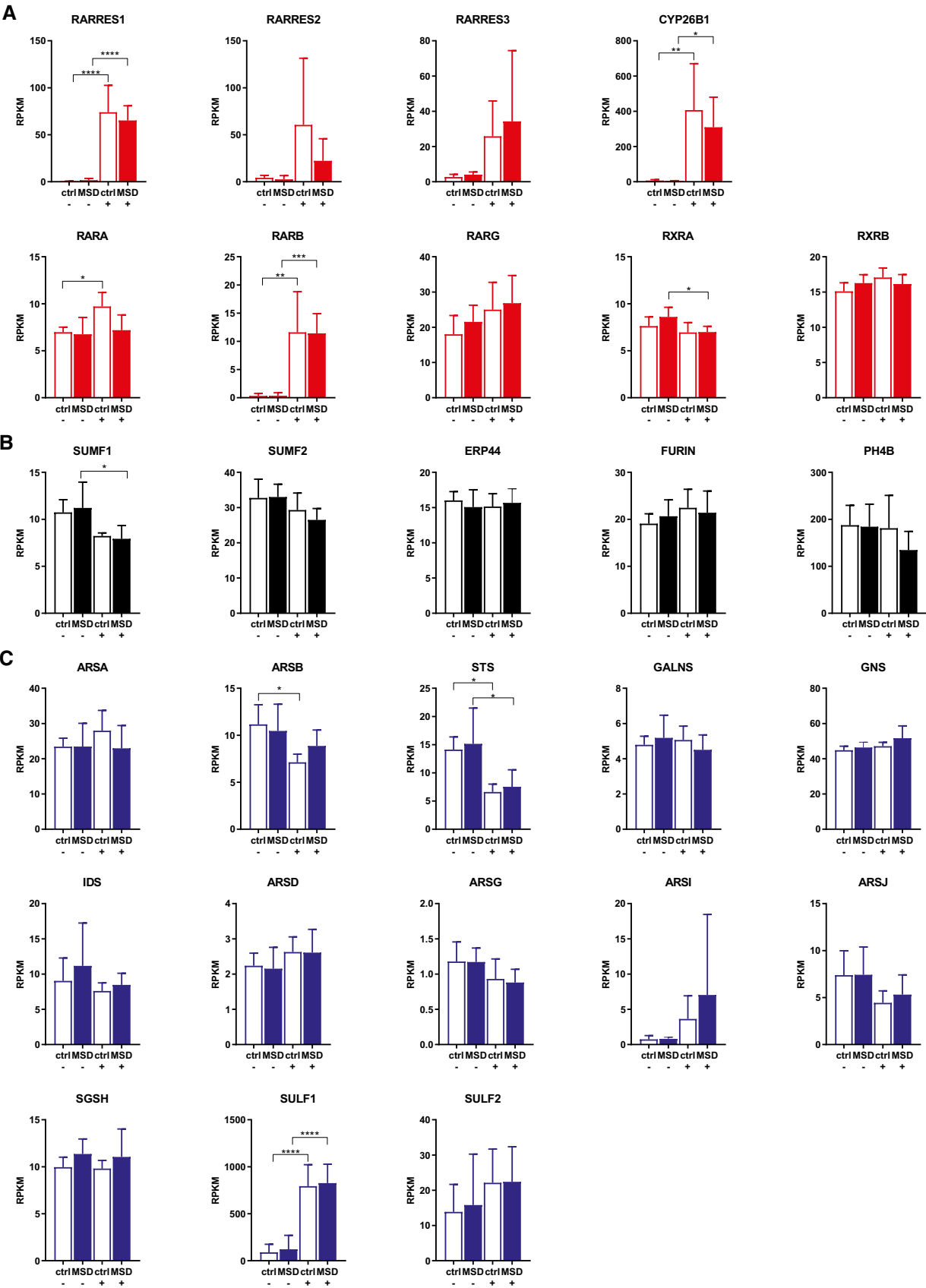


Figure EV3.

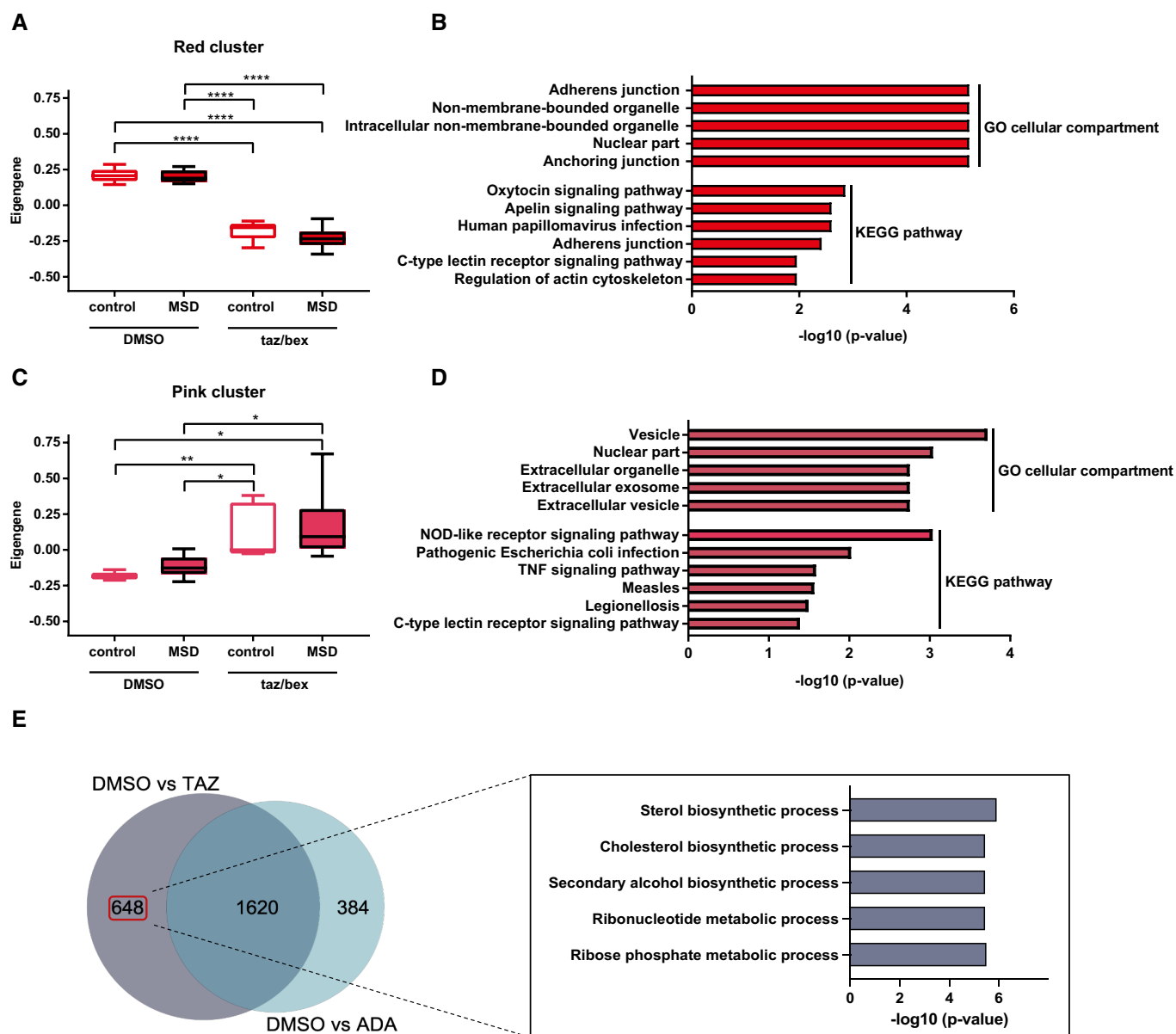


Figure EV4. Transcriptional response upon tazarotene and bexarotene treatment in MSD and control fibroblasts and differential transcriptional response in MSD fibroblasts upon treatment with tazarotene and adapalene.

- A Eigengene analysis of the red gene cluster as determined by WGCN analysis after RNA sequencing of six different MSD primary fibroblast lines and five different control fibroblast lines and treatment with tazarotene/ bexarotene 10/20 μM or DMSO only, respectively, for 6 days. Data represent min to max box and whisker blots of Eigengene values \pm SD of three independent experiments (biological replicates). One-way ANOVA test followed by Tukey's test for multiple comparisons. **** $p < 0.0001$. See details on P -values in Appendix Table S39.
- B GO and KEGG pathway analysis of genes in the red cluster and \log_{10} value of P -values. GO and KEGG pathway analysis of genes in the yellow cluster and their \log_{10} value of P -values as the display for changes in gene expression.
- C Eigengene analysis of the pink gene cluster as determined by WGCN analysis after RNA sequencing of six different MSD primary fibroblast lines and five different control fibroblast lines and treatment with tazarotene/bexarotene 10/20 μM or DMSO only, respectively, for 6 days. Data represent min to max box and whisker blots of Eigengene values \pm SD of three independent experiments (biological replicates). One-way ANOVA test followed by Tukey's test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$. See details on P -values in Appendix Table S40.
- D GO and KEGG pathway analysis of genes in the red cluster and \log_{10} value of P -values.
- E Differential gene expression analysis after treatment of seven MSD primary fibroblast lines with tazarotene (sulfatase activity response) and adapalene (no sulfatase activity response) in triplicates for 6 days. Treatment with DMSO served as a negative control. Venn diagram and number of exclusively regulated genes for tazarotene treatment (TAZ) versus DMSO condition (left) and adapalene treatment (ADA) versus DMSO (right), as well as the number of overlapping genes identically regulated by both tazarotene and adapalene. GO pathway analysis and \log_{10} value of P -values for tazarotene-only regulated genes.

Source data are available online for this figure.

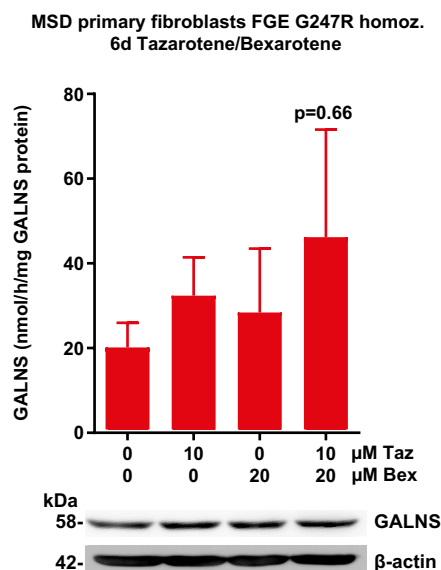
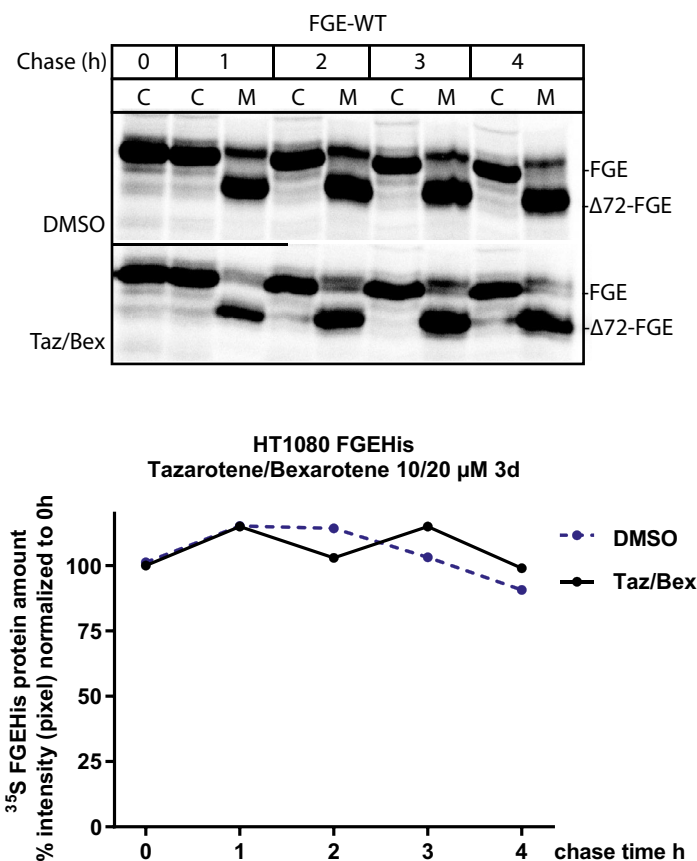
A**B**

Figure EV5. Sulfatase-specific activity and protein expression and protein stability of wildtype FGE upon treatment.

- A GALNS protein amount quantification after treatment of MSD primary fibroblasts (variant FGE Gly247Arg homozygous) with tazarotene, bexarotene, and tazarotene/bexarotene in combination for 6 days referred to β -actin amounts and calculation of GALNS activity based on GALNS protein amount (specific GALNS activity). Data represent mean \pm SD three independent experiments (biological replicates). One-way ANOVA followed by Tukey's test for multiple comparisons.
- B Pulse-chase-experiment in HT 1080 FGE wild-type (wt) cells after pretreatment with tazarotene/bexarotene and DMSO (control) for 3 days. Upper panel: autoradiogram of intracellular (full-length FGE, C) and cleaved and secreted (Δ 72 FGE, M) 35 S isotope labeled FGE protein in either condition with a chase time of 4 h. Lower panel: Quantification of the autoradiogram, $n = 1$ experiment.

Source data are available online for this figure.