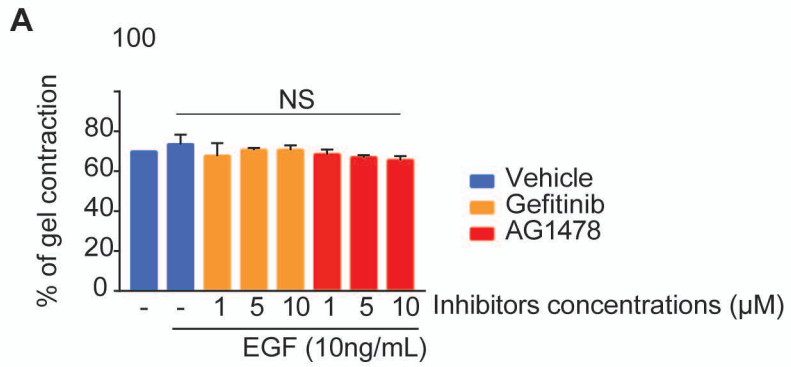

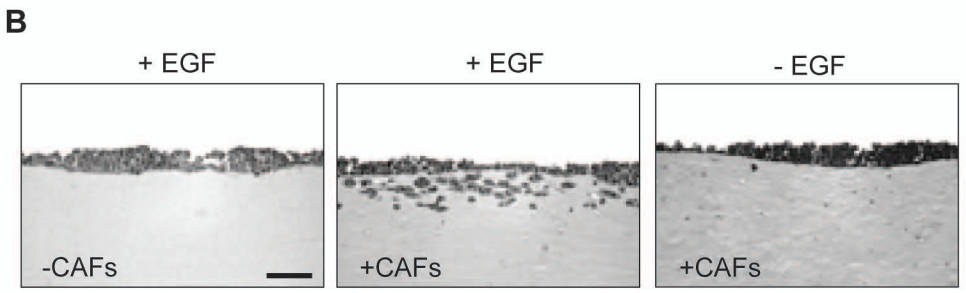

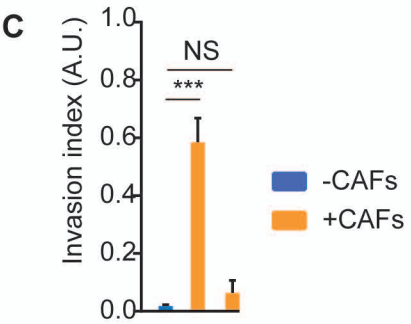

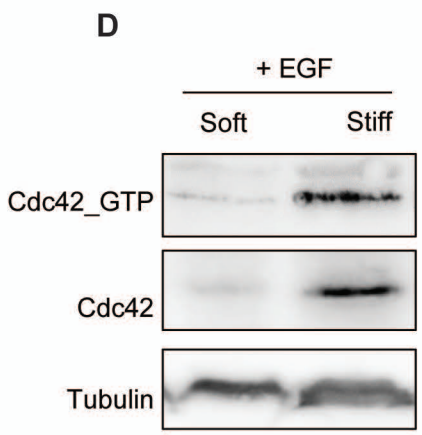

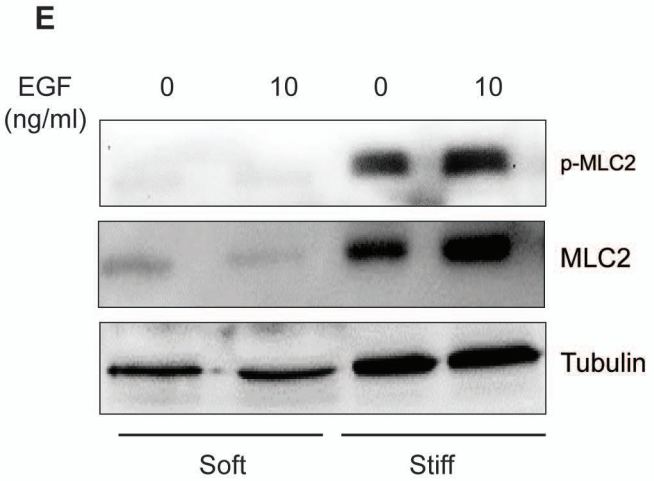

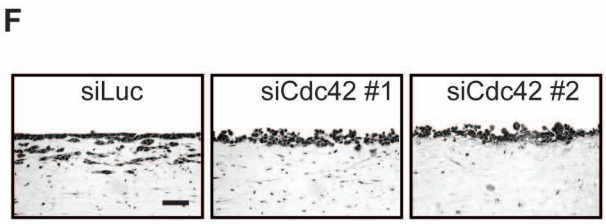

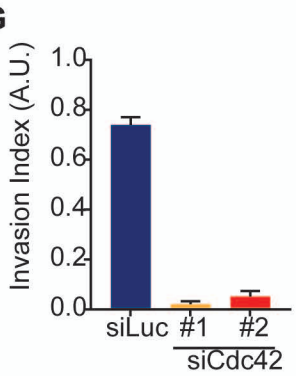

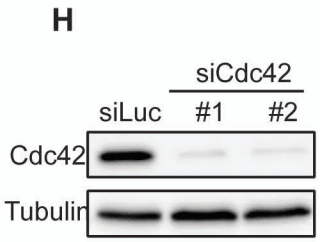

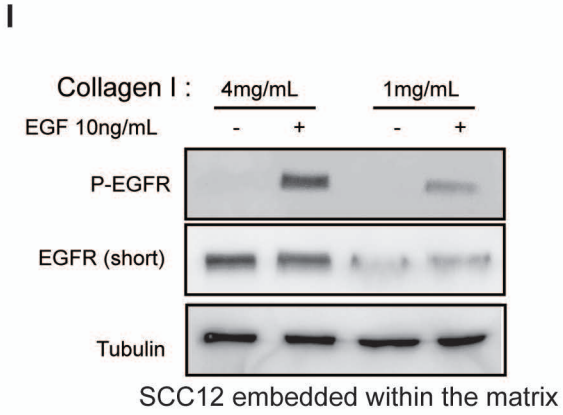

Supplementary Figure 1

Supplementary figure 1: A) Quantification of matrix remodeling by CAF compare to DMSO with or without EGF and EGFR TKi (Gefitinib, AG1478). (n=3 independent experiments performed in triplicate, mean + SD). **B)** H&E coloration of paraffin-embedded sections of SCC12 cells collective invasion in control or CAF remodeled organotypic culture in presence or not of EGF. Scale bar, 100 µm. **C)** Quantification of SCC12 cells invasion index shown in B. (n=3; mean + SD). **D)** Immunoblot of cdc42-GTP loaded and total cdc42 in SCC12 cells plated on soft or stiff matrix in presence of EGF for 5min. Tubulin is shown as control loading. **E)** Immunoblot of p-MLC2 and total MLC2 in SCC12 cells plated on soft or stiff matrix in presence or absence of EGF for 1h. Tubulin is shown as control loading. **F)** H&E coloration of paraffin-embedded sections of organotypic invasion assay with SCC12 cells transfected with siRNA against Cdc42 (2 sequences). siRNA against luciferase used as control. Scale bar, 100 µm. **G)** Quantification of SCC12 cells invasion index shown in F. (n=3; mean + SD). **H)** Immunoblot of Cdc42 in SCC12 transfected with siRNA against luciferase (siLuc, control) or siCdc42 (2 sequences). Tubulin used as control. **I)** Immunoblot of p-EGFR and EGFR in SCC12 cells embedded in a stiff (4mg/ml) and soft (1mg/ml) collagen I gel stimulated with EGF (10ng/ml). Tubulin used as control. For all data, paired samples were compared by 2-tailed Student's t test, while 1-way ANOVA and post-hoc Tukey's tests were used for group comparisons (NS: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).

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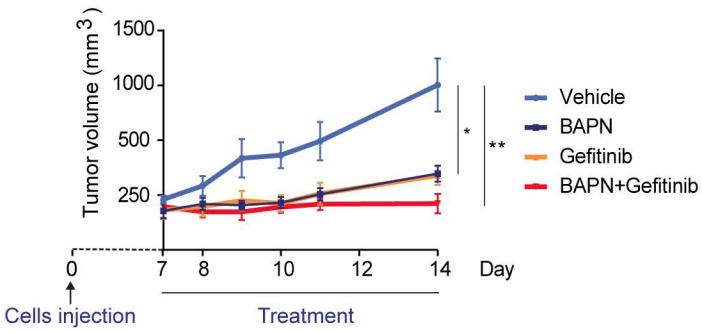
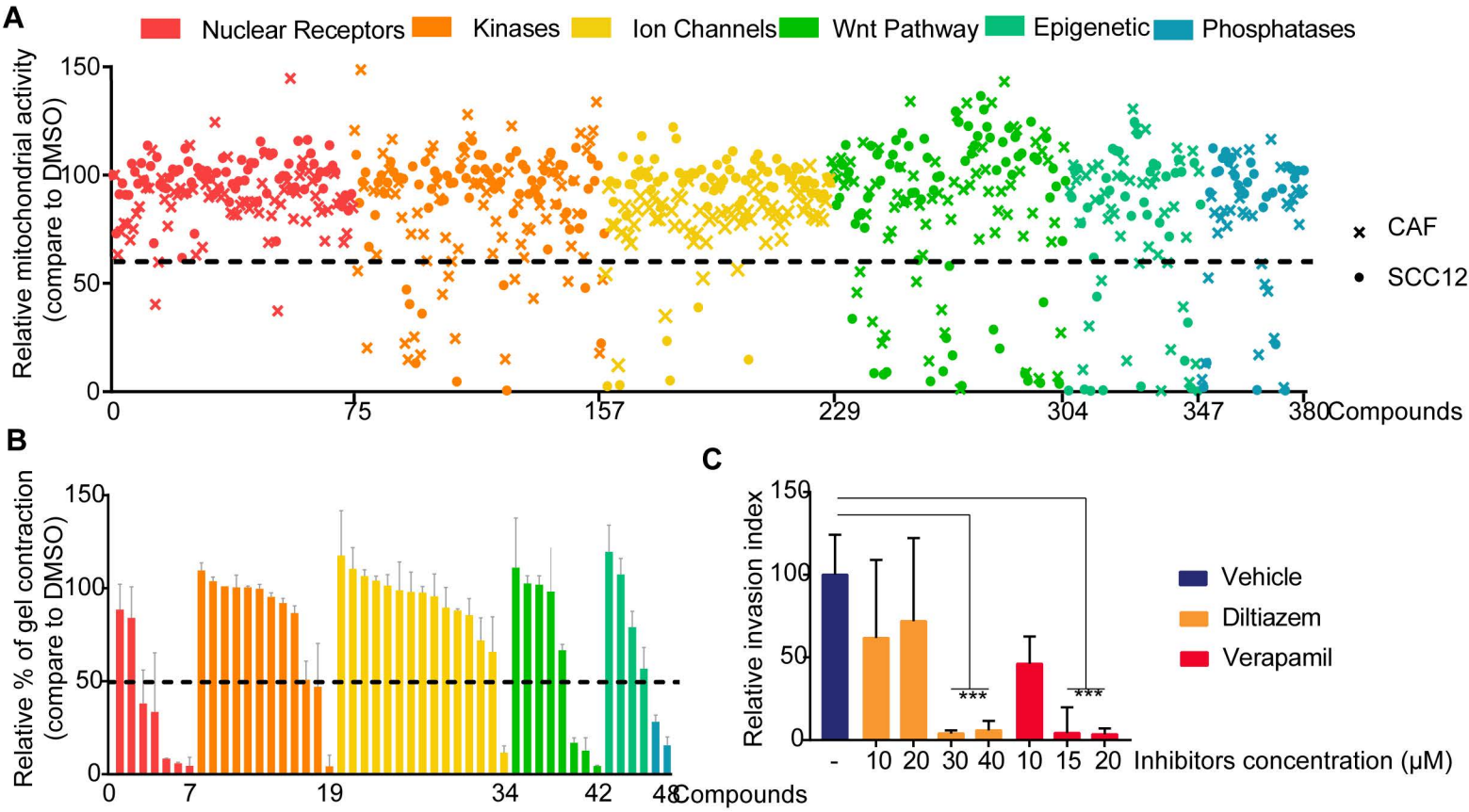
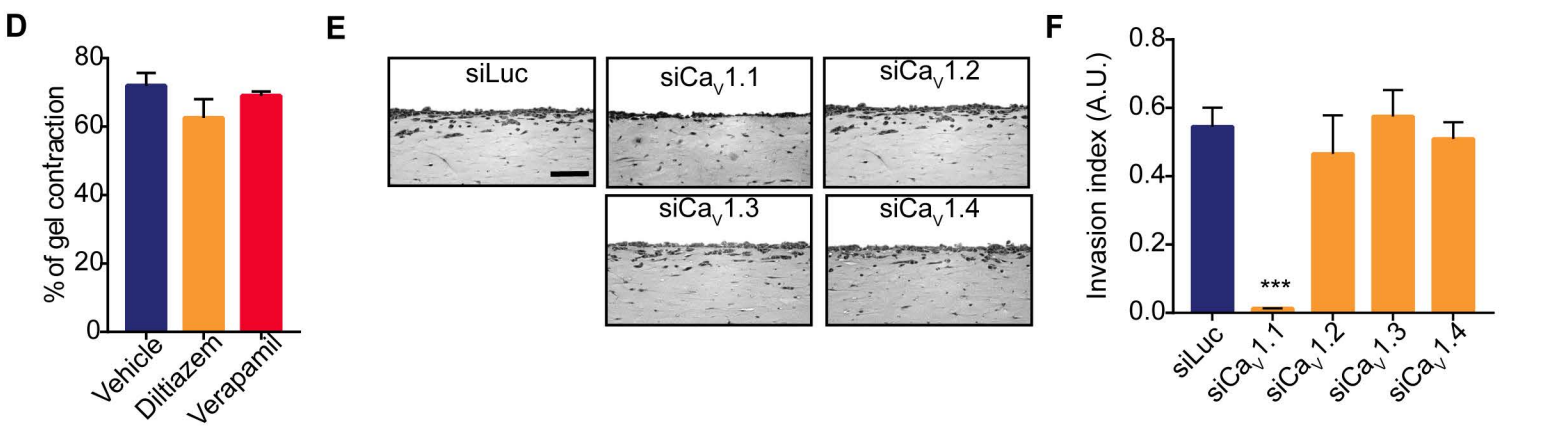


Supplementary Figure 2

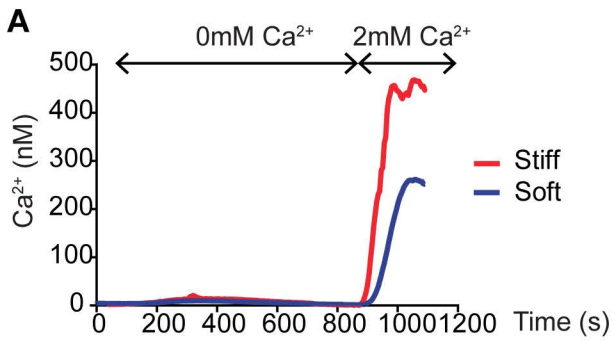
Supplementary figure 2: A) Quantification of mean tumor volume for 3 individual patient derived xenografts. Inhibitors treatment started at 7 days post-injection. (n=2 for 3 individual PDX, mean ± SEM). For all data, paired samples were compared by 2-tailed Student's t test (NS: not significant, **p<0.01, ***p<0.001).

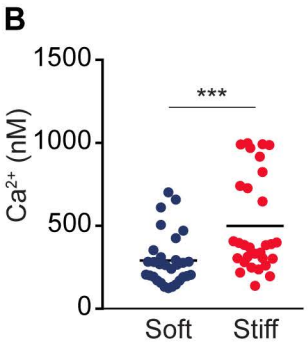


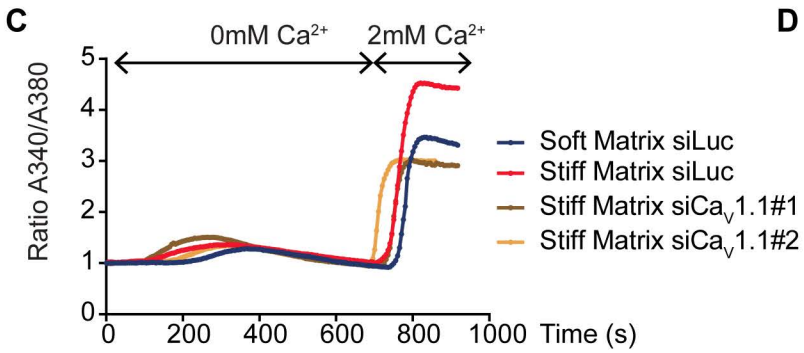


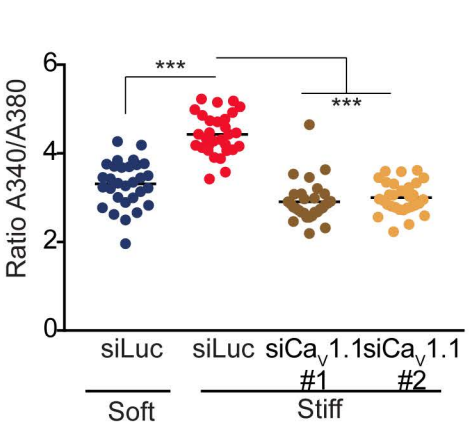
Supplementary Figure 3

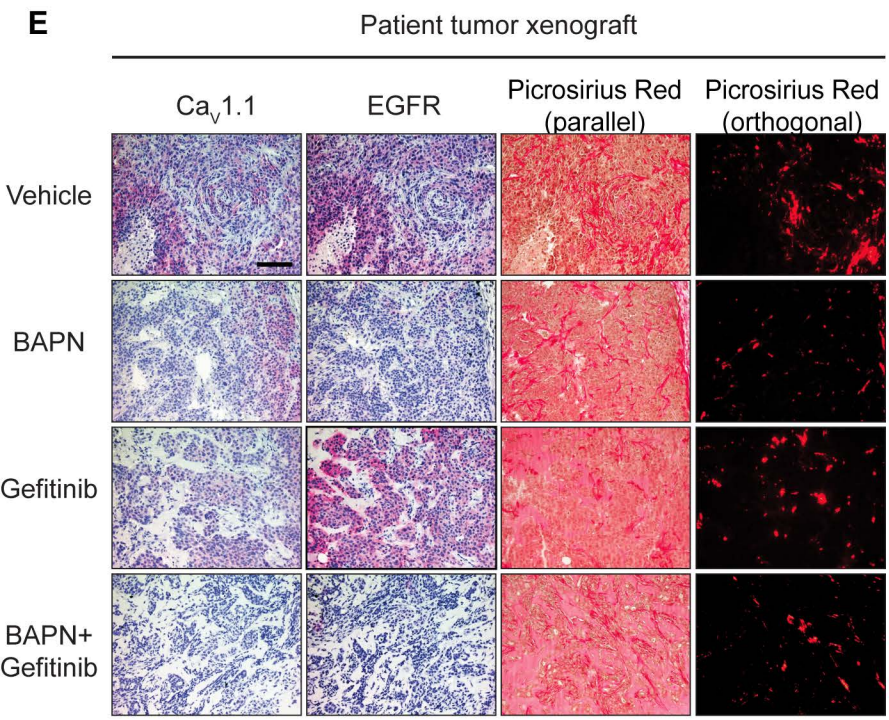
Supplementary figure 3: A) Relative mitochondrial activity measurements in SCC12 cells and CAF compare to DMSO for the 380 compounds tested (10 µM final concentration during 96 hours) and classified between libraries. Dotted bar represent the threshold (60 % of inhibition) used for toxicity determination. Each dot or cross represents the mean of 3 independent experiments performed in triplicate for SCC12 cells and CAF respectively. **B)** Quantification of relative matrix remodeling by CAF compare to DMSO with all inhibitors identified for blocking SCC12 invasion within the screening. Dotted bar represents the threshold used to select molecules that block CAF matrix remodeling (50 % of inhibition). (n=3 independent experiments performed in triplicate, mean + SD). **C)** Quantification of SCC12 cells invasion index of organotypic cultures in response to different doses of diltiazem or verapamil. (n=3; mean + SD). **D)** Quantification of relative matrix remodeling by CAF with or without diltiazem (30 µM) or Verapamil (15 µM). (n=3 independent experiments performed in triplicate, mean + SD). **E)** H&E coloration of paraffin-embedded sections of organotypic invasion assay with SCC12 cells transfected with siRNA against the different Ca_V1 α-subunits ($Ca_V1.1$, $Ca_V1.2$, $Ca_V1.3$, $Ca_V1.4$). siRNA against luciferase used as control. Scale bar, 100 µm. **F)** Quantification of SCC12 cells invasion index shown in E. (n=3; mean + SD). For all data, paired samples were compared by 2-tailed Student's t test (NS: not significant, ***$p<0.001$).

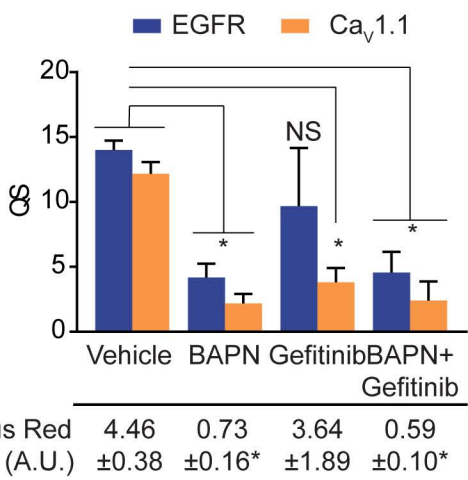








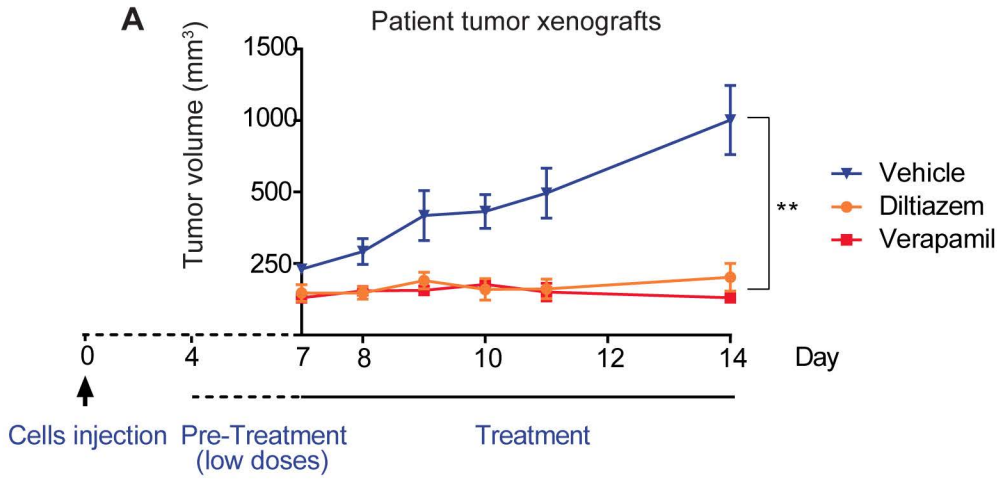




	Vehicle	BAPN	Gefitinib	BAPN+ Gefitinib
Picrosirius Red Intensity (A.U.)	4.46 ±0.38	0.73 ±0.16*	3.64 ±1.89	0.59 ±0.10*

Supplementary Figure 4

Supplementary figure 4: A) Ca^{2+} entry in SCC12 cells plated for 3 days on soft or stiff matrices, stimulated by 5 ng/mL of EGF during the experiment. Representative experiment of 3 independent experiments. **B)** Intracellular Ca^{2+} concentration measured at the end of the experiment shown in A. Bars corresponds to the mean and each dot represents Ca^{2+} measurement in a cell (n=30 cells at least). **C)** Ca^{2+} entry in SCC12 cells transfected by siRNA against luciferase (siLuc, control) or $Ca_V1.1$ (2 different sequences are used), plated for 3 days on soft or stiff matrices and stimulated by 5 ng/mL of EGF during the experiment. Representative experiment of 3 independent experiments. **D)** Representation of Ca^{2+} level measured at the end of the experiment shown in C. Bars corresponds to the mean and each dot represents Ca^{2+} measurement in a cell (n=30 cells at least). **E)** Representative pictures of $Ca_V1.1$, EGFR immunostaining and Sirius Red stained collagen bundles observed under polarized light of patients tumor xenograft represented in Figure 2. Scale bar, 200 µm. **F)** Quantification of $Ca_V1.1$ and EGFR staining shown in E (Quick Score method). Picrosirius Red intensity under polarized light is indicated under the graph. (n=2 for 3 individual PDX, mean + SEM). For all data, paired samples were compared by 2-tailed Student's t test, while 1-way ANOVA and post-hoc Tukey's tests were used for group comparisons (NS: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).



Supplementary Figure 5

Supplementary figure 5: A Quantification of mean tumor volume of 3 individual PDX. Diltiazem or verapamil Inhibitors treatment started at 4 days post-injection with low doses (20 mg/kg/day), final doses started at 7 days (50 mg/kg/day). (n=2 for 3 individual PDX, mean ± SEM). For all data, paired samples were compared by 2-tailed Student's t test, while 1-way ANOVA and post-hoc Tukey's tests were used for group comparisons (NS: not significant, *$p<0.05$, **$p<0.01$, ***$p<0.001$).