Preclinical efficacy of targeting FGF autocrine signaling in mesothelioma with the FGF ligand trap, FP-1039/GSK3052230

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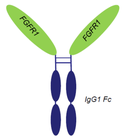
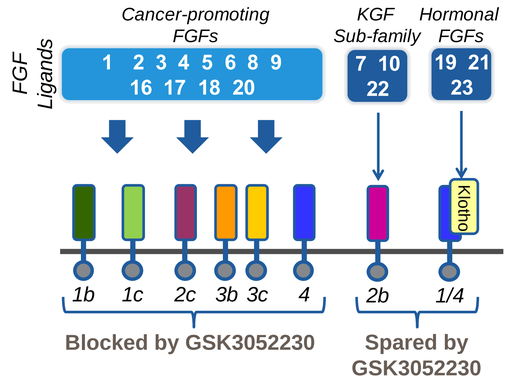
FP-1039/GSK3052230 Background

- FGF Ligand Trap composed of the extra-cellular domain of Fibroblast Growth Factor Receptor 1 (FGFR1 isoform α-IIIc) linked to the hinge and Fc regions of human IgG1



- Harding TC et al. *Sci. Transl. Med.* 2013;5:1-9

GSK3052230 has a distinct selectivity profile in blocking multiple FGFRs



- GSK3052230 binds to multiple FGFs and blocks activation of several FGF receptors
  - Affects FGF ligand-dependent pathways in cancer
- Does not block hormonal FGF signaling, avoiding the hyperphosphatemia, renal failure, retinal toxicities, and oral pain that have been observed clinically with small molecule pan-FGFR kinase inhibitors

Identification of biomarkers that predict sensitivity to GSK3052230

Table 2. RNA levels of FGF ligands and receptors correlated with FP-1039 efficacy in xenograft models.

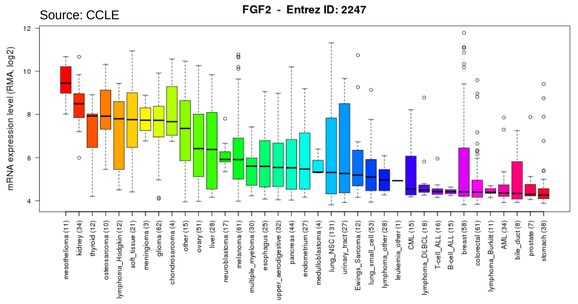
Gene	Ratio*	p†
ETV4	2.897	0.01639
FGFR1	2.447	0.01669
FGFR3c	9.863	0.01944
FGF18	6.915	0.02227
FGF2	247.7	0.03569
FGFR1c	3.647	0.0431

*Gene expression ratio was determined by median gene expression in FP-1039 responders/median gene expression in nonresponders. †P value was determined by Mann-Whitney.

Harding TC et al. *Sci. Transl. Med.* 2013;5:1-9

- FGF2 mRNA expression ratio was the highest of all statistically significant expression levels across all tumor xenografts
- Provides an opportunity for patient selection
- **Provided the rationale to explore tumor types where FGF2 expression levels are high**

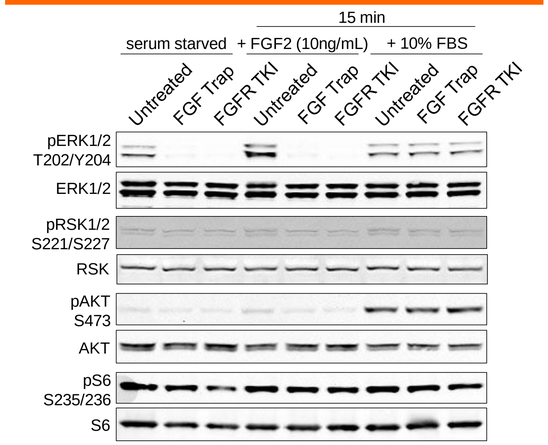
FGF2 mRNA expression in cancer cell lines



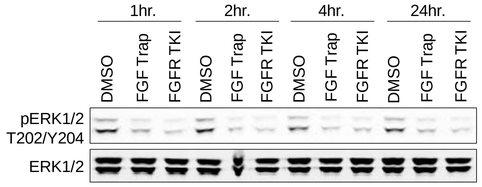
- FGF2 mRNA expression levels are highest in mesothelioma cell lines
  - NCI-H226: 9.9
  - MSTO-211H: 10.6

  RMA, log2 (see above)
- Overexpression (>4-fold over median) also observed in ~50% of 1˚ mesothelioma specimens (not shown)

FGF/FGFR pathway signaling in NCI-H226 mesothelioma cells

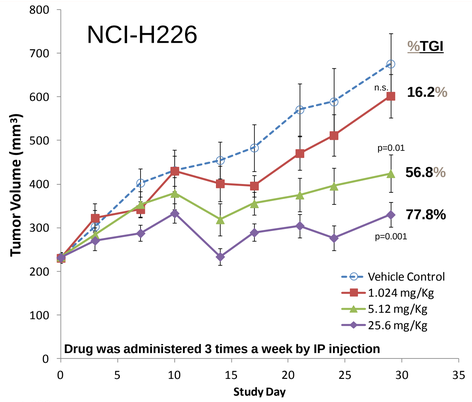


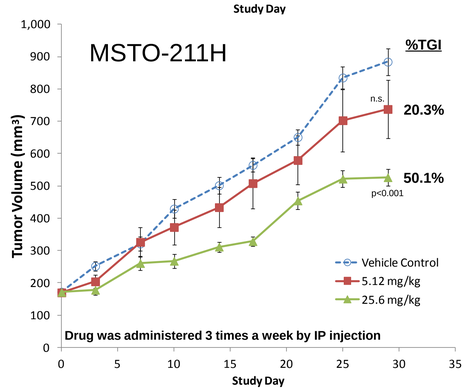
- FGF Trap (GSK3052230) and FGFR TKI (small molecule pan FGFR kinase inhibitor) inhibit basal phospho-ERK levels and FGF2-induced phospho-ERK levels, yet both were ineffective at inhibiting signaling induced by acute serum (10% FBS) stimulation



- Decreased phospho-ERK levels observed under full serum conditions (10% FBS) with both molecules.
- Similar results seen in MSTO-211H cells (not shown)

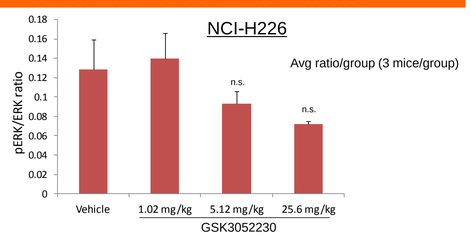
GSK3052230 inhibits tumor growth in mesothelioma tumor xenografts

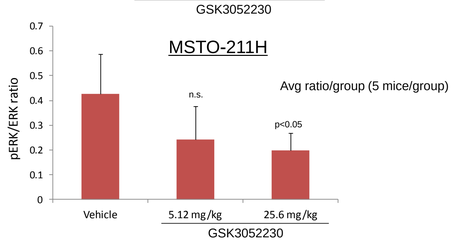




p-values calculated by two sample (independent group) t-test assuming unequal variance; n.s: not significant

GSK3052230 reduces pERK levels in both NCI-H226 and MSTO-211H tumors

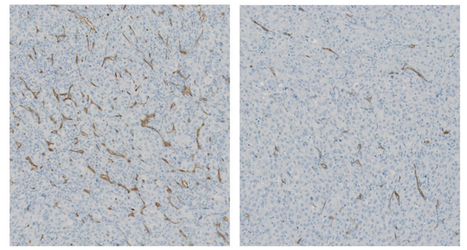




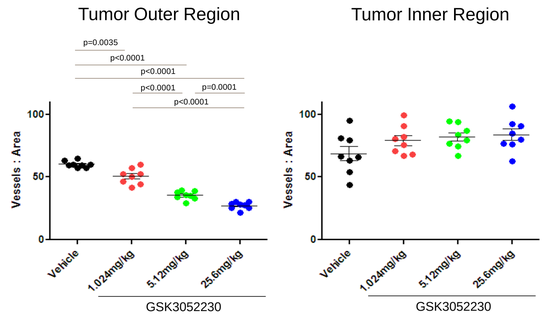
- pERK/ERK protein level ratios were determined by densitometry of western blot data

p-values calculated by two sample (independent group) t-test assuming unequal variance; n.s: not significant

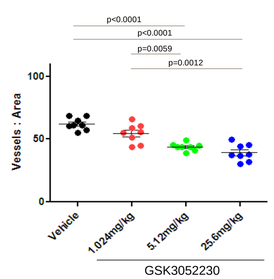
GSK3052230 reduces tumor vessel density in NCI-H226 xenografts



- Representative photomicrographs of vehicle-treated or GSK3052230-treated NCI-H226 xenograft tumors (outer region) stained for MECA-32 by IHC



Whole Tumor Mass



- Quantification of endothelial cell MECA-32 IHC staining of NCI-H226 tumors from efficacy study
- Dose-dependent and statistically-significant reductions in tumor vessel density observed in the outer region and whole tumor mass data sets

p-values calculated by one-way ANOVA assuming unequal variance. Bonferroni's multiple comparison test was used to adjust for the multiple comparisons.

Conclusions

- GSK3052230 inhibits tumor growth in mesothelioma xenografts that overexpress FGF2 by reducing FGF autocrine signaling and by inhibiting angiogenesis
- These data support the clinical evaluation of this drug in mesothelioma patients in a Phase Ib trial (NCT01868022)

All studies were conducted in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals and were reviewed by the Institutional Animal Care and Use Committee either at GSK or by the ethical review process at the institution where the work was performed.