Inhibitor-sensitive fibroblast growth factor receptor mutations in lung squamous cell carcinoma

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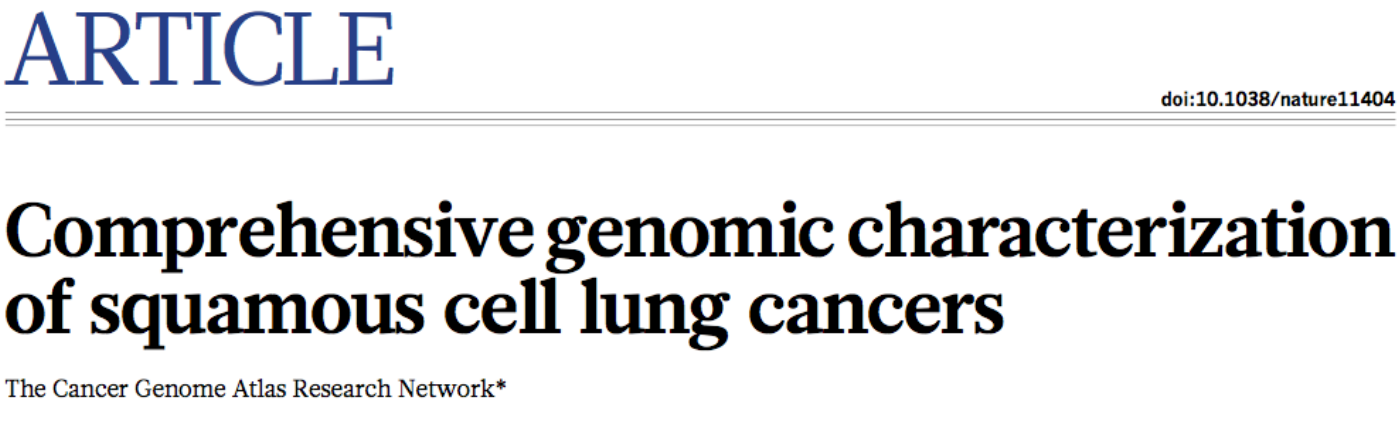
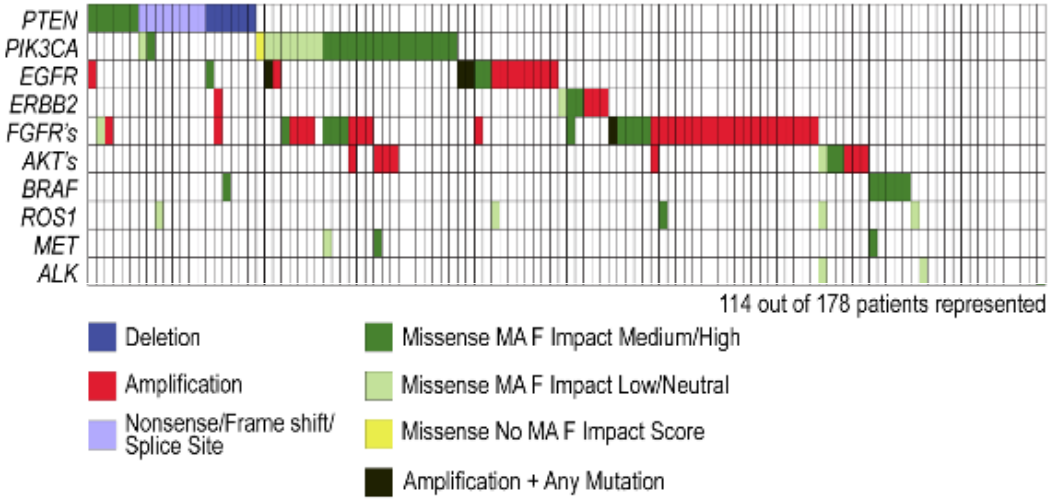
Squamous cell carcinoma of the lung: a disease without treatment options

- Adenocarcinoma of the lung has seen many targeted therapy advances in the past decade (EGFR, EML4-ALK, ERBB2), while
- Squamous cell carcinoma had few targets and no targeted therapies—and the clinical burden is great

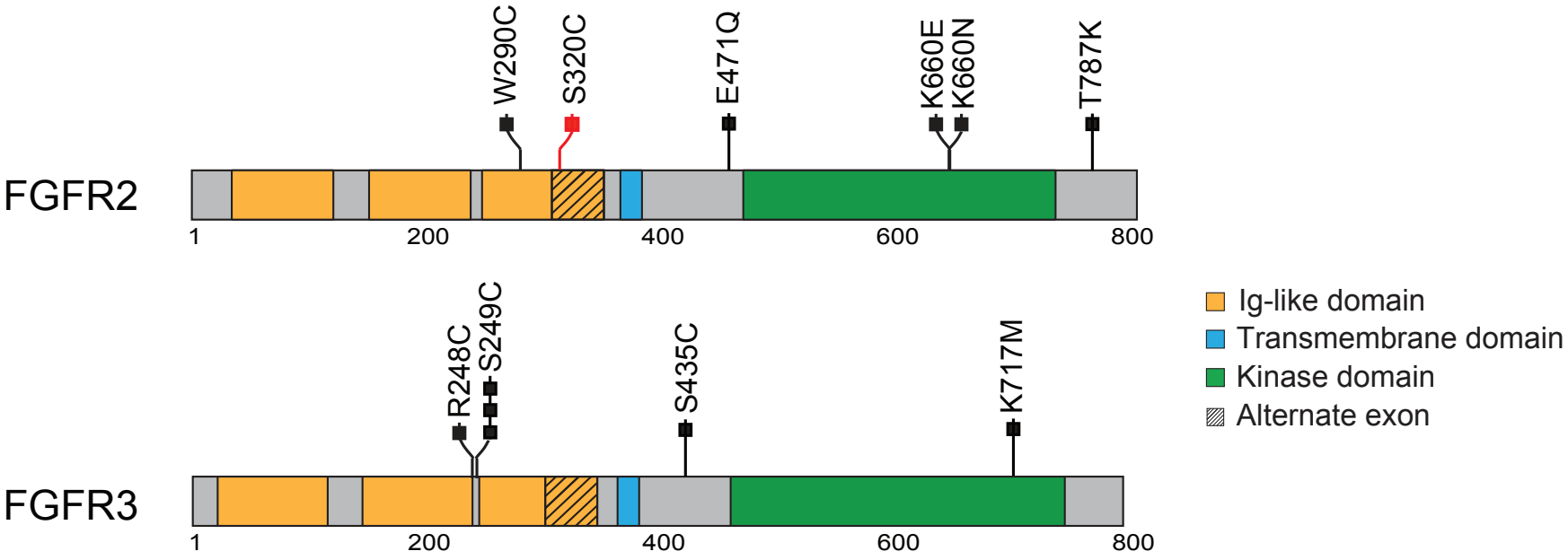


FGFR events in the TCGA Lung Squamous Cell Carcinoma sequencing project

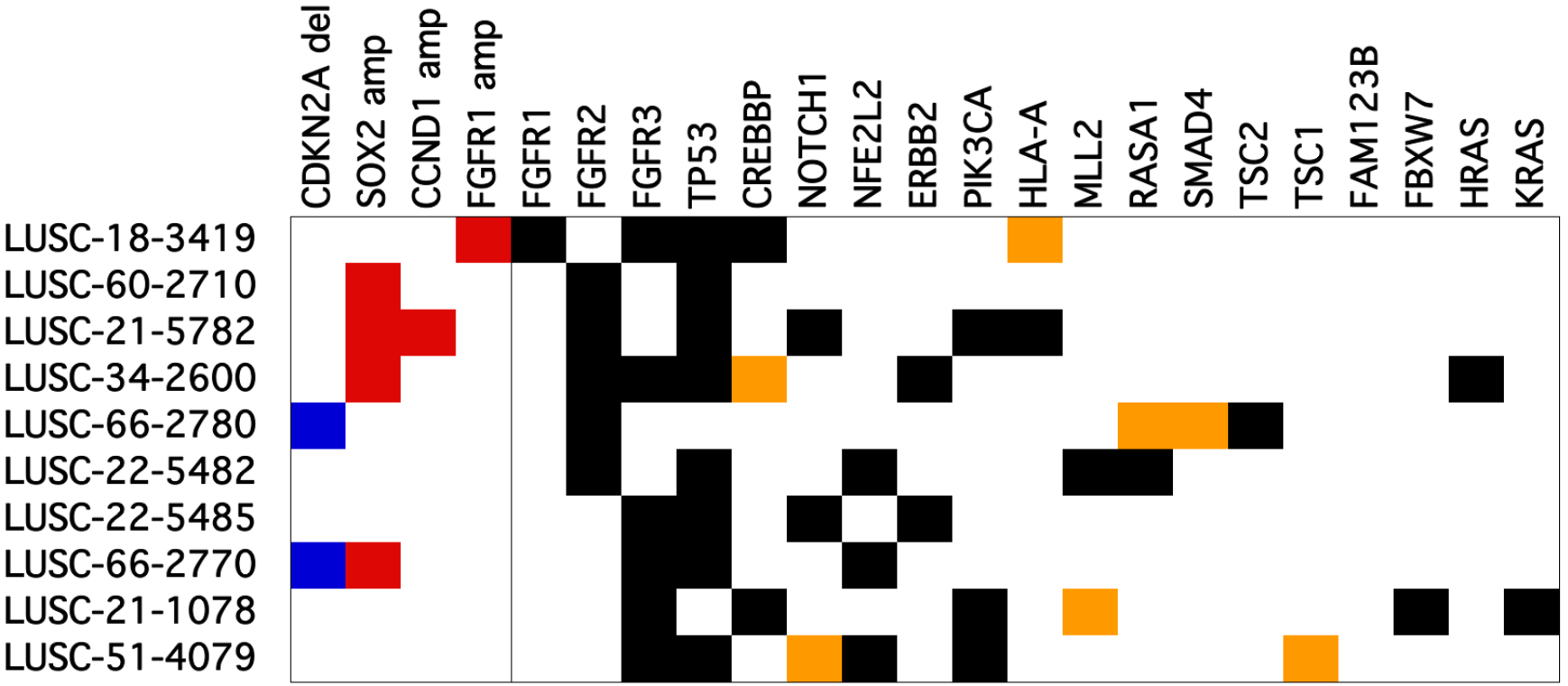
- ~10% focal amplification of FGFR1
- ~8% mutation across the four receptors
  - 3% FGFR2, 3% FGFR3
- Not significantly mutated across th dataset



FGFR2 and *FGFR3* mutations are observed in lung SqCC

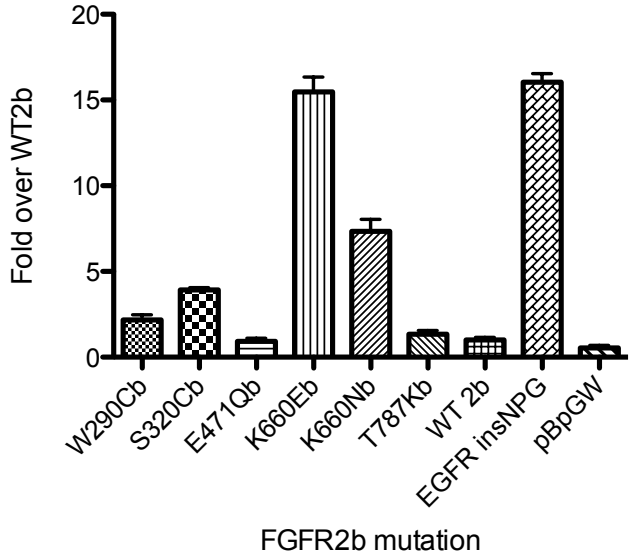


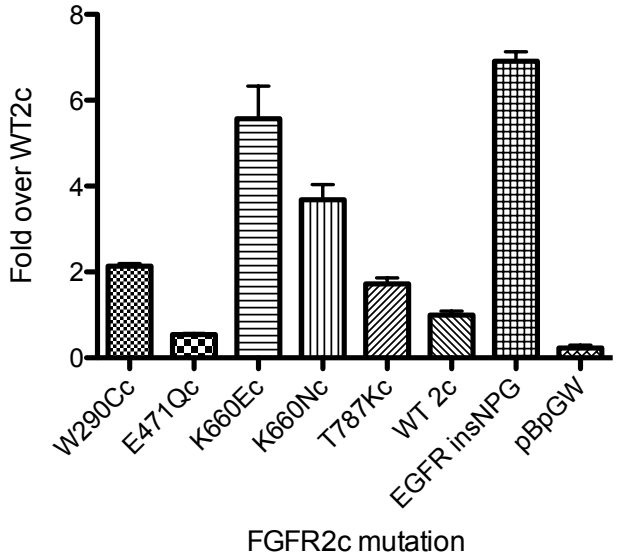
FGFR2 and *FGFR3* mutations do not repeatedly co-occur with other events except *TP53* mutation

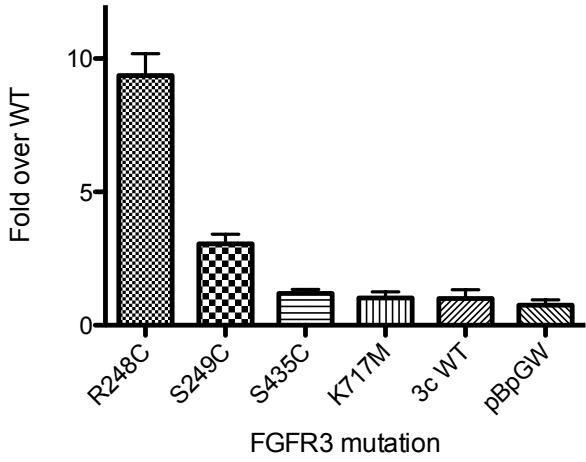


Trevor Pugh

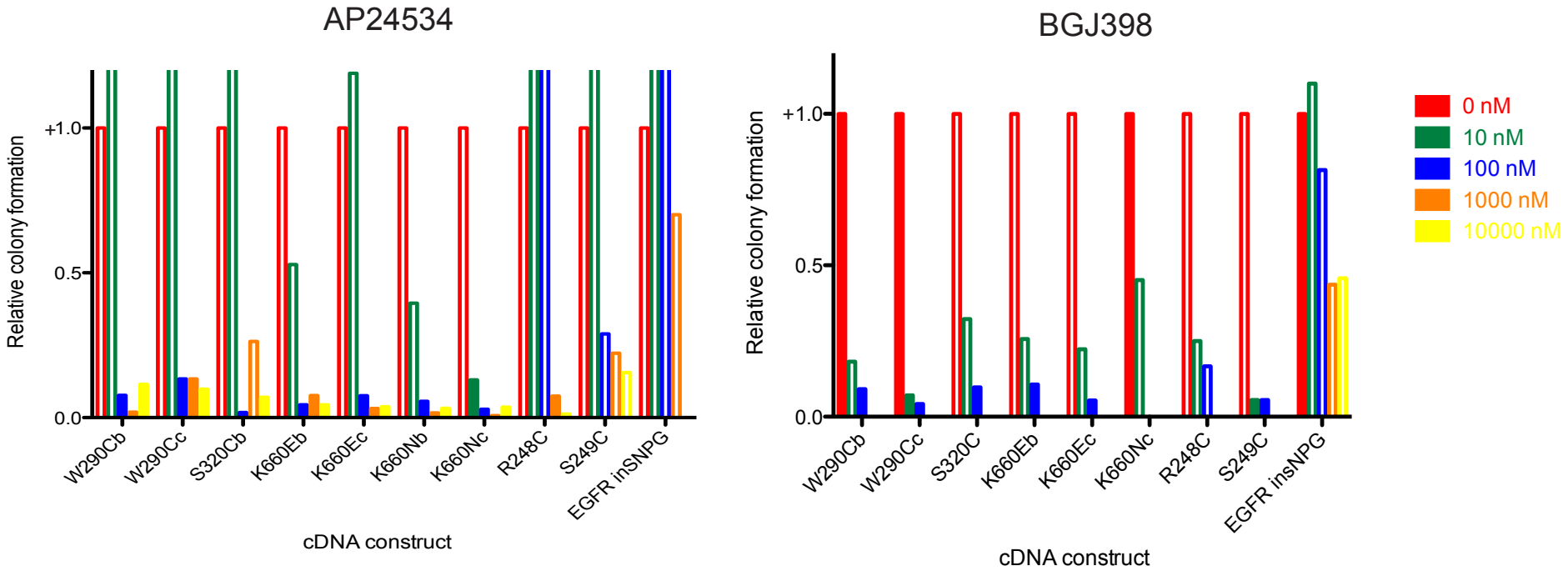
FGFR2/3 mutations are transforming in an anchorage-independent growth assay



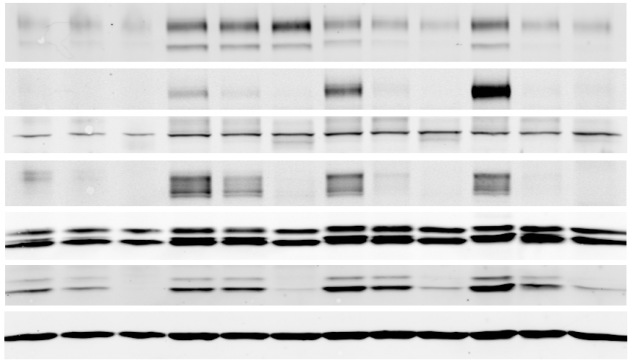




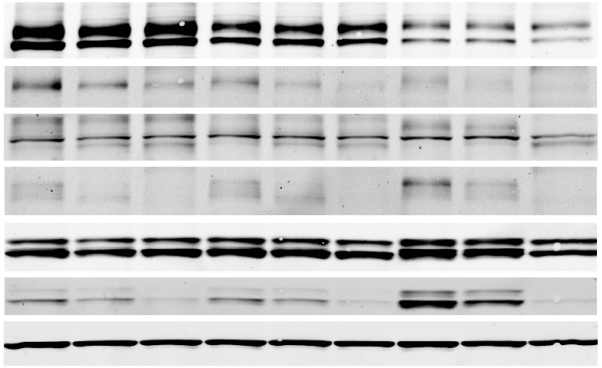
FGFR2/3 transformation can be blocked by FGFR inhibitors



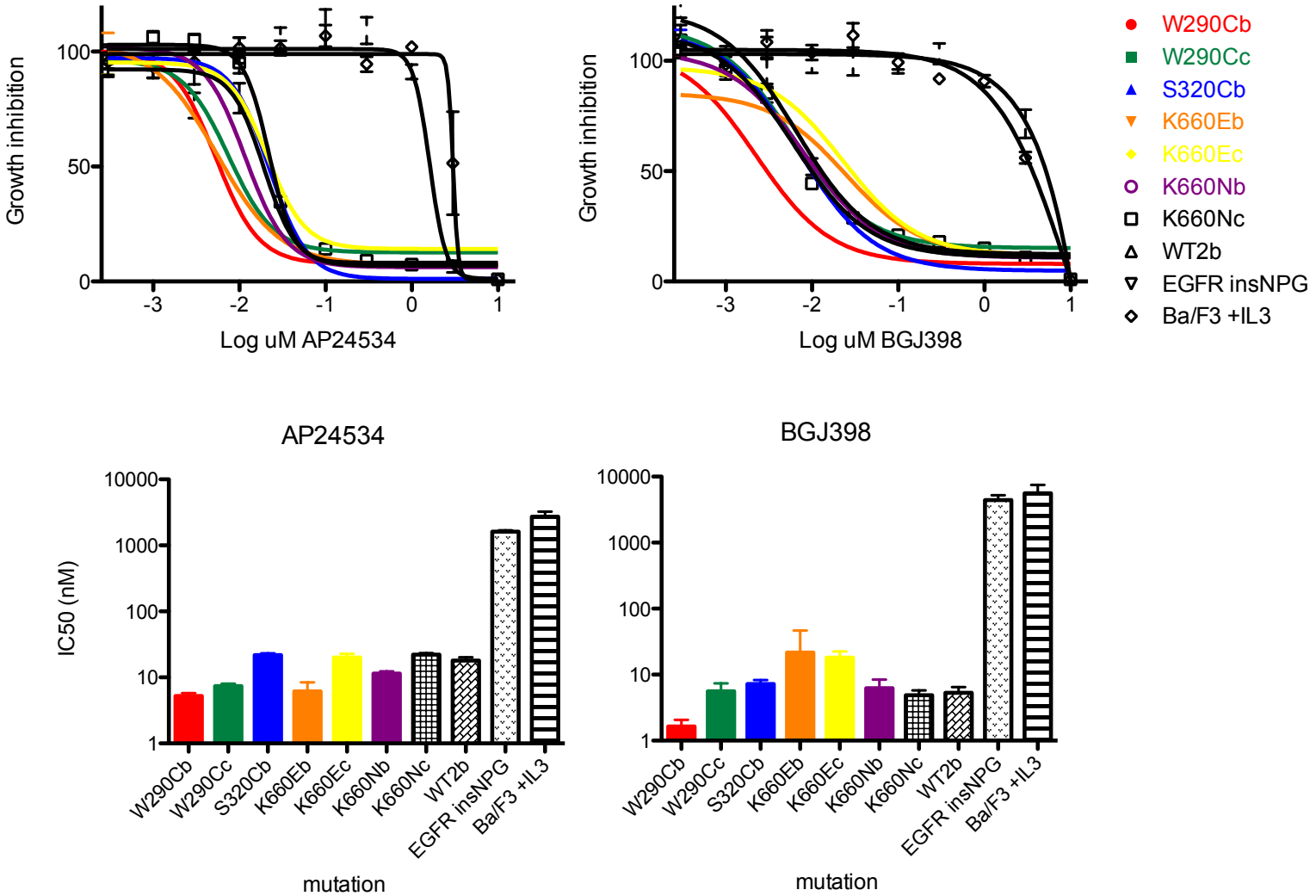
Loss of transformation correlates with loss of phosphorylation



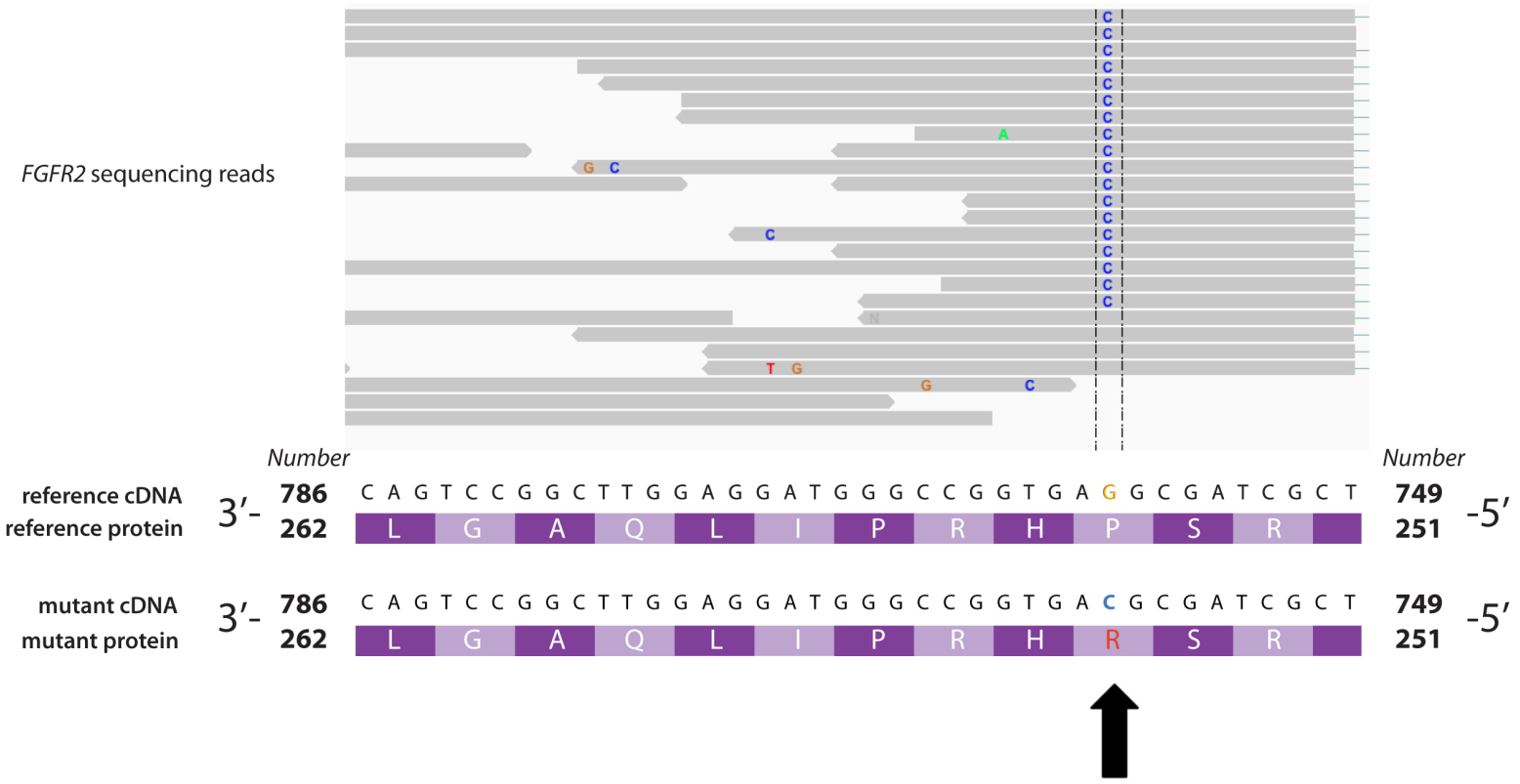
actin



Cells exhibiting dependency on the FGFR pathway are sensitive to FGFR inhibitors



A clinical case



FGFR2 mutation in the coding sequence at p.P253R

An *FGFR2*-positive tumor regresses upon pazopanib treatment

2 weeks pazopanib

Liao et al. Figure 5

Conclusions

- FGFR2/3 mutations observed in lung SqCC are sufficient to drive transformation in the NIH-3T3 cell line model, and the transformation phenotype can be reversed by FGFR small molecule inhibition
- Ba/F3 cells dependent on FGFR2/3 signaling for proliferation can be growth inhibited by FGFR small molecule inhibition
- A clinical success confirms that these findings provide a rationale for further study of patients with FGFR events in their tumors
- TCGA data have been used effectively to find new driving, targetable events in tumors (though these events do not always meet the threshold of statistical significance)

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FGFR biology

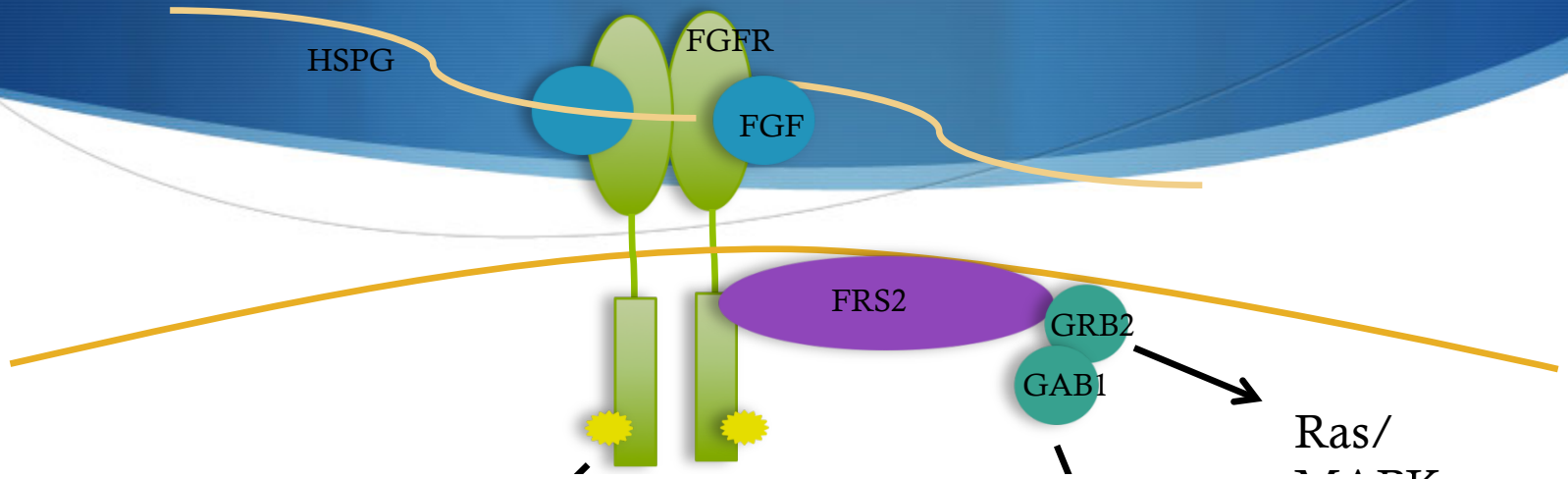


Table 1
Ligand specificities of FGFR isoforms

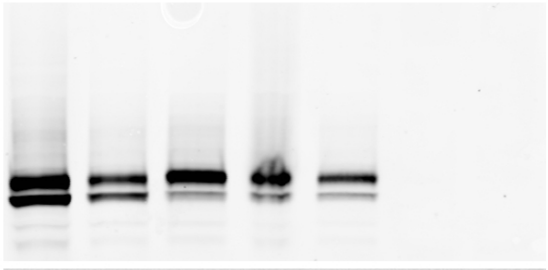
FGFR isoform	Ligand specificity
FGFR1b	FGF1, -2, -3 and -10
FGFR1c	FGF1, -2, -4, -5 and -6
FGFR2b	FGF1, -3, -7, -10 and -22
FGFR2c	FGF1, -2, -4, -6, -9, -17 and -18
FGFR3b	FGF1 and -9
FGFR3c	FGF1, -2, -4, -8, -9, -17, -18 and -23
FGFR4	FGF1, -2, -4, -6, -8, -9, -16, -17, -18 and -19

Disulfide bonding observed in ECD mutations to Cys

FGFR2
dimer

FGFR3
dimer

unreduced



FGFR3
monomer

reduced

actin