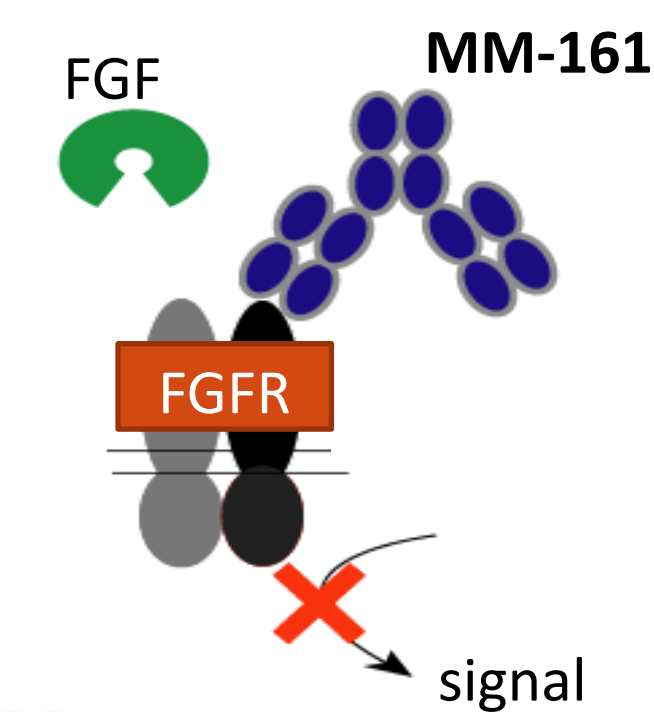


Introduction

- FGF receptor signaling plays a role in cell proliferation, differentiation, survival angiogenesis and regulation of vitamin D and phosphate homeostasis.
- Aberrant activation of the FGFR pathway has been shown to promote tumorigenesis and angiogenesis across multiple cancer indications.
- FGFR amplifications are frequently found in breast, gastric, ovarian, urothelial, colorectal and other squamous cancer.
- FGFR diversity has hampered the development of effective FGFR pathway inhibitors due to the need to block the activation of multiple receptors.
 - (FGFR1-FGFR2-FGFR3-FGFR4)
- Selective targeting this complex pathway of receptors has proven difficult due to tolerability associated with blocking endocrine FGF ligands. (FGF19, FGF23)
- We disclose for the first time a novel FGFR targeted antibody, MM-161, designed to block ligand-dependent signaling driven by all four FGF receptors.
- We present data illustrating that inhibition of multiple FGFRs is desirable to achieve full pathway inhibition and tumor regression.
- Specifically, MM-161 was designed to target the IIIc-isoforms of all four FGFRs.

MM-161 Design

- Antibody designed to block ligand binding to c-isoform FGFRs
- Offers greater specificity than small molecule FGF pathway inhibitors
- MM-161 is a potent inhibitor of the FGF pathway activation in preclinical models of lung, renal, breast, ovarian and other cancers

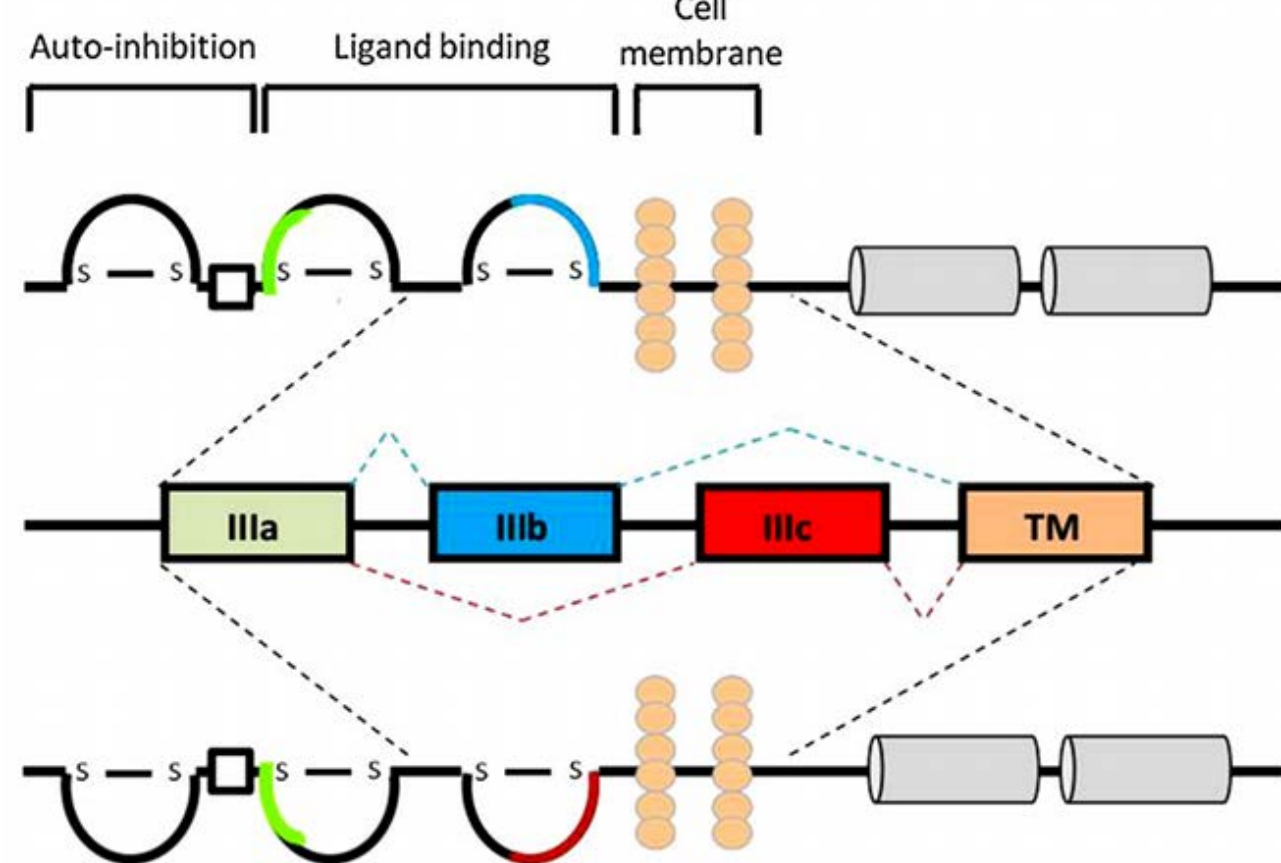


IIIb isoform

- expressed in epithelial cells
- FGFR2-IIIb thought to be a tumor suppressor

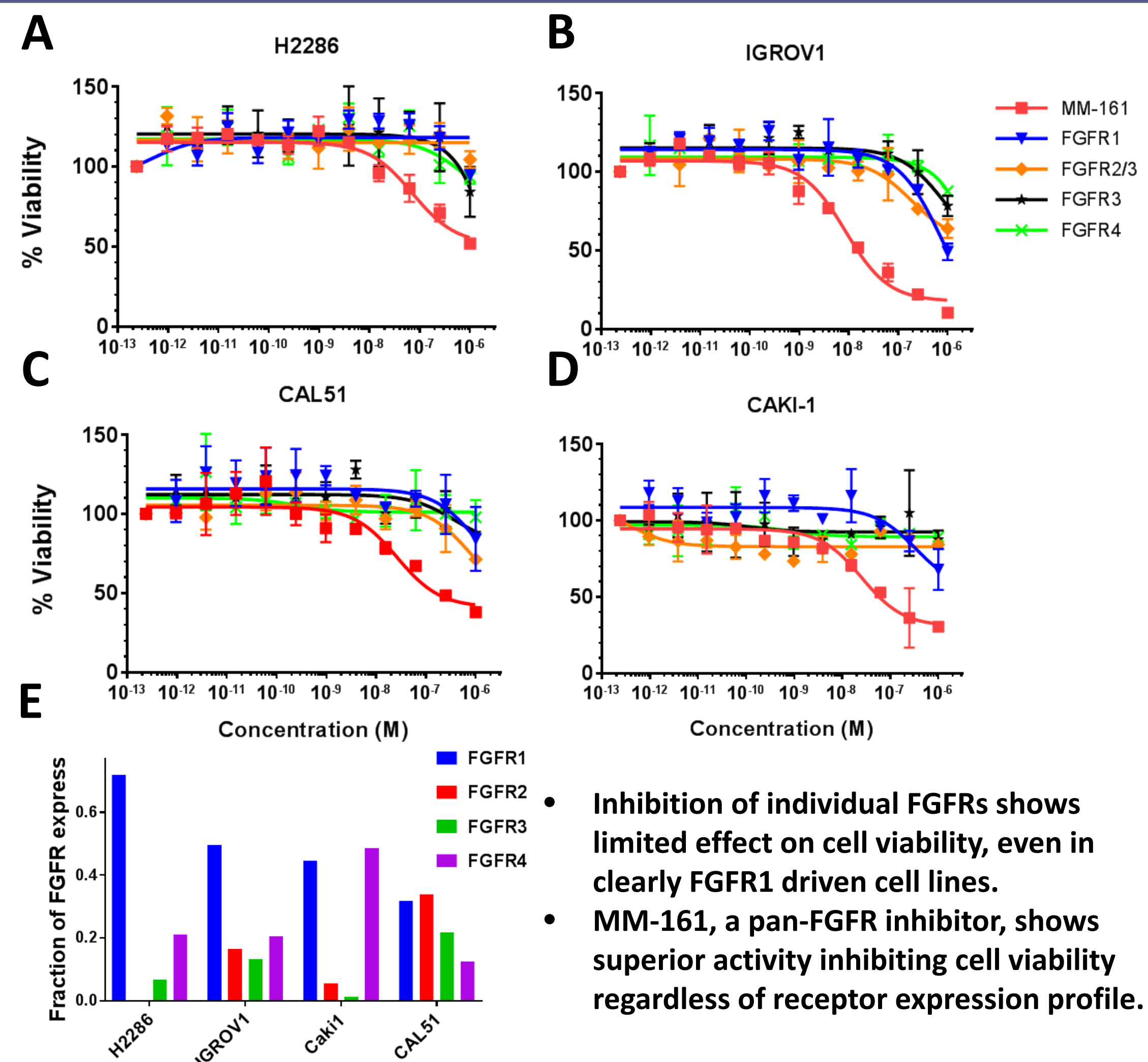
IIIc isoform

- expressed in mesenchymal cells
- Associated with more aggressive tumors
 - Due to broader ligand specificity?
- For FGFR2: switch from IIIb to IIIc is a marker of EMT

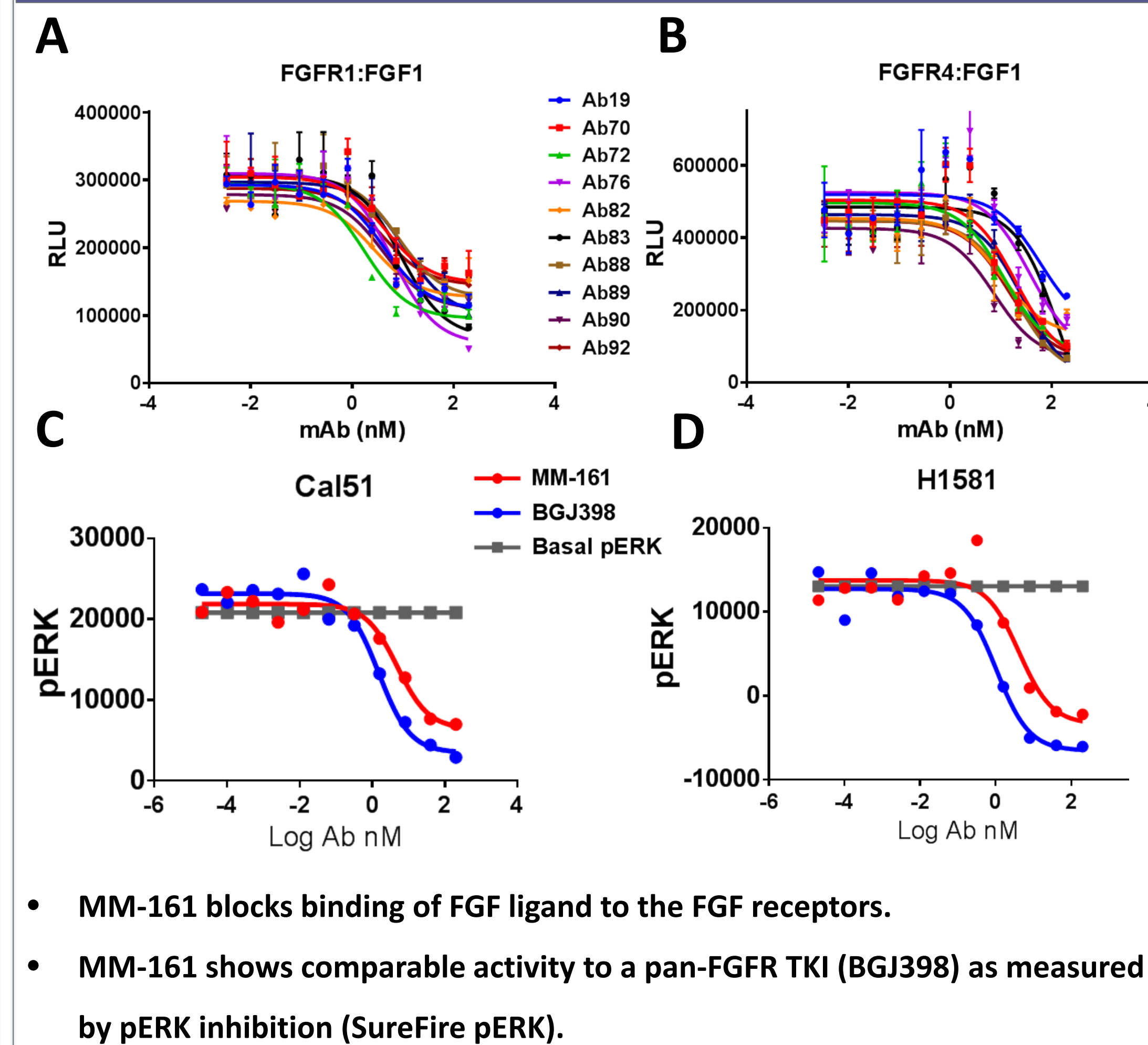


A.E. Fearon et al. / The International Journal of Biochemistry & Cell Biology 45 (2013) 2832–2842

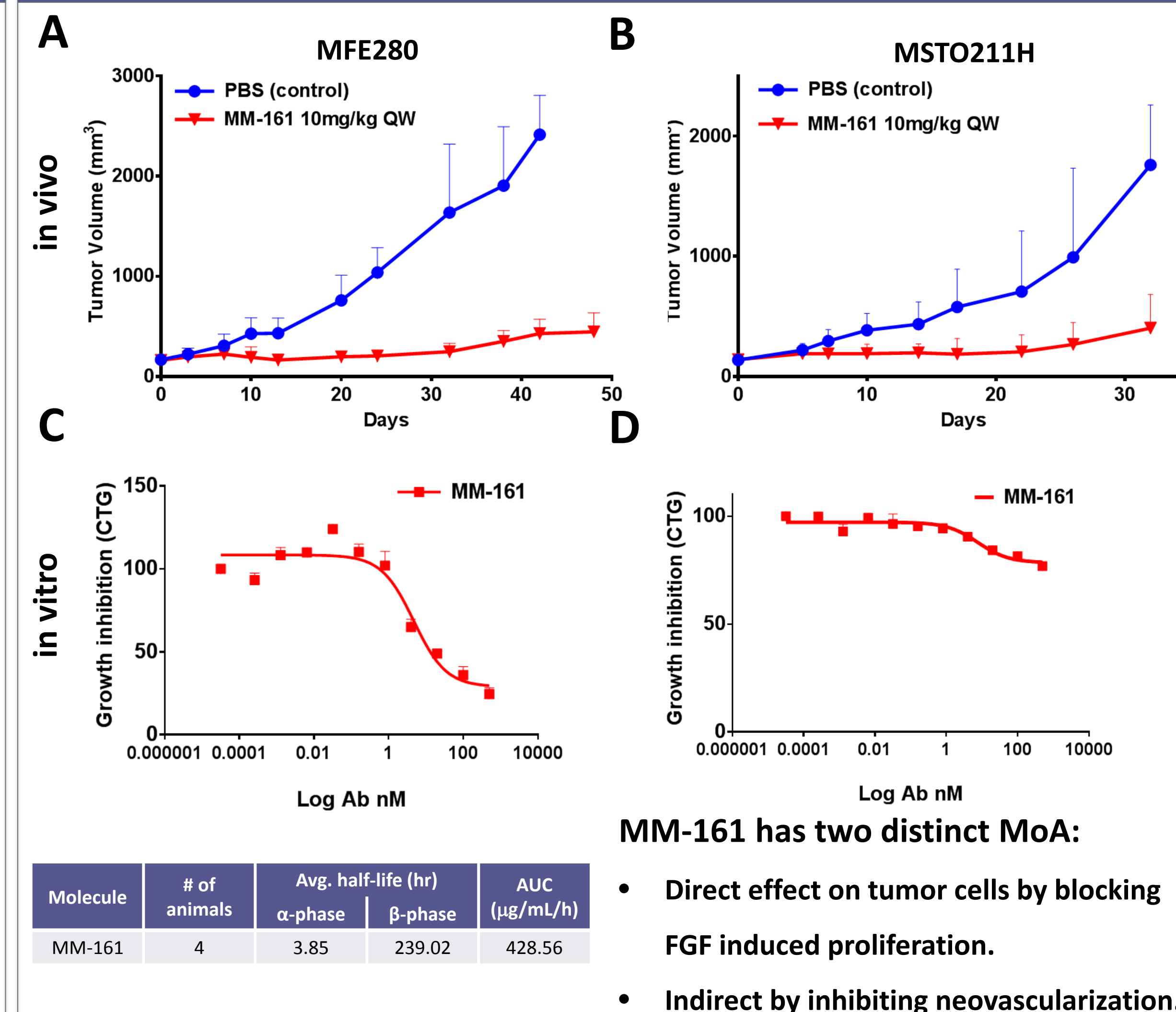
Targeting of Multiple FGF Receptors is Required for Maximal Growth Inhibition In Vitro



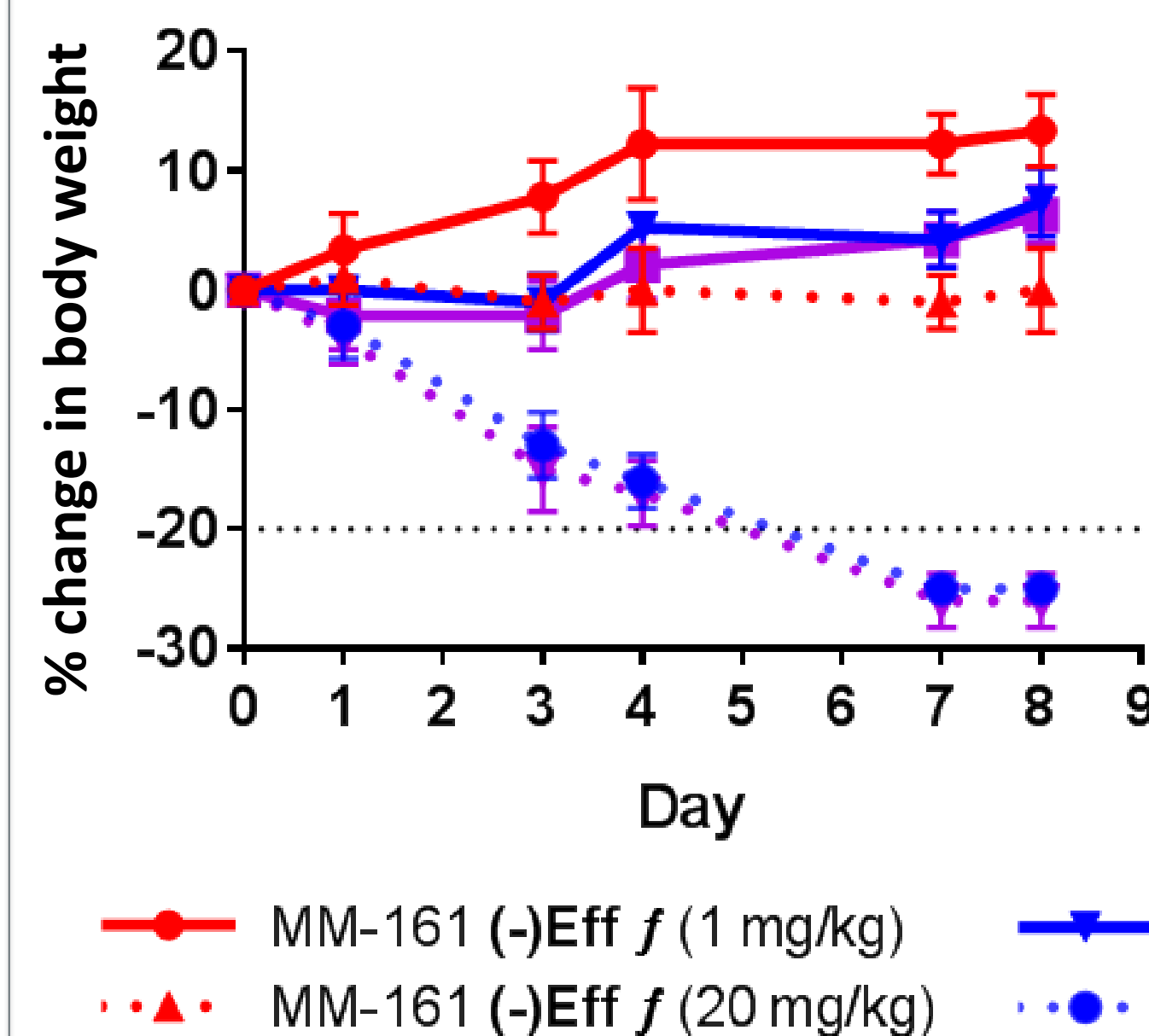
MM-161 is an Active Ligand Blocker and Inhibits Downstream Activation of pERK



MM-161 Inhibits Tumor Growth in Xenograft Models by Two Independent Mechanisms of Action



MM-161 is Well Tolerated in Animal Models



Sun *et al.* previously reported that systemic delivery of the antagonist FGFR1 antibody caused potent but reversible hypophagia and weight loss in rodents and monkeys.

Here we generated MM-161 molecules with various levels of effector function:

- full (+ Eff-f)
- partial (+/- Eff-f)
- no (- Eff-f)

MM-161 with full or partial effector function cause substantial weight loss within 2 days of the first dose. Importantly the effector less lead molecule does not affect food intake and weight stays stable even at high doses of 20mg/kg.

Summary

- MM-161 is well tolerated in mice and cynomolgus monkeys with no significant weight loss observed in either species.
- MM-161 does not cause hypoglycemia or hyperphosphatemia in mice or cynomolgus monkeys.
- MM-161 monotherapy leads to significant tumor growth inhibition or tumor regression of xenografts of human lung, renal and endometrial cancer amongst others.
- MM-161 has a dual mechanism of action by inhibiting both proliferation and angiogenesis.

Taken together, our preclinical data strongly supports the clinical evaluation of MM-161 in cancer patients.