Autocrine c-Met/HGF HCC PDX: Evaluation of a Biologic Targeting c-Met

Dawei Chen[1], Ziyong Sun[1], Likun Zhang[1], Mengmeng Yang[1], Jie Cai[1], Davy X. Ouyang[1], Jean-Pierre Wery[1], and Henry Q.X. Li[1,2]*

[1]Crown Bioscience, Inc., 3375 Scott Blvd, Suite 108, Santa Clara, CA 95054, [2]State Key Laboratory of Natural and Biomimetic Drugs, Peking University. *: presenting author

INTRODUCTION

The mesenchymal-epithelial transition factor (c-Met) represents an important target for cancer therapy. Aberrant activation of c-Met is associated with oncogenic transformation in several human tumor types, where tumor cell growth depends on constitutive activation of this tyrosine kinase receptor through binding to its high-affinity ligand, hepatocyte growth factor (HGF).

A c-Met/HGF experimental cancer model is critical to evaluate c-Met targeting therapies such as tyrosine kinase inhibitors (TKIs) or antibodies. Patient-derived xenografts (PDX) usually lose human stroma over time, which is the main source of HGF; moreover HGF produced by murine stroma is incapable of triggering paracrine signaling because of a lack of cross reactivity with the human c-Met expressed by the tumor. Some PDX grow independently of paracrine c-Met/HGF signaling, thanks to the presence of c-Met activating mutations or gene amplifications that provide constitutive c-Met activation, and autocrine signaling. These PDX models can be used to evaluate the antitumor efficacy of TKIs; however, they are not suitable to assess biologic agents such as antibodies, which work by disrupting the receptor-ligand interaction. Here we tested whether a PDX model with autocrine c-Met activation could be used to evaluate an antibody therapy against human c-Met. We identified a unique hepatocellular carcinoma (HCC) PDX, the LI0801 model, which relies on autocrine c-Met/HGF signaling for tumor growth, and we confirmed that a human c-Met antibody results in significant tumor response in this model.

METHODS

- LI0801 was engrafted subcutaneously in immunocompromised mice; the grafted tumor was derived from a male HCC patient (HBV++, early hepatocirrhosis, chronic cholecystitis, cholelithiasis).
- The tumor expression of human HGF and c-Met was assessed by RNAseq. The tumor expression of human vimentin, Met, and HGF was assessed by IHC.
- LI0801 was treated with a novel and highly specific c-Met TKI (M101) and a novel c-Met antibody (M102).

RESULTS

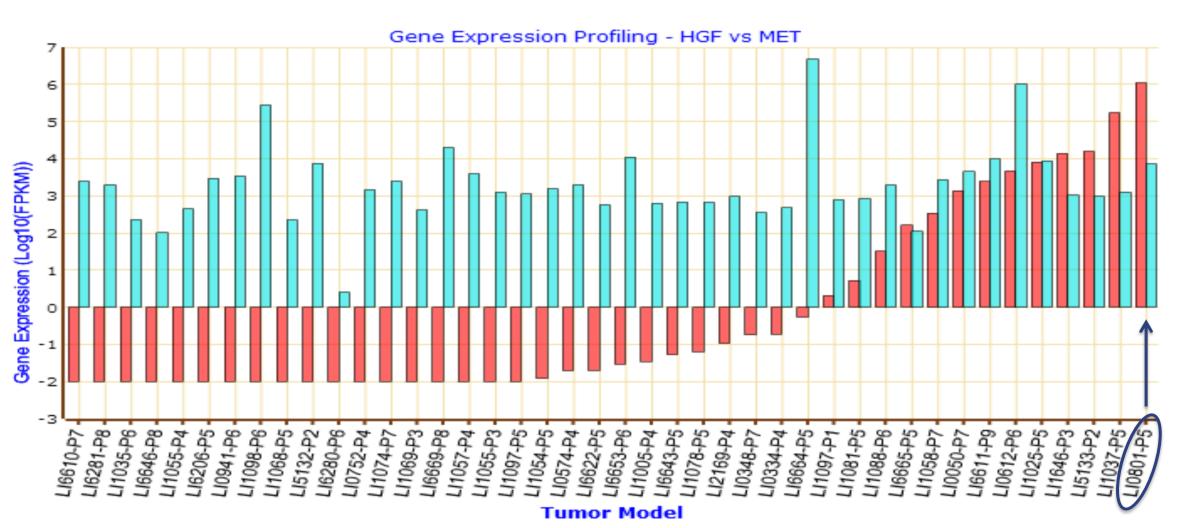**Figure 1. Mutational analysis and H&E staining of the LI0801 model.**

Figure 2: HGF/c-Met mRNA levels in a panel of HCC PDXs.
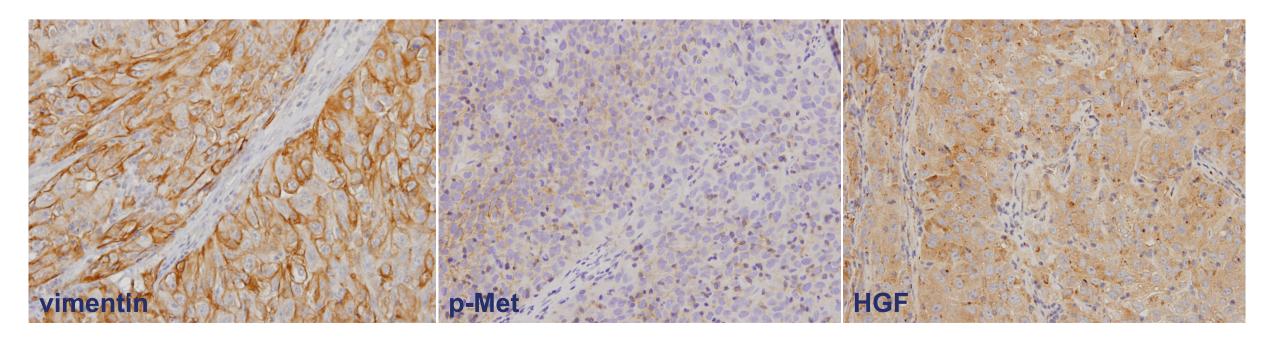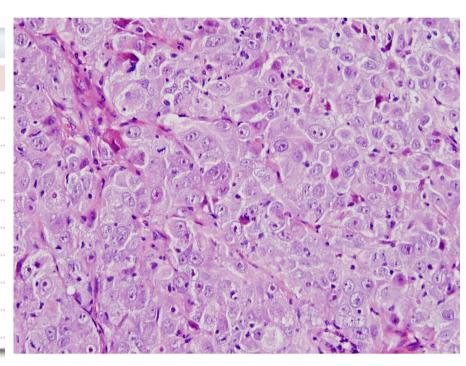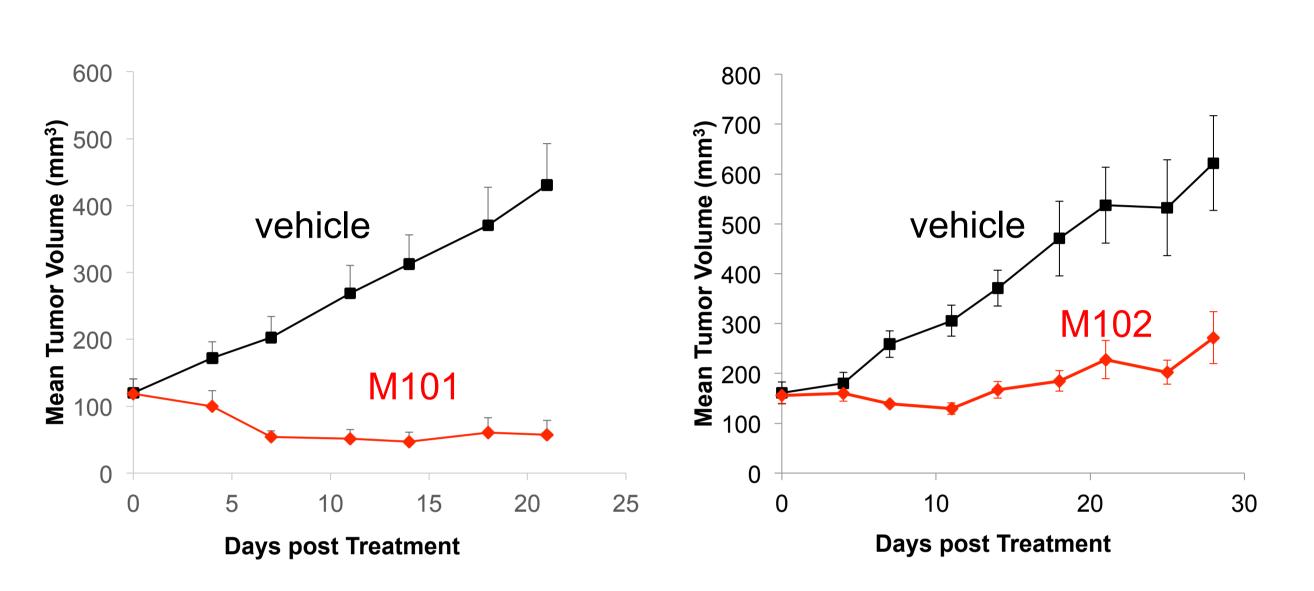Both genes are overexpressed in the LI0801 model.

Figure 3: IHC for human markers in LI0801 tumors.

Figure 4: Evaluation of the antitumor efficacy of a novel c-Met TKI M101 (left) and antibody M102 (right) in the HCC LI0801 xenograft model.
Tumor grafted subcutaneously in Balb/c nude mice.

CONCLUSIONS

1. LI0801, an HCC PDX, expresses high levels of both HGF and c-Met.

2. LI0801 grows via c-Met/HGF autocrine signaling in absence of human stromal cells.

3. LI0801 is sensitive to both a TKI and a monoclonal antibody targeting human c-Met.

4. Our data suggest that a model of autocrine c-Met/HGF signaling is suitable to evaluate both small molecule TKIs and antibody therapies.

Contact: Henry Li, henryli@crownbio.com