Development of a Novel Combination Therapy targeting MET and LGR5 to overcome Colorectal Cancer Resistance

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INTRODUCTION
Therapy-induced resistance and recurrence contribute to a majority of the challenges encountered in the clinical management of colorectal cancer (CRC). The chief culprits behind colorectal tumor relapse are cancer stem cells (CSCs). CSCs promote tumor progression and clonal heterogeneity owing to their self-renewability, plasticity, and differentiation capacity. Upon therapy termination, CSCs exit dormancy and circulate to secondary sites where they spawn metastases leading to disease-induced mortality. Leucine rich repeat-containing G protein-coupled receptor 5 (LGR5) is highly expressed in CRC and is a bona fide marker of functional CSCs. LGR5+ CSCs are often responsible for tumor initiation and metastatic outgrowth, however their conversion into a chemo-resistant LGR5 state is vital for metastatic dissemination. LGR5-targeted therapy results in tumor regression, yet LGR5 eventually relapse due to plasticity. Successful elimination of CRC tumors can be achieved by targeting both LGR5+ CSCs and LGR5- CRC cell populations. LGR5 CRC cells, at least in part, rely on the MET/STAT3 pathway to evade therapy. MET is a well-characterized plasticity- and promoter associated with poor prognosis in many solid tumor types, including CRC. For this project, we are generating MET-targeted antibody-drug conjugates (ADCs), which will act as guided missiles to deliver cytotoxic agents to CRC cells expressing high levels of MET, including therapy-resistant LGR5 CRC cells.

WORKING MODEL
Figure 1. ADCs can serve as guided missiles that deliver potent therapeutic agents to drug resistant colorectal cancer cells. The cytotoxic drug is released upon ADC internalization and lysosomal trafficking in tumor cells. The combination of MET and LGR5-targeted ADCs should effectively destroy both LGR5+ CSCs and LGR5 CRC cell populations.

DISCUSSION
- In addition to c-MET overexpression in a majority of CRC patients, it’s downstream activation upon LGR5 expression confers resistance to therapy. 
  - Both ABT-737 and MC8 c-MET mAbs demonstrate high binding affinity, internalization and lysosomal colocalization in human colorectal cancer cells.
  - Ongoing studies include conjugation with different cytotoxic payloads and validation in a wider panel of CRC cell lines and patient derived xenografts.

RESULTS
- The RNAseq results shown here are in whole or partly based upon data generated by the TCGA Research Network. 
  - This work is funded by NIH/NCI R01CA226894 and R21CA270716, and Cancer Prevention Research Institute of Texas (CPRIT) RP190542 to K.S. Carmon.
  - Preliminary data obtained from "Loss of LGR5 through plasticity or gene ablation is associated with therapy resistance and enhanced MET-STAT3 signaling in colorectal cancer cells." Posey TA, Jacob J, Parkhurst AN, Subramanian S, Francisco LE, Liang Z, and Carmon KS. bioRxiv doi: 10.1101/2022.03.01.482539

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