

Table 2. Patient assessment for those undergoing unsedated colonoscopy

Patient #	Required Rescue Analgesia	Repeat Colonoscopy with VD	Comments
1	No	Yes	"When pain is worst VD does not help. VD is useful in lower pain zones."
2	No	Yes	"Knowing the insertion was the most painful helped. Really no pain at all."
3	No	Yes	"Images could be sharper, talking from doctors were important and helped a lot"
4	Yes, 50 mcg Fentanyl (Group 3)	No	N/A
5	Yes, 75 mcg Fentanyl (Group 2)	Yes	"Would pursue in future. Was only difficult at the turns in the colon where the pain relievers were easily sufficient"
6	No	Yes	"Most helpful part of the procedure was staff talking"
7	No	Yes	N/A
8	No	Yes	"It reduced areas of most discomfort"
9	Yes, 50 mcg Fentanyl (Group 2)	Yes	"I liked to know what was going on"
10	No	No	"With VR there is too much going on to pay attention!"

Sa1110

INHIBITION OF HGF MATURATION OVERCOMES CETUXIMAB RESISTANCE IN COLORECTAL CANCER

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We have previously identified that activation of receptor tyrosine kinases (RTKs), MET and RON contributed to resistance to the EGF receptor (EGFR)-directed therapeutic antibody, cetuximab. These findings originated from our *in vitro* 3D type I collagen cultures of human colorectal cancer (CRC) cell line HCA-7 derivatives CC, SC, and CC-CR. CC are sensitive to cetuximab, while SC and CC-CR are resistant. Both *de novo* and acquired modes of cetuximab resistance in SC and CC-CR, respectively, could be overcome by crizotinib, a multi-RTK inhibitor that also targets MET and RON. Conversely, exogenous administration of MET ligand, HGF could transiently induce cetuximab resistance which could be further overcome by crizotinib addition. HGF/HGFL are synthesized as inactive precursors and require cleavage by proteases (HGFA, Matriptase, and Hepsin) to be biologically active. To inhibit HGF/HGFL cleavage in cetuximab-resistant cells, we employed inhibitors of HGF/HGFL proteases (ZFH7116 and VD2173) and were able to overcome both *de novo* and acquired cetuximab resistance. A survey of TCGA datasets indicated that HGF/HGFL were overexpressed in several CRC CMS subtypes. We next expressed human HGF in cetuximab-sensitive CC cells and observed that HGF overexpression imparts cetuximab resistance. Moreover, cetuximab resistance induced by HGF overexpression could be overcome by the downstream MET inhibition (with crizotinib), and we are now testing if the upstream inhibition of HGF proteases (with ZFH7116/VD2173) also overcomes cetuximab resistance. Combined these results indicate that inhibition of HGF cleavage and maturation may be a novel way to overcome resistance to EGFR-targeted therapies in CRC.

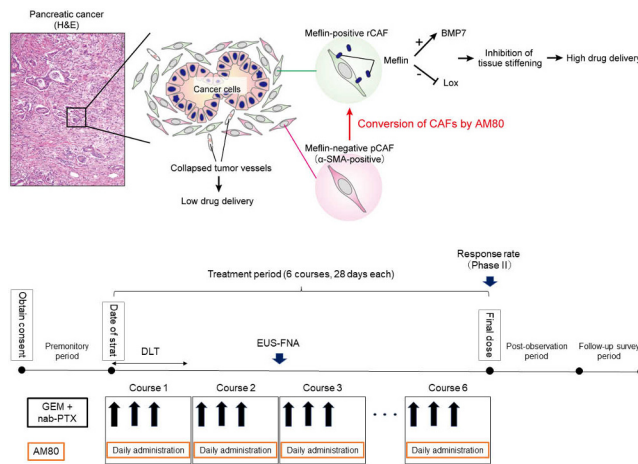
Sa1111

SAFETY AND EFFICACY OF AM80 IN PATIENTS WITH ADVANCED PANCREATIC CANCER: A STUDY PROTOCOL FOR AN OPEN-LABEL PHASE I/II INVESTIGATOR-INITIATED CLINICAL TRIAL BASED ON A DRUG REPOSITIONING APPROACH THAT REPROGRAMS THE TUMOR STROMA

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Background Cancer-associated fibroblasts (CAFs) are an important component of the tumor microenvironment. Recent studies revealed CAFs are heterogeneous and CAF subset(s) that suppress cancer progression (cancer-restraining CAFs [rCAFs]) must exist in addition to well-characterized cancer-promoting CAFs (pCAFs). However, the identity and specific markers of rCAFs are not yet reported. We recently identified Mefflin as a specific marker of rCAFs in pancreatic and colon cancers. Our studies revealed that rCAFs may represent proliferating resident fibroblasts. Interestingly, a lineage tracing experiment showed Mefflin-positive rCAFs differentiate into α -smooth muscle actin-positive and Mefflin-negative CAFs, which are generally hypothesized as pCAFs, during cancer progression. Identifying rCAF marker helped us develop new strategies to convert or reprogram pCAFs to rCAFs. Using a pharmacological approach, we identified AM80, a synthetic unnatural retinoid, as a reagent that effectively converts Mefflin-negative pCAFs to Mefflin-positive rCAFs. AM80 administration improved the sensitivity of pancreatic cancer cells to chemotherapeutics in a preclinical pancreatic cancer mouse model. Thus, conversion of pCAFs to rCAFs may represent a new strategy for pancreatic cancer treatment. We aimed to investigate the efficacy of a combination of AM80 and gemcitabine (GEM) and nab-paclitaxel (nab-PTX) in patients with advanced pancreatic cancer. **Methods** The phase I part is a 3+3 design, open-label, and dose-finding study. The dose-limiting toxicity (DLT) of these combination therapies would be evaluated for 4 weeks. After the DLT evaluation period, if no disease progression is noted based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or if the patient has no intolerable toxicity, administration of AM80 with GEM and nab-PTX would be continued for up to 24 weeks. The phase II part is an open-label, single-arm study. The maximum tolerated dose (MTD) of AM80 with GEM and nab-PTX, determined in phase I, would be administered until intolerable toxicity or disease progression occurs, up to a maximum of 24 weeks, to confirm efficacy and safety. The primary endpoints are frequency of DLT and MTD of AM80 with GEM and nab-PTX in the phase I part and response rate based on the RECIST in the phase II part. Given the historical control data, we hope that the response rate will be over 23% in phase II. **Discussion** Strategies to convert pCAFs into rCAFs have

been developed in recent years. We hypothesized that AM80 would be a promising enhancer of chemosensitivity and drug distribution through CAF conversion in the stroma.



Sa1112

THERAPEUTIC POTENTIAL OF MIR-198 TO SUPPRESS MC38 COLONIC ADENOCARCINOMA GROWTH

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Introduction: Colon cancer occurrence is steadily increasing. Immunotherapies target immune checkpoints, such as PD1/PD1-L and CTLA-4/B7. While successful, these immunomodulators are posing challenges in colon cancer due to their lack of efficacy, tumor resistance, and induction of autoimmune responses, which thus demonstrates the need for additional therapeutics. Recently, thousands of non-coding microRNAs have been identified which have critical roles in human diseases, particularly in cancer. MiR-198 is a microRNA that regulates multiple targets and plays a seminal role as a tumor suppressor in several cancers. Our objective was to investigate the potential tumor suppressor effect of exogenous miR-198 in colon cancer mouse models. **Methods:** The C57Bl/6 MC38 adenocarcinoma cell line was transfected with a synthetic hsa-miR-198 mimic condensed with lactic co-glycolic-acid-modified polyethylenimine (LGA-PEI) to form miR-198-loaded-LGA-PEI nanoparticles (LPNP-198) or blank controls (LPNP-Ctrl). After 24 hours, the transfection medium was replaced with DMEM containing 5% FBS or additionally oxaliplatin (3 μ M). Cell growth was quantified using a cell counter. As an alternative to achieve slow, targeted release of LPNP-198, a non-immunogenic jellyfish collagen Type 0 hydrogel was added to the transfection medium. SYBR Green qPCR for murine E-cadherin was performed. Additionally, *in vivo* subcutaneous flank, intraperitoneal and orthotopic colonic MC38 cell injection models are being used. **Results:** Cultured MC38 cells demonstrated a significant suppression in tumor cell growth after transfection with LPNP-198 and even a more significant growth inhibition when treated with LPNP-198 containing hydrogel (% inhibition: LPNP-198=42.6 \pm 4.8, LPNP-198+hydrogel in 3D culture=76.5 \pm 1.9, and LPNP-198+hydrogel in monolayer=97.1 \pm 0.4). Additionally, LPNP-198 demonstrated an additive suppressive effect on MC38 cell growth when combined with oxaliplatin (% inhibition: miR198=28.2 \pm 7.9, oxaliplatin=61.4 \pm 14.7, miR198+oxaliplatin=78.1 \pm 3.1). Interestingly, tumor expression of the anti-metastatic prognosticator E-cadherin was increased in MC38 cells after LPNP-198 transfection (relative expression: mock= 3.6x10⁻⁸ \pm 7.3x10⁻⁹ vs. LPNP-198=7.6x10⁻⁸ \pm 2.1x10⁻⁸). *In vivo* LPNP-198 transfection in the subcutaneous flank, intraperitoneal and orthotopic colonic MC38 cell injection models is being evaluated. **Conclusions:** The results demonstrate that *in vitro* LPNP-198 has the potential to suppress MC38 tumor cell growth in culture with it being more effective when adding a hydrogel to the transfection medium. Additionally, the LPNP-198 induced tumor suppression was additive when combined with oxaliplatin. These *in vitro* experiments demonstrate the therapeutic potential of LPNP-198 as an adjuvant cancer therapeutic.

Sa1113

A SINGLE-CELL RESOLUTION, MULTI-OMIC SPATIAL ATLAS OF COLONIC TUMORIGENESIS DRIVEN BY C. DIFFICILE FROM HUMAN COLORECTAL CANCER-ASSOCIATED BIOFILMS

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Emerging evidence strongly supports a causal role for specific pro-carcinogenic driver bacteria within the colonic microbiota. Simultaneously, invasive biofilm formation in the colon may initiate or accelerate colorectal cancer (CRC) directly through epithelium-autonomous mechanisms or indirectly by inducing pro-tumorigenic inflammation. To better understand these host-microbe interactions during the earliest stages of tumorigenesis, we have combined single-cell RNA-sequencing (scRNA-seq), spatial transcriptomics, and multiplex immunofluorescence to define the molecular spatial organization of colonic tissue from germ-free *Apc^{Min}* + mice colonized with bacteria from human biofilm-associated CRC. Drewes *et al.* have previously presented unpublished data suggesting toxigenic *C. difficile* as a critical species within biofilms driving distal colon adenoma formation in this model. Here, we focus on