epithelial cells (HCECs) and peripheral blood mononuclear cells (PBMCs) with PEGylated-PLGA-ZL0513, ZL0591, and ZL0742 overnight. No apparent increase in cell death was detected in HCECs or PBMCs even at 40 μM. Furthermore, oral administration of our nano-encapsulated BRD4 inhibitors at the dosage of 2 mg/kg effectively block colonic inflammation in both IBD animal models of dextran sulfate sodium (DSS)-induced colitis and oxazolone (OXA)-induced colitis.

Collectively, our compelling *in vivo* efficacy data support that our nano-encapsulated BRD4 inhibitors effectively block colonic inflammation in animal models of IBD. Local delivery of nanoparticle-encapsulated BRD4 inhibitors may offer superior pharmacotherapy for IBD patients.

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STOCHASTIC INTERINDIVIDUAL MICROBIOME VARIATION MAY GUIDE PROTECTIVE PERINATAL PROBIOTIC DEVELOPMENT AGAINST IBD

Mahesh Krishna, Melinda Engevik, Karen Queliza, Savini Britto, Rajesh Shah, Wenly Ruan, Hangtao Wang, James Versalovic, Richard Kellermayer

The purpose of our experiment was to explore how stochastic inter-individual variation in the mammalian gut microbiome may link to inflammatory bowel disease (IBD) susceptibility, and guide the development of a perinatal preventative probiotic.

Dextran sodium sulfate (DSS) was introduced to C57BL/6J mice to induce acute colitis as a model of IBD. Potentially protective bacteria were identified using a discovery-validation cohort approach towards stochastic DSS susceptibility. *Lactobacilli* (two different cocktails of *L. reuteri* and *L. johnsonii* strains) or control media were supplemented by mouth to dams prior to delivery and during lactation (i.e. perinatal probiotic). The pups were evaluated for DSS susceptibility at young adulthood.

Fecal *Lactobacillus* was increased in the DSS-resistant mice in both the discovery and validation cohorts. Maternal supplementation of female offspring with an *L. reuteri* cocktail (strains 6798-1, 6798-jm, and 6798-cm) induced progressive microbiome separation and protection against colitis by young adulthood.

Maternal supplementation of *L. reuteri* could confer protection against DSS colitis in young adult female mice. This work is the first to exploit stochastic mammalian microbiome variation to guide microbial therapeutic identification. Our findings underscore neonatal microbiome plasticity and set the stage for the potential development of perinatally deliverable protective probiotics against human IBD.

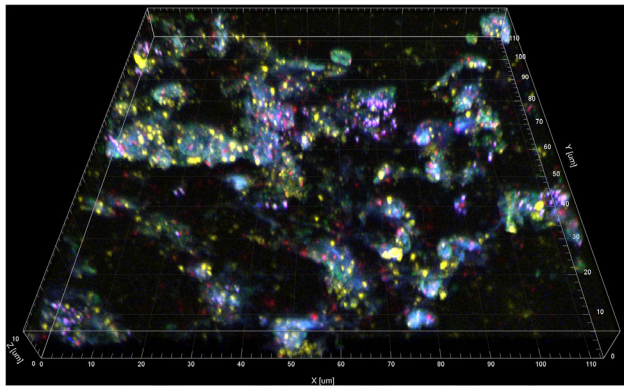
THE ROLE OF MYELOPEROXIDASE AND NEUTROPHIL EXTRACELLULAR TRAPS IN THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

Belal Chami, Gulfam Ahmad, Angie Schroder, Patrick San Gabriel, Paul Witting

Neutrophils are short-lived immune cells that represent the major cell type recruited to the inflamed bowel releasing their azurophilic granules containing enzymes myeloperoxidase (MPO). Fecal and serum MPO levels has previously been shown to correlate to disease severity in IBD patients. MPO, in the presence of H2O2 and free Cl- undergoes a halogenation cycle, yielding the two-electron oxidant, hypochlorous acid (HOCl) - a potent bactericidal agent. However, chronic intestinal exposure to MPO/HOCl due to perpetual inflammation may cause secondary host-tissue injury and cell death. Neutrophil Extracellular Trap (NET)osis is a specialised form of neutrophil death where MPO is entrapped in a DNA scaffold and continues to elicit HOCl activity and may further contribute to host-tissue injury.

We investigated the presence of NETs in surgically excised ileum samples from CD and healthy patients using advanced confocal microscopic techniques and found MPO, Neutrophil Elastase (NE) and Citrullinated Histone h3 (CitH3) - critical components of NET formation, individually positively correlate to the severity of histopathological intestinal injury. Furthermore, multiplex Opal™ IHC performed using LMS880 Airyscan-moduled microscopy with z-stacking revealed colocalization of NE, MPO, CitH3 and DAPI indicating the extensive presence of NETs in severely affected CD tissue. Using two pharmacological inhibitors of MPO in a dextran sodium sulphate (DSS) model of murine colitis, we demonstrated the pathological role of MPO in experimental colitis. MPO inhibitors, TEMPOL and AZD3241 delivered via daily *i.p* significantly rescued the course of colitis by abrogating clinical indices including body weight loss, disease activity index, inhibiting serum peroxidation, and preserving colon length, while significantly mitigating histoarchitectural damage associated with DSS-induced colitis. We also showed that MPO inhibition decreased neutrophil migration to the gut, suggesting MPO may play a role in perpetuating the inflammatory cell by further recruiting cells to the inflamed gut.

Collectively, we have shown for the first time that MPO is not only an important clinical marker of disease severity but may also play a critical role in perpetuating host-tissue damage and inflammation.



TOXICOLOGICAL FINDINGS OF A RECOMBINANT CHOLERA TOXIN B SUBUNIT VARIANT WITH THERAPEUTIC POTENTIAL IN ULCERATIVE COLITIS

Micaela Reeves, Daniel Tuse, Krystal Hamorsky, Joshua Royal, Nobuyuki Matoba

Background: The cholera toxin B subunit (CTB) is the nontoxic and homopentameric component of the holotoxin. Upon binding to GM1 ganglioside on the surface of epithelial cells, CTB mediates entry and retrograde transport through the endomembrane system and disengages the catalytic A subunit in the endoplasmic reticulum (ER). EPICERTIN (EPT) is a recombinant variant of CTB with a non-native C-terminal extension harboring an ER-retention motif, KDEL. We have found that increased ER-retention time resulting from this modification allowed EPT to induce an unfolded protein response and TGF-β signaling in colon epithelial cells, triggering wound healing activity in preclinical colitis models. The unique epithelial repair activity of EPT hints at its therapeutic potential in ulcerative colitis.

Objective: We aim to develop data supporting a first-in-human clinical trial with an EPT enema indicated for ulcerative colitis. Here, we evaluated the efficacy and toxicity of intrarectal (IR) administration of EPT in preclinical rodent models.

Results: IR administration of EPT at 0.1 and 1 μM to female C57/BL6 mice (0.6 and 6.1 μg/animal) with acute dextran sodium sulfate (DSS)-induced colitis resulted in decreased disease activity index scores and increased body weight recovery, supporting a target therapeutic dose of ≤1 μM for clinical administration. A dose-escalation study was performed following a single IR exposure at 1, 2 and 5 μM (61.4, 122.8 and 307 μg/animal) in male and female Sprague Dawley rats. No drug-related adverse effects were evident in clinical observations, including clinical pathology and gross necropsy, even at the highest dose tested. A pharmacokinetics study was performed in male and female mice dosed with a 1 or 10 μM (6.1 and 61.4 μg/animal) IV bolus of EPT. Plasma samples were collected periodically for up to 24 h postdose. EPT concentrations were highest at first collection and decreased steadily until unquantifiable by 4 h. The elimination phase half-life was 0.26 to 0.3 h. When healthy and DSS-induced colitic mice (n = 72) were dosed with 1 or 10 μM EPT IR, marginal amounts of EPT were found in only 4 plasma samples scattered across groups and time points, suggesting that systemic exposure after IR administration is negligible.

Conclusion: These data support further development of EPT as a potential therapeutic for ulcerative colitis.

Comparative Effectiveness Studies

COMPARATIVE EFFECTIVENESS AND SAFETY OF VEDOLIZUMAB AND ANTI-TUMOR NECROSIS FACTOR AGENTS IN OLDER ADULTS WITH INFLAMMATORY BOWEL DISEASES IN MEDICARE ADMINISTRATIVE CLAIMS DATABASE

Bharati Kochar, Virginia Pate, Michael Kappelman, Millie Long, Ashwin Ananthakrishnan, Andrew Chan, Robert Sandler

Background: The number of older adults with inflammatory bowel diseases (IBD) is increasing. Older adults with IBD are less likely to receive effective immunosuppression. We aimed to determine efficacy and safety of biologic therapies in older adults with IBD.

Methods: We conducted a retrospective cohort study using an active comparator, new user design in a 20% random sample from the 50 state Medicare claims

database between May 2014 and December 2018. We included patients who initiated vedolizumab or an anti-tumor necrosis factor (TNF)-α agent (infliximab, adalimumab, golimumab or certolizumab) following 12-months of continuous enrollment in Medicare fee-for-service Parts A/B/D without either study drug. Patients were required to be ≥65 years old and have ≥2 international classification of disease (ICD) codes of Crohn's disease (CD) or ulcerative colitis (UC). We excluded patients who received other biologic therapies and/or those who had ≥2 codes for other immunologic conditions. Pertinent co-variates included were age, sex, race Charlson Co-morbidity Index (CCI), predicted probability of frailty, healthcare utilization and baseline IBD medications. The outcomes of interest were hospitalizations, IBD-related surgery and new corticosteroid use ≥ 60 days after drug initiation. We described the study population, assessed health care utilization and use of other IBD medications. We estimated crude incidence rates and hazard ratios (HR) adjusted for the covariates using standardized mortality ratio (SMR) weights.

Results: We identified 488 vedolizumab users and 2,213 anti-TNF users. The median age was 72 years in the vedolizumab cohort and 71 years in the anti-TNF cohort; 12% of both cohorts were aged ≥80 years. Differences in the two cohorts existed with regards to sex, race, baseline healthcare utilization and IBD-related medications, but all the baseline differences were balanced by weighting measured by a standardized mean difference (SMD) <0.1 (Table 1). After weighting, vedolizumab users were less likely to be hospitalized in the 12 months after biologic initiation (HR: 0.81, 95% CI: 0.68 – 0.96). While there was no significant difference in IBD related hospitalizations, older adults with IBD were less likely to have an infection-related hospitalization (HR: 0.39, 95% CI: 0.23 – 0.65). There were no significant differences in IBD related surgery and steroid use after induction (Table 2).

Conclusions: In this large, retrospective cohort study of older IBD patients who were new users of vedolizumab and anti-TNF agents, we found that older patients initiated on vedolizumab were significantly less likely to have an infection-related hospitalization. However, there were no significant differences in IBD-related hospitalizations, IBD-related surgery or corticosteroid use after biologic induction.

Table 1: Characteristics of Inflammatory Bowel Disease (IBD) Patients ≥65 Years Initiating Vedolizumab or an Anti-Tumor Necrosis Factor (TNF) Agent in the United States Medicare Claims Database

Characteristic	Vedolizumab	Anti-Tumor Necrosis Factor	SMD
n	488	2,213	
Median Age (IQR)	72 (68-76)	71 (68-76)	0.05
% ulcerative colitis	43%	44%	0.03
% Female	55	59	0.08
% White	91	94	0.10
Charlson Comorbidity Index			
% CCI = 0	25	24	0.04
% CCI = 1	24	21	0.07
% CCI ≥2	51	55	0.09
Median # Outpatient Visits (IQR)	16 (11-24)	15 (10-22)	0.17
Median # of ED visits (IQR)	1 (0-2)	1 (0-2)	0.11
Baseline IBD medications:			
% Mesalamine	43	65	0.46
% Budesonide	28	26	0.06
% Systemic Corticosteroid	57	71	0.28
% Immunomodulator	28	33	0.12
Concomitant IBD medications:			
% Budesonide	11	11	<0.01
% Systemic Corticosteroid	33	44	0.22
% Immunomodulator	17	21	0.10

SMD: Standardized Mean Difference
IQR: Inter-Quartile Range
ED: Emergency Department
Baseline: the 12 months prior to biologic initiation
Concomitant: at or after biologic initiation

Table 2: Outcomes for Inflammatory Bowel Disease (IBD) Patients =65 years Initiating Vedolizumab compared with an Anti-Tumor Necrosis Factor (TNF) Agent in the United States Medicare Claims Database

Outcome	Drug	Crude Incidence	SMRW aHR (95% CI)
All Cause Hospitalization	Vedolizumab	0.34	0.81 (0.68 – 0.96)
	Anti-TNF	0.36	
IBD-related Hospitalization	Vedolizumab	0.06	0.77 (0.53 – 1.12)
	Anti-TNF	0.07	
Infection-related Hospitalization	Vedolizumab	0.03	0.39 (0.23 – 0.65)
	Anti-TNF	0.05	
IBD-related Surgery	Vedolizumab	0.04	0.78 (0.49 – 1.22)
	Anti-TNF	0.04	
New Corticosteroid Prescription =60 days after Biologic Initiation	Vedolizumab	0.58	1.01 (0.86 – 1.18)
	Anti-TNF	0.47	

SMRW: Standardized Mortality Ratio Weighted
aHR: adjusted Hazard Ratio

Controlled Clinical Trials in Humans

A POPULATION-BASED APPROACH TO DIGITAL OUTREACH, TRIAGE, AND MONITORING OF IBD PATIENTS DURING THE COVID-19 PANDEMIC

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Background: In March 2020, the Mount Sinai Health System Inflammatory Bowel Disease (IBD) center reported an increase in telephone call volume, with many IBD patients expressing anxiety about being on immunosuppressive agents during the COVID-19 pandemic. Consistent with GI society and CDC recommendations, we leveraged the Rx.Universe platform (Rx.Health, New York, NY) to rapidly design and deliver a population-based digital navigation program (DNP) to provide outreach, remote COVID-19 symptom monitoring, triage, and Telehealth to IBD patients.

Methods: After identifying all IBD patients seen in our IBD center from Electronic Health Records (Epic Systems), we "bulk prescribed" the DNP (Rx.Health, New York NY) to 6100 patients' smartphones. Patients were asked to reply to the prompt if they had new or worsening COVID-19 symptoms and opted-in to regular digital monitoring through an electronic patient reported outcome (ePRO) instrument. Patient data was screened by our clinical coordinators, who directly contacted patients via phone calls and scheduled testing and Telehealth visits with IBD practitioners when appropriate.

Results: Of the 6100 patients who were sent the DNP, 1829 patients opted-in to be regularly monitored using text-based electronic patient reported outcome (ePRO) instruments. Of those who responded affirmatively, 145 patients were identified requiring additional medical attention and were triaged using Telehealth visits. Compared to patients who chose not to opt-in, patients who opted-in were more likely to be female, white, married, on biologics, and had high inflammatory markers (Table 1).

Conclusion: As demonstrated by the 30% of patients who opted-in to regular COVID-19 symptom monitoring, a digital navigation program population approach is an effective and efficient approach to provide continuity of care and to mitigate COVID-19 exposure in a high-risk, immunosuppressed IBD population. This scalable approach serves as a model for providing high quality, remote monitoring to patients during COVID-19 and beyond, as well as achieving "Treat to Target" goals.

Clinical Factor Analysis of Patients Who Opted-in and Non-Participants of Regular Digital Monitoring

Clinical Factors		Opted-In (n=1829)	Percent	Non-Participants (n=4271)	Percent
Gender(p = 0.000115)	Female	1005	54.95	2118	49.59
	Male	823	45.00	2153	50.41
	Indeterminate	1	0.06	0	0.00
Race(p = 0.00001)	African American	61	3.34	219	5.13
	White	1393	76.16	2916	68.27
	Other/Unknown	375	20.50	1136	26.60
Smoking status (p = 0.192043)	Current smoker	69	5.07	199	6.46
	History of smoking	256	18.82	581	18.88
	Don't smoke	1035	76.10	2297	74.65
Marital Status (p = 0.000025)	Married/Significant other	753	49.83	1432	42.82
	Single	694	45.93	1733	51.82
	Divorced/Separated/Widowed	64	4.24	179	5.35
Age (p = 0.000835)	18-30	551	30.13	1462	34.23
	31-50	703	38.44	1530	35.82
	51-65	367	20.07	735	17.21
	65>	208	11.37	544	12.74
Biologics (p = 0.00001)	YES	1124	61.45	2249	52.66
	NO	705	38.55	2022	47.34
Language (p = 0.242757)	English	1813	99.13	4219	98.78
	Other than English	16	0.87	52	1.22
CRP (p = 0.026648)	<=5	1075	73.78	2341	70.63
	>5	382	26.22	973	29.36
ESR (p = 0.029728)	<=30	1118	82.50	2511	79.71
	>30	237	17.50	639	20.29
Phenotype (p=0.003517)	UC	620	33.90	1419	33.22
	CD	1079	58.99	2434	56.99
	Indeterminate	130	7.11	418	9.79

A TRANSLATIONAL PHASE I STUDY OF TAUROURSODEOXYCHOLIC ACID (TUDCA) TO REDUCE SYMPTOMS AND ER STRESS IN ACTIVE ULCERATIVE COLITIS

Katherine Huang, Ruishu Deng, Ta-Chiang Liu, Anas Gremida, Parakkal Deepak, Chien-Huan Chen, Nicholas Davidson, Randal Kaufman, Matthew Ciorba

Background: Emerging evidence has demonstrated that protein misfolding in the endoplasmic reticulum (ER), i.e., ER stress, plays fundamental roles in IBD development in humans. Patients with active Crohn's disease and ulcerative colitis exhibit signs of ER stress in their ileal and/or colonic epithelium. Human genetic studies of IBD have identified primary genetic abnormalities in several genes that encode proteins associated with ER stress. We recently reported that oral delivery