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Gastrointestinal: New frontiers in therapeutics for GI diseases and disorders — from microRNAs to novel pharmaceuticals, to low FODMAP diets and microbiome★

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Introduction — overview of the GI section

While we have made great strides in developing new therapeutic strategies to treat certain GI diseases such as hepatitis C, much more is necessary! There is a dire need for new therapies for complex diseases such as motility disorders, IBD, obesity, cancer, constipation and diarrheal disorders, iatrogenic diseases such as postoperative ileus, visceral pain, GERD and other esophageal disorders. Because children are not small adults, the challenges are even greater in developing drugs for children and infants. As highlighted in this issue, gaps in our fundamental understanding of the basic mechanisms of some GI diseases also limit progress. Some examples include GI disorders, GI cancer, GERD, obesity and brain-gut disorders. More consideration should be given to placebo effects of drugs for GI therapies in clinical trials. Emerging areas include pharmacogenomics, the interaction between pharmacotherapy and gut microbiome, special diets (i.e. low FODMAPs), purinergic drugs, opioid mechanisms of drug tolerance and constipation and microRNA's.

Review in Gastroenterology of costs/morbidity associated with gut disorders and diseases provide a sobering reality of the magnitude of the problem and underscore the need for more options for treatment. There is an alarming trend for escalating costs for health care, to treat these illnesses and reduce morbidity and in some cases mortality (associated with colorectal and pancreatic cancer for instance). A recent review article in Gastroenterology (2015) by Anne F Peery *et al.* focused on the burden of GI, Liver and pancreatic diseases in the United States. They are a substantial burden and cost. There are an estimated 7 million diagnoses of GERD in one year in the ambulatory setting. Functional and motility disorders accounted for nearly 1 million emergency department visits in one year, and most of them were for constipation. Hospitalizations and associated charges for IBD, *Clostridium difficile* infection and chronic liver disease increased substantially over the past 20 years. The prevalence of immune-mediated conditions such as celiac disease and eosinophilic esophagitis (EoE) has also increased dramatically in the last 20 years, and emerging new therapies are in the horizon. Finally the leading GI cause of death is colorectal cancer.

★The paper 'Therapeutic implications of the gastrointestinal microbiome' by Purna C Kayshap and Eamonn M M Quigley will be published later in Volume 38 (Neuroscience issue).

Conflicts of interest

No conflicts of interest.

With this in mind, this issue covers selected high-impact recent advances in gastrointestinal disorders. These advances cover a spectrum of novel therapeutics and emerging drug targets for the functional GI disorders, intestinal and hepatic diseases, IBD and GERD. Non-conventional drug targets include *micro-RNAs*, *low FODMAP diets*, *hypoxia-induced factor-2α (HIF-2α)* and *microbiome therapeutics*. The spectrum of novel targets is shown in Figure 1.

Adil E. Bharucha *et al.* discuss novel pharmacological approaches for managing functional bowel disorders, which probably affect approximately 10% of the population. These conditions can substantially impair quality of life. There is a considerable unmet need for newer drugs that target these conditions. Future trials should evaluate the incremental utility of newer therapies over older drugs, many of which are effective and less expensive.

Shanti and colleagues cover the role of low FODMAPs (fermentable oligosaccharides, disaccharides, 53 monosaccharides, and polyols) in the management of irritable bowel syndrome (IBS). These foods are poorly absorbed in the small intestine, are osmotically active, and fermented in the colon. While selected foods have been recognized to cause gastrointestinal symptoms in some people for many years (e.g., lactose intolerance), the term FODMAPs was introduced in 2004 to encompass a variety of foods. The review nicely covers the mechanisms by which FODMAPs are absorbed and cause symptoms, the implementation, pros and cons of low FODMAP diets, and the limitations of low FODMAP clinical trials. The incremental benefit of low FODMAP diets over standard dietary advice for IBS is unclear. Comparisons of low FODMAP diets to other therapies for IBS are necessary.

Harmeet and Michael describe the mechanisms of bile acid-mediated signaling in the enterohepatic communication, the use of bile acid sequestrants for diarrhea, and the remarkable advances in therapies that modulate bile acid signaling for intestinal and hepatic diseases. Obetichloic acid, a FxR agonist, is approved for primary biliary cholangitis, and is undergoing trials for other conditions. Several other agents are in the pipeline. The therapeutic benefits of FxR and FGF19 agonists are offset by hyperlipidemia.

Sang Hyoun Parka *et al.* clearly highlight the critical issues in a rapidly expanding area — that is, the treatment of inflammatory bowel disease with biologic agents. The treatment goal has moved from symptom control towards inflammation control (i.e., ‘deep remission’). In addition to the latest drugs, their review covers biosimilar agents, therapeutic drug monitoring and the ‘treat-to-target’ strategy. Site-specific drug delivery may overcome some of the issues with biologics. The next generation of small molecules with potential for oral administration and intestinal drug delivery may have advantages over biologics, and these are being considered for the treatment of inflammatory bowel disease.

Geoffrey Burnstock *et al.* highlight the role of purinergic signaling in the normal gut, enteric neuropathies and GI diseases. Purines regulate all levels of gut motor reflexes. Alterations in the expression or function of the purinergic receptors, or enzymes involved in the metabolism of purines, is associated with GI dysfunction, and in particular inflammation-mediated damage to enteric neurons in inflammatory bowel disease. Work from

Gulbrensan's lab provides evidence that glia release ATP, which contributes to neuron death and gut motor dysfunction in colitis via a P2X7-dependent neural-glia pathway and a glial purinergic-connexin-43 pathway. Emerging data suggest that enteric glia contribute to several gastrointestinal motility disorders. Studies in pre-clinical models provide convincing evidence for the potential therapeutic use of purinergic drugs for GI diseases and disorders, and a study in CD patients demonstrates that a P2X7R antagonist AZD9056 may be of some potential benefit. Indeed, carefully designed clinical trials are needed to 'test feasibility, safety and efficacy' of purinergic drugs in GI diseases. There is also a medical need for more potent, less toxic P2X7R antagonists and drugs targeting other purinergic mechanisms — innovative use of mini-antibodies or nanobodies for P2X7R may 'rise to the challenge'. Advances in medicinal chemistry are also paving the way for more selective agents, and hopefully, increased availability of a 'pipeline of purinergic drugs' will uncover effective drugs in humans.

It is difficult to imagine a class of drugs that has received more coverage in the media in recent years than opioids, due to the opioid crisis in this country. Hamid Akbarali and William Dewey review recent advances in our understanding of tolerance to opioid-related analgesia and identify enteric glial cells as a novel target of chronic morphine induced constipation (OIC). An interesting new development is that the gut microbiome may be a contributing factor in opioid tolerance to analgesia. The concept is forwarded that chronic morphine administration alters the gut microbiome and disrupts the epithelial barrier by causing intestinal inflammation. Bacterial translocation through a leaky barrier activate toll-like receptors and signaling on enteric glia to cause amplification of the connexin-43 — purinergic pathway. In addition to contributing to morphine induced constipation by altering intrinsic neural-motor function, inflammatory mediators released by 'reactive glia' may influence extrinsic sensory afferents located in the gut (with their cell bodies in the dorsal root ganglia) to induce tolerance to opioids. Relevant studies in patients are needed to confirm these innovative concepts on the role of 'activated glia' on OIC and tolerance to analgesia. Evidence presented also highlights the 'complexity of the different mechanisms between opioid-induced constipation and analgesia'.

The microbiome is a field of considerable clinical interest with tremendous implications for modern medicine and therapeutics in a wide variety of diseases. Next generation sequencing technologies have provided a platform for 'an in depth investigation of the microbiome and its implications to human health and disease. Kashyap Purna and Eamonn Quigley provide a timely and informative review covering clinically relevant aspects of the gut microbiome. The success of fecal microbiota transplantation (FMT) or stool transplantation is evident in the management of *C. difficile* infection, which is a major clinical problem. Probiotics may be beneficial in inflammatory bowel disease, necrotizing enterocolitis, and irritable bowel syndrome among others. The review highlights the important role played by the microbiome in inter-individual responses to drugs, and in the metabolism of medications to alter the efficacy or incidence of adverse events — many relevant examples of drugs are discussed. The review stresses that the microbiome is a rich source of potential novel therapeutics and pharmabiotics for GI diseases and disorders with many clinical trials in progress. This is a field of intense investigation and exciting possibilities, and many challenges.

Maite Solas *et al.* explore the role of gut microbiota in neuroinflammation that may link obesity, a disease of low level inflammation, to cognitive dysfunction, with plausible implications for pharmacological interventions down the road. Obesity is an epidemic, worldwide. The authors postulate an exciting putative link between nutrition, gut microbiome, obesity and cognitive decline and suggest potential therapeutic targets. This research deserves much further consideration, especially in the elderly, and those that are more likely to develop cognitive decline or impairments, that is patients that undergo major surgeries associated with anesthesia/postsurgical neuroinflammation, post-operative cognitive decline (POCD) and delirium. Whether obesity increases the risk of cognitive decline in this or other vulnerable populations remains to be determined. The review raises the attractive but unproven concept of ‘precision nutrition’ medicine designed to influence the microbiota and brain–gut axis. The potential for development of novel therapies for diseases associated with neurocognitive decline by targeting the gut microbiome is rather appealing.

MicroRNA’s are non-coding regulators of gene expression. Micro RNA’s have been implicated in gastrointestinal diseases, and in particular inflammatory bowel disease and colorectal cancers that are linked to inflammation. Esmerina Til and Carlo Croce provide a superb in depth review and update on the role of microRNA’s in IBD and related cancers. The focus is on microRNA targeting of transcripts encoding proteins of the intestinal barrier (i.e. tight junction proteins) and their regulators to produce gut pathologies — indeed, the review covers an area that has not received much attention till now. Clearly, the intestinal barrier is a critical target for health and disease of the GI tract. Gut Inflammation disrupts the intestinal barrier in IBD, and also induces changes in intestinal epithelial microRNA expression that can lead to gut tumor development. As discussed, this is an area of intense investigation and great hope to someday develop new drugs, to ‘*directly deliver microRNA mimics or antisense inhibitory RNAs (antagomiRs) to pathologic cells, ultimately leading to truly personalized medicine.*’ A number of phytochemicals included in our diets may be beneficial by regulating microRNA levels. Restoration or maintenance of normal microRNA expression in intestinal epithelia should be beneficial. A challenge is to develop new drugs that can modulate ‘on demand’ the expression of microRNA’s to minimize side effects.

Eosinophilic esophagitis, which was recognized as a distinct entity in the mid-1990s, is one of the most common causes of dysphagia in adults. Celiac disease possibly affects 1% of the United States white population. Both conditions are characterized by chronic immune-mediated gastrointestinal mucosal inflammation, resulting from eosinophils in EoE and lymphocytes in CeD and gastrointestinal symptoms. Currently, the cornerstones of therapy are proton pump inhibitors and topical steroids for EoE and strict adherence to a gluten-free diet for CeD. The review by Rok Seon and colleagues covers critical issues related to standard therapy and also highlights several exciting drugs, including biological agents, that are being tested in clinical trials. However, none are superior to standard therapy or ready for approval.

Rhonda F Souza and colleagues explore a new paradigm for GERD pathogenesis — the traditional concept is that refluxed acid and bile salts cause a chemical burn/injury in the esophagus. Rather, they postulate the novel concept that refluxed acid and bile salts activate

the NADPH oxidase/ROS/PHD signaling pathway to stabilize hypoxia induced factor — 2 α (HIF-2 α) that can translocate to the nucleus to induce transcription of pro-inflammatory cytokines. In turn these cytokines, and the inflammatory response, drives the development of reflux esophagitis. Small molecule inhibitors of HIF-2 α exhibit favorable selectivity, potency, pharmacokinetic and toxicity profiles, and clinical trials with these drugs for treatment of HIF-2 α — driven kidney cancers are in progress. The potential for utilizing HIF-2 α inhibitors to treat GERD is discussed, although further studies using HIF-2 α inhibitors in pre-clinical models of reflux esophagitis are clearly warranted.

Our understanding of GERD in infants lags behind adults. Mohamed A El-Mahdy *et al.* provide a succinct update of current pharmacological management of GERD in infants, highlighting additional challenges in premature-born high risk infants and those with neuro-aerodigestive pathologies in treatment options. As discussed, data from well designed clinical studies on aerodigestive problems and GERD symptoms in infants is lacking, making it difficult to develop guidelines and recommendations for therapy. A better understanding of the underlying pathogenic mechanisms of GERD, and in infants or premature infants with neuro-aerodigestive pathologies is also desperately needed.

Novel designs and paradigms to study the placebo and nocebo responses in carefully designed clinical trials in gastroenterology is the topic of a review written by Paul Enck *et al.* This is a complex and important topic that does not get nearly enough attention in the literature. The authors discuss placebo (improved symptoms with treatment) and nocebo (worse symptoms after treatment) effects and, their mechanisms, in gastroenterology. The authors nicely cover animal models of placebo response and analgesia, as well as pharmacological and neurochemical mechanisms. They attempt to demystify how placebo and nocebo effects occur, and discuss novel study designs to overcome limitations of traditional randomized and placebo-controlled study designs in drug testing in the field, and focus on visceral pain and nausea for their implementation and application in gastroenterology.

Final thoughts

Many thanks to the authors for their insightful reviews—exciting new realms of therapeutic strategies are in the horizon for GI disorders and diseases that are often not associated with the traditional pharma drug therapies. There is indeed much hope for optimism in novel therapeutics, but there is still much work to do along the path from bench-side to bedside and many opportunities exist for young trainees, basic and clinical investigators alike on this journey.

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Figure 1.
New frontiers in therapeutics for GI diseases and disorders. Spectrum of novel therapeutics covered in the gastrointestinal section.