



Penn Digestive & Liver Center

# GASTROENTEROLOGY NEWSLETTER

## RESEARCH IN GASTROINTESTINAL MEDICINE AT PENN

### Introduction

Gastrointestinal research has been an important focus historically at the University of Pennsylvania. Thus, this edition of the *Division of Gastroenterology Newsletter* focuses on the division's substantial contribution to the field of clinical research and the rapid translation of that research into improved care at the Hospital of the University of Pennsylvania.

As a partner to one of the nation's top academic research institutions, the Division of Gastroenterology has realized dramatic growth in the past five years. With a cadre of junior faculty recruited from among the nation's finest research institutions, and the many developed within Penn, a consequent increase in the number, complexity and diversity of research has occurred throughout the institution.

Funding for the division's research programs has seen significant increases, as well. Apart from private foundation grants and grants from industry, NIH grants make up nearly 95% of the research portfolio at Penn. The GI division is currently home to one of only 14 NIDDK P30 GI/Liver Centers in the United States, as well as the nation's only NCI P01 program project in esophageal cancer and over 15 R01 grants.

The division also receives a variety of training and lectureship grants to support the education of clinical investigators and physician scientists. The numerous educational initiatives underway at the division include a highly esteemed undergraduate student scholar program; a "sabbatical" program that permits Penn medical students to devote a year of their education to research supported by the NIH; a GI pathophysiology module for medical students; and the division's renowned GI fellowship program. Supported by two NIH training grants, the GI fellowship program at Penn attracts the best medical residents in the country.

As the division's research programs continue to evolve at Penn, additional space is being acquired or designated to foster both the growth of these programs and recruitment. Beginning in 2009, the Ruth and Raymond Perelman Center of Advanced Medicine (?list website) will house all of Penn's gastroenterology team, including specialists in gastroenterology, gastrointestinal surgery, medical oncology, radiation oncology and pathology, along with nursing and nutritional staff. This will permit the continued expansion of the research program.

I hope you find this report, which contains a summary of important research efforts within the division of Gastroenterology at Penn, both informative and useful.

**Anil K. Rustgi, MD**  
T. Grier Miller Professor of Medicine & Genetics  
Chief of Gastroenterology

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### LOCATIONS

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PENNSYLVANIA  
HEALTH SYSTEM**



## CHIEF'S CORNER



**ANIL K. RUSTGI, MD**  
T. Grier Miller Professor of Medicine & Genetics  
Chief, Division of Gastroenterology

Beginning in late 2008, the Penn Gastroenterology division will move from the Hospital of the University of Pennsylvania into new quarters at the Ruth and Raymond Perelman Center for Advanced Medicine. An outpatient facility of approximately 360,000 square feet adjacent to HUP, the Perelman Center is the largest capital project in the history of the University of Pennsylvania Health System.

Concentrating the outpatient clinics, outpatient endoscopy unit and specialists in gastroenterology and gastrointestinal surgery at the Perelman Center will result in a variety of significant advantages for both patients and clinicians. Patients who once traveled between sections of the GI division for appointments or to separate hospital departments

for diagnostic and therapeutic procedures will now proceed from one appointment to the next with optimal convenience. Cancer patients will find medical oncology, radiation oncology and pathology services at the Perelman Center, as well, and a dedicated nursing and nutritional staff who work with patients and physicians to develop a full treatment plan for patients.

The future holds great promise, as well. In 2009, the Perelman Center for Advanced Medicine will house the Roberts Proton Therapy Center for the treatment of cancer. The largest and most comprehensive proton therapy center in the world (and one of only six in the country), the Roberts Proton Center will offer the unique ability to fully integrate conventional radiation treatment with proton radiation, a modality that precisely targets tumors while leaving surrounding, healthy tissue unaffected.

### RESOURCES

For Penn's GI division academic website: <http://www.med.upenn.edu/gastro/>  
For the Penn Abramson Cancer Center website: [www.penncancer.org](http://www.penncancer.org)  
For Penn's GI division academic website: <http://www.med.upenn.edu/gastro/>  
For the Penn Abramson Cancer Center website: [www.penncancer.org](http://www.penncancer.org)

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## RECENT PUBLICATIONS

### RESEARCH AT THE DIVISION OF GASTROENTEROLOGY

*This selective overview of the many clinical trials published in the last year by the faculty of the Division of Gastroenterology at Penn includes two key areas of clinical investigation, inflammatory bowel disease and gastrointestinal cancers. For an overview of ongoing research at Penn, visit the Office of Human Research website at: <http://www.med.upenn.edu/ohr>.*

#### Inflammatory Bowel Disease (IBD)

Penn has been at the forefront of research into the origin and management of IBD for more than two decades. Within the last year, researchers with the GI division have published a variety of reports focusing on innovative therapies for ulcerative colitis (UC) and trends in comorbid disease and hospitalization rates for patients with the disease.

#### Treatment

GI division researchers reported on a number of novel therapeutic agents in various indications for UC in 2007 and early 2008, including rosiglitazone, BBIC and MMX mesalazine. Each of these randomized double-blind, placebo-controlled clinical trials was supported by NIH funding.

Lewis, et al,<sup>1</sup> found the thiazolidinedione ligand rosiglitazone efficacious in the treatment of mild to moderately active UC, achieving clinical response in 44 percent of patients and remission in 17 percent of patients; adverse events were rare. In a separate report,<sup>2</sup> the authors determined that BBIC, a soy extract, achieved beneficial trends in rates of remission (P = 0.082) and clinical response (P = 0.22) in patients with active UC, without apparent toxicity. The third study, by Lichtenstein, et al,<sup>3</sup> examined three doses of MMX mesalazine in patients with mild to moderately active UC. In this study, clinical and endoscopic remission at week eight was achieved by 34.1 percent and 29.2 percent of patients receiving MMX mesalazine 2.4 g/day b.i.d. and 4.8 g/day QD, respectively, versus 12.9 percent receiving placebo (P < .01).

#### REFERENCES

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2. Lichtenstein GR, Deren JJ, Katz S, et al. Bowman-Birk inhibitor concentrate: a novel therapeutic agent for patients with active ulcerative colitis. *Dig Dis Sci*. 2008;53:175-180.
3. Lichtenstein GR, Kamm MA, Sandborn WJ, et al. MMX (trade mark) mesalazine for the induction of remission of mild-to-moderately active ulcerative colitis: efficacy and tolerability in specific patient sub-populations. *Aliment Pharmacol Ther*. 2008. Postprint; doi: 10.1111/j.1365-2036.2008.03688.x.

#### Disease Trends

In 2007, Aberra, et al<sup>1</sup> of the Penn GI division published the results of a retrospective cohort study to determine the incidence of active tuberculosis in the IBD population before the advent of infliximab. After adjusting for confounders, corticosteroid use and smoking in a population consisting of 16,213 IBD subjects and 66,512 controls, the team determined that the relative risk for active tuberculosis among patients with IBD compared to the general population was 1.88 (95 percent confidence interval, 0.68-5.20). Immunosuppressant medications were considered the main reason for this increased risk.

Bewtra, et al,<sup>2</sup> reported in May 2007 that rates of IBD hospitalization and surgery have not decreased in the United States since 1990. After examining hospitalization and surgery rates in the US over a 14 year period among patients with a primary diagnosis of IBD, the research team (which included members from the GI division and Penn Department of Medicine) noted a significant increase in hospitalizations for CD (P = .0002), with stable rates of bowel resection surgery for CD and hospitalization and surgery for UC.

#### REFERENCES

1. Aberra FN, Stettler N, Brensinger C, et al. Risk for active tuberculosis in inflammatory bowel disease patients. *Clin Gastroenterol Hepatol*. 2007;5:1070-1075.
2. Bewtra M, Su C, Lewis JD. Trends in hospitalization rates for inflammatory bowel disease in the United States. *Clin Gastroenterol Hepatol*. 2007;5:597-601.

#### Gastrointestinal Cancers

Gastrointestinal cancers are a significant cause of cancer mortality in the United States. With the division of Hematology-Oncology at Penn, the division of Gastroenterology is leading the effort to discover the mechanisms of these cancers, as well as to develop new and better therapies for their treatment and prevention.

#### Genetic Studies

The GI Division at Penn has become a powerhouse for basic and clinical research into the genetics of gastrointestinal cancers. Much of this research is focused upon understanding genetic involvement in the progression from precancerous lesions to cancer, according to GI Division Chief Anil Rustgi, MD.

“Understanding the genetics of GI cancer has great potential to improve the ways we diagnose and treat these diseases,” Dr. Rustgi explains. “The hope, of course, is that genetic research will someday lead to innovative therapeutic approaches that target certain genes in cancer cells.”

A 2007 report by Crissey, et al,<sup>1</sup> concerning the oncogenic behavior of the intestine-specific transcription factor Cdx1 is typical of the complexity and depth of clinical research within the GI division. Although previously determined by Penn researchers to be an antiproliferative, Cdx1 has been implicated as an oncogene in other studies. To evaluate the transgene's oncogenic potential, GI division researchers used murine villin promoter to ectopically express Cdx1 in the small intestinal villi and colonic surface epithelium of normal mouse intestine. No subsequent changes in intestinal architecture, cell differentiation, or lineage selection were observed. In a separate murine model for colitis-associated cancer, moreover, the Cdx1 transgene decreased the number of adenomas and expression of endogenous and transgenic Cdx1 proteins was largely absent in polyps. These results led the team to conclude that Cdx1 is not an oncogene in normal intestinal epithelium. Subsequent reports linking Cdx1 to oncogenesis, however, suggest that the transgene's fate will remain at issue.<sup>2,3</sup>

A second report issued in 2007 concerned the oncogenicity of epidermal growth factor receptor (EGFR) in human esophageal squamous cell cancer.<sup>4</sup> Produced by an international team of researchers that included Anil Rustgi, MD of Penn, this study used epidermal growth factor receptor (EGFR) as a platform to recapitulate esophageal squamous cell cancer. The catalytic subunit of genes frequently altered in human esophageal squamous cell cancer, EGFR was found to have a profound influence when introduced via retroviral-mediated transduction into human esophageal epithelial cells. When compared to control cells, these cells demonstrated increased migration and invasion. Moreover, when placed within the in vivo-like context of an organotypic three-dimensional (3D) culture system, the cells formed a high-grade dysplastic epithelium, with malignant cells invading the stromal extracellular matrix (ECM). Compounded with alterations in key oncogenes and tumor suppressor genes in esophageal epithelial cells, these features led

the team to conclude that the composition and activation of fibroblasts and the components of the ECM conspire to regulate the physical and biological properties of the stroma.

This effort is part of a unique National Cancer Institute funded Program Project on esophageal cancer in the country.

The genetic pathogenesis of hereditary nonpolyposis colon cancer (HNPCC) has been the focus of clinical research at Penn's GI division at for many years. Discussed by Dr. Rustgi in a prominent 2007 review of HNPCC,<sup>5</sup> these studies were the foundation for subsequent investigations at Penn aimed at improving diagnosis in patients with HNPCC. A recent prospective cohort study performed by the GI division, for example, assessed men and women from 11 extended HNPCC families to determine adherence to colorectal screening recommendations following genetic counseling and testing.<sup>6</sup> After controlling for clinical factors and pretest screening practices, HNPCC mutation carriers were found significantly more likely than test decliners to have colonoscopy—suggesting that genetic testing may motivate increased colonoscopic screening among this population.

#### REFERENCES

1. Crissey MA, Guo RJ, Fogt F, et al. The homeodomain transcription factor Cdx1 does not behave as an oncogene in normal mouse intestine. *Neoplasia*. 2008;10:8-19.
2. Bonhomme C, Calon A, Martin E, et al. Cdx1, a dispensable homeobox gene for gut development with limited effect in intestinal cancer. *Oncogene*. 31 March 2008; doi: 10.1038/onc.2008.78.
3. McKinney-Freeman SL, Lengerke C, Jang IH, et al. Modulation of murine embryonic stem cell-derived CD41+c-kit+ hematopoietic progenitors by ectopic expression of Cdx genes. *Blood*. Prepublished online Feb 5, 2008;2008 Feb 5. doi:10.1182/blood-2007-11-124644.
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