Penn Digestive & Liver Center
Penn Medicine

WINTER 2010 | VOLUME 3 | ISSUE 1
ANNUAL RESEARCH REVIEW

GASTROENTEROLOGY NEWSLETTER

RESEARCH IN GASTROINTESTINAL MEDICINE AT PENN

Introduction

This edition of the Gastroenterology Newsletter reviews the Division's substantial contribution to the field of clinical research and the rapid translation of that research into improved care.

The Division of Gastroenterology (GI) has realized dramatic growth in the past five years. The recruitment of a cadre of junior faculty from the nation's finest research institutions and the development of many superb investigators at Penn has resulted in a consequent increase in the number, complexity and diversity of research throughout the Division.

Funding for the Division's research programs has seen significant increases. Apart from grants originating from private foundations and industry, NIH grants make up nearly 95 per cent of the division's 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 more than 15 R01 grants and the nation's only NCI P01 program project in esophageal cancer. It has several U01 grants (consortium or multi-center) in therapy of hepatitis C, drug-induced liver injury, immunology of hepatitis B, intestinal stem cells and the tumor microenvironment. Total research funding is about $13 million per year.

The Division also receives a variety of training and lectureship grants to support the education of clinical investigators and physician scientists. The numerous educational programs 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.

In 2008, the Ruth and Raymond Perelman Center for Advanced Medicine became the home of Penn's gastroenterology team, including specialists in gastroenterology, gastrointestinal surgery, medical oncology, radiation oncology and pathology, along with nursing and nutritional staff. This consolidation has permitted 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 Research
Chief of Gastroenterology at the Division of Gastroenterology

LOCATIONS

The Ruth and Raymond Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
Philadelphia, PA 19104
Phone: 215.349.8222

Penn Presbyterian Medical Center
38th and Market Streets
218 Wright-Saunders Building
Philadelphia, PA 19104
Phone: 215.662.8900

Penn Medicine at Radnor
250 King of Prussia Road | Module B
Radnor, PA 19087
Phone: 610.902.1500

RECENT PUBLICATIONS

RESEARCH BY THE DIVISION OF GASTROENTEROLOGY

This selective overview of the many studies published in the last year by the faculty of the Division of Gastroenterology at Penn includes two representative areas of basic and clinical investigation: molecular pathogenesis of pancreatic cancer and the association between diet and the gut microbiome in Crohn's disease. For an overview of ongoing research at Penn, visit the Office of Human Research website at: http://www.med.upenn.edu/gastro.

NOTCH SIGNALING IN PANCREATIC CANCER

Pancreatic cancer is the fourth leading cause of cancer death in the United States. Treatment options are limited, and most standard approaches using chemotherapy and radiation have failed to provide any clinical benefit. Several investigators have begun to approach certain cancers, including pancreatic cancer, from a "developmental biology" approach. Since embryonic development constitutes a period of extremely rapid tissue growth, signaling pathways utilized by developing organs may be "exploited" by neoplastic cells during cancer progression.

One signaling pathway that plays an important role in the embryonic development of the pancreas is the Notch pathway. The Notch pathway mediates cell-cell interactions, resulting in the maintenance of cells that receive the signal in a stem cell-like state. While the Notch pathway is normally quiescent in the adult pancreas, it is activated during premalignant progression as well as aggressive cancers. Small molecules have been developed which inhibit a critical step in the pathway — an enzyme called γ-secretase — and these γ-secretase inhibitors (or GSIs) can be used to determine whether targeting Notch signaling could be an effective way of preventing or treating pancreatic cancer.

1. Plentz R, Park JS, Rhim AD, et al. Inhibition of γ-secretase activity inhibits tumor progression in a mouse model of pancreatic ductal adenocarcinoma. Gastroenterology. 2009; 136:1499-1502.

A multicenter team of investigators that includes members of the Penn Gastroenterology and Abramson Family Cancer Research Institute has completed a study determining the role of Notch signaling in pancreatic ductal adenocarcinoma (PDAC). The study's findings were published in *Gastroenterology* in May 2009. Ben Z. Stanger, MD, PhD, of the Division of Gastroenterology, was the co-corresponding author. (This study was done in collaboration with Nabeel Bardeesy at Massachusetts General Hospital).

INHIBITION OF γ-SECRETASE ACTIVITY INHIBITS TUMOR PROGRESSION IN A MOUSE MODEL OF PANCREATIC DUCTAL ADENOCARCINOMA

OBJECTIVES – This study sought to investigate the role of Notch signaling the pathogenesis of PDAC.

METHODS – To determine the role of Notch signaling in PDAC, the investigators tested the effects of a γ-secretase inhibitor (or GSI) in human PDAC cell lines and in two groups of mice, a treatment group engineered to recreate the genetics and histopathogenesis of the human disease, and wild-type controls. Human PDAC cell lines were obtained. Murine pancreatic duct cells and PanIN cells were derived and cultivated from the pancreata of the wild-type mice and the genetically engineered mice, respectively. The cell lines and treatment mice were exposed to a GSI prepared in suspension. Control animals received the suspension alone.

RESULTS – Notch signaling was activated in PDAC precursors and advanced tumors. The GSI inhibited the growth of premalignant pancreatic duct-derived cells in a Notch-dependent manner. Additionally, in a panel of over 400 human solid tumor-derived cell lines, PDAC cells, as a group, were more sensitive to the GSI than any other tumor type. Finally, the GSI completely inhibited tumor development in the genetically engineered model of invasive PDAC ($P<.005$, $\chi 2$ test; compared with controls).

CONCLUSIONS– These results suggest that Notch signaling is required for PDAC progression. Pharmacologic targeting of this pathway offers therapeutic potential in this treatment-refractory malignancy.

INFLUENCE OF DIET AND GENOTYPE ON THE GUT MICROBIOME WITH IMPLICATIONS IN CROHN'S DISEASE AND ULCERATIVE COLITIS

The microbiome, or the total microbial population, its genomes and interactions within a defined environment, is of great interest to gastroenterological research. Recent studies show substantial differences in human gut microbiome between obese and lean people, suggesting that the composition of the gut microbiome is affected principally by host diet, phenotype and genotype.

Investigators from the Divisions of Gastroenterology and Endocrinology and the Department of Microbiology at the University of Pennsylvania School of Medicine, in collaboration with researchers from the University of Colorado, Boulder, examined the effects of diet and genetics on the gut microbiome.

HIGH-FAT DIET DETERMINES THE COMPOSITION OF THE MURINE GUT MICROBIOME INDEPENDENTLY OF OBESITY[1]

OBJECTIVES – The study investigators compared mice receiving standard nutrition to mice on a high-fat diet to determine the contribution of diet, host genotype, and host phenotype (obesity) to alterations observed in the composition of the total microbial population (microbiome) of the gut.[1]

METHODS – The investigators took advantage of the phenotype of genetically engineered knockout (KO) mice, which in the cohort studied, remained comparatively lean on the high-fat diet relative to wild-type controls. To determine gut microbiome composition, fecal pellets were harvested after both groups of mice had received standard chow for a period of time and again after 21 weeks on a high-fat diet. DNA was isolated from these fecal pellets and deep sequencing was performed to characterize 25,790 ribosomal DNA (rDNA) sequences from uncultured bacterial communities.

RESULTS – Analysis of gut bacterial communities from both wild-type and genetically engineered KO mice on the standard and high-fat diets showed a drastic change in the detectable rDNA sequences. These alterations were observed irrespective of the degree to which mice gained weight on a high fat diet, suggesting that the diet, and not host phenotype (in this case obesity) was the principal determinant of gut microbiome composition.

Characterization of bacterial gene content of fecal DNA isolated from the wild-type controls showed that gene types associated with energy metabolism decreased while those associated with signal transduction, cell motility and membrane transport increased. A collection of genes identified with nutrient transporters also increased, particularly among transporters for sugars, lipids, peptides and metals. Collectively, these alterations suggest that the reduction of carbohydrates in the high-fat diet may have resulted in a state of nutrient stress on the gut microbiome.

CONCLUSIONS – The results of this study emphasize the importance of diet as an important determinant of gut microbiome composition. As an extension of these findings, as well as work by other investigators in the field, Frederic Bushman, PhD, James Lewis, MD, Gary Wu, MD and Hongzhe Li, PhD, at the University of Pennsylvania as well as Robert N. Baldassano, MD and Nicholas Stettler, MD, at the Children's Hospital of Philadelphia are currently examining the effect of diet on the composition of the human gut microbiome and its implications on dietary interventions currently used to treat patients with Crohn's disease. This study is supported by a UH2 grant from the National Institutes of Health entitled, "Diet, Genetic Factors, and the Gut Microbiome in Crohn's Disease."

1. Hildebrandt MA, Hoffmann C, Sherrill-Mix SA, et al. Gastroenterology. 2009;137:1716-1724.

RESOURCES

- Penn GI division patient website: **PennMedicine.org/GI**
- Penn GI division academic website: **www.med.upenn.edu/gastro**
- Penn Abramson Cancer Center website: **PennMedicine.org/abramson**
- Cancer information: **www.oncolink.org**
- NCI program project on esophageal cancer at Penn: **www.med.upenn.edu/gastro/nci**

CHIEF'S CORNER

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

The gastroenterology team at the University of Pennsylvania School of Medicine and Penn Medicine is nationally recognized for clinical research and superlative care for its patients. I am pleased to announce the following honors and awards by our faculty:

JOHN LYNCH, MD, PHD, Assistant Professor of Medicine (GI), has received an NIH U01 grant to be in the Intestinal Stem Cell Consortium (ISCC), a coordinated effort to accelerate research on stem cells of the intestinal epithelium. The goals of the ISCC include the establishment of a network of individual research projects and a Coordinating Center committed to the isolation, characterization, validation and comparison of stem cell populations from the intestinal epithelium. The latter are important to understanding clinical diseases such as colon polyps and cancer development, different types of infectious colitis and inflammatory bowel disease. Information will be shared between projects in the ISCC—as well as biomaterials, models, reagents, resources and methods—and made publicly available through a web site to be created by the coordinating center.

BEN Z. STANGER, MD, PHD, Assistant Professor of Medicine (GI), has been elected as a 2009 Pew Scholar in the Biomedical Sciences. As a Pew Scholar, Dr. Stanger will receive a $240,000 award over four years to support his research. His research will provide insights to develop therapies for pancreatic cancer.

AMERICAN RECOVERY & REINVESTMENT ACT OF 2009 (ARRA)

The Division of Gastroenterology has submitted 32 ARRA applications and to date has been awarded $1.5 million. Participating faculty included **KYONG-MI CHANG, MD; JONATHAN KATZ, MD; JOHN LYNCH, MD, PHD; HIROSHI NAKAGAWA, MD, PHD; MICHAEL PACK, MD; ANIL RUSTGI, MD; REBECCA WELLS, MD;** and **GARY WU, MD.**

Non-profit Org.
U.S. Postage
PAID
Phila., PA
Permit No. 2563

Penn Medicine
3600 Market Street, Suite 210
Philadelphia, PA 19104

GASTROENTEROLOGY NEWSLETTER
2010