

Gastrointestinal Cancer Research

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According to the American Cancer Society, there were more than 250,000 cases of gastrointestinal cancer anticipated in the United States in 2005, with more than 135,000 deaths from these diseases. Gastrointestinal malignancies include cancers of the esophagus, stomach, hepatobiliary system, pancreas, and small and large intestines. The most common gastrointestinal cancer in men and women is colorectal cancer. This preventable cancer, which is highly curable when detected early, remains the second leading cause of cancer death in the United States, with 56,000 deaths anticipated annually. While less common, more than 30,000 patients are diagnosed with pancreas cancer each year, and the vast majority will succumb to this disease. While relatively uncommon in the United States, gastric and liver cancers are among the most common malignancies in other parts of the world. Thus, GI cancers are a major public health problem worldwide, and improved methods

of detection, prevention, and treatment are required. Members of the Fox Chase scientific community conduct a broad range of clinical and laboratory-based gastrointestinal cancer research that include studies of screening, prevention, pathogenesis, risk assessment and genetics, and treatment. This section of the *Scientific Report* will highlight some of these efforts. More comprehensive presentations by individual principal investigators can be found throughout the *Scientific Report*.

Gastrointestinal cancer therapeutics. *Meropol, Sigurdson, in collaboration with Blanchard,^a Burtness, Cheng, S. Cohen, Damjanov, Engstrom, Freedman, Goldberg, Hoffman, Joseph, Konski, Lewis, Scott, Watson, Weiner*

Given the relative resistance of GI cancers to standard chemotherapeutic agents, a major emphasis of the GI cancer program at Fox Chase Cancer Center involves development of novel systemic approaches. Overall goals of the program are to: 1) develop treatments with improved target selectivity; and 2) identify tumor and patient characteristics that will permit improved treatment selection. A major emphasis in the past several years has been the development of agents that target the epidermal growth factor receptor and vascular endothelial growth factor receptor pathways. This work has contributed to the integration of these inhibitors into routine clinical practice in patients with colorectal cancer.

Several methods of non-invasive pharmacodynamic monitoring are underway. As a platform for the early prediction of treatment response, and *in vivo* assessment of pharmacodynamic endpoints, S. Cohen and N. Meropol are leading a multicenter study of circulating tumor cells from patients with metastatic colorectal cancer. This study includes both enumeration of circulating cells as well as characterization of gene expression. In addition, S. Cohen is exploring the use of circulating endothelial cells as markers of treatment effect in a clinical trial of the effect of bevacizumab on coagulation parameters in patients with pancreas cancer. S. Cohen and O. Haluszka are studying the use of shed cells in biliary fluid for the monitoring of patients with hepatobiliary cancers. A. Konski is exploring the predictive value of PET scanning in patients with esophagus and rectal cancers.

Clinical trials over the past year have included a variety of investigational agents and technologies. J. Cheng is conducting a study of talabostat, an inhibitor of the stromal dipeptidyl peptidase fibroblast activation protein

(FAP), in patients with metastatic colorectal cancer. This year, J. Cheng reported an inverse relationship between FAP and tumor stage in colorectal cancer. S. Cohen is conducting a CTEP-sponsored study of bortezomib in patients with biliary tract cancers, with correlative studies of proteasome inhibition in bile. S. Cohen is also conducting studies in pancreas cancer with amplimexon, a glutathione inhibitor, and an yttrium-labeled monoclonal antibody against PAM4. A clinical trial of sunitinib (SU011248) in patients with neuroendocrine tumors is underway (Meropol). N. Meropol presented the final results of a phase II trial of panitumumab, a human antibody inhibitor of the epidermal growth factor receptor, in patients with advanced colorectal cancer. In an effort to improve local control with reduced toxicity, G. Freedman is conducting a study of intensity-modulated radiation therapy in patients with locally advanced rectal cancer.

N. Meropol and R. Blanchard^a reported an association of UGT1A7 and UGT1A9 low activity polymorphisms with improved antitumor activity and decreased toxicity in colorectal cancer patients treated with irinotecan plus capecitabine. Of note, there was no association of UGT1A1*28 polymorphisms with toxicity in this phase II trial (1).

Members of the gastrointestinal cancer program at Fox Chase have lead roles in cooperative group trials: 1) B. Burtness, ECOG 8200, a randomized phase II trial of irinotecan, docetaxel and cetuximab, in patients with metastatic pancreas cancer; 2) E. Sigurdson, ECOG 4298, a study of hepatic chemoembolization in patients with neuroendocrine and hepatocellular cancers; 3) J. Hoffman, ECOG 1200, a multimodality neoadjuvant study in patients with marginally resectable pancreas cancers; and 4) N. Meropol, ECOG 3200, a multicenter, randomized phase III study for patients with metastatic colorectal cancer. This is the first study to demonstrate a survival advantage associated with the use of bevacizumab in the second-line metastatic setting, and the first to demonstrate

a survival advantage associated with the use of bevacizumab in combination with oxaliplatin-based therapy. Meropol has a randomized study (ECOG 4203) in which treatment selection is prospectively assigned based upon tumor expression of thymidylate synthase. This is the first ECOG colorectal trial to base treatment on tumor phenotype. Meropol and A. Bellacosa[§] are investigating the association of somatic *MED1* mutations (DNA repair gene with glycosylase activity) with prognosis and treatment response in patients with colorectal cancer in collaboration with the Eastern Cooperative Oncology Group. Meropol also has a randomized trial testing the hypothesis that bevacizumab will increase survival in the adjuvant setting in patients with locally advanced rectal cancer (ECOG 5204). Meropol is also leading a prospective, randomized phase II cooperative group trial of multimodality neoadjuvant therapy in patients with locally advanced resectable rectal cancer (RTOG 0247).

Gastrointestinal Tumor Risk Assessment Program. Meropol, Klein Cabral, Sheth, in collaboration with Balshem,[§] Bellacosa,[§] Cooper,[§] Daly,[§] Engstrom, Godwin,[§] Manne,[§] Ross,[§] Weinberg[§]

Identification of risk factors for colorectal cancer (CRC) and other GI cancers permits screening strategies based upon individual patient characteristics. Influences on CRC risk include diet, family history, personal history of CRC or polyps, and inflammatory bowel disease. In addition, germline mutations in genes such as *APC*, *MLH1*, *MSH2*, *PMS2*, *MSH6*, and *MYH* which are responsible for familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC), have been identified, and clinical testing is available for suspected affected individuals. The availability of genetic testing for cancer predisposition raises a variety of ethical, legal, and social issues for individual patients, their families and society at large. The GI Tumor Risk Assessment Program was designed with two major objectives: 1) to provide a service to patients wishing to undergo risk assessment, counseling and screening; and 2) to conduct laboratory, epidemiologic, and psychosocial studies of hereditary and familial GI cancers. The members of this program comprise a multidisciplinary team including gastroenterologists, genetic counselors, medical oncologists, pathologists, laboratory and clinical

scientists, and health educators. Services offered include education, individual risk assessment, counseling, and recommendations regarding screening, including the appropriateness, risks, and benefits of genetic testing. An Institutional Review Board (IRB)-approved registry and tissue bank for collection of family health history information and psychosocial data, as well as germline and tumor DNA from affected and non-affected members of 'high risk' cancer families, serves as a resource for multidisciplinary research of cancer risk.

Development & evaluation of a Web-based tool for genetic risk counseling and education: Internet Risk Assessment Program (IRAP).

Meropol, Klein Cabral, Sheth, in collaboration with Daly,[§] Manne,[§] Zubarev,[§] Manion[§]

The identification of hereditary cancer syndromes and the availability of clinical genetic testing heighten the importance of risk assessment and counseling. In particular, the decision of whether to pursue genetic testing requires a careful risk assessment, which ideally involves not only individuals but also their family members. Unfortunately, families are frequently geographically dispersed, with many individuals not having access to appropriate professional expertise in cancer genetics. The purpose of this project is to develop and evaluate an internet-based method for provision of live, on-line cancer risk assessment and education for families at increased risk for colorectal, breast, or ovarian cancers. Recruitment to this study has begun. Participants at remote locations are provided a webcam and software to permit their connection via the Internet to a risk assessment session at Fox Chase Cancer Center. All subjects view an on-line prerecorded educational presentation, followed by a live counseling session with a genetic counselor. Outcomes include feasibility, acceptability, and impact on risk perception, anxiety, and genetic knowledge.

Informed decision making regarding microsatellite instability testing. Meropol, Sheth, Klein Cabral, in collaboration with Manne,[§] Cooper,[§] Godwin,[§] Driesbaugh,[§] Catts,^b Chung,^c Petrelli,^b Shannon,^c Manning^d (See [Manne report in Population Science](#))

Germline defects in several DNA mismatch repair genes, including *MSH2* and *MLH1*, pre-

dispose people to a hereditary form of colorectal cancer (CRC) called hereditary nonpolyposis colorectal cancer (HNPCC). HNPCC accounts for approximately 5% of all colorectal cancers. Microsatellite Instability (MSI) testing and immunohistochemistry (IHC) for DNA mismatch repair proteins are commonly used as screening tests for hereditary nonpolyposis colon cancer (HNPCC) before proceeding to germline mutation analysis. Before undergoing MSI/IHC testing at Fox Chase and other centers, patients routinely provide written informed consent. The purpose of this study is to improve knowledge and understanding of the MSI and IHC tests, and overall patient satisfaction with the process of informed consent for this testing. In collaboration with investigators from Massachusetts General Hospital and Triad Interactive, Inc., we are conducting a randomized clinical trial to evaluate the impact of standard consent versus a CD-ROM education intervention.

Brief excerpts of selected gastrointestinal cancer research underway at Fox Chase. The following is not meant to be an exhaustive list of gastrointestinal research at the Center. Detailed descriptions and collaborator institutions are provided by the individual principal investigators elsewhere in the *Scientific Report*.

A. Bellacosa[§] Our main interest is to further characterize the molecular genetics of hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), as well as of sporadic colorectal cancer (CRC). A major focus of the laboratory involves the DNA repair protein MED1, which encodes an interactor of MLH1 and exhibits glycosylase activity on G:T and G:U mismatches. Recent studies indicate that MED1 has a marked preference for halogenated pyrimidines and suggest that MED1 may play a significant role in the cytotoxicity of 5-fluorouracil and of the radiosensitizing agent 5-iododeoxyuridine. Additional studies employ laser-capture microdissection, microarray analysis and animal models to identify early molecular changes induced by APC mutations, and the role of the PI3 kinase/AKT signaling axis in CRC.

J. Cheng The goal of my research program is to identify novel stromal targets for therapeutic interventions aimed at disrupting the tumor-stromal interface. We have utilized Fibroblast

Activation Protein (FAP), a stromal selective serine protease, as a platform to investigate stromal contributions to tumor growth. We plan to determine the biologic effects resulting from disruption of the bidirectional interactions between tumor cells and the stromal cells that are found in tumors.

M. Clapper[§] Significant efforts within the Chemoprevention Program are focused on the development of a chemopreventive regimen for individuals at high risk for colorectal cancer, both heritable and inflammatory bowel disease (IBD)-associated cancer. Unique animal models of colorectal carcinogenesis that have been developed by Clapper, H. Cooper,[§] R. Coudry,[§] and W.-C. Chang[§] are being used to both detect early molecular changes associated with the carcinogenesis process and identify promising chemopreventive agents. Recent progress has included the discovery that 5-aminosalicylic acid (5-ASA), the first line therapy for IBD, can reduce the multiplicity of colonic dysplasias in mice with dextran sulfate sodium (DSS)-induced colitis by approximately 50%. Additional studies are in progress to determine the clinical relevance of these findings.

E. Cukierman[§] We have recently established an *in vivo*-like 3D stromal system for culturing normal and tumor-associated fibroblasts within microenvironmental settings that are reminiscent of desmoplastic stroma (M.D. Amantangelo et al., *Am. J. Pathol.* 167: 475, 2005). In the above-mentioned study, we demonstrated that normal fibroblast can differentiate into desmoplastic fibroblast in a tumor-associated extracellular matrix dependent manner. K Brown and R. Quiros, in our laboratory, are engaged in isolating human primary pancreatic fibroblasts in two collaborative efforts with: 1) S. Cohen, O. Haluszka,[§] and J. Tokar,[§] utilizing endoscopic-guided fine needle aspirates; and 2) J. Hoffman and J. Watson, utilizing surgical pancreatic samples. Both types of samples will serve to establish a human pancreatic stroma 3D system derived from fibroblasts associated with tumors at different stages of neoplastic development. This stromagenic system is being used to study both stroma-progression, with the goal of identifying targets effective in preventing or inhibiting pancreatic stromagenesis, as well as stroma permissiveness during pancreatic tumor development, progression, and metastases.

A. Knudson[§] A main area of research involves a multi-investigator study of sites (colon, kidney, breast, and ovary) targeted by mutations causing hereditary predisposition to cancer. We are searching for aberrant genomic and proteomic expression of cells cultivated *in vitro*, and testing whether putative chemopreventive agents can reverse any such changes.

S. Manne[§] Our research focuses on evaluating methods of improving quality of life for cancer patients and improving acceptance of screening practices among cancer patients and their families. We are currently conducting two studies in individuals at risk for developing colorectal cancer. In the first study, described above, we are attempting to improve the informed consent process for microsatellite instability (MSI) testing. We are evaluating whether a CD ROM educational tool can improve satisfaction with decision making and knowledge about the MSI test. In another study we are evaluating a tailored intervention utilizing print material and telephone counseling in siblings of young (<55 year old) colorectal cancer patients. The primary objective is to improve screening compliance in this at-risk population.

M. Murphy[§] Research in our laboratory is aimed at elucidating the impact of coding region polymorphisms in the p53 tumor suppressor gene on cancer risk, prognosis, and the efficacy of therapy. There are two coding region polymorphisms in p53 that alter its apoptotic function. Because the development and treatment of pancreatic cancer is known to be directly controlled by apoptosis induced by p53, we are crossing mouse models of wild type p53, and these two polymorphic variants, to a well-characterized model of murine pancreatic cancer, in which cancer development is controlled by conditional activation the Ki-ras proto-oncogene. These studies will test the contribution of altered apoptotic function on pancreatic tumor development, progression, and treatment.

D. Weinberg[§] Members of the Gastroenterology Section lead or participate in multiple studies directed at cancer risk stratification,

prevention or control. Weinberg is interested in utilizing combinations of genes and different environmental factors to predict sporadic CRC risk as well as novel molecular markers that might improve CRC staging or post-operative surveillance. J. Tokar[§] and O. Haluszka[§] employ interventional endoscopy techniques to study pancreatic cystic lesions to see what molecular or proteomic factors may predict malignancy, while M. Nguyen[§] focuses on predictors of treatment response for patients with HCV infection. The GI section is also participating in a Mayo Clinic-led study comparing several oral chemopreventive agents in patients with a prior history of CRC or advanced adenoma.

Y-N. Wong[§] New therapies for colorectal cancer, while promising, are costly. We have developed a Markov model to examine the cost-effectiveness of new chemotherapy and biologic agents for metastatic disease. In addition, we are participating in a National Comprehensive Cancer Network (NCCN) outcomes project in colorectal cancer. This project includes collection of detailed information regarding the comorbidities, diagnosis, treatment and outcomes of patients treated at Fox Chase. The goal of the database is to provide quality improvement data, including the Center's concordance with NCCN guidelines.

A. Yeung[§] Our GI research is focused on proteomic studies in colon cancer and pancreatic cancer. Proteomics examines thousands of proteins and peptides in a cell at the same time to provide insights about the biology of the cell. In the colon cancer project, Yeung and collaborators (Li,[§] Patel,[§] Patterson,[§] Blagoi,^a Seeholzer,[§] Chaudry,[§] Knudson,[§] Bellacosa,[§] Clapper,[§] Litwin,[§] Ross,[§] Cooper,[§] Boman,^e and Zhang^e) compare patients with a mutation in the colon cancer gene, *Adenomatous Polyposis Coli*, with normal patients, in terms of the colon crypts and the colon fibroblasts. The goal is to uncover changes that occur prior to cancer. In pancreatic cancer research, Yeung and collaborators (Tokar,[§] Haluszka,[§] Hoffman, Watson, Weinberg, Nguyen,[§] S. Cohen, Meropol, and Litwin[§]) use the proteomes of pancreatic cyst fluids as indicators for early cancer detection.

Publications

Only N.J.M. publications are included below. References of other gastrointestinal cancer researchers are included throughout the *Scientific Report*.

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