

# Gastrointestinal Program

The Gastrointestinal Program, led by Gagandeep Singh, M.D., focuses on a wide variety of tumors, including colon, rectal, pancreas, stomach, liver and esophagus cancers. In collaboration with the Department of Molecular Oncology, great strides have been made to further understand the molecular mechanisms important in gastrointestinal cancers growth and spread. This has been the result of national and international collaborative research cooperation between the Institute and other well-known cancer centers.

The Gastrointestinal Program focuses on improving disease staging by molecular genetic techniques and understanding the fine points of disease development. The studies are highly translational and relate to current surgical oncology approaches and therapy.

## Colorectal Cancer

The Department's international connections and collaborations continue with a strong program in association with the Dutch Colorectal Cooperative Group (DCCG). JWCI is collaborating with the DCCG to study specimens from colorectal cancer trials from Europe. Other areas our scientists are exploring include research on the multidisciplinary approach to patients with colon and liver cancers, in particular colorectal and neuroendocrine liver metastases, research pertaining to the

importance of finding the smallest cancer cells in both colon and liver cancer, and examining the importance of meticulous surgery and adequate lymph node retrieval — research that is likely to have a major impact on how gastrointestinal cancers are managed.

In collaboration with the Department of Experimental Therapeutics, scientists are delving into a new theory that could account for the high degree of “intrinsic” drug resistance that is a characteristic of colorectal cancer.

Colon cancer cells have the ability to sequester anticancer agents such as cisplatin within tiny vesicles, making the drug unavailable to the nucleus where chemotherapy often acts. This “isolation” of the drug is likely to play a functional role in drug trafficking and lessen treatment efficacy. A new project underway in the Department of

Experimental Therapeutics is assessing techniques that could dismantle this mechanism, making the drug available to target key points.

## Liver and Pancreatic Cancers

Department researchers are developing innovative, minimally invasive techniques for liver and pancreatic cancers. Surgical expertise now extends beyond the classic open approach to leading edge laparoscopic surgical resection and, more recently, robotic surgery when deemed suitable. These include all forms of complex liver resections, complex pancreatic surgery with vascular reconstruction, radio frequency, ablation and microwave ablation. From a clinical research perspective, surgically our physicians are now developing a model for extending the limits of liver resection to greater than 80 percent of total liver volume. Although this is still in its infancy



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and undergoing thorough evaluation in the laboratory, if successful, this model would directly translate into the clinical world — providing hope for thousands patients nationwide who currently are deemed unresectable.

Diagnosis of pancreatic cancer is often associated with a dismal prognosis. The availability of validated and efficient diagnostic, prognostic and predictive biomarkers is virtually nonexistent for pancreatic cancer. Our physicians and scientists are addressing this critical problem with several studies. Epigenetic biomarkers in the form of hyper- and hypo-methylation of promoter CpG islands of tumor-related genes play a significant role in solid tumor development and progression. Epigenetic changes can silence and turn on specific genes that are related to cancer proliferation, invasiveness, metastasis and

differentiation status. In preliminary studies done at the John Wayne Cancer Institute, our team has demonstrated the assessment of some of these epigenetic changes. Gagandeep Singh, M.D., and Dave S. B. Hoon, Ph.D., are now collaborating to make this a reality for patients with pancreatic cancer. The long-term goal would be to extend this to all gastrointestinal tumors — to identify these epigenetic changes which in turn would provide new diagnostic and prognostic biomarkers for pancreatic cancer, and ultimately improve management and survival.

One of the most exciting areas of research involves “pulling the plug on cancer cells” (i.e. preventing the tumor from developing new blood vessels [angiogenesis]) — thus preventing tumor growth and possible complete involution. Tumor growth and metastasis are depend-

ent on this angiogenesis via release of various proangiogenic factors. Novel targets that have been recently identified by one of our collaborating scientists allow our team to target maturation of tumor vessels dependent on EphB4-EphrinB2 interactions.

Researchers are currently studying the expression and availability of these targets in various gastrointestinal tumors, and have very encouraging results for colorectal cancers and colorectal liver metastasis. The Department’s ongoing research efforts would include study of and creating tumors of pancreas, liver, colon, stomach and esophagus in murine models, and testing these targets with soluble EphB4 as a candidate for therapy in these cancers. This is independent of most existing pathways and would be a novel approach in the pursuit of finding a “cure” for cancer.