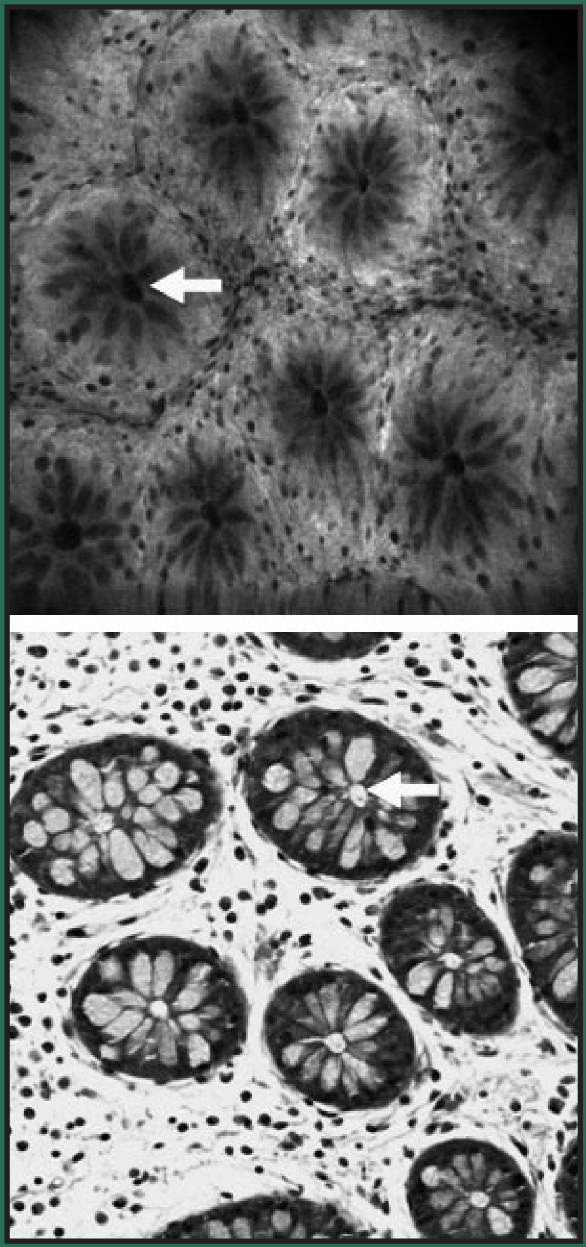

Endomicroscopy (upper) and histologic section (lower) of normal human colon crypts. New imaging technologies, such as confocal endomicroscopy, can enable more accurate diagnosis and monitoring of digestive diseases, such as colorectal cancer in high-risk patients.

Image courtesy of Dr. Ralf Kiesslich. Reprinted from Gastroenterology, *132, Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis, pp. 874-882, Copyright 2007, with permission from Elsevier.*

Bioengineering, Biotechnology, and Imaging

SUMMARY OF RESEARCH GOALS

The luminal structure of the gastrointestinal (GI) tract and the inherent regenerative capacities of many cell types within the organs of the digestive system afford significant opportunities for the development of innovative technologies and approaches to the diagnosis and treatment of digestive diseases. The Commission recommends several research goals that are intended to capitalize on emerging technologies and facilitate medical and surgical care of digestive disease patients. Ready access to much of the digestive tract is permitted by endoscopic or minimal access approaches for biopsy or resection of tissue. Research is needed to evaluate the risks and benefits of such procedures compared to conventional surgical techniques. Advances in stem cell biology and regenerative medicine could be applied to foster the repair and regeneration of diseased tissue within the digestive system. Innovative scaffolds to guide the growth of complex digestive organ structures will need to be developed in order to realize the potential of promising tissue engineering approaches. The development of advanced imaging technologies and interactive simulators that allow surgeons to plan and practice procedures using patient-specific images would reduce the risk of trauma to healthy tissue during treatment. Collectively, these research goals will lead to innovative technologies that have the potential to significantly improve patient outcomes and enhance treatment efficacy for many digestive diseases.

INTRODUCTION AND BACKGROUND

Detection, diagnosis, and treatment of digestive diseases present both challenges and opportunities for technology development given the diverse anatomy of the digestive organs. Procedural techniques and imaging strategies must be designed for both luminal and solid organs. Advances in technology require scientific collaboration among multiple clinical and scientific disciplines, including gastroenterology, surgery, radiology, engineering, mathematics, physics, computational science, and others.

Luminal structures: The most common disorders of the GI tract develop from the cells that line the intestinal lumen—the mucosa. This is the site of origin of GI cancers, benign ulcers, and a variety of inflammatory disorders that occur in all age groups. While the foregut (esophagus, stomach, and duodenum) and colorectum are readily accessible to endoscopic evaluation, the small bowel remains a vast organ that is largely inaccessible to repeat endoscopic evaluation and treatment of the luminal surface. The luminal surfaces of the colon, rectum, and foregut can be visualized, allowing abnormalities to be biopsied, ablated, or resected using endoscopic approaches or provide needed data to plan surgical procedures. New technologies for imaging the intestinal lumen have yielded improved diagnostic capability, although their therapeutic applications remain limited. CT and MRI imaging techniques have improved to evaluate structural disorders of the intestinal wall and peritoneal cavity, allowing the use of minimal access surgical technologies in lieu of conventional operative procedures.

Solid organ structures: The liver, biliary system, and pancreas remain common sites of malignant and inflammatory disorders. Enhanced application and utilization of CT, MRI, and PET imaging modalities have improved the ability to make accurate structural assessments of tumors and inflammatory processes in these organs. Endoscopic access to the pancreatic and biliary systems is now routine, allowing more accurate diagnosis and therapeutic options for patients with benign ductal disorders or with malignant conditions. Three-dimensional reconstructive imaging has improved pre-operative procedural planning to predict residual hepatic volume after resection and to more accurately stage patients with malignant tumors. Multimodality imaging of the liver, including real-time ultrasonography, has facilitated the application of ablation technologies for selective treatment of tumors in some patients. Increasing knowledge of the molecular characteristics of tumors metastatic to liver disease, such as gastrointestinal stromal tumors (GIST) and neuroendocrine tumors, enables assessment of the efficacy of chemotherapeutic agents, including imatinib or octreotide, in the management of these patients.

Imaging: Advances in imaging technology are revolutionizing the noninvasive detection of digestive diseases. Improvements in CT technology have enabled the delivery of high-resolution images for three-dimensional reconstructive imaging that mimics endoscopic observations. Emerging technologies—fusion of ultrasound and CT imaging, for example—allow precise, real-time interventions and improved procedural planning. New contrast agents and agents that reflect metabolic activity of tissues, such as PET imaging, have improved the ability to detect otherwise occult lesions in solid organs or in the peritoneal cavity.

Emerging technologies: Advances in device development have led to remarkable new tools for manipulating the GI tract and peritoneal structures. Based on the evolution of these manipulable devices from a remote operating platform, new procedures such as natural orifice transluminal endoscopic surgery (NOTES) are being implemented in the clinic. Clinical trials are in progress to introduce an operating endoscope via the mouth for passage through the stomach wall into the abdominal cavity to remove or repair an organ. Both trans-vaginal and trans-gastric cholecystectomies (removal of the gallbladder) have been reported. Linking robotic surgical devices, whereby a surgeon manipulates fine instruments in a patient from a console with high-definition three-dimensional imaging, is increasingly applied to surgical procedures of the abdomen, with the result that surgeries can be performed with more precise and miniaturized instruments to reduce trauma to healthy tissue.

Tissue engineering/regenerative medicine: The field of tissue engineering and regenerative medicine has just begun to be explored in the GI luminal and solid organs with the goal of reconstructing functionally and structurally normal tissues. The identification of the intestinal stem cell niche provides a vital first component to this work, as this cell type will be a progenitor for growth of a new mucosal structure to replace a damaged small intestine. Similarly, the development of appropriate scaffolds on which to grow new liver cells, pancreas cells, and intestinal tissue will be necessary to create replacement organs for those patients with hepatic, pancreatic, or intestinal failure. The structural diversity and complexity of the digestive tract pose a significant challenge for the development of regenerative therapies for digestive diseases.

Simulation training: Preparing the GI endoscopy and surgical workforce for the future requires sophisticated educational platforms. The development of simulators capable of mimicking highly complex GI procedures to allow physicians and surgeons to gain needed practice and expertise before proceeding to patient procedures will foster improved patient safety and quality of care in rapidly changing new technologies. Recent advances in computational science and haptic technology have allowed the initial delivery of simulators with high-fidelity to create virtual environments for these educational purposes. As the pace of technological innovation in procedural technologies is rapid, simulators that keep pace with this change to maintain the skill sets of the gastroenterology and surgical workforce will need to be developed. Advances in technology will also enable the combination of pre-procedural, patient-specific simulation, so that a surgical team can plan and practice the procedure using images of patient-specific anatomy. It is conceivable that simulators will also be used as part of privileging programs to assess procedural competency of gastroenterologists and surgeons.

RECENT RESEARCH ADVANCES

Image-enhanced endoscopy

Advances in optical imaging have greatly expanded the sensitivity and specificity of endoscopic observations. High magnification chromoendoscopy, confocal microscopy, autofluorescence imaging, narrow band imaging, and optical coherence tomography have enhanced the ability to detect areas of mucosal abnormalities, including pre-malignant changes of dysplasia and early cancers. These technologies have allowed enhanced detection of areas of flat and depressed colorectal neoplasia, enhanced identification of Barrett's epithelium with dysplasia, and identification of dysplastic mucosa in the stomach.

Technological advances have allowed endoscopic procedures to replace more invasive surgical procedures in several complex areas of GI disease. Improved design, materials, and delivery tools for endoluminal stents have provided improved palliation for malignant strictures, refractory fistulas, and complex post-operative surgical disorders with lesser morbidity than conventional surgical approaches.

The development of operating endoscopes with multiple ports to allow improved endoscopic techniques, including suturing, injection, and manipulable instruments, has facilitated endoscopic treatment of luminal conditions that once required surgical approaches.

Effective technologies for mucosal ablation

For those areas of the GI tract amenable to endoscopic reach, a variety of ablation tools have been developed to treat benign and malignant conditions. For patients with pre-malignant disorders of the foregut and colorectum (including Barrett's esophagus and others) and those with more advanced neoplasms who are otherwise not candidates for major surgical procedures, a variety of ablation technologies, such as photodynamic therapy, radiofrequency ablation, and sclerosing agents, now offer new treatment options. For patients with GI bleeding disorders or lesions, enhanced devices and agents to treat these lesions via the endoscope have been developed, sparing patients considerable morbidity associated with major surgical procedures.

New technologies to detect colorectal neoplasia have been developed. While screening colonoscopy of the prepared colon remains the gold standard, significant advances in detection of pre-malignant and adenocarcinoma of the colon have been developed, such as the use of CT colonography (virtual colonography, colonoscopy), video capsule endoscopy, quantitative immunochemical fecal occult blood testing, and fecal DNA analysis.

Development of the endoscopic ultrasound (EUS) probe

The development of an ultrasound probe capable of being passed into the GI tract with the endoscope has made possible the examination of the mucosa, bowel wall, and adjacent organs with enhanced specificity. The ultrasound probe has revolutionized the evaluation of periampullary lesions, allowing more accurate identification and definition of pancreatic and distal biliary masses, more precise tissue sampling with fine needle aspiration biopsy, and improved staging of malignancy for pre-operative evaluation. Submucosal and mural lesions of the GI tract from the esophagus through the first portion of the duodenum—regions that were previously occult to conventional imaging and endoscopy—are readily evaluated by EUS. Intrarectal ultrasound has standardized staging of rectal cancers, allowing appropriate application of neoadjuvant strategies for patients with rectal cancer and identifying those patients amenable to local resection.

Evaluation of the small bowel lumen

The introduction of the video capsule endoscope has revolutionized imaging of the small bowel mucosa. This once hidden luminal structure is now readily evaluated for many common disorders, including Crohn's disease, idiopathic inflammatory diseases of the small bowel, and malignancy. Occult bleeding from the small bowel may be identified, addressing a long-standing, unresolved clinical dilemma prior to this technology.

Combined modality imaging and molecular imaging

Recent studies have established that FDG-PET allows identification of peritoneal and lymph node metastases for colorectal and other GI cancers. The use of specific, targeted molecular agents to silence metabolic activity of tumors has been particularly valuable in conjunction with FDG-PET as the tracking modality. Patients with imatinib-sensitive GIST tumors or octreotide-sensitive neuroendocrine tumors exhibit molecular silencing on FDG-PET scanning, which provides a valuable marker of efficacy of these agents.

Tissue engineering/regenerative medicine (TE/RM) in the GI tract

The regenerating intestinal epithelium with its inherent stem cell population offers unique opportunities for TE/RM efforts. The most significant progress of TE/RM research in the GI tract has been in the creation of functional liver tissue. Significant advances have been made in the ability to isolate functional hepatocytes and maintain their phenotype and functionality *in vitro*; the ability to isolate biologic scaffolds that support functional hepatocytes; and in understanding the appropriate growth factors and cytokines needed to maintain hepatic growth *in vitro*.

GOALS FOR RESEARCH[18]

Research Goal 12.1: Define the optimal procedural approach for patients with digestive disorders amenable to endoscopic, image-guided, or minimal access surgery.

Innovations in minimally invasive surgery offer several potential advantages over traditional surgical techniques or endoscopic procedures. Rigorous evaluation of these new procedures is needed to determine their cost-effectiveness and efficacy in improving patient outcomes.

Objectives:

- Evaluate efficacy and outcome measures, including quality-of-life, for innovative surgical technologies.
- Perform a cost analysis of new surgical methods compared to traditional procedures.
- Conduct rigorous studies of physiologic and immunologic response to minimal access surgery to determine whether biologic advantage exists for these procedures.

Research Goal 12.2: Develop innovative technology for the diagnosis and treatment of luminal disease.

In addition to surveillance and detection of disease, endoscopic techniques are used to biopsy or resect diseased tissue. Endoscopic improvements would further reduce the risks of the procedure and augment the therapeutic applications of the technology.

Objectives:

- Develop and validate a method to perform “molecular” biopsy of luminal abnormalities in real time.
- Develop improved instrumentation for therapeutic endoscopy.
- Develop improved virtual endoscopy technology to access the luminal space of the GI tract.

Research Goal 12.3: Use tissue engineering and regenerative medicine approaches to develop innovative treatments for digestive diseases.

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[18] *Research Goals are numbered for ease of reference only; the numbers do not indicate prioritization of scientific topics.*

Advances in stem cell biology provide an opportunity to transform the treatment of digestive diseases. The stem cell population that supports ongoing regeneration of the intestinal epithelium can be harnessed to regenerate tissues of the GI tract. To reach this goal, better understanding of the stem cell niche and development of biologically compatible scaffolds that can direct the growth of the complex structure of the GI tract are needed. The esophagus, in particular, would benefit from regenerative approaches, as there are limited surgical options for repair of this organ. The small intestine represents another prime target for stem cell-based approaches to the treatment of short bowel syndrome, inflammatory bowel diseases, and other conditions.

Objectives:

- Identify and isolate local stem cell populations in the GI tract for tissue engineering applications.
- Develop scaffolds, both naturally occurring and synthetic, to support growth and differentiation of cell populations indigenous to the GI tract.
- Develop tissue engineering and regenerative medicine methods to treat diseases of the digestive organs.

Research Goal 12.4: Expand the application and integration of imaging and procedural technologies to deliver targeted interventions with minimal tissue injury to patients with digestive disorders.

Image-guided therapeutics can accurately and specifically deliver treatments to diseased tissue and minimize damage to surrounding healthy tissue. Novel agents to visualize markers of disease must be tested and validated in human patients. New devices that facilitate noninvasive imaging and manipulation of tissues could minimize trauma to the patient and improve therapeutic efficacy.

Objectives:

- Develop new PET tracers for clinical use, including markers of proliferation, tumor-specific antigens, and markers of apoptosis and inflammation.
- Develop intraoperative high-energy gamma and beta detectors to enhance intraoperative localization.
- Develop energy delivery and real-time tracking devices to optimize local image-guided interventions.
- Develop improved devices for facilitating single port laparoscopic procedures, intraluminal procedures, and natural orifice surgeries.

Research Goal 12.5: Develop high-fidelity interactive simulators of the digestive system.

Advances in computer simulation provide an opportunity to transform technical and cognitive training in GI endoscopy and surgery. Virtual environments can be used for training, prior to initiation of patient procedures. Simulators could facilitate the acquisition of new procedural skills by physicians who have completed training and also could be used for certification and testing to ensure procedural quality.

Objectives:

- Define the optimal use of simulation in training the procedural workforce, including metrics, transference, competency assessment, and acquisition of new technologies.
- Define the value of simulation in developing new procedures to facilitate procedural design and the prediction of outcomes.
- Develop high-fidelity simulators to allow multimodality procedural rehearsal.

MAJOR CHALLENGES AND STEPS TO ACHIEVE THE RESEARCH GOALS

Translational and clinical research: A critical challenge for the field is finding ways to attract and support translational clinicians—physicians who interact with patients and can bridge the basic science questions and technologies. Training of new investigators in the area of technology feasibility and assessment could also be encouraged. In addition, enhanced support for randomized clinical trials, including studies of advanced endoscopic and other technologies, would accelerate the validation of new, state-of-the-art procedures. Increased inclusion of endoscopists and surgeons on study sections is critical for ensuring appropriate review of proposals for testing new technologies.

Academia-industry collaboration: Small technology companies working to develop imaging or intraprocedural guidance technology often do not have sufficient capitalization, and value is based primarily on a small amount of academically based intellectual property. Finding ways to foster collaboration between academia and small industry would encourage development and testing of new devices and technologies arising from translational research. Management of conflict-of-interest and intellectual property issues are key matters to address.

Regenerative medicine: The GI tract lags behind other tissues in terms of tissue engineering/regenerative medicine research. Fostering research on this topic and translation of results into clinical trials would accelerate progress in the field.

Fostering research teams: A multicenter consortium for the evaluation and treatment of luminal disease could be established. Such collaboration among expert users of advanced or novel technologies would enhance the design and execution of randomized, controlled trials in human patients. Further, the development of multidisciplinary centers for technology design, development, and testing would promote scientific investigation among relevant areas of expertise that include GI medicine and surgery, engineering, imaging, chemistry, computer science, and others. Inclusion of scientific expertise that is traditionally considered to be outside of the biomedical sciences would promote rapid progress in the field. Finally, creation of a patient registry would encourage collaboration and sharing of resources. These challenges could be addressed by a workshop to convene investigators for an early assessment of promising new technologies and to identify key questions and studies for implementation in the near future.