Circulating tumor cells (CTCs) are extremely rare cancer cells circulating in the peripheral blood of individuals with invasive cancers. For every one billion blood cells, there is approximately one CTC. CTCs may break off from a primary tumor or its metastases, signaling the spread of disease to distant sites and rendering it all too often incurable.

The isolation and study of CTCs is an emerging field, but one that has been limited by the technology for isolation of rare cells from the blood. Although a commercial device is available for CTC isolation (Veridex’s CellSearch), it is hampered by low yields, typically yielding only one CTC per spoonful of blood, in only half of all patients with known metastatic cancer.

Recently, a Massachusetts General Hospital team co-led by Center for BioMicroElectroMechanical Systems (BioMEMS) Director Mehmet Toner, PhD, and Cancer Center Director Daniel A. Haber, MD, PhD, developed a groundbreaking technology that makes use of microfluidics to enable the efficient and sensitive isolation of CTCs. This new approach not only effectively isolates rare CTCs from patients with a variety of epithelial cancers, but it also allows for the study of their genetic makeup.

CTC Chip Technology

The microfluidic technology developed by scientists at the Mass General Cancer Center is a device called the CTC Chip. It is a small silicon chamber filled with 80,000 micro-posts, each of which is covered with antibodies against EpCAM, a virtually universal marker on the surface of CTCs. As whole blood flows through the chip, CTCs bind to the posts while normal blood cells flow through unimpeded. Cells are then imaged using fluorescent antibodies or subjected to nucleic acid analysis for genotypes. The majority of cells captured by the CTC Chip remain intact, which offers the promise of functional or other detailed analyses.
Circulating Tumor Cells Reveal Lung and Prostate Cancer Biology

Advances in Targeted Therapies for Lung Cancer

Testing of the CTC Chip began at Massachusetts General Hospital in 2005. Led by senior investigators Shyamala Maheswaran, PhD; Sunitha Nagrath, PhD; and Lecia Sequist, MD, MPH, a research team comprised of bioengineers, molecular biologists and clinicians demonstrated that the device can successfully identify CTCs in the peripheral blood of patients with metastatic lung, prostate, pancreatic, breast and colon cancer. Following up on the discovery that lung cancer patients whose tumors have a mutation in the epidermal growth factor receptor (EGFR) gene exhibit dramatic responses to EGFR kinase inhibitors, the Mass General team demonstrated the presence of EGFR mutations in the CTCs isolated using the CTC Chip. While these findings suggest the potential for rapid blood-based genotyping of tumor cells, the most important implications relate to the potential for serial monitoring of tumor genotypes during the course of therapy.

The development of drug resistance to targeted therapies remains a major challenge in treating lung cancer. It is difficult to harvest repeated tumor samples to monitor the various mechanisms leading to the acquisition of drug resistance. Advancing treatment in the face of drug resistance requires the appropriate selection of second-line targeted agents directed against the acquired pathways mediating drug resistance. Both processes require repeat biopsies. Given the risks associated with repeated tumor biopsies, there is a need for noninvasive biopsies, which may become possible through molecular analysis of circulating tumor cells.

Indeed, the Mass General investigators were able to demonstrate the appearance of defined EGFR mutations that confer resistance to the first generation EGFR inhibitors (erlotinib and gefitinib), in effect demonstrating the evolution of tumor genotypes as a result of successful initial targeted therapy. These efforts are vital to the design of second generation agents capable of circumventing the acquisition of resistance to these targeted agents.

Application of the CTC Chip to Prostate Cancer

Cancer Center investigators, including Dr. Maheswaran and genitourinary oncologist Richard J. Lee, MD, PhD, along with researchers Shannon Stott, PhD; Sunitha Nagrath, PhD; David Miyamoto, MD, PhD; and others, are using the CTC Chip to explore the biology of metastatic prostate cancer. Prostate cancer has several features that present challenges for molecular characterization. The primary tumor is often multifocal, making it difficult to know which lesion is responsible for the eventual metastatic spread of the disease. Once it does spread, prostate cancer often metastasizes to the bone, where it is difficult to biopsy. Here again, the analysis of CTCs offers great potential.

Key Points

- Circulating tumor cells (CTCs) are extremely rare cancer cells circulating in the peripheral blood of individuals with invasive cancers. For every one billion blood cells, there is approximately one CTC.

- Massachusetts General Hospital, under the direction of Cancer Center Director Daniel A. Haber, MD, PhD, and Center for BioMicroElectroMechanical Systems (BioMEMS) Director Mehmet Toner, PhD, has developed a groundbreaking technology called the CTC Chip that not only effectively isolates rare CTCs, but also allows for study of their genetic makeup.

- The CTC Chip can successfully capture CTCs in the peripheral blood of patients with metastatic lung, prostate, pancreatic, breast and colon cancer.

- The Mass General Cancer Center has been a leader in personalized treatment for lung cancer. The CTC Chip will allow researchers to better target therapies for patients based on specific gene mutations by allowing serial testing of lung cancer patients throughout treatment.

- Mass General researchers are launching exploratory studies using the CTC Chip to analyze the genetics of metastatic prostate cancer and identify biomarkers that may help predict who may or may not respond to a particular therapy.

- The Mass General Cancer Center was recently awarded a $15 million research grant from the Stand Up to Cancer campaign to help accelerate cancer research with the CTC Chip.
promise for molecular characterization of metastatic disease.

Early studies from the Mass General team have shown that prostate cancer CTCs can be isolated using the microfluidic technologies in numbers that cannot be achieved with standard technologies. Defining molecular characteristics, such as the TMPRSS2-ERG chromosome translocation, are readily detected. Even more importantly, staining for the Ki67 proliferation marker allowed for the first time the measurement of a “CTC proliferative index.”

The microfluidic technology is sensitive enough to allow detection of CTCs in some patients with localized prostate cancer prior to surgical resection. The Mass General team is now initiating a clinical trial involving 200 patients undergoing prostatectomy for localized prostate cancer. These patients will be monitored for the presence of preoperative CTCs and the rate of decline of CTCs following surgical resection. This may help determine if CTC analysis can identify men who will have earlier recurrence of the disease as well as provide information that could result in better management of the disease.

The Future of CTC Chip Technology

The Massachusetts General Hospital Cancer Center was recently awarded a $15 million research grant from the Stand Up to Cancer campaign to help accelerate cancer research with the CTC Chip. Through a multi-institution collaboration, the Mass General Hospital technology will be rolled out to four other cancer research centers—Massachusetts Institute of Technology, Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center and MD Anderson Cancer Center—so as to enable joint clinical and technological research efforts.

The Mass General team has already developed a second generation platform with increased CTC capture, imaging and molecular analysis, and is making progress toward studying CTCs in patients with breast cancer, melanoma and brain tumors. While still in its infancy, this revolutionary technology has the potential to change the way oncologists detect, monitor and treat cancer.

Selected References


Contributors

Daniel A. Haber, MD, PhD
Director, Massachusetts General Hospital Cancer Center
Isselbacher/Peter D. Schwartz Professor of Oncology, Harvard Medical School
dhaber@partners.org

Richard J. Lee, MD, PhD
Medical Oncologist, Bertucci Center for Genitourinary Cancers, Massachusetts General Hospital Cancer Center
Instructor of Medicine, Harvard Medical School
rjlee@partners.org

Lecia V. Sequist, MD, MPH
Medical Oncologist, Center for Thoracic Cancers, Massachusetts General Hospital Cancer Center
Assistant Professor of Medicine, Harvard Medical School
lvsequist@partners.org


Confocal Laser Endomicroscopy Makes Possible In Vivo Diagnosis in Digestive Cancers

Despite improvements in diagnosis and treatment approaches, gastrointestinal (GI) cancers remain some of the most deadly malignancies. Five-year survival rates for esophageal and pancreatic cancers in advanced stages, for example, are less than 5 percent. In addition, occurrence of such cancers is growing. Incidence of esophageal cancer has risen 500 percent over the last 15 years, making it the most rapidly increasing cancer in the United States.

Given the difficulty in managing GI cancers after invasion and metastases occur, early detection remains an extremely important clinical objective. Now, a novel approach called confocal laser endomicroscopy (CLE) holds the potential to allow real-time in vivo diagnosis of esophageal and other digestive cancers. Currently being investigated at Massachusetts General Hospital and a few other centers worldwide, this procedure aims for the same degree of accuracy as conventional histology, challenging traditional pathology techniques.

Surpassing Traditional Diagnostic Approaches

Most GI cancers develop over a period of several years and are characterized by changes in tissue architecture and cellular structure before invasion and metastasis. Traditional white light endoscopy imaging is often nonspecific for the diagnosis and detection of these malignancies. Histology, typically derived through endoscopic biopsy, can provide the necessary cellular and subcellular resolution and remains the gold standard for diagnosis. However, conventional histology has potential drawbacks.

Histology typically is based on a forceps biopsy. Histopathological processing of the tissue samples often can be time consuming, delaying a definite diagnosis. In addition, invasive tissue sampling carries some, albeit rare, risk of bleeding and infection. While still investigational, CLE offers the potential to speed up this process and reduce the number of required biopsies by allowing for the diagnosis and treatment of GI malignancies in real time through in vivo imaging.

Mass General pathologists predict that once CLE protocols have been established through further clinical trials, the procedure could reduce the need for biopsy of tissue that is unmistakably “normal.” Pathologists could then focus their efforts on “targeted biopsies.”

Diagnosing Cancers In Vivo

CLE is a newly developed imaging tool that uses laser light and optical technology to visualize living tissue at the cellular level. Epithelial structures magnified 1,000-fold appear in real time on a computer screen, which enables detection of changes in cellular morphology without the need for a biopsy. CLE allows in vivo histology of the whole mucosal layer of up to 250 µm infiltration depth. As a result, CLE can help identify mucosal areas that are suspicious for neoplasia, inflammatory lesions, Barrett’s esophagus or other mucosal anomalies. This real-time in vivo diagnosis capability allows for immediate, targeted biopsy or endoscopic therapy to remove the cancerous lesions.

Ideally, it also allows for much greater accuracy during endoscopy, eliminating the need to repeatedly rescan the same tissues over the course of multiple procedures to ensure that all questionable tissue has been identified. Instead, any suspicious tissues can be diagnosed and resected immediately.

Achieving Subcellular Resolution

Confocal microscopy is an adaptation of white light microscopy in which the light has to pass through a system of two consecutive pinholes before an image is detected. CLE provides better spatial resolution than conventional fluorescence microscopy as the images are not contaminated by light scattering from the other planes. It permits observation of fine

A confocal laser endomicroscopy (CLE) image of normal gastric glands.

A confocal laser endomicroscopy (CLE) image of normal duodenal villi.

Key Points

- Confocal laser endomicroscopy (CLE) is applicable for many kinds of gastrointestinal (GI) cancer diagnostics, including esophageal, gastric and colorectal cancer.
- Using an endoscope or a probe, CLE magnifies structures 1,000-fold in real time on a computer screen, allowing in vivo imaging of living GI tissue at the cellular and subcellular level.
- When perfected and performed by a specially trained gastroenterologist, this real-time in vivo diagnosis capability allows for immediate biopsy or endoscopic therapy to remove the cancers.
- Massachusetts General Hospital is partnering with other institutions to advance CLE research and define the accuracy of the technique compared with conventional histology.
cellular detail in conjunction with fluorescent labeling techniques or vital dyes, even in cells located below the tissue surface.

Fluorescein sodium is the most commonly injected agent used to achieve high-contrast images during CLE. It binds to serum albumin, and remaining unbound dye molecules pass across the systemic capillaries and enter the tissue, highlighting the extracellular matrix. It yields cellular and subcellular details, and it permits the evaluation of connective tissue and vessel architecture at a high resolution but does not stain nuclei.

Currently, two CLE techniques are available: a scope-based platform (referred to as endoscopic CLE) and a probe-based system. Endoscopic CLE integrates a confocal laser microscope within the distal tip of a flexible endoscope. Probe-based CLE employs a microfiber probe that is inserted within the biopsy channel of a standard diagnostic flexible endoscope. Both systems provide excellent image clarity.

CLE can be used like a regular endoscope, taking advantage of the standard endoscope accessory channel. A laser beam is delivered at the surface of the mucosa, allowing targeted endomicroscopic images to be captured. Images can be collected by sectioning down through the mucosa in 7 µm increments to a depth of 250 µm. Endoscope stabilization using suction is necessary to obtain high-quality images. Tissue biopsies can be targeted to the area of imaging using the site of the suction polyp found next to the imaged area.

Diagnosing and Treating Aggressive GI Cancers

Gastroenterologist William R. Brugge, MD, of the Digestive Healthcare Center at Massachusetts General Hospital, is helping to pioneer the development of CLE in the United States. Working with oncologists and pathologists at the Tucker Gosnell Center for Gastrointestinal Cancer at the Mass General Hospital Cancer Center, Dr. Brugge is leading the investigation of CLE for surveillance of patients with Barrett’s esophagus and dysplasia who are at high risk of developing esophageal cancer.

However, CLE can be used for almost any GI cancer. The ability to obtain high-resolution images at the cellular level of the duodenum, stomach and colon makes the technique applicable for many kinds of diagnostics, including the following:

**Barrett’s Esophagus**

CLE is used in conjunction with endoscopic mucosal resection (EMR) to treat Barrett’s esophagus. Now, in preliminary work being done in collaboration with Mass General pathologists, resection margin is established by probing with CLE, and then a frozen-section biopsy is done to confirm the margins. Once perfected, this technique would eliminate the need for multiple biopsies to establish “clean” margins.

**Gastric Cancer**

Confocal laser endomicroscopy allows real-time in vivo diagnosis of mucosal neoplasia or preneoplasia in the stomach. CLE can be used to identify early neoplasia and guide biopsies to microscopically suspicious areas. Precursor lesions, such as intestinal metaplasia, can be visualized by CLE during endoscopy.

**Colorectal Cancer**

Another common paradigm for CLE is in patients who are at high risk for colon cancer. Such patients undergo screening that can include taking mini-biopsies throughout the colon. Typically, this requires a large number of biopsies because the colon is a very long organ. With CLE, physicians can use the scope to closely examine many different areas during the screening itself and detect abnormalities more quickly. As with esophageal cancer, this early detection makes it possible to remove the malignancies by means of immediate endoscopic resection.

**Setting a New Standard of GI Cancer Care**

New technologies in endoscopy often take five to 10 years to become widely adopted. Today, major academic medical centers are evaluating CLE to determine its accuracy and which methods may potentially have the most impact on patient care. However, while CLE offers tremendous promise, some barriers remain to its widespread adoption.

Selected References


Contributor

William R. Brugge, MD
Director of Endoscopy, Digestive Healthcare Center, Massachusetts General Hospital
Professor of Medicine, Harvard Medical School
wbrugge@partners.org
Tumor Genotyping Brings Personalized, Targeted Therapies to Patients

Physicians at the Massachusetts General Hospital Cancer Center have become leaders in the development of personalized medicine for cancer patients. Specifically, years of collaborative research among clinicians, pathologists and molecular biologists have led to the development of better and faster methods to “genotype” cancers and identify the genetic abnormalities that drive particular tumors. In turn, these methods are giving rise to new treatment paradigms focused on genetic mutations that may be shared by different tumors, irrespective of their tissue of origin.

Building on the rapidly advancing understanding of how cancer develops at the molecular genetic level, physicians at Mass General are working with pharmaceutical scientists to develop and bring into clinical use new “smart” drugs that can de-activate genetic abnormalities and arrest the disease process.

Dissimilar Cancers Share Genetic Mutations

Through tumor genotyping, researchers can detect the genetic abnormalities that give rise to particular tumors. It is these mutations that appear to “drive” healthy cells to become tumor cells. Diverse cancers may share the same genetic abnormalities. For example, some lymphomas and lung cancers share genetic abnormalities of the ALK gene, while some breast and gastric tumors have an amplification of the HER2 gene. These mutations can have a major impact on patient outcomes.

The genetic abnormality HER2 first brought genotyping into focus for the oncology community. About 30 percent of breast cancers have the HER2 amplification, whose activity can be shut off by the drugs Herceptin (trastuzumab) and Tykerb (lapatinib). Using such personalized, targeted therapy in early cases of breast cancer, physicians have been able to nearly cut in half the number of patients who will ultimately relapse and die from their disease.

Physician-researchers at Mass General identified a genetic mutation of the EGFR gene in lung cancer patients in 2004. In the United States, 10 percent of lung cancers—and 50 percent of those in nonsmokers—carry this mutation. More than 70 percent of EGFR-mutant tumors respond to the oral EGFR inhibitors Iressa (gefitinib) or Tarceva (erlotinib). Recent international trials have shown that initial treatments of EGFR-mutant lung cancers with EGFR inhibitors have far better outcomes than initial treatment with traditional chemotherapy.

Accelerating Tumor Profiling

To accelerate clinical trials in which patients may benefit from molecularly targeted therapies, the Mass General Cancer Center has established a dedicated translational research laboratory in which tumor specimens are genotyped for key mutations that may affect the selection of targeted agents. While many of these mutations are relatively rare in any given type of cancer, their identification by a systematic approach and in “real time” is essential for the ability to rapidly match individual patients’ tumors with the novel therapeutic agents to which they may be responsive. As additional genetic information is generated, and as additional targeted drugs become available for testing, this strategy becomes critical for clinical trials. Currently, the Mass General Cancer Center routinely screens most lung, colorectal and brain tumors, and in the coming months, it plans to expand tumor genotyping to melanoma, breast and ovarian tumors.

Developing the technical capacity to screen large numbers of patients was a major effort that took two years and involved collaboration among scientists, pathologists and oncologists at the Cancer Center.

One of the first steps was establishing the Molecular Pathology Translational Research Lab (TRL) through a collaboration between Mass General’s Pathology Department and the Cancer Center. Led by A. John Iafrate, MD, PhD, director of diagnostic molecular pathology at Mass General and by Cancer Center oncologist and breast cancer researcher Leif Ellisen, MD, PhD, the TRL has developed a streamlined process that allows researchers to extract and test DNA from tumors collected through routine biopsies.

A few years ago, Dr. Ellisen and Dr. Iafrate realized they needed to develop more robust genetic tests that would apply to clinical specimens, which are often heterogeneous and contain impurities. As a result, the team developed a protocol for DNA purification made more powerful through the application of precise robotic technology.

The tumor genotyping process at Mass General Cancer Center works as follows:

- A standard tumor sample is taken by biopsy or surgery.
- Samples are sent to the pathology laboratory, where surgical pathologists confirm the diagnosis and forward the sample to the TRL.

These tumor cell nuclei (blue) display the ALK mutation. Normal ALK gene copies appear as overlapping (yellow) or adjacent green and red probes. Unpaired red probes (arrows) indicate a broken segment of the ALK gene joined to another part of the genome, creating a mutation that can be targeted therapeutically.
• In the TRL, a piece of tumor is removed from the sample. The tumor DNA is purified and genotyped using proprietary software that screens for 122 mutations that have been identified.

  The robotic protocol developed at Mass General permits initial processing of up to 100 specimens a day. Without this protocol, only a few of these labor-intensive tests could be completed each day.

  Currently, Mass General is involved in a consortium funded by the National Institutes of Health to determine the best, and most rapid, protocols for conducting this kind of molecular analysis. The consortium effort is focused on lung cancer. Additional research efforts are under way to develop larger and more comprehensive genotyping approaches.

  Due to limited capacity, the Cancer Center does not offer outside reference testing, but it is actively engaged in disseminating the technology to enhance diagnostic testing at other institutions and diagnostic providers.

  Developing Targeted Therapies: BRAF and Melanoma

  To further support the development of personalized medicine, physician-researchers at Mass General have focused on clinical trials of genotype-directed therapies. Their work with “smart” drugs that shut off the abnormally activated molecular pathways in tumor cells is aimed at causing cancer cell death while minimizing side effects to normal cells.

  Research by medical oncologist Keith T. Flaherty, MD, has centered on melanoma patients with a BRAF mutation. BRAF is a key component of MAP kinase, the central signal transduction pathway for cancer. The BRAF mutation was identified in 2002, and it is prevalent in 7 percent of all cancers. But it is especially common in melanoma: scientists estimate that 40 to 60 percent of melanomas harbor these mutations. BRAF mutations also occur in 5 to 20 percent of colorectal cancers.

  Dr. Flaherty is leading the first-in-human trial of PLX4032, a new oral drug designed to inhibit BRAF. Early data in melanoma indicates that as many as 80 percent of patients whose tumor has the BRAF mutation have responses. The Cancer Center is currently enrolling patients for trials testing PLX4032 given alone, and another selective inhibitor of BRAF (GSK218426) in combination with an inhibitor of MEK, another key component of the MAP kinase pathway. A review of BRAF co-authored by Dr. Flaherty, is in press with the New England Journal of Medicine for publication in 2010.

  ALK and Lung Cancer

  Another promising genotype-directed approach under active research at Mass General involves the EML4-ALK gene rearrangement, found in a subset of lung cancers. Like EGFR, activated ALK is a tyrosine kinase receptor that promotes the growth and transformation of cells. While EGFR activation results from point mutations in the gene, the ALK gene is rearranged and abnormally fused to the EML4 gene, resulting in its ability to act as an oncogene.

  Chromosomal translocation of the ALK gene (to another partner gene) was first identified in lymphomas, and point mutations in ALK have been discovered in pediatric neuroblastoma. However, it is in lung cancers with the EML4-ALK rearrangement, that clinical investigators first demonstrated the effectiveness of anti-ALK therapy.

  A multi-institutional collaboration led by Mass General medical oncologists continued on the next page
Tumor Genotyping Brings Personalized, Targeted Therapies to Patients

Leif W. Ellisen, MD, PhD
Co-Director, Molecular Pathology Translational Research Lab, Massachusetts General Hospital Cancer Center
Associate Professor of Medicine, Harvard Medical School
lellisen@partners.org

Keith T. Flaherty, MD
Director of Developmental Therapeutics, Massachusetts General Hospital Cancer Center
Lecturer, Department of Medicine, Harvard Medical School
kflaherty@partners.org

Alice T. Shaw, MD, PhD
Medical Oncologist, Center for Thoracic Cancers, Massachusetts General Hospital Cancer Center
Assistant Professor, Department of Medicine, Harvard Medical School
ashaw1@partners.org

Eunice Kwak, MD, PhD, and Jeffrey Clark, MD, along with Dr. Iafrate, tested the effectiveness of an ALK inhibitor developed by Pfizer in patients with lung cancer. ALK gene rearrangements are rare, estimated to occur in approximately 4 percent of lung cancers; however, given the prevalence of lung cancer, this small percentage represents many patients.

Furthermore, additional research has shown that the ALK gene rearrangement is present in approximately 20 percent of lung cancers arising in nonsmokers. The team tested lung cancers for the ALK rearrangement, and patients whose tumors harbored the abnormality were enrolled into an early-phase clinical trial of an ALK inhibitor.

Approximately 85 percent of enrolled lung cancer patients with the mutation benefited from treatment, with many cases experiencing dramatic and long-lasting tumor shrinkage. This study not only demonstrates a new treatment option for a subset of patients with lung cancer, but it also shows the effectiveness of prescreening large numbers of tumors for a specific genetic abnormality, and then directing a clinical trial to that subset of patients most likely to benefit from a targeted inhibitor.

Clinical trials of ALK-positive lung cancer are ongoing at the Mass General Cancer Center. Medical oncologist Alice T. Shaw, MD, PhD, is leading the international phase 3 registration clinical trial of the ALK inhibitor, now called crizotinib (PF-02341066).

Future Research Efforts

In addition to their work on the ALK mutation in lung cancer and the BRAF mutation in melanoma, physician-scientists at the Cancer Center are actively studying other drugs targeting the following genes:

- MEK in patients whose tumors harbor the BRAF mutation (such as colon, lung and thyroid cancers)
- C-Kit in melanoma and gastrointestinal stromal tumor patients
- HER2 in gastric, lung and breast cancer patients
- KRAS in colon cancer patients

Physicians at the Cancer Center expect that tumor profiling through genotyping will become more integrated with clinical practice in the future.
Hepatocellular carcinoma (HCC), the primary malignancy of the liver, is the fifth most common cancer worldwide and the third most common cause of cancer-related mortality. In 2009, more than 22,500 Americans were diagnosed with primary liver cancer and the incidence of HCC in the United States continues to rise.

At least 70 to 80 percent of patients with HCC have underlying cirrhosis of the liver, which creates significant challenges in disease management. Cirrhosis is most often caused by hepatitis B or C infections or chronic alcohol abuse. Nonalcoholic fatty liver disease, which could be related to obesity or diabetes mellitus, may also increase the risk for cirrhosis. Heightened awareness of risk factors, coupled with regular surveillance of at-risk individuals, can have significant implications on treatment outcomes. HCC is curable by resection or liver transplantation if detected in its early stages.

Unfortunately, the vast majority of individuals with HCC present with late-stage disease and their prognosis is poor. HCCs are heterogeneous and are generally unresponsive to systemic chemotherapies. Innovative research and novel treatment approaches are necessary to meet the complex and challenging needs of this patient population.

Multidisciplinary Approach Ensures Optimal Treatment Direction

The Massachusetts General Hospital Cancer Center is a national leader in liver cancer research, care and treatment. The Cancer Center offers complex surgical and nonsurgical treatment options, as well as clinical trial opportunities, to provide patients with the best outcomes possible.

Patients are evaluated by a multidisciplinary team devoted to liver malignancies, including medical and surgical oncologists, transplant surgeons, radiation oncologists, vascular radiologists, gastrointestinal radiologists, hepatologists and others. The team meets to review each case collaboratively and provides definitive treatment recommendations. For patients wading through the many treatment options available, this offers a significant benefit.

Leading-Edge Surgical Treatments at the Massachusetts General Hospital Cancer Center

Surgical intervention in localized liver cancer is considered the gold-standard of care, resulting in an approximate 50 percent cure rate. Led by Division of Surgical Oncology Chief Kenneth K. Tanabe, MD, the Mass General Cancer Center’s highly specialized liver surgeons perform more liver tumor resections than any other center in Massachusetts. The Cancer Center also offers a highly experienced liver transplant program.

The Cancer Center continues to refine advanced surgical approaches, providing complex surgical patients with the most...
curative treatment options. The following are some of the advanced techniques presently performed at the Mass General Cancer Center:

Laparoscopic Liver Resection
Massachusetts General Hospital pioneered the development of laparoscopic surgery. Laparoscopic liver resections are performed by a skilled team in selected patients and offer a significant benefit in recovery. In addition to faster recovery, these patients have less postoperative pain, wound complications and scarring, allowing them to pursue any necessary adjuvant chemotherapy more expeditiously.

Inferior Vena Cava and Hepatic Vein Resections
Liver tumors that involve the inferior vena cava or all three of the hepatic veins are traditionally considered inoperable. However, the Mass General Cancer Center is one of a few centers in the country offering an aggressive, leading-edge surgical solution to appropriate patients. Surgical oncologists, working with cardiac perfusionists, use veno-veno bypass to redirect blood flow from the lower extremities and kidneys back to the heart. This provides surgeons a relatively bloodless field to remove tumors that involve the inferior vena cava or hepatic veins. The inferior vena cava and/or hepatic veins can then be reconstructed. To prevent ischemic liver damage, in some cases, the liver is cryopreserved within the body—filled with a protective solution and packed with ice.

Deceased and Live-Donor Liver Transplants
Most HCC tumors occur in cirrhotic livers. Therefore, liver transplantation and replacement of the cancerous liver with a new liver removes both the cancer as well as underlying cirrhosis, providing a successful treatment option for HCC patients with unresectable tumors. (Due to organ shortages, only patients with favorable survival rates, based on specific tumor size and number, are eligible for organ transplantation from the national donor list.)

In addition to providing organ transplants from deceased donors, the Massachusetts General Hospital Transplant Center provides live-donor liver transplants in one of the most active and established programs in the region. For appropriate patients with a suitable living-related donor, the program can help avoid prolonged waiting periods for transplantation, providing patients with a partial liver from a suitable donor.

Radiofrequency Ablation
In 1996, surgical oncologists at Mass General Hospital performed the first radiofrequency ablation of a liver tumor in the United States. Mass General continues to be a leader in this technique. Radiofrequency ablation (RFA) is a minimally invasive procedure performed on an outpatient basis. Using advanced imaging, a thin electrode is inserted through the abdominal skin and into the center of a liver tumor. The electrode passes an electric current to the tumor, destroying the tissues. RFA has been shown to be as effective as surgery in some early-stage liver cancer tumors.

Transcatheter Arterial Chemoembolization
The Mass General Cancer Center uses the transcatheter arterial chemoembolization (TACE) procedure alone or in combination with radiofrequency ablation to slow blood flow to HCC tumors. TACE blocks
blood flow to the targeted tumors and enriches the concentration of chemotherapy drugs. This can result in tumor shrinkage, potentially making surgical resection possible.

**Proton Beam Radiation**

The Cancer Center’s Francis H. Burr Proton Therapy Center is the only facility in the Northeast and one of just a few select centers in the country to offer proton beam radiation for HCC. This type of radiation, which requires the use of a highly specialized proton beam radiation machine, allows physicians to provide a higher dose of radiation to a more targeted area, almost completely sparing healthy liver tissue. Proton beam therapy allows treatment of hard-to-treat liver tumors, including larger tumors and tumors with portal vein thrombosis.

**Promising Therapies through Research**

With a team of investigators led by Andrew X. Zhu, MD, PhD, director of liver cancer research, the Mass General Cancer Center maintains a strong research focus to further understand and overcome the challenges of HCC. The Cancer Center has conducted numerous clinical trials, including large phase 3 trials, to further research to this end. A few current research initiatives are discussed here:

**New Systemic Treatments: Targeted Therapies**

The Massachusetts General Hospital Cancer Center is one of the most active centers nationwide working to develop and test new molecular targeting agents to improve systemic treatment of HCC. Currently, sorafenib is the only FDA-approved target agent for HCC; however, the benefits have been only moderate for most patients. In addition to researching new agents as well as novel ways of using sorafenib effectively, the Cancer Center’s research team continues to explore the mechanism of these agents and why they benefit specific patients. This information will help guide the development of targeted agents in the future.

**Using Engineered Virus to Destroy Tumors**

The Cancer Center is currently conducting a clinical trial to test the effectiveness of an engineered herpes virus to destroy primary and secondary liver tumors. The virus, developed at Massachusetts General Hospital, is designed to robustly replicate within and destroy tumor cells.

**Exploring Prevention Strategies**

Oncologists at the Mass General Cancer Center are aggressively exploring prevention strategies for HCC. Researchers led by Dr. Tanabe have identified a variant in the epidermal growth factor (EGF) gene that significantly increases the chance of HCC developing in those with underlying cirrhosis. Further studies in animal models have revealed that the EGF receptor can be blocked with the drug erlotinib, halting cell growth and improving the underlying condition of the liver. The Mass General Cancer Center maintains a strong liver cancer research, the Mass General Hospital, is designed to robustly replicate within and destroy tumor cells.

**The Future of HCC**

The Mass General Cancer Center is aggressively addressing the needs of individuals with HCC—a growing patient population largely considered untreatable. Our surgical oncologists and transplant surgeons continue to refine complex techniques to effectively treat patients with liver tumors. Ongoing research focuses on proton therapy and ablative therapies that include RFA and TACE, molecularly targeted therapies, novel viral gene therapies, blockage of the EGF gene to address the underlying cirrhosis that is often a precursor to liver cancer and minimally invasive approaches, including laparoscopic liver resection.

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**Selected References**


**Contributors**

**Kenneth K. Tanabe, MD**

Chief, Division of Surgical Oncology, Massachusetts General Hospital

Deputy Clinical Director, Massachusetts General Hospital Cancer Center

Program Director, Tucker Gosnell Center for Gastrointestinal Cancer

Director, Massachusetts General Hospital Liver Surgery Program

Professor of Surgery, Harvard Medical School

ktanabe@partners.org

**Andrew X. Zhu, MD, PhD**

Director, Liver Cancer Research, Massachusetts General Hospital Cancer Center

Associate Professor of Medicine, Harvard Medical School

azhu@partners.org
Cancer Center Priorities Fund: Investing in Breakthrough Research and Innovative Programs

With rising economic pressures and waning federal support for biomedical research, the need for unrestricted resources to support key Cancer Center initiatives has never been greater. The Cancer Center Priorities Fund fills this gap, supporting early research, underfunded initiatives and novel scientific concepts. The Fund’s investment in Cancer Center initiatives focuses on the following five guiding principles:

- To Discover the Fundamental Causes of Cancer as a Guide to Prevention, Early Detection and Treatment
- To Target Early Cancers Through Precision Surgery and Focused Radiation
- To Target Complex and Advanced Cancers Through Molecularly Designed Therapies
- To Accelerate the Delivery of Research Discoveries to People with Cancer
- To Sustain a World of Care by Treating the Patient, Supporting the Family and Educating the Community About Cancer

New Physician Leaders at the Cancer Center

A number of new physicians joined the Cancer Center staff this year, including some who have become key clinical team leaders. They are Michael J. Birrer, MD, PhD, new director of medical gynecologic oncology and the Gynecologic Cancer Research Program; John O. Schorge, MD, new division chief of gynecologic oncology for Massachusetts General Hospital Obstetrics and Gynecology, and clinical director of the Gillette Center for Gynecologic Oncology; Lori Julin Wirth, MD, new director of medical oncology at the Center for Head and Neck Cancers; Keith T. Flaherty, MD, new director of experimental therapeutics; and Inga T. Lennes, MD, new director of clinical quality.

José Baselga, MD, PhD, Named Chief of Hematology Oncology and Associate Director of the Massachusetts General Hospital Cancer Center

Massachusetts General Hospital Cancer Center Director Daniel A. Haber, MD, PhD, has announced the appointment of José Baselga, MD, PhD, as chief of hematology oncology and associate director of the Mass General Cancer Center.

A renowned clinical scientist, Dr. Baselga is relocating to Boston from Barcelona, Spain, where he has been the chairman of the Medical Oncology Service and director of the Division of Medical Oncology, Hematology and Radiation Oncology at the Vall d’Hebron Institute of Oncology.

His career is focused on the development of targeted therapies, especially for HER2 positive breast cancers. He has been actively involved in the clinical development of several new and targeted agents, as well as the identification of novel mechanisms that may resist current therapies.

“Dr. Baselga is an exceptional leader and commands international respect for his research and vast accomplishments in the field of clinical oncology,” says Dr. Haber. “We are confident that he will be an integral part of our exceptional team and will work to ensure that our commitment to the close integration of research and clinical care remains a priority.”

Dr. Baselga received his medical degree from the Universidad Autònoma de Barcelona in 1982. He did his internal medicine residency at both Vall d’Hebron University Hospital in Barcelona, Spain, and at the State University of New York in the United States. He completed a fellowship in medical oncology at Memorial Sloan-Kettering Cancer Center in New York, where he remained a faculty member until returning to Spain in 1996.

Dr. Baselga is the current president of the European Society of Medical Oncology (ESMO). He serves on several committees for the American Association for Cancer Research (AACR) and is a past member of the board of directors of the American Society of Clinical Oncology (ASCO).

José Baselga, MD, PhD, is the new chief of hematology oncology and associate director of the Massachusetts General Hospital Cancer Center.
New Clinical Director at the Cancer Center

David P. Ryan, MD, has assumed the position of clinical director of the Massachusetts General Hospital Cancer Center. Dr. Ryan also continues to serve as associate chief of hematology oncology and as clinical director of the Tucker Gosnell Center for Gastrointestinal Cancer. The principal focus of his clinical research is the design and implementation of phase 1 and 2 trials in gastrointestinal malignancies.

Bruce A. Chabner, MD, stepping down as clinical director and chief of hematology oncology at the Massachusetts General Hospital Cancer Center, will serve as director of clinical research. Under his leadership since 1995, the Cancer Center has grown from a modest cancer program into a comprehensive cancer center with one of the nation’s leading clinical research programs. Dr. Chabner has mentored many of the leading oncologists now practicing in the Northeast.

As director of clinical research, Dr. Chabner will work closely with the Cancer Center’s clinical trials and research training efforts, while continuing to mentor junior faculty. A former director of the Division of Cancer Treatment of the National Cancer Institute (NCI), he is associate director for clinical science for the Dana-Farber/Harvard Cancer Center (DF/HCC) and was recently appointed NCI National Cancer Advisory Board Chairman.

Divjak Family Underwrites New Warshaw Pancreatic Cancer Research Institute

The family of Zdravko Divjak has committed $5.25 million in funding to establish the Andrew L. Warshaw, MD, Institute for Pancreatic Cancer Research (WIPCR). The gift will both build on the Cancer Center’s research strengths and enhance what is already the largest pancreatic cancer treatment center in the Northeast.

Further development of a database and tissue bank will help determine why some pancreatic cancers evolve slowly while others are highly aggressive. Dr. Warshaw predicts WIPCR investigators will use a genetic marker or circulating tumor cell technology to isolate pancreatic cancer cells, characterize their genomic fingerprint and determine which tumors are good candidates for surgery, while also working to personalize drug therapies for individual forms of the cancer.

“The tools to understand cancer biology are very different now from just five years ago,” adds David P. Ryan, MD, clinical director of the Massachusetts General Hospital Cancer Center. “With the ability to characterize the genetic pathways important for pancreatic cancer cells to survive and flourish, we will also learn ways to shut down these pathways.”

The institute will also provide seed money to investigators whose work shows promise but is too early in development to attract NIH support.

From the Bench: Research News

Study Finds Engineered Mutation in Bone Stem Cells Can Disrupt Blood Cell Formation

Working with mouse models to study how bone precursor stem cells modulate blood cell formation, a research team led by David T. Scadden, MD, director of the Massachusetts General Hospital Center for Regenerative Medicine and Harvard Stem Cell Institute co-director, has discovered that introducing a specific Dicer1 genetic mutation into bone precursor cells induces bone marrow dysfunction and myelodysplasia, a precursor to leukemia. The team’s findings, reported in a March 2010 Nature study, support the idea of niche-induced oncogenesis and offer new insight into stem cell signaling as a potential therapeutic target.

Researchers Find Cell Resistance to Cancer Drugs Is Reversible

Tumor cells resistant to cancer drugs can lose their resistance, Mass General Cancer Center researchers reported in April 2010 in the journal Cell. They found that such drug tolerance requires IGF-1R signaling, and that IGF-1 receptor inhibitors or chromatin modifying agents can disrupt the resistance. Jeffrey Settleman, PhD, former Massachusetts General Hospital Cancer Center scientific director, was senior study author. Other Cancer Center researchers included Sridhar Ramaswamy, MD, and Shyamala Maheswaran, PhD, along with researchers from Dana-Farber/Brigham and Women’s Cancer Center.

STO International Conference

The Society for Translational Oncology (STO) will convene its 2010 international conference in Boston in November, launching a three-city, global consortium with Amsterdam and Belfast. With a yearly meeting that draws oncologists worldwide, STO is committed to speeding the discovery and translation of important new cancer treatments into global clinical practice. Hosted by Massachusetts General Hospital Cancer Center, the 2010 conference will focus on collaboration between academic medicine and the pharmaceutical industry.

STO publishes The Oncologist and develops educational programs to improve physician competencies and strategies for cancer screening, prevention, treatment and management, with a focus on enhancing performance in practice.
New Collaborations Link Mass General Cancer Center with Florida Hospitals

Florida’s Holy Cross Hospital in Fort Lauderdale and Massachusetts General Hospital Cancer Center have launched a collaboration to expand oncology services for South Florida residents. Holy Cross Hospital CEO and President John C. Johnson hails the new relationship as an opportunity to build on the comprehensive cancer care Holy Cross patients already receive, through access to “new clinical treatments and an additional network of nationally and internationally recognized specialists …while they continue their care at home in South Florida.”

David P. Ryan, MD, clinical director of the Mass General Cancer Center says the new collaboration enhances care for South Florida residents by providing “rapid access to subspecialty cancer care, genetics counseling and early phase clinical trials.”

A new collaboration also has been announced between the Mass General Cancer Center and Lee Memorial Health System’s Regional Cancer Center in Fort Myers, Florida, which is expected to enhance and expand access to oncology services for residents in that area. “Our relationship with the Mass General Cancer Center will give our patients access to new clinical protocols and treatments, as well as timely referrals for second opinions and improved coordination of care,” says Sharon MacDonald, vice president for Lee Memorial’s Regional Cancer Center.

Paul M. Busse, MD, PhD, clinical director of radiation oncology at Massachusetts General Hospital, also welcomes the new collaboration. “Novel approaches and treatments, such as genetic testing, genotyping, targeted drugs, proton beam radiation, stem cell therapies and bone marrow transplant, will be available through Mass General to Lee Memorial patients, including those Mass General patients who reside part time in Florida.”

Szostak Discovery of Telomere Function Wins Nobel Prize

Mass General Hospital researcher Jack Szostak, PhD, of the Department of Molecular Biology, won a Nobel Prize last fall for his work on two cellular components, telomeres and telomerase, which play vital roles in cell division.

Telomeres are regions of repeating DNA sequences at the ends of chromosomes; they protect chromosomes from deterioration during cell division. The enzyme telomerase adds extra DNA repeat sequences to telomeres, maintaining them during continuing cell division cycles. When telomerase is blocked, as it is in most cells, telomeres shorten, leading to cell aging and, eventually, cell death.

Dr. Szostak’s work has spawned investigations worldwide aimed at further understanding how telomeres and telomerase prevent the chromosome deterioration that leads to normal cell death, thereby permitting the unabated cell proliferation that characterizes cancer.

“One of the things cancer cells do to keep dividing is to turn this enzyme back on,” Dr. Szostak says. Finding a way to block or turn off the enzyme could yield a critical breakthrough in halting cancer.

Dr. Szostak shared the Nobel Prize with Elizabeth Blackburn, PhD, of the University of California in San Francisco, and Carol W. Greider, PhD, of the Johns Hopkins School of Medicine.

Dr. Blackburn was studying telomere DNA from a pond organism, Tetrahymena. Together they succeeded in putting Tetrahymena telomeres into yeast, which was more amenable to biologic study. Dr. Greider identified telomerase a year later, after Dr. Szostak and Dr. Blackburn predicted the existence of an enzyme that added new DNA to chromosome ends, keeping them intact.

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THE TELOMERE Function and Synthesis

Physician Awards and Honors

Two Cancer Center Researchers Named to Institute of Medicine

Each year, the Institute of Medicine (IOM) of the National Academies elects up to 65 new members and five foreign associates. They are chosen for their professional achievements and for their willingness to actively consult on IOM initiatives.

This year, two Mass General Cancer Center researchers were named members of the IOM. They are Cancer Center Director Daniel A. Haber, MD, PhD, Howard Hughes Medical Institute investigator and Kurt J. Isselbacher/ Peter D. Schwartz Professor of Medicine at Harvard Medical School; and Mass General Center for Systems Biology Director Ralph Weissleder, PhD, MD, professor of systems biology and radiology at Harvard Medical School.
New Roles for Thoracic Cancer Experts
Thoracic oncologist Panos Fidias, MD, has been appointed the clinical director of the Cancer Center’s new Inpatient Nurse Practitioner Oncology Service. While stepping down from his role as clinical director of the Center for Thoracic Cancers, he will continue his active clinical practice. Thoracic oncologist Jennifer Temel, MD, has been appointed the new clinical director of that center.

Cancer Center Online CME Offerings
The Mass General Cancer Center’s 2009 archive of Continuing Medical Education (CME) programs is available online at mgacademy.org/enduring. Users must register, then scroll down to access individual programs.

Offerings include:
Treatment Approaches for Metastatic Non-Small-Cell Lung Cancer  
Date: July 8, 2009; 1 hour

Targeted Agents: Tyrosine Kinase Inhibitors and Monoclonal Antibodies Against EGFR and VEGF  
Date: August 12, 2009; 1 hour

GI Cancer—The Role of Chemotherapy, Chemoradiation or a Combination  
Date: December 18, 2009; 2 hours

Key Advances in the Management of Lung Cancer  
Date: December 18, 2009; 2 hours

Treating Breast Cancer in the Era of Targeted Therapy  
Date: December 18, 2009; 2 hours

Assessment of Chemotherapeutic and Hormonal Options Based on Individualized Risk Assessment  
Date: December 23, 2009; 1 hour

Open Clinical Trials
The Massachusetts General Hospital Cancer Center conducts about 350 clinical trials in collaboration with the Dana-Farber/Harvard Cancer Center. Selected Mass General trials currently enrolling new cancer patients are listed here.

**BREAST CANCER**

| 06-325 | A Two-Arm, Randomized, Open-Label Phase 2 Study of CP-751,871 in Combination with Exemestane Versus Exemestane Alone as a First Line Treatment for Postmenopausal Patients with Hormone Receptor Positive Advanced Breast Cancer  
Phase 2  
Paua Ryan, MD, PhD  
617-726-5046 |

| 09-279 | A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women with Early-Stage HER2/neu Overexpressed/Amplified Breast Cancer  
Phase 3  
Beveloy Moy, MD, MPH  
617-643-1897 |

**GASTROINTESTINAL CANCERS**

| 06-248 | Study of Neoadjuvant Accelerated Short Course Radiation Therapy with Proton Beam and Capecitabine for Resectable Pancreatic Cancer  
Phase 1/2  
Theodore S. Hong, MD  
617-724-1159 |

| 2009P001471 | In Vivo Confocal Endomicroscopy (EUM) for Improved Diagnosis of Barrett’s Esophagus (BE) and Associated Neoplasia: A Multicenter Randomized Controlled Trial of Diagnostic Yield and Clinical Impact  
Phase 3  
William R. Brugge, MD  
617-724-0462 |

**GENITOURINARY CANCERS**

| 04-139 | A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Early Versus Standard Zoledronic Acid to Prevent Skeletal-Related Events in Men with Prostate Cancer Metastatic to Bone  
Phase 3  
Mattheow R. Smith, MD, PhD  
617-724-5257 |

| 09-285 | Multicenter, Single-Arm Study Evaluating Carboplatin/Gemcitabine in Combination with BSI-201 in Patients with Platinum-Sensitive Recurrent Ovarian Cancer  
Phase 2  
Michael J. Birrer, MD, PhD  
617-724-4800 |

| 08-331 | CALGB 10502: Dose Escalation Study of Bortezomib (IND#58443, NSC#681239) Added to Standard Daunorubicin and Cytarabine Therapy for Patients with Previously Untreated Acute Myeloid Leukemia (AML) Ages 60–75  
Phase 2  
Eyal C. Attar, MD  
617-726-8743 |

| 09-002 | Everolimus in Combination with Rituximab for Relapsed/Refractory Diffuse Large B-Cell Lymphoma  
Phase 2  
Jeremy S. Abramson, MD  
617-726-8743 |

| 08-032 | A Phase 1 Safety Study of LY2127399 in Combination with Bortezomib in Patients with Relapsed or Refractory Multiple Myeloma  
Phase 1  
Noopur Raje, MD  
617-726-0711 |

| 09-089 | Study of AZD2171 and Whole Brain Radiation Therapy in Patients with Brain Metastases from Non-Small-Cell Lung Cancer  
Phase 1  
April Eichler, MD  
617-726-7851 |
Confocal Laser Endomicroscopy Makes Possible In Vivo Diagnosis in Digestive Cancers

First, the endoscopist using the instrument must undergo training to perform the procedure. Mechanically, CLE does not differ substantially from conventional endoscopic techniques. However, endoscopists who are accustomed to seeing the GI tract as it appears to the naked eye must learn how to interpret the much higher resolution images they obtain during the procedure. Effectively, they must become well trained in histology to understand how to use the instrument appropriately. A collaboration with the Mass General Pathology Department is aimed at developing a histological image archive to help set these standards. In addition, CLE is still a new technology and a substantial investment, costing approximately $200,000 for the instrument alone, so it requires significant commitment from the institution.

Nevertheless, the potential advantages of CLE—particularly in terms of the speed of diagnosis and the reduction in the number of biopsies—are too great to ignore.

As a result, it is likely that CLE will eventually become a standard of care in GI surveillance and cancer detection, as well as in guiding endoscopic resection of early malignancies in the esophagus and throughout the GI tract. Mass General will continue to play a central role in advancing this field.

Currently, Mass General is participating in a consortium along with Johns Hopkins University, the University of Pennsylvania and Ralf Kiesslich, MD, chief of endoscopy at the University of Mainz, Germany, who pioneered the use of CLE in the GI tract. The consortium is working under a grant to evaluate the accuracy of CLE compared with traditional techniques. Ultimately, continued leadership by Mass General and others in this field through multicenter investigations such as this one will help promote more widespread application.

Announcing ADVANCES at the MASS GENERAL CANCER CENTER

Welcome to the first issue of ADVANCES at the MASS GENERAL CANCER CENTER, a new physician publication of the Massachusetts General Hospital Cancer Center. This newsletter will update you twice a year on how Mass General Cancer Center researchers and clinicians are helping to transform cancer care by approaching new thresholds in treatment that help us better understand the disease.

We hope you enjoy this first issue. If you would like to receive this publication by e-mail, please contact us at: MGHADVANCESinCANCER@PARTNERS.ORG.