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.
• 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 (GSK2118426) 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
continued from the previous page

Tumor Genotyping Brings Personalized, Targeted Therapies to Patients


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.

Selected References

Contributors

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