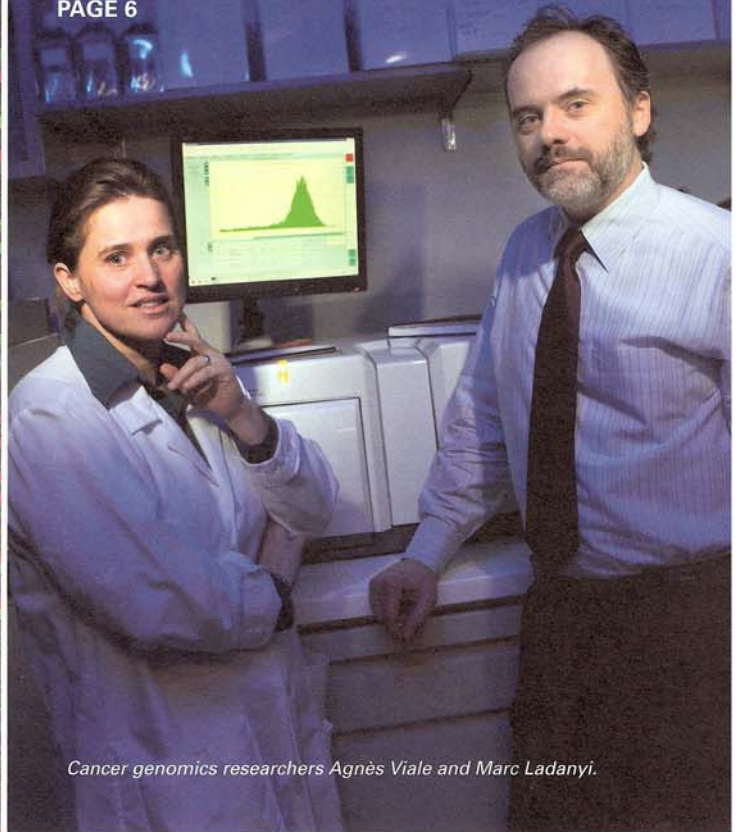


A reconstructed microarray image analyzing DNA from a glioblastoma tumor shows whether the number of copies of various genes has been gained (red) or lost (green), or has indeterminate status (blue). The array is designed to map one important type of genetic change that is found in this aggressive form of brain cancer, one of three cancers being studied at MSKCC as part of The Cancer Genome Atlas pilot project. (Image by Cameron Brennan, MD)

## PROBING THE GENOMIC BASIS FOR CANCER

*MSKCC Leads Efforts to Understand the Key Genetic Changes in Many Types of Cancer*

PAGE 6



Cancer genomics researchers Agnès Viale and Marc Ladanyi.

**PLUS** CANCER RISK SHOWN TO VARY WIDELY AMONG CARRIERS OF *BRCA1* AND *BRCA2* GENE MUTATIONS **3**  
INTERVIEW WITH STEM CELL BIOLOGIST LORENZ STUDER **4** MSKCC ETHICS COMMITTEE ROLE EXPANDS **10** MSKCC  
SOCIETY DISTRIBUTES GIFTS TO PATIENTS **14** THREE MSKCC FACULTY NAMED TO ENDOWED CHAIRS **16**



3



4



10



14



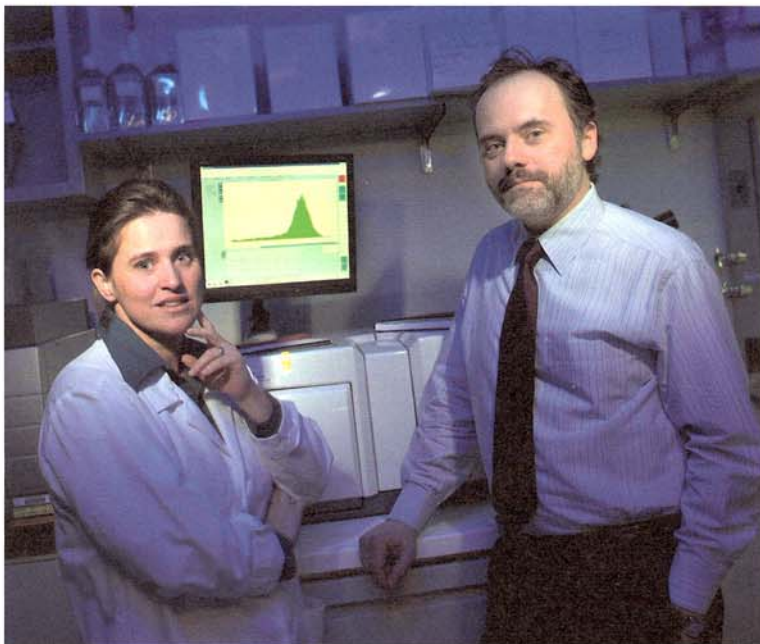
16



Memorial Sloan-Kettering  
Cancer Center

## Probing the Genomic Basis for Cancer

*Memorial Sloan-Kettering Is Leading Efforts to Understand the Key Genetic Changes in Many Types of Cancer*



*Agnès Viale and Marc Ladanyi collaborate with many members of MSKCC's research community on a variety of projects related to cancer genomics. Here they are pictured with a 454, a so-called next-generation DNA sequencer, which is changing the way investigators learn about tumors and their genetic defects.*

Imagine a day when a patient could have a biopsy taken from a tumor, have the entire genome of the tumor characterized, and then be treated with drugs and other therapies that are tailored to the exact genetic changes present in the tumor cells. The scenario is not science fiction, but a goal that investigators at MSKCC and other institutions have recognized as one of the most promising avenues for treating cancer.

**T**he future of oncology is going to be in large part a drive toward more personalized medicine, which is more effective and has fewer side effects," said medical oncologist William Pao. "It would be similar to the way we treat infections today: We take cultures, identify the organism causing the infection, and figure out exactly which antibiotic to give. We can now envision something similar in cancer: obtain a tumor sample, identify the molecular lesions causing that tumor, and give specific targeted agents to kill it," said Dr. Pao, who is a member of

the Human Oncology and Pathogenesis Program (HOPP).

"As we learn more about the genetic abnormalities in human cancers, we will find there are many different subtypes among tumors that, using conventional pathology techniques, might look quite similar," said molecular pathologist Marc Ladanyi. "However, more detailed analysis will reveal subsets of a certain cancer that can benefit from a particular drug. Even if the subgroup doesn't immediately connect to a known drug, it may help us determine which tumors are likely to behave more aggressively and which patients are therefore candidates for more intensive

conventional therapy." Dr. Ladanyi is a HOPP member, and he leads the Center's contribution toward a nationwide effort to catalog comprehensively the genetic changes involved in human cancer. (See page 8.)

For a few types of cancer, this concept is starting to become a reality. Several years ago, Dr. Pao and MSKCC President Harold Varmus, as members of an MSKCC team called the Lung Cancer Oncogenome Group (LCOG), helped determine molecular reasons why some lung adenocarcinomas (a subtype of non-small cell lung cancers) are either sensitive or resistant to the targeted therapies gefitinib (Iressa®) and erlotinib (Tarceva®).

## Using next-generation sequencing, investigators are able to sequence each individual DNA molecule separately, rather than combining the sequences of all fragments, as older sequencing machines do.

The team found that highly sensitive tumors harbor mutations in a gene called *EGFR*, whereas resistant tumors often contain mutations in a gene called *KRAS*. About 10 percent of patients with lung adenocarcinomas have *EGFR* mutations, and about one-quarter of lung adenocarcinomas have *KRAS* mutations. Based on these findings, testing for these mutations has become a part of routine care for lung cancer patients at MSKCC to help guide treatment decisions regarding the use of targeted therapies.

The knowledge gained from studying these lung cancer drugs — along with the success of other targeted therapies — illustrates why this area of research is becoming so important. Currently, for most types of cancer, there is still much to be learned about their molecular characteristics, including the genetic changes that cause them to form, grow, and spread (metastasize) and that make some tumors more aggressive and resistant to therapy than others. Identifying a genetic change that leads to the formation of a certain tumor, however, does not necessarily mean there will be compounds available today to counteract

the defect. But identification of these changes could spur the development of such agents.

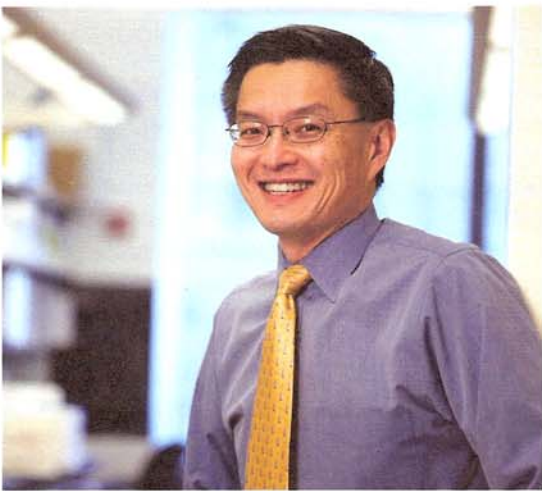
One of the strengths that has put MSKCC at the forefront of the search for genomic changes in cancer is its extensive tumor bank, directed by molecular pathologist and HOPP member William L. Gerald. As early as the 1980s, MSKCC surgeons, led by then-Department of Surgery Chair Murray F. Brennan, began saving thousands of tumor specimens collected from patients with all different types of cancer. These specimens are stored anonymously to protect patient confidentiality but are linked to clinical information about the patients, such as whether they responded to certain treatments, where the cancer metastasized (if it did), and whether the patients were ultimately cured. The tumor bank already has contributed to significant findings, including work by cancer biologist Joan Massagué pinpointing genes that mediate the metastasis of breast cancer to the lungs and bones.

Another resource that gives Memorial Sloan-Kettering a distinct advantage in the field is its Genomics Core Laboratory and its DNA Sequencing Core Laboratory. The latter recently received a huge boost in sequencing capabilities through the purchase of an instrument called a 454 — a “next

generation” DNA sequencer. Both facilities are led by Agnès Viale. The genomics lab analyzes tumor cells using various microarrays (also called “chips”), which can monitor thousands of genes at the same time to look for changes in the number of copies of a gene or determine whether a gene is expressed, for example. Data from these microarrays might explain differences between tumor cells and normal cells or distinguish different subtypes of the same cancer.

Using next-generation sequencing, investigators are able to sequence each individual DNA molecule separately, rather than combining the sequences of all fragments, as older sequencing machines do. “What this means,” explained Dr. Viale, “is that if only 1 percent of cells in a tumor have an additional mutation that confers resistance to a drug treatment, we can find it. That small number of cells is what likely would be responsible for disease recurrence, and up until now we had no way to detect that rare additional mutation. This technology is beautiful, absolutely cutting edge.”

Recently the Center’s tumor analysis capabilities were further enhanced by the creation of the Geoffrey Beene Translational Oncology Core Facility, under the leadership of Adriana Heguy. The facility, which is part of HOPP, extracts DNA from patient tumor samples, prepares the DNA for sequencing, and then outsources the material to high-volume sequencing facilities. It also performs mutation detection and data analysis using software designed by MSKCC’s bioinformatics team



*William Pao's research is focused on the genetic changes present in lung cancer cells.*

# MSKCC Plays Important Role in National Cancer Genome Discovery Efforts

In 2005, 15 years after the start of the Human Genome Project and two years after the full human genome sequence was completed, the National Cancer Institute and the National Human Genome Research Institute (two components of the National Institutes of Health) announced the launch of the pilot phase of The Cancer Genome Atlas. Known as TCGA—the initials also represent the four chemical building blocks in DNA (thymine, cytosine, guanine, and adenine)—the project seeks to accelerate the understanding of the molecular basis of cancer through the application of a variety of genome analysis technologies.

MSKCC President Harold Varmus was director of the NIH during much of the time that the Human Genome Project was under way. More recently, he also was a member of the working group that recommended the formation of a project to analyze the human genome comprehensively in many types of cancer.

“The cancer genome project was conceived to create a catalog of every type of genetic change that can lead to cancer, and to link these changes to clinical data,” Dr. Varmus said. “As with the Human Genome Project, all of the information is being placed in a free public data repository so that any researcher worldwide can access it.”

TCGA is initially focusing on three types of cancer that are especially difficult to treat: ovarian cancer; squamous cell non-small cell lung cancer; and glioblastoma, the most common and aggressive type of primary brain tumor. The goal is to study 500 samples from each tumor type. The first phase of the pilot project must meet clear milestones and goals before a large-scale effort for additional types of cancer is initiated.

Cancer Genome Characterization Centers (CGCCs) were established at seven institutions around the country to study different types of genetic changes in the same tumor

samples, and Memorial Sloan-Kettering was funded to house one of these CGCCs, under the leadership of molecular pathologist Marc Ladanyi. The CGCC is located in MSKCC's Genomics Core Laboratory.

“The idea is to do a definitive, comprehensive, fully integrated profiling of all the genomic alterations in these samples,” Dr. Ladanyi said. “We can't anticipate what genomic profiling might look like in the future, but today this would be the state-of-the-art, most detailed, exhaustive view of all the genetic alterations that are present in these three cancers.”

The CGCC at MSKCC is one of four centers that are studying changes in the number of copies of genes — whether particular bits of the genome are gained (have extra copies) or have been delet-



ed (have lost copies) in a given tumor sample. “When you do this in hundreds of samples of the same cancer,” Dr. Ladanyi explained, “you see that there are characteristic genetic changes that occur over and over again, in tumors from different patients.” The other centers looking at copy numbers are using different approaches and in some cases different technologies. “The idea is that each technology has its own advantages and disadvantages, and by using several methods to measure the same thing, you can get the most accurate picture of this class of genetic

abnormalities,” Dr. Ladanyi said.

Other characterization centers are looking at additional aspects of genetic changes in tumors, including patterns of gene expression, changes in microRNAs (which regulate gene expression), and alterations called DNA methylation (a modification that does not change the gene sequence but alters expression of neighboring genes). There are also three Genome Sequencing Centers that use high-throughput methods similar to those used for the Human Genome Project, and a bioinformatics center to analyze all of the data that is being generated.

Some members of the research community have criticized TCGA's approach, questioning whether it is the most efficient way to find genetic changes related to cancer and expressing concern about the cost of the project in relation to the amount of data it is likely to generate. One alternative that's been suggested is a so-called func-

**“Ultimately, the more data we have about all the genes that play a role in cancer, the faster we will be able to develop drugs that will benefit patients.”**

**MSKCC PRESIDENT HAROLD VARMUS**

tional genomics approach, which looks for normal cellular pathways that play a role in cancer by using molecules called short hairpin RNAs (which are engineered to target and suppress specific genes) and studying the response of cancer cells.

“The various approaches to learning more about cancer genes complement each other,” said Dr. Varmus. “Ultimately, the more data we have about all the genes that play a role in cancer, the faster we will be able to develop diagnostic procedures and drugs that will benefit patients.”

and maintains a centralized database.

“The goal of our core is to identify novel mutations in different cancer types, as well as to characterize the samples for known mutations that can ultimately translate to new options for patient care,” Dr. Heguy said. “Our laboratory has been in operation for less than six months, and we are already collaborating with a large number of researchers across MSKCC who are utilizing our technology in diverse tumor types.”

The Center’s research on genomic changes in lung adenocarcinoma is moving forward. A multidisciplinary team of clinicians and basic scientists, led by medical oncologist Mark G. Kris, has received a large grant from the National Institutes of Health to expand the work started by the LCOG. Members of the team are working on a variety of projects, including the development of newer targeted therapies; the search for additional genes that cause the formation of lung cancer, as well as genes that mediate the metastasis of lung

Members of MSKCC’s lung team also have participated in the Tumor Sequencing Project (TSP), a federally funded, multi-institutional collaboration that is seeking to map genomic changes in lung adenocarcinoma. In November 2007, the TSP team published a paper in *Nature* identifying more than 40 previously unknown genomic regions that are frequently altered in lung adenocarcinoma. The paper was based on a different approach than the one used by LCOG, a technique called single nucleotide polymorphism (SNP, pronounced “snip”) profiling, which allows investigators to look for changes in the number of DNA copies that occur in tumors on a genome-wide level.

Another type of cancer on which the Center is focusing its genomics efforts is soft tissue sarcoma, a broad category of rare but aggressive tumors that affect tissues such as fat, muscle, and nerves. Through a joint project with the Broad Institute of Harvard and MIT, now



*Samuel Singer is working to characterize the genetic changes that occur in the most common types of soft tissue sarcoma.*

to target with new therapies,” said surgical oncologist Samuel Singer.

“We’re analyzing patient samples to look for genes that are altered or amplified to see if they promote sarcoma formation,” he elaborated. So far, the team has studied more than 200 sarcoma samples across seven subtypes for changes in the number of gene copies and changes in gene transcription.

Investigators have sequenced more than 225 genes in 48 tumor samples and have identified mutations that may serve as potential therapeutic targets. They plan to expand the mutational analysis to additional genes and additional sarcoma samples. “Now we need to determine which mutations are the most significant, in terms of those that can be targeted with drugs, as well as those that can teach us more about how tumors behave,” he said.

In collaboration with several clinical departments at MSKCC, Dr. Gerald has begun a similar project with prostate cancer. The group is studying approximately 250 genes in 200 prostate tumor samples, and data generation is expected to be completed later this spring. Likewise, a project initiated by immunologist Alan N. Houghton seeks to characterize genomic changes that occur in melanoma cell lines.

“We have the expertise and resources at MSKCC to make an important contribution to the cancer genome efforts,” Dr. Ladanyi said. ⚙

For most types of cancer, there is still much to be learned about their molecular characteristics. Identification of genetic changes in tumors could spur the development of new targeted therapies.

cancer to the brain; and the study of genes related to disease persistence.

“Disease persistence means that even in patients for whom targeted therapies like gefitinib and erlotinib induce massive tumor shrinkage, you never get rid of all the cancer,” explained Dr. Pao. “So we’re trying to figure out why these cells persist.”

funded by a grant from the Starr Cancer Consortium, MSKCC scientists are characterizing the genetic changes in several subtypes of soft tissue sarcoma, which together make up about three-quarters of all cases. “Most types of sarcoma are not sensitive to traditional chemotherapy, and that is why we set out to look for molecular changes that we might be able