
Memorial Sloan Kettering Cancer Center

Michael Berger, PhD (left), Agnès Viale, PhD, and David Solit, MD, will lead Memorial Sloan Kettering's Center for Molecular Oncology.

and many others where it is not currently part of routine care," he says.

The center plans to genetically profile the tumors from every patient with metastatic disease at MSKCC, totaling more than 10,000 patients each year. Solit says the long-term goal is to also analyze the tumors of patients with earlier-stage disease.

Hundreds of tumors have already been analyzed using a test that can screen for mutations in 341 cancer-associated genes. Even in cancers for which genetic profiling is now standard, only a handful of genes are typically sequenced, Solit says.

Some patients are then matched with approved cancer drugs that target the mutations fueling their tumors. Others are enrolled in clinical trials called basket studies that use agents targeted to a specific mutation, regardless of cancer type. Basket studies allow patients with a driver mutation that has not yet been studied in their tumor type to receive a targeted agent.

The center has several basket studies currently under way, Solit notes. One is testing neratinib (PB272; Puma Biotechnology) in patients with a *HER2* or *HER3* mutation, while another is using vemurafenib (Zelboraf; Genentech) in patients with a *BRAF* mutation. "We have already observed some dramatic responses on these basket studies," he says.

Another CMO initiative uses MSKCC's extensive collection of tumor samples to discover new mutations and drug targets. Researchers are, for example, retrospectively analyzing tumors of exceptional responders, patients who had a sustained response to a treatment in a clinical trial in which nearly all other participants did not.

Solit recently discovered that a mutation in *TSC1* was responsible for an advanced bladder cancer patient's remarkable response to everolimus (Afinitor; Novartis), a targeted drug approved for kidney cancer. Solit is now finalizing plans for a basket study to test everolimus in patients whose tumors test positive for a *TSC1* mutation.

MSKCC is not alone in its quest to bring the genomic revolution into patient care. Earlier this year, San Diego, CA–based Human Longevity Inc. launched a similar effort to understand the molecular underpinnings of cancer and other diseases, as did the Broad Institute of MIT and Harvard in 2004.

What sets the CMO apart is its ability to apply molecular insights in real time to guide clinical practice. "Most of the sequencing that's been reported to date has been performed as part of retrospective studies," Solit says. "The CMO will use next-generation methods to prospectively profile patients who are actively receiving treatment in the clinic now." ■

Glioma a Downside of Long Telomeres

Long telomeres may protect against cardiovascular disease and promote longevity. They may also raise the risk of glioma, a new study in *Nature Genetics* reveals (Nat Genet 2014 June 8 [Epub ahead of print]).

In the popular view of telomeres, longer is better. Indeed, studies have linked truncated telomeres to reduced life span and increased vulnerability to heart disease and stroke. Research on the relationship between telomere length and cancer risk, however, has provided mixed results. For some cancers, including pancreatic and lung cancers, short telomeres correlate with greater susceptibility. For other cancer types, such as colon and breast, the opposite holds true.

Lead author Kyle Walsh, PhD, a genetic epidemiologist at the University of California, San Francisco, and colleagues weren't looking for a telomere connection when they began searching for new single-nucleotide polymorphisms (SNP) associated with glioma. The researchers first searched out SNPs in genotype data from 1,013 glioma patients and 6,595 healthy individuals. They then verified their findings by analyzing an additional 631 patients and 1,141 controls from independent sources. Most of the patients in both groups suffered from glioblastoma, the most common and most aggressive form of glioma.

The team found that a SNP with a large effect on glioma risk lies near the gene *TERC*, which encodes the RNA component of telomerase, the enzyme that lengthens telomeres. They also analyzed two previously identified SNPs that are located in the genes *TERT* and *RTEL1*, which encode proteins that spur telomere extension. Both SNPs showed a robust association with glioma risk.

To determine the relationship between these SNPs and telomere dimensions, the scientists turned to a 2013 genome-wide association study on leukocyte telomere length in more than 37,000 people of European ancestry. The SNP residing near *TERC* and the SNP in *TERT* showed a strong correlation with longer telomeres. In contrast, the SNP in *RTEL1* was moderately associated with shorter telomeres.

The team also found that other glioma-linked genes, such as *EGFR,* didn't correlate with telomere length. That finding suggests there are multiple mechanisms for glioma development, not all of which involve telomeres.

"We have evidence that for glioma, longer telomeres are a risk factor or are a biomarker for risk," says Walsh. However, researchers did not measure telomere length in glioma patients. If long telomeres do promote the development of glioma, how they accomplish it is unclear.

Walsh notes that *TERT* variants turn up in many kinds of cancer. However, researchers have uncovered cancer-associated variants of *TERC* only in colon cancer, multiple myeloma, and glioma. This similarity between disparate cancers suggests they have a common mechanism that might depend on telomere length, he says. ■

Choosing Biomarkers Wisely

The explosion of genomic data means that scientists who are planning clinical trials can consider more molecular information than ever before. An international team of experts has

drawn up a new risk-management strategy to help cancer researchers incorporate biomarkers into clinical trials and avoid potential pitfalls.

Five experts from the European Organization for Research and Treatment of Cancer (EORTC), the NCI, and the National Cancer Research Institute in the UK decided to draw up the recommendations because they all were seeing the same problems with biomarker use in clinical trials. "We want to raise key points to the principal investigators who design and conduct the trials," says co-author Jacqueline Hall, PhD, former head of translational research at the EORTC and coordinator of the working group.

The authors advocate a risk-management approach because which biomarkers a clinical trial includes and how they are measured can have an impact on patients' health, the trial's outcome, and even the future usefulness of the biomarkers. For example, relying on a poorly chosen biomarker could mean that some patients receive inadequate treatment. If the biomarker is uncommon, the trial could languish because of the difficulty of recruiting subjects.

The recommendations, which the authors describe in *The Lancet Oncology*, emphasize a step that seems self-evident but that many researchers skimp on: planning (Lancet Oncol 2014;15:e184–93). "The main difficulty generally is that people don't start early enough, and they don't begin with the end in mind," says study co-author Tracy Lively, PhD, deputy associate director of the Cancer Diagnosis Program at the NCI.

Lively and her colleagues advise researchers who design clinical trial protocols to focus on issues like the justification for a particular assay, the qualifications of the lab that will conduct the tests, and the experience of the biobank that will hold the samples. To make good decisions about biomarkers, the authors note, clinical researchers need to consult with other experts, including pathologists and statisticians.

Once the trial has begun, the authors add, researchers need to continue their efforts, monitoring assay performance and sample banking, for instance. Once the trial concludes, they must still deal with issues like access to banked samples.

Although following the recommendations will increase the amount of time and intellectual effort that researchers have to put into planning clinical trials, doing so is as important as setting appropriate drug doses and treatment schedules, says Lively.

Hall adds that she and her co-authors hope the recommendations will be adopted by agencies that review proposed clinical trials and that they'll spur cancer researchers to improve the use of biomarkers. "It's a call to the community to get involved," she says. ■

T-Cell Therapy for Cervical Cancer

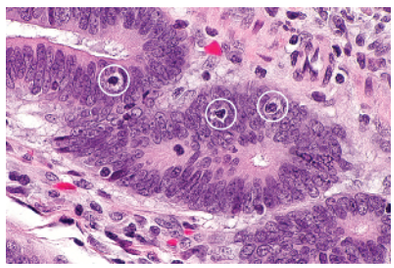
Pitting the immune system against human papillomavirus (HPV) may be a promising strategy for treating women with advanced cervical cancer, according to a small, federally funded phase II study. The results were reported by Christian Hinrichs, MD, an assistant clinical investigator at the NCI in Bethesda, MD, during the American Society of Clinical Oncology's Annual Meeting in Chicago, IL, May 30–June 3.

More than 4,000 women in the United States die from cervical cancer each year. Their median survival is 13 months on chemotherapy and 17 months if bevacizumab (Avastin; Roche) is added.

In this study, researchers used an approach called tumor-infiltrating lymphocyte (TIL) therapy, which has had some success in treating metastatic melanoma and B-cell malignancies. They isolated T cells from patients' tumors and selected those with reactivity with HPV oncoproteins E6 and E7. The TILs were then expanded and infused back into each patient, along with IL2, a T-cell growth factor.

All 9 patients in the study had either HPV-16 or HPV-18 infections, which together cause about 80% of cervical cancers. Two women with widespread metastases and chemotherapy-resistant disease achieved complete and lasting remissions of 11 and 18 months, respectively, at the time of analysis.

"This provides the first proof-of-principle that HPV-targeted TIL therapy can induce regression in cervical cancer," Hinrichs said.



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Researchers are testing an approach called tumor-infiltrating lymphocyte (TIL) therapy in various cancers, including melanoma, cervical cancer, and colorectal cancer (above). TILs are circled in white.

Hinrichs cautioned that HPV-TIL therapy "is still considered experimental and associated with significant side effects," mainly bone marrow suppression and an increased infection risk due to neutropenia. However, he added, "these toxicities are fully reversible, and it's a one-time treatment."

One challenge associated with personalized immunotherapy is that the antigens targeted by T cells often exist in cells elsewhere in the body, not just in cancer cells. However, the E6 and E7 viral oncoproteins make "extremely attractive targets," said Hinrichs, because they are expressed only in infected tissue.

The study's results are limited but striking. "These are young women who failed multiple attempts at tumor-directed therapy," said Steven O'Day, MD, an immunologist at the University of Southern California's Keck School of Medicine in Los Angeles. "By ignoring the cancer cells and, instead, activating T cells, we've provoked a few durable responses in a disease generally not seen well by the immune system."

Hinrichs is now exploring why this therapy was highly effective in only some women. "The next step, to better clarify the response rate, is to treat more patients—we're expanding to 35," he said. "We've also added a patient cohort with noncervical, HPV-positive cancers to this study." ■

Study Supports Routine Lung Tumor Genotyping

Using multiplex genotyping to identify oncogenic drivers and match patients to individualized therapies has the potential to transform drug