

PEOPLE



St. Jude Children's Research Hospital

James R. Downing, MD, was appointed CEO of St. Jude Children's Research Hospital in Memphis, TN, effective July 15. He succeeds William E. Evans, PharmD,

who is retiring from the position after 10 years to pursue pharmacogenomics research full time.

Downing joined St. Jude in 1984 and became its scientific director and executive vice president in 2004 and deputy director in 2011. Richard J. Gilbertson, MD, PhD, who directs the institution's cancer center, has now assumed the role of scientific director as well.

A world leader in pediatric cancer research, Downing studies the genetic basis of cancer and has overseen the Pediatric Cancer Genome Project, which produced groundbreaking discoveries for four types of brain tumors, four subtypes of childhood leukemia, and other cancers.



E. Cantor-Smith

James P. Allison, PhD

The first Tang Prize for Biopharmaceutical Science has been awarded to **James P. Allison, PhD**, chairman of immunology at The University of Texas MD Anderson Cancer Center, and **Tasuku Honjo, MD, PhD**, professor of immunology and genomic medicine at Kyoto University in Kyoto, Japan, for their research leading to cancer immunotherapy. Established in

2012, the biennial prize provides a cash award of about \$1.3 million and a research grant of about \$350,000.

Allison was one of two scientists who identified CTLA-4 as an inhibitory receptor on T cells, and he developed an antibody to block it. An FDA-approved drug based on his antibody (ipilimumab; Yervoy) is now used to treat melanoma. Honjo discovered PD-1, another immune checkpoint receptor on T cells. PD-1 inhibitors are under development for the treatment of cancer.



E. Cantor-Smith

Tasuku Honjo, MD, PhD

NIH to Require Both Sexes in Preclinical Studies

The NIH announced a new policy in May that will require federally funded scientists to include both males and females in cell and animal studies. The requirement will affect some of the more than 300,000 researchers awarded competitive grants each year by the NIH, which invests about \$30 billion annually in medical research.

In a commentary published in *Nature* explaining the policy, Francis Collins, MD, PhD, director of the NIH, and Janine Clayton, MD, director of the agency's Office of Research on Women's Health, advise scientists to include more female lab animals and cells in their experiments. "The over-reliance on male animals and cells in preclinical research obscures key sex differences that could guide clinical studies. And it might be harmful: women experience higher rates of adverse drug reactions than men do," they write (*Nature* 2014;509:282-3).

One reason cited for the avoidance of female animals is an unwarranted concern that reproductive cycles and hormone changes would confound study results. Another reason is decades of laboratory conventions that have relied on male-only models.

Cancer researchers may be conducting gender-biased preclinical studies, but not in the way suggested by the NIH commentary, says Norman Sharpless, MD, director of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center in Chapel Hill and co-lead of UNC's Mouse Phase 1 unit.

"I do not believe they considered studies in oncology, where we use female mice considerably more often than male rodents. So it's a valid point both ways—to use only males or only females is not representative," he says.

In Sharpless's lab, where mice are used to study cancer and aging, female mice considerably outnumber male mice. The reason is cost: Male mice are more likely to fight, so it's cheaper to use female mice that can be housed long-term at greater density, Sharpless says.

The NIH will roll out the new policy in phases beginning in October 2014.

Researchers seeking NIH grants must report their plans for including and comparing male and female animals or cells unless their research qualifies for an exception, such as research on reproductive organs. Reviewers will consider those plans when awarding grants, and the NIH will monitor whether grantees comply with such plans.

The agency also says it will work closely with publishers of scientific journals to encourage reporting of sex and gender analyses from NIH-funded research.

To help offset the added expense of studying both sexes, Sharpless predicts cancer researchers may use smaller cohorts of male and female animals. "If males and females can be pooled in the analysis—and often they can be—then the statistical power will not be decreased," he says.

Smaller sample sizes would however make studies less powerful if males and females are affected differently, Sharpless adds. "If sexes can't be pooled, we should be studying females and males independently, which is exactly the point of the policy."

Sharpless says his main concern is an overly heavy-handed enforcement of the new policy. "I'm worried someone will have a proposal that has brilliant science, but they won't get funded because they forgot to include a paragraph in their grant about inclusion of males and females," he notes. "Having said that, this is still a good idea." ■

MSKCC Launches Center for Molecular Oncology

Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, launched in May the Center for Molecular Oncology (CMO), a program its leaders say will deliver personalized treatment options to more cancer patients.

Established with a \$100 million gift from Marie-Josée and Henry R. Kravis, the CMO expands the ability to perform genetic profiling in the clinic beyond cancers such as lung and colon for which profiling is standard of care, says CMO director David Solit, MD. "The center will allow us to offer genetic testing for cancers such as bladder, prostate, ovarian, endometrial,



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