RESEARCH PROFILE

Alea Mills

On a cold Sunday afternoon many months ago, CSHL Professor Alea Mills did what many scientists do when facing a grant application deadline — she put off writing and escaped to the lab. A new experiment had just reached a critical stage and she was eager to check on the results, which happened to be a newborn litter of genetically engineered mice.

Throughout her career, Mills has strived to understand human disease by modeling it in mice. When programmed to carry the same genetic abnormalities found in patients with a disease, mice not only become an extraordinarily powerful source of information about the genetic and molecular forces that drive that disease, they can also stand in as test subjects in the development of new diagnostic methods, novel therapies, and better drugs.

Although Mills cut her investigative teeth building mouse models of cancer, the mice that claimed her attention that day had been created with a different human condition in mind — autism. In 2007, Dr. Michael Wigler, also a professor at CSHL, had discovered a link between autism and a small section of chromosome 16. Called 16p11.2, this region has since gained notoriety as a genetic hotspot with links to developmental delay, mental retardation, and schizophrenia.

While about 1% of children with autism have one less copy of 16p11.2 — humans normally have two copies, one inherited from each parent — duplications of this segment have also been found in a few autism cases and more commonly in schizophrenia. But even as these details emerged, one crucial question remained unanswered: were the 16p11.2 copy number variations (CNVs), as these deletions and duplications are called, actually causing autism and the other syndromes?

A "eureka!" moment for autism research

One way to find out would be to check whether clipping out the mouse equivalent of human 16p11.2 or adding more copies of it causes autism-like features to appear in mice. With financial support from the Simons Foundation Autism Research Initiative, Mills used her expertise in a technique called chromosome engineering to do just that.

Invented in the mid-1990s by Mills' postdoctoral mentor Dr. Allan Bradley, the technique involves making a series of precise molecular maneuvers in mouse embryonic stem cells growing in a dish. The cells are then used to create mice that can pass on the engineered chromosome to their progeny. Mills, who helped develop some key shortcuts of this process while in Bradley's lab, had successfully used it before to create cancer and schizophrenia models. But she also knew that "there were no guarantees that we would see anything interesting" this time.

That wintry afternoon, however, one look at the mice gave Mills a "eureka!" moment. The mice that carried one less copy of 16p11.2 "behaved completely different" from the normal mice, which had both copies, and the mice that had an extra copy. Exactly how different would become apparent over the next few months, when Postdoctoral Fellow Dr. Guy Horev set up a one-of-a-kind infrared camera system to track and quantify mouse behavior.

The deletion caused mice to have many of the features used to diagnose autism in children: extreme hyperactivity, difficulty adapting to new environments, sleeping deficits, and restricted, repetitive behaviors. MRI scans of the animals' brains showed that eight different regions of the brain were larger than they should be.

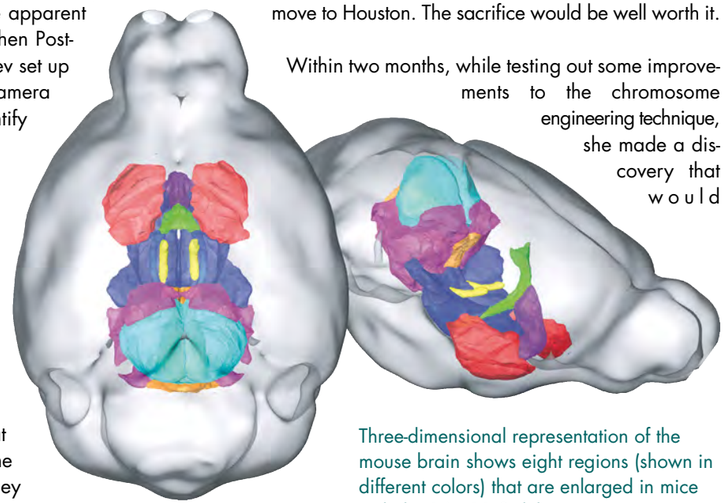
Mills' presentation of these results at a conference at MIT in December 2010 created a huge buzz among the experts that was amplified in the news media when her study was published this October. In addition to all that they might reveal about the biology of autism, the mice can guide Mills and others toward diagnostic markers for autism, and perhaps even point them toward the best mode of treatment — advances that can, among other things, transform the current discussion about autism in society.

Big risks, bigger pay-offs

"If you don't take on high-risk projects that have a chance for a big pay-off, then you're just going to make small, incremental discoveries forever," says Mills. This bold view has served her well during her career, starting with graduate school at University of California, Irvine. There, Mills convinced her advisor Dr. Eric Stanbridge — one of the first proponents of the existence of tumor suppressors, proteins that put the brakes on cancer — to let her develop cancer models using gene-targeting approaches "that no one at the university had tried before."

This experience led to a postdoctoral job offer from Bradley, then based at Baylor College of Medicine in Houston. Mills jumped at the chance to learn from the guru of mouse modeling, even if it meant giving up an enviable California lifestyle on her beloved sailboat to move to Houston. The sacrifice would be well worth it.

Within two months, while testing out some improvements to the chromosome engineering technique, she made a discovery that would



Three-dimensional representation of the mouse brain shows eight regions (shown in different colors) that are enlarged in mice with the 16.p11.2 deletion.

A chromosome-engineered mouse.

open a whole new field of cancer research. That discovery was the *p63* gene, a relative of the famous *p53*, the powerful "master" tumor suppressor. The *p63*-deficient mice engineered by Mills revealed the gene's necessity for the correct formation of limbs and epithelial tissue.

Since her appointment to the faculty at CSHL in 2001, Mills has uncovered *p63*'s role in slowing aging and its ability to control cellular senescence, a form of growth arrest that guards against tumor formation. Her more recent work showing that *p63* produces some protein versions, or isoforms, which suppress cancer and others that promote it, has steered the field in new directions. Earlier this year, her team showed how one of these isoforms stimulates a specific population of stem cells in the skin to form carcinomas, a deadly form of skin cancer.

A second important cancer-related gene that Mills has discovered is one that others had hunted for unsuccessfully for more than 30 years. Looking for this "holy grail" of tumor suppressors, a gene that was known to be missing in many human cancers, was deemed so challenging that Mills couldn't get independent funding to pursue it. But with starter funds from CSHL, where senior staff including President Bruce Stillman firmly backed her work as well as her chromosome engineering skills, Mills's team succeeded in identifying *CHD5* as the elusive tumor suppressor.

Her subsequent work, defining *CHD5*'s role as a circuit breaker that controls the tumor-preventing power inside a cell, continues to have a major impact in the cancer field. CHD5 status — the amount of CHD5 protein a patient has — is now appreciated as a predictor of treatment outcome for cancer patients.

"Because of its supportive atmosphere and its lack of bureaucratic shackles, CSHL is probably the only place where I could have succeeded with this project," says Mills, who encourages a similar free-enterprise type of work ethic within her own group. Her approach seems to have paid off.

At her team's Christmas party last year, postdoc Guy Horev, the behavior analyst working on the autism project, and graduate student Assaf Vestin, working on *CHD5*'s role in living mice, surprised her with a present — the results of an experiment that they had jointly decided to set up. Horev had used his unique camera system to record the *CHD5*-deficient mice. The footage showed some striking, completely unexpected behaviors, hinting at an unexpected link between a cancer-related gene and a neurological syndrome. These are the kinds of paradigm-shifting results spurred by out-of-the-box approaches, and Mills is excited about where this might lead. "When there are no constraints and people work together, research leaps ahead," she says.

Hema Bashyam

A passionate educator

In addition to graduate and postdoctoral researchers, Mills also regularly mentors the youngest scientists at CSHL — high school seniors selected by the Lab's Partners for the Future (PFF) program to spend part of their school year in one of the 50 labs on campus. Mills, who finds the Partners' enthusiasm for learning lab work infectious, is keen to "give them the opportunity to make real contributions to research and advance it."

She also co-teaches a class called Scientific Exposition and Ethics at CSHL's Watson School of Biological Sciences. "We want the students to realize that understanding how their work impacts society and being able to explain their science to the world-at-large in an understandable way is just as important as doing great experiments," she says.

Mills and high school senior Victoria Lellis of Harborfields High School set up an experiment.