

## Bedside Inspiration

A NEW GROUP OF HHMI INVESTIGATORS TACKLES BASIC RESEARCH QUESTIONS BY SPLITTING TIME BETWEEN THE LABORATORY AND THE CLINIC.

A 1992 ENCOUNTER WITH A TODDLER WHOSE EYES WERE FROZEN in a downward gaze led pediatric neurologist Elizabeth C. Engle to discover a trove of previously unrecognized congenital disorders. Over the last 16 years she has explored the clinical and genetic features of these syndromes, caused by errors in brain-stem motor-neuron development, which rob patients of normal control of their eye movements.

Engle's commitment to both patient care and research was just what HHMI had in mind when she and 14 other patient-oriented researchers were selected as HHMI investigators last fall. The new HHMI investigators represent 13 institutions from across the United States. In all, 40 finalists were chosen from among 242 applicants, and 15 were selected to become HHMI investigators. The Institute has committed approximately \$150 million to their first term of appointment.

These physician-scientists "have demonstrated extraordinary creativity and innovation," says Institute President Thomas R. Cech, and they "are changing the way we think about—and treat—a variety of diseases."

### *Toward a Treatment for the Eyes*

When Engle first met her young patient at Children's Hospital Boston, she simply wanted to diagnose the child's problem. Ophthalmologists thought it was congenital fibrosis of the extra-ocular muscles, a rare birth defect generally believed to result from rigid scar tissue replacing the muscles that pull the eyeball down. Engle agreed that the patient fit the clinical description for this disorder; however, she was left wondering if his eye movement disorder might result from an error in neuron development rather than primary muscle fibrosis.

Learning that the boy's extended family had 20 similarly affected members, Engle worked with the Children's Hospital laboratories of Alan Beggs and HHMI investigator Louis Kunkel to conduct a systematic study that combined clinical and genetic analyses.

The family would notify her when an elderly relative died of other causes, and she would then examine the deceased's

eyeballs and their surrounding muscles. Engle found that while the muscle that pulled the eye down was defective, it was not a mass of scar tissue; the muscle was simply contracted, keeping the eyeball pointed at the ground. Moreover, the muscles that pulled the eye upward were absent altogether, and so was the cranial nerve connecting them to the brain stem. Muscle fibrosis was not the correct diagnosis after all.

Looking for case reports and families with similar conditions, Engle pored over journals and contacted clinicians around the world, ultimately locating more than 700 families affected by this newly described disorder or others related to it. Then, using DNA linkage and mutation analysis, she identified the genetic causes for a series of these disorders, each of which perturbed development of one or more cranial nerves. The syndromes, now termed "congenital cranial dysinnervation disorders" (CCDDs), include Duane syndrome, horizontal gaze palsy, Moebius syndrome, and congenital ptosis.

Engle and her colleagues found that CCDDs were caused by two kinds of mutations—in genes that encode transcription factors crucial to cranial motor-neuron development, and in genes for proteins that help growing nerve axons connect to appropriate targets. The mutation passed down to some members of the original toddler's family, for example, scrambles the gene for a particular kinesin—a motor molecule that shuttles nutritional and structural

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ELIZABETH ENGLE

cargo through nerve cells. When it is defective, the nerves are starved of critical resources and fail to develop normally.

Engle is now using her findings to develop mutant mice that may help reveal the details of such breakdowns. “My colleagues and I are excited by the light these studies may shed on the



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normal development and targeting of cranial motor neurons,” she says, “and on why these neurons seem particularly vulnerable to specific gene mutations.”

#### **Back on the Radar Screen**

Vulnerable neurons, particularly in very young patients, are also on the mind of another new HHMI investigator, David H. Rowitch of the University of California, San Francisco (UCSF). Rowitch, who treats premature infants at UCSF, rattles off stats he calls “completely unacceptable”: nearly 800,000 people in the

United States have cerebral palsy, a neurological condition that causes permanent loss of muscle coordination beginning early in life. Health care for patients with the disorder—a potential consequence of premature birth—costs nearly \$35 billion a year.

“We actually have a higher incidence of cerebral palsy now than in the 1960s, but this disease has fallen off the radar screen,” he says. According to Rowitch, rates are up because more extremely low birth-weight babies, born as early as 6 months gestation, are surviving.

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Rowitch, whose laboratory in the UCSF Institute for Regeneration Medicine investigates the biology of the brain's stem cells, is in a position to reduce those numbers. In order to change the standard of care for protecting newborns at high risk for cerebral palsy, he is exploring the basic biology behind the disease, of which little is known.

“Recent studies reveal that up to 50 percent of babies born between 24 and 26 weeks’ gestation (about 6 to 6 1/2 months into a pregnancy) will have some degree of cognitive impairment because this is a very important period of brain development,” says Rowitch. “While the field of neonatology has made real advances in treatments supporting heart and lung function, when it comes to the brain, we have no therapy to improve outcomes in babies born at these early stages.”

Cerebral palsy is usually attributed to an early episode of brain damage, but evidence from Rowitch’s lab suggests that the problem is more likely inhibition of the mechanisms the brain normally uses to repair itself.

As he learns more about what goes wrong during brain development to cause the disorder, Rowitch will help establish a program at UCSF whereby new discoveries about the developing brain

occur when chromosomes inappropriately swap pieces of genetic material—a process called translocation. The “fusion” genes that result can spur rapid and uncontrolled cell division, as in chronic myelogenous leukemia (CML), which is caused by the fusion event involving the two genes *Bcr* and *Abl*. That finding led to targeted drugs, such as Gleevec, that have dramatically improved survival of patients with CML.

In 2005, when Chinnaiyan used DNA microarray technology and powerful computational tools to analyze biopsies from patients with prostate cancer, he was stunned to find that almost 80 percent exhibited translocation. The fusion gene resulted when a male hormone-regulated gene, *TMPRSS2*, joined certain DNA transcription factors to create an overactive “on” switch for growth-stimulating genes in prostate cells.

Because that discovery did not fit current dogma, “we didn’t believe our result at first, and we had to carry out further studies before we convinced ourselves it was true,” Chinnaiyan recalls. “We think this is the causative lesion—it’s the ‘*Bcr-Abl*’ in prostate cancer.”

The discovery inspired Chinnaiyan’s current ambitious plans to use high-throughput search methods to find fusion genes he believes may be the key to other solid tumors as well. “We’re working diligently in breast cancer, because we believe there is an estrogen-regulated gene fusion comparable to the androgen-regulated gene fusion we found in prostate cancer,” he says. By identifying gene fusions associated with these and other solid-tumor cancers, Chinnaiyan hopes to provide targets for new drugs that are more effective than current therapies.

What unites him with Rowitch, Engle, and the 12 other recent appointees is their calling as physician-scientists who spend their professional lives crossing the boundaries between the laboratory and the clinic, convinced that patient care informs and enhances their research. Says HHMI’s Cech: “With the appointment of these new investigators—who will also serve as mentors for the next generation of patient-oriented researchers—and our early-career awards to physician-scientists, we are sending a strong message that HHMI is committed to supporting the people who perform this vital work.” ■

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ARUL CHINNAIYAN

and nervous system can be applied to tiny patients. “You really need to have a specialized clinical setting that doesn’t yet exist for neonates—we’ll be the first in the nation. The hope,” he says, “is to do for the brain what we’re already doing for the heart and lungs.”

***Finding the Causative Lesion***

Another new HHMI investigator, pathologist Arul M. Chinnaiyan of the University of Michigan Medical School, also aims to devise novel treatments through a better understanding of the basic events that lead to a disorder—in this case, solid tumors such as cancers of the breast, colon, lung, and prostate.

Most solid tumors have traditionally been thought to result from mutations that affect one or more growth-regulating genes in the cell. This mechanism is different from what happens in blood cancers—such as leukemias and lymphomas—which

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FOR MORE INFORMATION: To read about the other new investigators, go to [www.hhmi.org/news/poz20071011.html](http://www.hhmi.org/news/poz20071011.html). To learn about HHMI’s early-career awards, visit [www.hhmi.org/news/20070815.html](http://www.hhmi.org/news/20070815.html).

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