

wanted the engine to be capable of high recall, so that nothing crucial would be missed, and to be precise, to avoid wasting time wading through irrelevant material.

“Initially, we were going to have just a couple of categories,” says Sternberg, “but then we realized it would be easier to do ‘everything.’ Even if it wasn’t perfect, we’d just learn from that.” He adds, only half in jest, that they even thought of having categories for “speculation” (so that users could determine whether someone had formed a hypothesis possibly worth exploring) and “gratitude” (reflecting acknowledgment in a paper by peers).

After nearly two years of hard work, Textpresso was launched in February 2003. The search engine, which currently receives an average of about 1,200 hits a day, covers more than 19,000 publications, including 4,420 full-text papers, over 11,000 paper and meeting abstracts, and nearly 3,000 abstracts from the *Worm Breeders Gazette* alone.

Sternberg says he can now do in seconds what used to take hours. Type in the name, say, of the gene *let-60*, and voilà: Textpresso delivers 3,741 matches in 572 publications. To refine the search,

he adds the categories “pathway” and “regulation,” which whittles the hits down to a more manageable 479 matches in 196 publications. In the interest of relevance to the user, papers are listed in descending order based on the number of matches.

“Textpresso is a significant step forward in doing searches that are both specific and sensitive for a model-organism database,” says Lynette Hirschman, a computer scientist at the MITRE Corporation, a government-funded think tank in Bedford, Massachusetts.

One measure of Textpresso’s effectiveness is that other geneticists are adapting the software for their own databases. “The software’s response time is great and it really helps focus the search,” says J. Michael Cherry, whose research team curates a yeast-genome database at Stanford University. Cherry’s lab recently launched *Tetrahymena* Textpresso—a database of information about ciliate protozoa, which are used extensively in genetics studies—and a similar resource for yeast, *Saccharomyces* Textpresso. Reporting that his applications of Textpresso are already receiving lots of positive feedback, Cherry says that “it’s definitely a useful tool for accessing biological knowledge.”

— LINDA MARSALA

How to sift through thousands of scientific papers? Paul Sternberg thought there must be a better way.



Brain Work at the Worm Shack

Researchers at the University of Alabama push undergraduates to take creative risks.

The lab-worker population in Guy A. and Kim A. Caldwell’s laboratory tends to double each weekday afternoon as undergraduates file in after classes to take their places at the bench. Although their daily chores may include feeding, counting, or observing tiny *Caenorhabditis elegans* roundworms, these students are not on hand merely to do the grunt work. They are bona fide researchers—advancing the lab’s agenda, cultivating their own scientific futures, and more than happy to explore the outer limits.

“You can take a crazy idea—like ‘Can worms have seizures?’—and take a chance on that research with an undergraduate without risking the career of a postdoc or graduate student,” says Guy Caldwell, coordinator of the HHMI Undergraduate Research Intern Program at the University of Alabama and assistant professor of biological sciences there. When you have a group of students eager to work hard in the lab even without getting published, they are willing to pursue riskier projects, he says. This can lead to greater rewards. For the past four years, for example, a Caldwell lab undergraduate researcher has been named to the elite list of the *USA Today* All-USA Academic Team.

Recently, the lab discovered a worm model of epilepsy, through the efforts of former undergraduate turned-Ph.D student Shelli N. Williams, who was aided by two HHMI undergraduate research interns, Andrea L. Braden and Cody J. Locke. The worms carry a mutation in the *LIS1* gene, which is linked to the human-brain birth defect called lissencephaly. Children with this rare (1 in 30,000) condition, in which the normally wrinkled surface of the brain’s cortex is smooth, have mental retardation and severe epilepsy. Similarly, the mutant worms are more susceptible than normal worms to having epilepsy-like convulsions—owing, the team found, to the mutation’s effect on specific

inhibitory neurons.

Because the number, placement, and organization of these neurons in the mutant worms appeared normal, the researchers looked at the nerve cells' ability to release the inhibitory neurotransmitter γ -aminobutyric acid (GABA), a chemical that normally prevents motor neurons from becoming "overexcited"; when it is not present in the correct amounts, convulsions can result.

When the Caldwell team examined the nerve cells of mutant worms, they noticed gaps in the lineup of the synaptic vesicles, tiny intercellular sacs, that store GABA and release it when the nerve fires. The working hypothesis now is that the mutated *LIS1* misdirects the movement of the synaptic vesicles at the ends of nerve cells, resulting in reduced release of the inhibitory neurotransmitter and a lowered convulsion threshold.

Caldwell hopes this *C. elegans* convulsion model will help decode mysteries of epilepsy and lead to better treatments for the seizures that affect some 2 percent of human beings. There is, of course, a long way to go. "Epilepsy—one of the worst parts of lissencephaly—is still a black



From left, colleague scientists at the University of Alabama: Shelli Williams, Cody Locke, Guy Caldwell, and Kim Caldwell, collaborators in the "Worm Shack." The work links scientists at various stages in their careers.

Having undergraduates in the lab keeps the lab's research agenda "young at heart."

—Guy Caldwell

box on a genetic level," he acknowledges. "But this work shows we can dissect out that part of the disease."

The team published its findings in the September 15, 2004, issue of *Human Molecular Genetics*.

Caldwell expects undergraduate researchers to assist with another major project—a large-scale worm-genome screen to find genes that may affect the aggregation and degradation of proteins associated with Parkinson's disease. The

lab's work in this area began with a freshman's research project to model another related human-movement disorder, called dystonia, in worms. In fact, current HHMI intern Amber Clark is performing the first funded screen for drugs that may affect dystonia protein activity.

Studying brain disorders in "brainless" worms might seem like, well, a no-brainer—unlikely to yield results applicable to human beings. But Caldwell is quick to explain why he believes worms are fitting for both neuroscience and undergraduate research. "The human brain has some 100 billion neurons, whereas the [adult] worm has only 302. We know each type of neuron and how they connect to each other," he says. Also, the lab's genetic screens involve a simple assay of feeding worms specially engineered bacteria, which inhibit specific genes, and then inspecting the

transparent worms under a microscope for defects. "In this way, a multitude of undergrads can carry out a sophisticated project where the day-to-day work is simple," notes Caldwell. This contemporary version of a mutant hunt is well suited to undergraduate work.

Incentives for students' participation run the gamut from eminently practical rewards to attractive outlets for their idealism. Locke points out that his experiences in the Worm Shack, as the lab is affectionately known, have "put me in a great position" for graduate school. And as Caldwell and his co-investigator wife, Kim, assistant professor of biological sciences and director of the university's HHMI-sponsored Rural Science Scholars Program, stress to their undergraduate students, they are contributing to the bigger picture of deciphering a major medical problem.

Meanwhile, practical and idealistic incentives apply as well to the Caldwells and their fully credentialed colleagues. The undergrads, says Guy Caldwell, "keep the lab's research agenda young at heart."

—KENDALL POWELL