MODEL BEHAVIOR

Simplicity is an ally for researchers studying the mechanisms of fundamental biological processes. Some of our diminutive domestic companions—bakers' yeast, the fruit fly, the mouse and the weedy arabidopsis—may mean big breakthroughs for CALS scientists tapping into their potential as model organisms.

By Sarah Thompson • Photos: Kent Loeffler

MUS MUSCULUS (THE HOUSE MOUSE)

Mankind and mouse are inextricably linked. Nearly every gene in the mouse genome has a counterpart in that of humans, and our organs and bodily systems work in similar ways. Like humans, mice are social mammals who care for their young, can learn, and are flexible in their behavior. They also develop diseases, such as hypertension and type 2 diabetes, in a similar way to humans. But what makes mice so indispensable for human biological research is how easily and precisely they can be genetically manipulated, with the resulting effects studied in the context of a whole living organism.

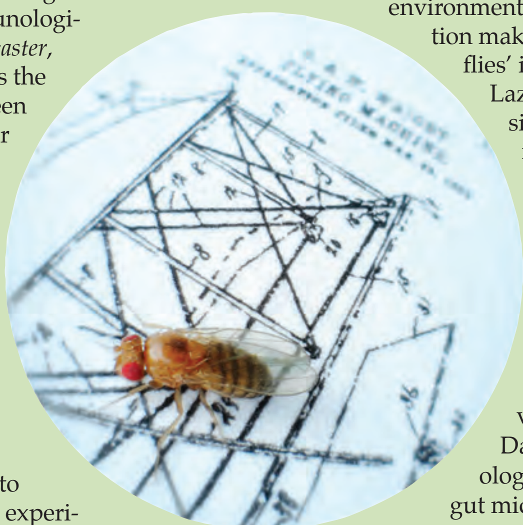
David McCobb, associate professor of neurobiology and behavior, uses mice to study animals' stress response and how it interacts with sex and species differences. Chronic stress can adversely affect every system in the body. According to McCobb, the problem is that humans' stress response evolved to trigger emergency reactions to acute threats. "But because we live longer and are less likely to be devoured by lions, our well-being is related more to how we deal with chronic threats, real or imagined," he said.

McCobb has found that cells in the adrenal gland of female mice are equipped to secrete adrenaline at higher rates than those of males, likely because females have higher levels of glucocorticoids, or stress steroids. But in male mice, more habitual aggressive behavior is probably driven by noradrenaline, a less intense relative of adrenaline. "In humans under chronic stress with elevated stress steroid levels, elevated adrenaline secretion—similar to that seen in female mice compared to males—may contribute to depression. These studies are part of the bigger picture of learning how to regulate our stress response better on a day-to-day basis," McCobb said.

Robin Dando, assistant professor of food science, is using mice to study how obesity changes animals' sensitivity to certain tastes. To do this, Dando will test different genetic strains of obese mice, each exhibiting different obesity-related

DROSOPHILA MELANOGASTER (FRUIT FLY)

Be careful which fly you swat. It could hold the genetic keys to unlocking the secrets of tissue regeneration or chronic metabolic and immunological diseases. *Drosophila melanogaster*, commonly called the fruit fly, is the one you should spare. It has been used as a model for research for more than a century, mostly because of its small size, fast development, and ability to lay thousands of eggs per year. Today, genetics and developmental biology researchers are attracted to the fruit fly's compact and easily manipulated genome, as well as its extensive genetic resources. Most importantly, the fruit fly allows researchers to conduct mechanistic biological experiments that can't be done in humans, or even in mice.

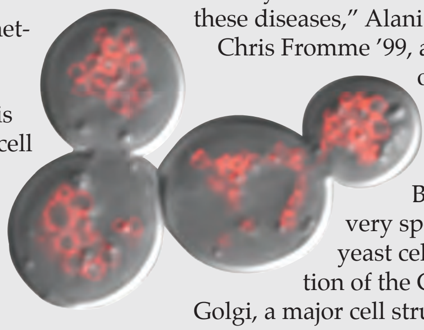


Brian Lazzaro, associate professor of entomology, understands the benefits of these insects in studying the genetic basis of immune system performance. Lazzaro has found that flies vary greatly in their ability to fight infection, due to both genetic and environmental reasons. High-sugar diets and nutrient deprivation make flies more susceptible to infection, while female flies' immunity drops significantly after mating. The Lazzaro lab is interested in deciphering the genetic basis for such unexpected interactions, many of which may also hold true in other animals, including humans. "This is where model systems really have an advantage," Lazzaro said. "Through these studies we're getting at mechanisms, including possible hormonal linkages among traits."

Our microbiota—the bacteria living in and on our bodies—affect our health and wellness. However, these relationships are difficult to study in complex organisms with highly diverse and variable microbiota. This led Angela Douglas, the Daljit S. and Elaine Sarkaria Professor of Insect Physiology and Toxicology, to turn to *Drosophila* to study how gut microbes affect nutrition. She found that fruit fly gut microbes are more stable and less diverse, with just five types of bacteria accounting for 90 percent of the total. When she grew germ-free flies, Douglas got a surprise: The flies weren't terribly

BAKER'S YEAST

Saccharomyces cerevisiae, or baker's yeast, is a cheap date. This single-celled fungi is low maintenance, microscopic, reproduces in under two hours, and has a small, completely sequenced genome.



Eric Alani, professor of molecular biology and genetics, is using it to help him answer a fundamental biological question: What is the role of genes in how a cell behaves? He is studying yeast cell "spell checker" proteins, which monitor cell reproduction and DNA replication, identify errors, and remove them before they become permanent after cell division. According to Alani, these highly conserved proteins—seen in bacteria, yeast, and humans—play a major role in maintaining genome stability. Defects in spell checker proteins have been identified in hereditary forms of colorectal and endometrial cancer. "However, there remain inherited colorectal cancers for which the underlying genetic defects are not known. Part of my lab's work is to identify the mutations associated with these diseases," Alani said.

Chris Fromme '99, assistant professor of molecular biology and genetics in the Weill Institute for Cell and Molecular Biology, generates very specific mutations in yeast cells to study the function of the Golgi apparatus. The Golgi, a major cell structure, is the cell's Grand Central Station–sorting proteins out to different locations in the cell. Mutations in Golgi proteins give rise to many human diseases. Fromme has identified a positive feedback loop by which different proteins interact to regulate the master molecular switch that turns the Golgi on and off.

"These same proteins in yeast cells are found in humans, so the assumption is this works the same in humans," Fromme said.

Assistant professor Marcus Smolka, another member of the Weill Institute, developed a new technology to better study how certain signaling proteins, called DNA damage checkpoint kinases, prevent cells with damaged DNA from dividing. Smolka identified one particular protein, Slx4, that kinases regulate in yeast cells. Initially thought to exist only in yeast, Slx4 has now been found in humans. It appears to have a major impact on the development of Fanconi anemia, a cancer predisposition syndrome. "If you are addressing a fundamental biological mechanism, it will eventually have an impact on humans," Smolka said.

symptoms, to find molecular evidence for these changes in the taste bud itself. For Dando, mice are ideal surrogates for the study of human feeding. Like humans, they are drawn to sweet, salty and protein-rich food; if fed a steady diet of these, mice—just like us—will get fat. But they can also slim down by exercising more and eating less. "However, a mouse will reach maturity in a matter of weeks, thus giving us access to a whole lifetime of data in a fraction of the time the study would take in humans," Dando said.

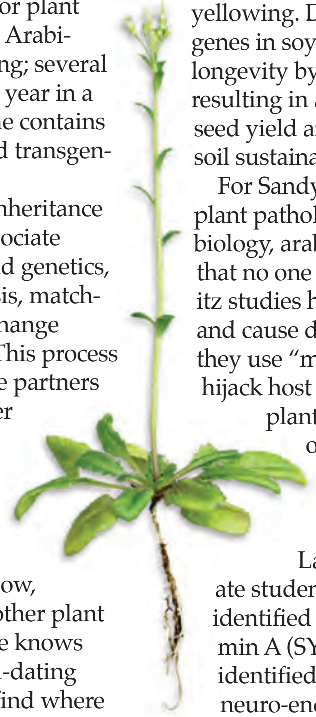
sick, but they had very high blood sugar and fat levels—the same traits seen in people with insulin resistance. Douglas is continuing experiments to see which of the fly's five main gut microbes are important for controlling fat and blood sugar levels.

Nicolas Buchon, assistant professor of insect immunology, also uses the fruit fly to study how the gut controls its own microbes, both good and bad, and how microbes affect the gut. Buchon found that bacterial infection changed the rate of cell turnover in the gut, which is powered by stem cells—specialized cells that can generate new cells of different tissue types. Buchon discovered that stem cell growth was ten times higher in infected flies, a clear demonstration that microbes can impact the division rate of stem cells, which could in part explain how microbes affect cancer initiation and progression.

ARABIDOPSIS THALIANA

Arabidopsis is a small unassuming plant, but it has power in numbers. In the past 20 years, scientists have rallied around arabidopsis as a main model for plant biology and genetics research. Arabidopsis is small and fast growing; several generations can be grown in a year in a small space; its concise genome contains almost no repetitive DNA; and transgenics and mutants abound.

To better understand how inheritance works, Wojtek Pawlowski, associate professor of plant breeding and genetics, studies meiosis. During meiosis, matching pairs of chromosomes exchange parts before recombination. "This process of finding correct chromosome partners is extremely important in order for inheritance to work," Pawlowski said. In meiosis, the genome does what Pawlowski describes as "a rock-and-roll dance," where chromosomes mix together. Now, by studying arabidopsis and other plant species, Pawlowski believes he knows why: "We think this is a speed-dating protocol for chromosomes to find where their appropriate parts are. We have evidence that this is in fact what's happening during meiosis."



Susheng Gan, associate professor of horticulture, is interested in how leaves are programmed to die. Since their main function is photosynthesis, the longer leaves stay green, the more sugars and other nutrients the plant can synthesize to fill seeds, store as biomass, or help root nodules live longer to fix more nitrogen in the soil. Using arabidopsis strains lacking certain genes, Gan identified several genes that regulate senescence, or leaf yellowing. Disabling one of these genes in soybeans increased leaf longevity by more than one week, resulting in a 44 percent increase in seed yield and significantly increased soil sustainability.

For Sandy Lazarowitz, professor of plant pathology and plant-microbe biology, arabidopsis opened doors that no one knew existed. Lazarowitz studies how viruses infect plants and cause disease, specifically how they use "movement proteins" to hijack host cell pathways to cross plant cell walls and infect other cells. While investigating the host proteins that work with these movement proteins, Lazarowitz and her graduate student Jenn Lewis, Ph.D. '05, identified one protein, Synaptotagmin A (SYTA), that had only been identified in animal brain and neuro-endocrine cells.

"When we identified SYTA in plants, people's reaction was, 'But plants don't have brains!'" Lazarowitz said. "Further studies revealed that SYTA regulates the cell-to-cell spread of a variety of plant viruses from diverse families. We now have the potential to engineer broad-based resistance to quite different, distinct plant viruses."