



Plants are Us

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Scientists are gaining critical knowledge of human biology from the study of—no kidding—plants. Fact is, we have lots of similarities, and plants are easier to deal with.

Gregor Mendel would no doubt be pleased.

Two centuries after the Augustinian monk crossed pea plants to probe heredity, an increasing number of molecular biologists are turning to plant models to unravel basic human biochemistry, understand disease, and improve nutrition worldwide. Several HHMI investigators are at the forefront of this green trend.

“About 20 years ago, most biomedical scientists were lukewarm on the benefits of plant research,” says HHMI investigator Joanne Chory, a plant biologist at the Salk Institute for Biological Studies. “But we’ve since found that we can freely manipulate genetics in plants, making transgenic varieties. I like to say that we can actually do gene therapy in plants because the plant genome can stably integrate and express introduced genes—and that has opened the way to new molecular insights.”

Of Mustard and Men

This bloom has emerged, in large part, because of the model mustard plant *Arabidopsis thaliana*. Its sequenced genome, published in 2000, showed that mustard and humans share some important biology. At least 139 known human disease genes have homologues, or counterparts, in *Arabidopsis*. Even more basic, perhaps, is a shared biochemistry that makes life possible. “Like almost all higher organisms, humans and plants have much in common,” says HHMI investigator Steven E. Jacobsen, a plant biologist at the University of California, Los Angeles. “Thanks to work in a number of labs, plant research is rapidly gaining more respect.”

Jacobsen, whose lab is one of those pushing plants to the forefront, grew up on a farm in Merced, California, and had originally planned to work in plant development. As a postdoctoral fellow at the California Institute of Technology, however, he stumbled upon a set of unusual mutations that changed developing flowers. Flowers with these mutations sprouted extra male sexual organs, or stamens. Yet, sister plants, sharing the same basic DNA, remained perfectly ordinary, with the usual six stamens.

Puzzled, Jacobsen compared his mutant and ordinary plants. He found a telling difference in a key gene, called *SUPERMAN*, that regulates flower development. The difference—and the launch of his career—was DNA methylation. As Jacobsen’s subsequent work has illustrated in detail, plant cells can turn off, or silence, particular genes by chemically attaching methyl groups to

their surface. With this trick, plants regulate gene expression to control cell growth and development. DNA methylation is a primary example of what’s called epigenetic gene regulation—or heritable changes in gene expression that do not modify the fundamental gene sequence.

In fact, what Jacobsen witnessed at the lab bench—the difference between ordinary flowers and blossoms bearing extra stamens—resembles a devastating biochemical process in humans: cancer. Like plant cells, human cells also methylate DNA. And some cancer cells inappropriately methylate tumor-suppressor genes in particular, effectively silencing them and allowing the cancer cells to grow unchecked.

“I realized then,” Jacobsen recalls, “that these plant mutations could give us a real genetic handle on DNA methylation, explaining the biochemistry with experiments that would be impossible to do in other models.” Key biomedical model organisms, such as the fruit fly, worm, and yeast, wouldn’t cut the mustard, so to speak, because they lack the DNA methylation feature. And “experimentally reducing DNA methylation kills embryos in other mammalian systems,” says Jacobsen. “But in plants, with their

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Clockwise from left: Joanne Chory, Steven Jacobsen, David Bartel, and Bonnie Bartel are all studying and manipulating plant genetics to answer some core questions about basic biochemical processes and regulatory factors in humans.

built-in biological redundancy, you can knock out various genes and the plants still thrive.”

Since his postdoctoral surprise, Jacobsen and colleagues have been systematically deconstructing DNA methylation. They used the hypermethylated *SUPERMAN* mutants (called *clark kent* mutants) to screen for genes that maintain proper patterns of DNA methylation. Using this trick, Jacobsen and colleagues cloned three genes—*CHROMOMETHYLASE3*, *KRYPTONITE*, and *ARGONAUTE4*—that further clarify methylation mechanics and the interaction of methylated DNA with modified histones (proteins that help wrap the DNA into tightly packed chromosomes) as well as with small RNA molecules that target methylation. Last summer, Jacobsen’s team described how plants use RNA interference

(RNAi), or RNA silencing, to target specific genes for DNA methylation.

Now, Jacobsen’s team is working to pinpoint every instance of DNA methylation in the *Arabidopsis* genome. The lab’s initial efforts were reported in the August 31, 2006, online edition of the journal *Cell*. With this model organism map, Jacobsen says, scientists will be able to find similar activity in the more complex human genome. “Although not identical, DNA methylation in plants and humans is sufficiently similar that we can glean useful information,” he says.

A Steppingstone to Animal Research

Scientists also have sidled up to the potting bench to analyze regulatory RNA. Over the past decade, regulatory RNA has won recognition as a major coordinator of gene expression in cells of various species. Indeed, the petunia,

streaked in different colors, provided some of the first evidence that regulatory RNA can silence pigment genes during development.

Today, HHMI investigator David Bartel, a biologist at the Massachusetts Institute of Technology, is studying plant regulatory RNA for insight into animal development. Bartel’s lab studies in particular how microRNAs (miRNAs) silence genes. In 2002, having found many miRNAs in animals, Bartel wondered whether these molecules might also exist in diverse species—namely, plants. He contacted an inside resource for *Arabidopsis* plants: his sister, Bonnie Bartel, a plant biologist at Rice University who became an HHMI professor this year. Teaming up, the sibling duo set about analyzing mustard plants for regulatory RNAs. They hit the jackpot.

“At the time, only three known targets of animal miRNA existed,” says David Bartel.

A Cabbage Kids Will Like

HHMI professor Richard M. Amasino, a biochemist at the University of Wisconsin–Madison, envisions whole classrooms of green thumbs. He sees students, from elementary school to college, breeding inexpensive and easy-to-grow plants to study flower development, plant size, and other basic processes. Amasino is working to adapt fast-flowering cabbages into a series of genetics lessons for students of different ages.

“If you really want kids to get it, they need to see genetics in action, without fancy equipment,” says Amasino. “They need to see interesting mutations that not only look cool, but also can be studied further. But while science students dissect frogs to understand anatomy or maybe worms to study development, how can they easily learn about genetics? *Arabidopsis* and *Drosophila* are challenging for most educators to use.”

Developing a classroom model of genetics from scratch is a tall order. Amasino is recruiting teams of undergraduates and his own lab members to dip seeds into mutation-causing solutions, hand-pollinate and water thousands of experimental plants, and monitor future generations of the plants to identify interesting variants. The teams will also help develop hands-on class activities to show K-12 students how genes pass from one generation to the next.

“My ultimate goal is to find a range of experiments so that advanced students could grow generations of plants, say, while third-graders breed simple mutants,” Amasino says. “The beauty of this project is that even if we produce just a handful of mutants, we’ll be ready to start developing classroom exercises.” — K.B.



Richard Amasino

“When we mapped just one miRNA (miR171) to the *Arabidopsis* genome, we turned up three different targets. That’s when it got exciting. Soon we had about 50 confidently identified targets and could begin to consider the broad functions of these regulatory RNAs.” Bartel, who had never worked with plants before, promptly hired several scientists to study plant miRNAs full-time.

The team has identified miRNAs in *Arabidopsis* that, for example, regulate embryonic and organ development, and analogous targets in animal models. The team also honed lab techniques for plants, such as high-throughput sequencing methods, before adapting them to animal studies. Interestingly, Bartel notes that although miRNAs in plants and animals have the same silencing effect, their mechanisms usually differ considerably. He speculates that miRNAs evolved at least twice, once in early plants and again in early animals. Today, *Arabidopsis* has at least 100 known miRNA genes, while humans have more than 400.

Studying Plants to...Make Better Plants

Beyond their service in elucidating the biology of other life forms, plants are of course worth study in their own right. Breakfast, lunch, and dinner come to mind. On the food front, HHMI supports plant research that could lead to hardier, more abundant crops—particularly in developing countries. With the world population expected to grow by 2–3 billion over the next 30 years, many regions could struggle to feed residents. “We urgently need more and better food,” says HHMI international research scholar Luis Herrera Estrella, head of Mexico’s National Laboratory of Genomics for Biodiversity of the Center for Research and Advanced

Studies at the National Polytechnic Institute in Irapuato, Mexico.

Estrella is working to develop transgenic plants that grow in acid soils, which represent roughly a third of the world’s arable land. In Latin America, he says, more than 450 million hectares of land are highly acidic yet otherwise prime for farming, with a good growing climate and available water. Acid soil contains toxic levels of aluminum, which inhibits the roots of growing plants, and low amounts of phosphorous, an essential plant nutrient. Rather than fight the poor soil, most farmers in the region simply allow cattle to graze on marginal pastures. Those that do plant crops such as corn and soybeans must apply costly amounts of lime and fertilizer.

If growers could cultivate crops on this acid soil, Estrella says, food production in Latin America could jump by 50 percent. With that goal, he and his colleagues have studied plants naturally adapted to acid soils, pinpointing their molecular talents for tolerating aluminum and efficiently using phosphorous. His lab is also working to design plants with shallow, highly branched root systems that can more efficiently use fertilizer in diverse kinds of soils. “If we can produce new plant varieties or hybrids that require less fertilizer,” he says, “we could cut farm costs, make agriculture more sustainable, and reduce harm to the environment.” The team is headed in that direction, with recent studies that identified key regulatory and metabolic genes that allow some varieties of maize and *Arabidopsis* to thrive in low-phosphate soils.

Despite their prodigious value to humans, sometimes plants can cause human health problems. HHMI investigator Daphne Preuss, who is one of HHMI’s first plant biologists, and her colleagues at the University of Chicago have recently identified genes that code for proteins that coat the pollen of *Arabidopsis*, a finding that is helping scientists learn how plants recognize pollen from their own species. Building on that research, Preuss is

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— JOANNE CHORY

working to identify the molecules within pollen that trigger allergies. This line of research, funded in part by the Arabidopsis 2010 Project (see sidebar), could lead to more effective treatments for the beleaguered millions who are allergic to airborne pollen.

Plants' Own Steroids

Back at Salk, Joanne Chory shifts her gaze skyward to explore how plants respond to different light environments. In particular, Chory focuses on signaling by brassinosteroids, plant-steroid hormones that are critical regulators of development in virtually all plant cells, including seeds, flowers, roots, leaves, stems, pollen, and young vegetative tissue. Because brassinosteroids control cell growth, they help determine whether a plant becomes a dwarfed knot of green, say, or a sleek stalk stretching high.

In two studies reported in the journals *Nature* and *Science* this year, Chory and

colleagues diagrammed how brassinosteroids trigger a cascade of biochemical events that ultimately activate the expression of diverse genes involved in plant development, from cell-wall metabolism to reproductive organs. “We are now in a position to modify steroid levels or the signaling pathway to either miniaturize or grow the plant bigger,” says Chory. The *Nature* study, in particular, generated significant media coverage, with the vision of grass that never needs mowing. Even more importantly, Chory adds, these findings could improve plant yield for agriculture worldwide.

In an earlier study, Chory and colleagues identified a gene that controls flowering when “shade avoidance” is triggered. Shade avoidance syndrome is a novel molecular mechanism activated when sun-loving plants, such as *Arabidopsis*, get stuck in the shade. Short on sunlight, the plant taps this pathway to elongate its stem, restrict leaf and root development, and—if all else fails—produce what Chory calls a “desperation flower” that allows the shade-stressed plant to set seeds and ensure survival of at least some offspring.

“All our studies—on brassinosteroids, auxin [another hormone that controls plant development], and the quality and quantity of light—suggest how plants grow in different environments,” says Chory. “In the next five years, we want to understand how these different systems interact.” During that time, she notes, basic research on plants will contribute to biofuels and to the creation of hardier, higher-yielding crop varieties with added nutritional content. “In fact, the study of plant genomes might contribute more to human health and well-being than the study of any animal genome.” ■

Arabidopsis 2010: Big Plans for a Little Genome

Even as biologists released the *Arabidopsis thaliana* genome sequence in 2000 they were launching another ambitious endeavor: Arabidopsis 2010, a project to map and explain by the year 2010 the function of each of the mustard plant's roughly 25,000 genes. Their goal is to outline nothing less than the complete workings of a flowering plant.

“The *Arabidopsis* genome is small enough that we can understand every gene,” says HHMI investigator Joanne Chory, a plant biologist at the Salk Institute and a principal author of the project's planning document. Ultimately, Arabidopsis 2010's goal is to build a body of knowledge—a kind of modern encyclopedia, with interactive tools—that plant biologists can tap as a central reference. Through 2005, Arabidopsis 2010 had funded 86 individual projects, primarily with support from the National Science Foundation. Participants, including HHMI investigators Steve Jacobsen, David Bartel, and Daphne Preuss, are building a toolkit of sorts, including valuable seed banks of modified *Arabidopsis* lines such as “knock-outs,” which lack a given gene. Other projects range from cell wall studies to microarray experiments that test gene function.

Biologists have already begun talk of Arabidopsis 2020, a program to build on this basic toolkit, with projects that not only extend basic research but may also serve practical applications in agriculture, environmental science, and other fields. — K.B.

For more information, see the “Mid-Course Assessment of the Arabidopsis 2010 Project” at www.nsf.gov/pubs/2006/bio0601/bio0601.pdf.