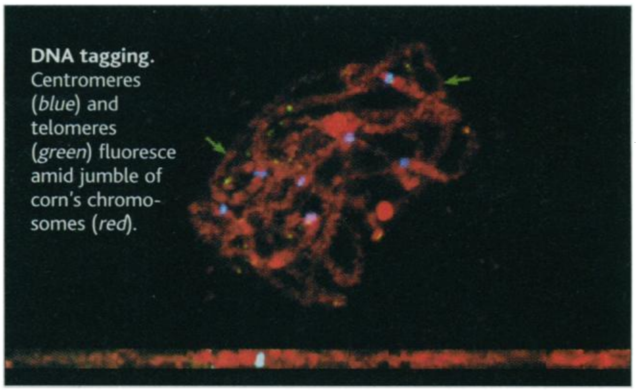
A Bonanza for Plant Genomics

NEWS

A new initiative could provide the biggest ever pot of government money for plant genomics

When the National Science Foundation (NSF) announced last year that it had some $40 million in its 1998 budget to launch a plant genome initiative, Virginia Walbot sent an e-mail to nine colleagues asking if they would be interested in applying jointly for a grant to analyze the corn genome. Ninety seconds later, she had her first affirmative response; within 2 hours, all had agreed to team up with Walbot, a plant molecular biologist at Stanford University. Similar partnerships were forming throughout the plant biology community to take advantage of this windfall. Last month, the networking paid off when NSF announced that Walbot and her colleagues, along with 22 other groups,* would receive the first grants from the new initiative: an assortment of projects from mapping the corn genome to determining the genes responsible for fruit development in tomato plants.


DNA tagging. Centromeres (*blue*) and telomeres (*green*) fluoresce amid jumble of corn's chromosomes (*red*).

These investments are just the initial installments of what promises to be a new bounty of plant research funds. Already, Congress has approved another $50 million for NSF's plant genome program in 1999, and there's talk of increasing funding for plant genomics—and adding an animal component—to $85 million in the year 2000. Plant scientists are thrilled by this new largess. Until now, U.S. government support for crop plant genomics has been sparse; the U.S. Department of Agriculture (USDA), for example, has provided only a few million dollars a year for such work. "We've been rather impoverished," says plant geneticist Chris Somerville of the Carnegie Institution of Washington at Stanford University. Now, says USDA's Ed Kaleikau, NSF's initiative will provide "the biggest infusion of money for plant biology, perhaps ever."

The initiative is the outgrowth of a proposal, originally made in 1995 by the National Corn Growers Association, that the U.S. government put $143 million into sequencing the genome of corn, the number one crop plant in the United States. Researchers welcomed the idea, but they worried that such an effort would sap funds from other genomics projects. In response, an Office of Science and Technology Policy committee—with representatives from NSF, USDA, the Department of Energy, the National Institutes of Health, and the White House Office of Management and Budget—held meetings with scientists from academia and industry and other experts to map out a structure for the effort (*Science*, 27 June 1997, p. 1960).

As a result, when Congress approved the $40 million add-on to NSF's fiscal year 1998 budget, it simply required that at least three-quarters of the funds be spent on genetic studies of economically important crops. That's what NSF has now done. In the first round of grants, $30 million will be devoted to work on key crops—primarily corn but also sorghum, tomato, cotton, and soybeans—while the remaining $10 million will speed up the sequencing of the genome of *Arabidopsis*, the favorite model plant for lab scientists. "If the [federal agencies] maintain this momentum and interest, which is long overdue, I think the benefits to researchers are going to be phenomenal," says Thea Wilkins, a molecular geneticist at the University of California (UC), Davis.


Gene hunter. Virginia Walbot hopes to find all of corn's genes.

Already, successes with genetically engineered strains of pest-resistant corn and herbicide-resistant cotton have convinced many of the value of using such technology to improve crop plants. Indeed, many companies are positioning themselves to cash in on the fruits of plant genomics (see p. 608). But further advances will depend on identifying genes for useful traits, such as the ability to survive stresses such as drought or to produce higher crop yields. The mapping and sequencing efforts should accelerate the discovery of such genes. "We think that [with genomics] higher yields will be possible with lower production costs," says Ryland Utlaut, president of the National Corn Growers Association, which calculates that each 3% increase in U.S. corn production leads to an increase of $1 billion in the U.S. economy.

Focus on corn

Although the new initiative is broader than it originally envisioned, the corn growers association has much to be pleased about. NSF has committed $37 million in the new initiative to corn genomics over the next 5 years. Some will go toward mapping and cloning efforts that set the stage for sequencing the genome; other work will help identify corn's genes or evaluate which genes are responsible for desirable traits, such as oil content.

The job of developing the infrastructure to analyze key parts of the corn genome will go to Edward Coe, a USDA plant geneticist at the University of Missouri, Columbia. Coe's team, including colleagues at Clemson University in South Carolina and at the University of Georgia, Athens, will make libraries of corn DNA fragments that can be used to build a physical map and as the raw material for sequencing. W. Zacheus Cande, a cell biologist at the University of California, Berkeley, has developed a labeling technique that makes specific genes visible on the long corn chromosomes, pinpointing their position. Meanwhile, Ron Phillips at the University of Minnesota, Minneapolis, will work on another type of physical map, called a radiation hybrid map.

This work, a prelude to large-scale sequencing, will take more than 5 years to complete. Many researchers think, however, that rather than sequence the full corn genome—which has a whopping 3 billion base pairs and is full of repetitive DNA that is hard to sequence—they will focus on regions likely to contain the most valuable information.

Meanwhile, Walbot's team—this year's biggest NSF winner with a grant of $12.6 million—will take a more direct approach to identify-

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* www.nsf.gov/bio/pubs/awards/genome98.htm

CREDITS: (TOP) PETE CARLTON/UNIVERSITY OF CALIFORNIA, BERKELEY; (BOTTOM) GRANT HEILMAN, INSET: STANFORD UNIVERSITY/PRESS SERVICE

Slow Start for U.S. Rice Genome Project

The United States has long been a leader in efforts to sequence the human, *Escherichia coli*, and *Arabidopsis* genomes. But it appears to be taking a back seat in an international effort to determine the genetic makeup of one of the world's most important crops, rice. U.S. researchers last year urged the government to pay half the cost of sequencing this plant's genome, but federal agencies now seem barely able to come up with the 10% (about $20 million) expected from the U.S. Department of Agriculture (USDA). This shortfall could undermine a cooperative effort to make rice genome data freely available to researchers, and it could cause an incipient international consortium to "fall apart as originally conceived," says Susan McCouch, a rice geneticist at Cornell University in Ithaca, New York.

The latest blow came last week, when the U.S. Congress killed a $120 million initiative that would have supported rice sequencing projects (*Science*, 16 October, p. 392). USDA, the National Science Foundation (NSF), and the Department of Energy are now cobbling together about $4 million for a small U.S. rice sequencing effort later in 1999, but "additional funding" will be needed to reach the $20 million level, says Ed Kaleikau, who runs USDA's plant genome program.

Plant biologists are not pleased. The loss of the USDA funds came 2 weeks after it became clear that none of the funds from NSF's new $40 million plant genomics initiative would support sequencing the rice genome (see main text). "I and my colleagues in this international effort truly believed that NSF [would] give top priority to the proposals for rice genome sequencing," says Takuji Sasaki of the National Institute of Agrobiological Resources in Tsukuba, Japan. "So many researchers in crop genomics were disappointed by the decision."

As with microorganisms and mammals, the prospect of having one plant genome in hand—*Arabidopsis* by the year 2000—has made researchers eager for more. Although a U.S. corn-lobbying group has been trying to get corn sequenced next, among researchers worldwide, "there's unified agreement that if [we're] going to sequence a second plant, it should be rice," says Chris Somerville, a plant geneticist at the Carnegie Institution of Washington lab at Stanford University. A key food for much of the world, rice has a relatively small genome—just 430 million bases, compared to corn's 3 billion or so. Like corn and other cereals, it is a monocot, and deciphering its genome could make gene-hunting easier in other crop plants.

Eager to get started, rice researchers had formed an international consortium last September* to sequence a Japanese rice cultivar called Nipponbare (GA3), the focus of 7 years' work by Sasaki. This group had finished an extensive physical map and, with $10 million per year from the Japanese government for the next decade, were poised to start sequencing. In the United States, Rod Wing and his colleagues at Clemson University in South Carolina had begun building a DNA library of bacterial artificial chromosomes (BACs) and sequencing their ends to determine which would be the best to use for genome sequencing. Novartis supported some of this work, but agreed to allow the BAC sequences to be freely available. Sasaki's team planned to do the same. Representatives from the United Kingdom, Korea, Japan, the United States, France, and China tentatively agreed to coordinate their efforts and to put sequence data in public databases.

Drooping support. U.S. funding lag could hurt international plan.

The United States seemed ready to join the team. In January 1998, a U.S. interagency committee recommended that the United States contribute $40 million and sequence 20% of the rice genome over the next 5 years, formally acknowledging the government's interest. And when NSF got $40 million in fiscal year 1998 for plant genomics, representatives of the consortium, who had been in close contact with NSF officials, assumed rice was a top priority and began building blue-ribbon scientific teams and applying for grants. But although the grants came through for corn, rice lost out. NSF program officer Machi Dilworth says no special consideration was given to any proposals based on plant species. Ben Burr, a plant geneticist at Brookhaven National Laboratory in New York, feels that the U.S. effort has been left with "egg on our face."

These setbacks make some researchers worry about the fate of the nascent international rice genome consortium. Thus far, only Japan has put substantial money behind this effort. Although France seems eager to support some work, the European Union will not consider substantial support for sequencing the rice genome for a year. Even then, "we've not got a firm commitment," says Michael Gale, a plant geneticist at the John Innes Centre in Norwich, U.K. Korea would like to be involved, but national economic problems may limit its participation. And China has decided to sequence a different rice cultivar, raising a question about its willingness to share data.

If the United States doesn't set up a rice-sequencing program in the next month or so, "we will have lost a lot of ground," warns McCouch. Japan began its sequencing program in April and could lose interest in an open-data policy if no one else is contributing. Even if Japan's commitment remains unchanged, the funding setbacks will have a chilling effect, giving the decade-long project a slow start. Given the importance of rice as a crop and as a model for studying other plant genomes, says Ronald Phillips, a plant geneticist at the University of Minnesota, Minneapolis, "it's really too bad that [rice] is not going to be the front and center of our plant genomics program."

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* www.STAFF.or.jp

ing corn genes. The researchers have genetically engineered corn plants with a piece of mobile DNA, called a *Mu* transposon, that jumps about the genome, disrupting the genes on which it lands. The team will then look for mutations such as stunted ears, superlong tassels, or purple-colored kernels in the offspring of the engineered plants.

Walbot's team uses a neat trick to identify the genes responsible for these changes: They tag the transposon itself with an antibiotic-resistance gene. The Stanford researchers extract DNA from a mutated plant, chop it into small pieces, add the pieces to bacteria, and grow the bacteria in a culture medium containing an antibiotic. The only bacteria that survive are those that take up a piece of DNA including the transposon and its antibiotic-resistance gene, all embedded in the gene they are looking for. Walbot eventually expects to have mutations in all the estimated 50,000 corn genes, together with seeds from the affected plants and bacteria containing the gene responsible. This approach "allows simultaneous study of gene sequence and function in a living corn plant," says Walbot. "It's a way to get more quickly into functional genomics."

The NSF initiative will support several variations on the transposon technique. Hugo Dooner, a geneticist at Rutgers University in Piscataway, New Jersey, plans to pull out about 100 genes using a transposon called *Activator*. At Cold Spring Harbor Laboratory in New York, Rob Martienssen will use a transposon system to create some 40,000 lines of corn mutants, each associated with a piece of altered DNA. Although his approach is similar to Walbot's, "having several groups use complementary approaches increases the likelihood that every important gene will be identified," says NSF's David Meinke.

A view across the field

Corn is the only crop plant in which transposons can be easily used to pull out genes. But researchers think they will be able to combine what they learn about the corn genome with data coming from the *Arabidopsis* sequencing project and also a rice genome project expected to be under way in Japan and other countries within the year (see sidebar on previous page). There appear to be enough similarities between the gene arrangements in different species that locating a particular gene in one will point to counterparts in the others. But first, says Cornell University plant molecular geneticist Steven Tanksley, "we need to find ways to connect [*Arabidopsis* and rice] genome information to other species."

To find those connections, Andrew Paterson, a plant molecular geneticist at Texas A&M University in College Station who is moving in January to the University of Georgia, Athens, will look for similar DNA landmarks in sorghum, rice, and corn. And Tanksley's team will be looking at genes involved in fruit development in wild and domestic tomato plants and comparing them with *Arabidopsis*, with an eye to evaluating how evolution has reshaped genomes. "All of these factors will merge into a picture of the interrelatedness that will tie one crop to another," Coe says.

While these groups are exploring the fundamental structure of plant genomes, others will jump into functional genomics—determining how patterns of gene expression vary under different conditions or in different mutants. Among other things, this should help identify genes that affect plant yields or responses to stresses such as high salt concentrations or infection by pathogens.

For example, plant geneticist Bertrand Lemieux of the University of Delaware, Newark, wants to find the genes that enable some corn varieties to produce more oil than others, and UC Davis's Wilkins will try to track down all the genes important to cotton fiber formation—information that could ultimately lead to improved cotton varieties. A team coordinated by Hans Bohnert, a biochemist at the University of Arizona, Tucson, will focus on identifying genes involved in salt tolerance, while Nina Fedoroff of Pennsylvania State University in University Park and her colleagues will look for genes that turn on or increase their activity when plants are subjected to high concentrations of ozone and damage by pathogens. "Rather than providing just [DNA] sequence, we're attacking a biological problem," Bohnert says.

Once identified, such genes might be used to genetically engineer plants with improved yields or resistance to the various stresses. Fedoroff hopes eventually to create inexpensive monitors that will let farmers detect when their crops are at risk. It may take years to achieve these goals, Fedoroff and Bohnert note. But in the meantime these projects will invigorate basic research. Genes involved in fiber formation, for example, will help plant physiologists understand cell growth in general, and there should soon be a wealth of new genes of all kinds to study in corn. Says Tanksley, "plant biology, like all biology, has embarked on a golden age." Or, as Gerald Tumbleson, a Minnesota corn farmer, said at a press conference announcing the NSF awards, "With this season of biology, we're going to be able to do things that we only dreamed of before. I just wish I was 20 years old, because I think this is fantastic." **–ELIZABETH PENNISI**

DNA Studies Challenge the Meaning of Race

NEWS

Genetic diversity appears to be a continuum, with no clear breaks delineating racial groups

Last year, the U.S. Office of Management and Budget (OMB) completed a contentious 4-year review of the racial and ethnic categories that will be used to define the U.S. population in federal reports, including the 2000 census. It finally settled on seven groupings: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian (added after OMB received 7000 postcards from Hawaiians) or Other Pacific Islander; White; Hispanic or Latino; and Not Hispanic or Latino. The categories could have enormous implications—from the distribution of government resources to political districting to demographic research. But as far as geneticists are concerned, they're meaningless.

"Ridiculous" is the word cultural anthropologist John Moore of the University of Florida, Gainesville, uses to describe such racial typing. This view is based on a growing body of data that indicates, as Moore says, that "there aren't any boundaries between races." Geneticist Kenneth Kidd of Yale University says the DNA samples he's examined show that there is "a virtual continuum of genetic variation" around the world. "There's no place where you can draw a line and say there's a major difference on one side of the line from what's on the other side." If one is talking about a distinct, discrete, identifiable population, Kidd adds, "there's no such thing as race in [modern] *Homo sapiens*." Indeed, the American Anthropological Association urged the government last year to do away with racial categories and, in political matters, let people define their own ethnicity.

You might think that this emerging view of genetic variation would help lower the temperature of discussions about race and ethnicity. But, ironically, researchers who want to extend their studies of genetic diversity are being stymied by the intense sensitivity surrounding the topic. A major international project to survey genetic diversity around the globe is on hold, having been opposed by activists. Moreover, a planned database of genetic polymorphisms is being constructed in a way that will prevent comparisons between different population groups, making it useless for exploring the gene frequency variations that do exist, according to researchers.

Anthropologists have long objected to the stereotypes that are used to classify human populations into racial groups. But the most potent challenge to such groupings has come from genetic studies of human origins. The field was "transformed" in the late 1980s, says anthropologist Kenneth Weiss of Pennsylvania State University in University Park, by an analysis of variations in mitochondrial DNA (mtDNA) begun by Rebecca Cann of the University of Hawaii, Manoa, Mark Stoneking of Penn State, and the late Allan Wilson of the University of California, Berkeley. These researchers reported that diversity in mtDNA genes was two to three times greater in Africa than in Europe or the rest of the world. Assuming that the rate of change in mtDNA was fairly constant, they concluded that Africans' mtDNA was older than that of non-Africans, and that modern humans originated from a small population that emerged from Africa and migrated around the globe.

Since the 1980s, other researchers have extended these studies by looking at diversity in nuclear DNA. Two years ago, for example, Kidd and his Yale colleague Sarah Tishkoff reported patterns of variation in the CD4 gene locus on chromosome 12 among 1600 individuals chosen from 42 populations from around the world (*Science*, 8 March 1996, p. 1380). They have since looked at 45 short tandem repeats across the entire nuclear genome in multiple populations. What they found, says Kidd, is "a lot of genetic variation in Africa, decreasing genetic variation as you go from west to east across Eura-