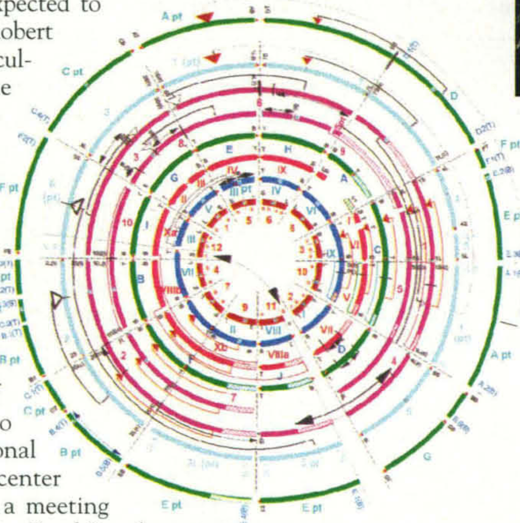
Corn Genome Pops Out of the Pack

Congress is poised to launch a corn genome project, but plant geneticists want to make sure other, related cereal grains aren't ignored

IRVINE, CALIFORNIA—In the next few weeks, key members of the U.S. Congress are planning to plant seed money into appropriations bills to launch a new genome project. This ambitious effort, focused on corn, or maize, the quintessential American food crop, could mean tens of millions of dollars for crop genetics research in the next few years.

The prospect of such an initiative has grabbed the attention of plant scientists, who hope it could do for crop genetics what the multibillion-dollar Human Genome Project is beginning to do for human genetics. By helping to unravel the multitude of genetic mysteries hidden in corn's crunchy kernels, the project could aid in understanding and combating common diseases of grain crops. It could also provide a big boost for efforts to engineer plants to improve grain yields and resist drought, pests, salt, and other environmental insults. Such advances are critical for a world population expected to double by 2050, says Robert Herdt, director of agricultural sciences at the Rockefeller Foundation. "Four species provide 60% of all human food: wheat, rice, maize, and potatoes," says Herdt. "And we don't have good strategies for increasing the productivity of plants."


S. MCCOUCH



Old friends. Rice, wheat, and corn—key grains on a list of grass genomes to be sequenced—are believed to have diverged some 60 million years ago.

SOURCE: M. GALE

Herdt was one of 50 plant scientists who gathered at the National Academy of Sciences' center here 2 to 5 June for a meeting billed as "Protecting Our Food Supply: The Value of Plant Genome Initiatives." Although there's widespread enthusiasm for a plant genome project focused on a crop, the meeting revolved around the question of how much emphasis should be put on corn—which has a huge, complex genome. Several researchers believe the project should intensively study rice, too, which has a much simpler genome, and several other species from the genetically similar grasses family.

Unlike many meetings in which scientists dreamily discuss prospects in their field, the talks at this one were integral to the policymaking process. One of the meeting's co-organizers, Ronald L. Phillips of the University of Minnesota, St. Paul, is also chief scientist for the competitive grants program at the U.S. Department of Agriculture (USDA) and chair of a task force preparing a report to Congress about how the government should proceed on such an initiative. "This is the only meeting that I knew was going to be important from the outset," said Michael Freeling, a University of California, Berkeley, geneticist and the meeting's co-organizer, at the opening session.

Ear ye, ear ye

As much as scientists would like to see a crop genome project that studies several grasses, organizing it around corn makes a great deal of political sense. Corn is a potent economic force, providing much of the feed for the country's livestock, basic ingredients for everything from drugs to ethanol, and up to $8 billion in exports. And the industry is represented by a formidable political lobby, the National Corn Growers Association.

Indeed, the idea for a publicly funded corn genome project began to take root late in 1995, when the growers' association put its muscle behind it. The sales pitch includes a 70-page business plan and a slick video promoting a "national corn genome initiative." They have won the backing of Senator Christopher "Kit" Bond (R–MO), who chairs the subcommittee that funds the National Science Foundation (NSF). "One of the reasons we're here [in Irvine] is because of the corn growers and the political momentum they created," said corn geneticist Joachim Messing of Rutgers University in Piscataway, New Jersey.

Bond says he is keeping an open mind about the project and that he welcomes input from scientists. "Give us a game plan," Bond told presidential science adviser Jack Gibbons and NSF director Neal Lane at a 22 April hearing on NSF's 1998 budget request. Bond asked Gibbons to assemble a panel to come up with such a plan, and the White House responded by creating the task force that Phillips chairs. An interim report is due this month, with a final report by December.

Several hundred academic researchers in the United States are studying corn genetics, estimated Ed Coe of the University of Missouri, Columbia, and three companies have projects under way to identify corn genes. But there is scant coordination between any of these efforts, and much of the data from the private companies are not widely available (see sidebar). The solution, according to the corn growers, is a federally funded, $143 million research program that would stitch together these varied efforts.

Given a chance to put science in the driver's seat, plant geneticists are trying to block out the key issues. The most fundamental question is the same one that faced researchers who launched the Human Genome Project a decade ago: What level of detail is needed? One group would like to fish out from corn and other model plants just the sequences of genomic DNA most likely to code for genes. That's typically a small part of any genome. Another camp says that sequencing the entire genome is the only way to find all the genes and understand their relation to each other. "This is 'déjà vu all over again,' " says David Cox, who co-directs a center working on the Human Genome Project at Stanford University. The lesson from the human experience, he says, is that "you need both."

However, the big problem with sequencing the entire corn genome is just that—it's big. Corn has about 3 billion pairs of bases (the building blocks of DNA), which makes it comparable in size to the human genome.

Please Pass the Data

IRVINE, CALIFORNIA—Deciphering the genetics of the mustard plant won't by itself meet the world's increasing demand for food. But plant biologist Christopher Somerville thinks that it can teach his colleagues a lot about sharing as they embark on a grain genome project (see main text).

Somerville is part of a coordinated, international effort to decode, or sequence, all of the DNA in the genome of *Arabidopsis* (*Science*, 4 October 1996, p. 30). But a slide he presented at a recent meeting on food crops (see below) makes clear that the extent of collaboration has been uneven. While several groups were sharing sequence information fully, he says, Japanese and European researchers had yet to put any sequences into public databases. "From the beginning, we've had a lot of international cooperation, and this is not in that spirit," says Somerville, who heads the Carnegie Institution of Washington's plant research branch in Stanford, California.

Leaders of both the Japanese and European *Arabidopsis* projects acknowledge the shortfall, but they say there's good reason. Michael Bevan of Britain's John Innes Centre, who heads the international consortium on the plant that Somerville and others contribute to, notes that European researchers, unlike their U.S. counterparts, don't release data until they have verified its accuracy. "The rapid release of highly accurate, annotated sequence is a goal we all aim to achieve," says Bevan. Satoshi Tabata, who heads the Japanese project at the Kazusa DNA Research Institute in Chiba, Japan, says money has been a big obstacle to the posting of data. Tabata says the project will begin releasing data next month and "will keep releasing data without delay after that."

Regardless of which view prevails, the *Arabidopsis* experience illustrates the obstacles to any effort to coordinate the sharing of genomic data. And even when scientists profess fidelity to the idea of sharing, the interests of industry and nationalism can be overwhelming. Michael Gale, a plant molecular biologist also at the Innes Centre, is much worried by what he says is recent pressure from the European Union (EU) to give industry first crack at any genome data. "The EU wants to protect its databases," says Gale. "It's something we should all fight very vigorously."

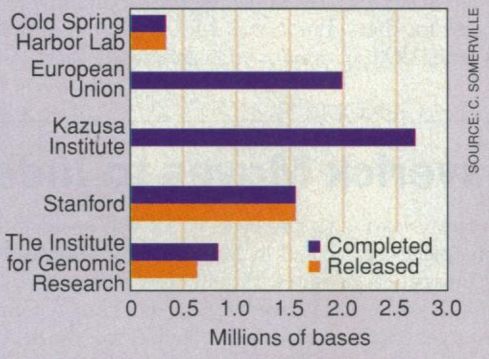
Rice genome researchers have long complained that Japan's 7-year-old rice genome project has been slow in sharing data (*Science*, 18 November 1994, p. 1187). While tensions have eased as the Japanese researchers have made their data and materials more widely available, similar concerns are being raised about the availability of data from a Chinese project. In particular, says Susan McCouch of Cornell University, Chinese researchers have had little interaction with foreign colleagues. "We have almost no information out of the Chinese project," said McCouch. "No one I know has ever seen any of that data."

Hong Guofan, director of the National Center for Gene Research at the Chinese Academy of Sciences in Shanghai, told *Science* that he expects the situation to improve shortly. An Internet site will offer data "as soon as the relevant financial arrangement has been settled." Hong noted that Chinese rice researchers also submitted an abstract of their work at a meeting in South Carolina last October and have a related paper in press. McCouch replies that Hong canceled his talk at the South Carolina meeting and again at a meeting held in San Diego this January. "As far as I am concerned, an abstract is not 'sharing data,'" says McCouch.

Other genomic data about grains are being held close to the vest because industry is directly funding the work. Three U.S. companies—Pioneer Hi-Bred, Monsanto, and DuPont—have corn genome projects under way. The highest profile belongs to Pioneer's project, a 3-year, $16 million deal with Human Genome Sciences of Rockville, Maryland, to pluck out pieces of corn genes and assemble them in a database.

Setting the rules for access to such databases can be tricky. Pioneer's Steven Briggs says the data, while not in the public domain, are available. "We've granted everyone's request for access," said Briggs about the project, which began in January 1996. Briggs urged the U.S. government to negotiate with industry to gain access to private databases.

James Cook of the U.S. Department of Agriculture had some advice for the feds, too: Be tough with collaborators who withhold information. "If our partners are not holding up their end, pull the plug," said Cook. For their part, most scientists prefer the carrot to the stick. "A data-release war [would be] a disaster for the genome project," says Rob Martienssen, who co-leads the *Arabidopsis* sequencing project at Cold Spring Harbor Laboratory in New York. "We can only encourage them and lead by example." –J.C.



SOURCE: C. SOMERVILLE

Unequal portions. *Arabidopsis* collaborators follow different practices about sharing databases.

It also has an abundance of repeated sequences, which probably contain worthless information. Rice, on the other hand, is the smallest of the crop grasses (see table), with only 430 million base pairs. Moreover, rice has a great deal in common with corn, wheat, oats, barley, and other members of the grasses family, says rice researcher Susan McCouch of Cornell University. "Rice is the closest thing to the ancestral version of the grass genome," says McCouch. "Yet it still embodies the essential set of genes for grasses."

Researchers have already found broad similarities between the genes of different members of the grass family (see circle diagram). "It's no longer OK for me to be a wheat geneticist and for you to be a rice geneticist," says Michael Gale, a plant molecular biologist from the John Innes Centre in Norwich, U. K. "We all have to be cereal geneticists." But he says "it's still an open question" how many genes the different grasses actually share.

Obtaining the entire rice sequence would clarify how much "synteny"—similar genes that appear in similar locations of the genome—exists between the grasses. But how to get the most bang for the bucks that researchers hope Congress will devote to the project is another question. "If we get $100 million, do we suck it all into the rice genome?" asked Jeff Bennetzen, a corn geneticist at Purdue University. "For me, whole-genome sequencing is a low priority." Timothy Helentjaris of Pioneer Hi-Bred emphasized that rice has little political muscle. "If you got down to details and said 70% [of the budget] is for rice sequencing, you'd set off red flags," said Helentjaris.

Cornucopia project

By the meeting's end, participants had cobbled together a plan that seemed to satisfy the majority. The first was a proposal for an international rice genome sequencing effort, with the United States putting up half of the money and inviting China and Japan, both of whom are funding rice genome projects, to join. The scientists also suggested building up a database of short sequences, called "expressed sequence tags" (ESTs), that can be used to identify expressed genes. They recommended sequencing 500,000 ESTs for corn and 100,000 each for rice, wheat, oats, barley, and sorghum. The group also called for computer databases to share data as they are generated and stock centers where researchers can freely receive the clones used to study the various plants.

COMPARATIVE GENETICS

Species	Genome size (millions of bases)	Predicted # genes
Mycoplasma genitalium	0.58	482
Haemophilus influenzae	1.83	1,727
Escherichia coli	4.72	4,307
Saccharomyces cerevisiae	12.50	6,000
Caenorhabditis elegans	100	13,100
Arabidopsis thaliana	150	20,000
Oryza sativa (rice)	430	30,000
Sorghum bicolor (sorghum)	760	30,000
Zea mays (corn)	2,000	30,000
Homo sapiens	3,000	100,000
Triticum aestivum (wheat)	16,000	30,000

SOURCE: SUSAN MCCOUCH/CORNELL

Gnats and giants. Grain genomes range in size, but are much larger than the nonhuman species being sequenced.

The plan won plaudits from government officials eager to avoid a congressional mandate. "I'm very enthusiastic about what I've heard at this meeting," said Mary Clutter, head of the biology directorate at the NSF. "That is, focus on the science and let us build a program" to present to Congress. Clutter would like several agencies to participate in a project led by the USDA, with NSF funding a steering committee that would draw up a request for the 1999 fiscal year that begins on 1 October 1998.

That's not soon enough for Kellye Eversole, a lobbyist for the corn growers at the meeting. "We don't want to spend another year on planning," says Eversole. "We want to see this get off the ground in 6 to 7 months." But James McLaren of Inverizon International, which drew up the business plan for the corn growers, signaled a willingness to be flexible about the scope of the project. "If you all tell me the best way to improve corn is to sequence rice, I'll support you," said McLaren. "But you'd better be right, because [the corn growers] are standing out front."

Congress also seems eager to get started. A staffer in Bond's office who asked not to be named told *Science* that legislators plan to designate $10 million for the effort in two separate parts of the spending bill for the agriculture department. Another earmark might appear in the appropriations bill that funds NSF. But Clutter takes issue with that approach. "Earmarking … is anathema to the Administration," said Clutter. "It means taking away money from something planned."

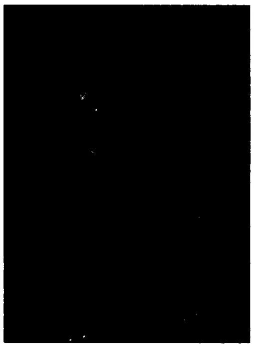
Indeed, says Cliff Gabriel of the White House's Office of Science and Technology Policy, starting a genome project means curbing or ending an existing program. And although he didn't propose any candidates for the chopping block, he told the group that the Administration supports a grain initiative. "The time is right to do something," he said.

–Jon Cohen

GENOMICS

Alzheimer's Maverick Moves to Industry

Since 1994, the British drug company Glaxo Wellcome has been buying bits and pieces of U.S. biotech firms as part of a push into genetics. On 17 June, the company announced a surprising choice to direct its growing genetics empire: Allen Roses of Duke University, a prominent neuroscientist and controversial Alzheimer's disease researcher. Roses will run this $47 million directorate from Glaxo's U.S. headquarters in Research Triangle Park, North Carolina.



LES TODD/DUKE UNIVERSITY

Glaxo-bound. Roses will head genetics program.

Roses, an outspoken researcher whose ideas about the genetics of Alzheimer's have drawn a mixed reception from his peers, has been at Duke for 27 years and was named director of the university's Center for Human Genetics in 1996. He says the main reason he took the job with Glaxo is that "We are at a point now in the understanding of Alzheimer's disease [at Duke] that we are targeting" therapeutic products. "Universities don't make drugs and governments don't make drugs," Roses says, but "Glaxo Wellcome does." Glaxo Wellcome has funded Roses's work at Duke, and he says his research program will "be accelerated by my being inside" the company. Glaxo has agreed to allow Roses to continue some research at Duke as an adjunct professor.

As director of Glaxo's international genetics program, Roses will command a program based in labs in three countries (the United States, Britain, and Switzerland), comprising 150 researchers. According to Glaxo, the staff is expected to double over the next 18 months, as new departments are created to "ensure that genetics plays its part not only in drug discovery but also in development and in the commercialization of medicines." Roses's job will be to forge a coherent strategy, linking combinatorial chemistry at Affymax Research Institute of Palo Alto, California (purchased by Glaxo in 1995), gene expression research at Incyte Pharmaceuticals Inc. of Palo Alto (as of last month, a partner of Glaxo's), and clinical genetics studies at Spectra Biomedical of Menlo Park, California (purchased by Glaxo this month).

Roses says one of the reasons the company chose him is that he's not a fence straddler. Indeed, he notes, some of his peers have called him a "street fighter." For example, he recently spoke out at a Senate subcommittee hearing about what he called lack of vision in the public biomedical funding agencies. He says his grant requests to the National Institutes of Health received poor ratings from "narrowly focused scientists" with "dogmatic belief systems." His lab would have closed, he added, had it not received funding from Glaxo Wellcome.

Roses may be best known for showing that a protein involved in cholesterol transport (apolipoprotein E) is a factor in Alzheimer's disease. Roses and his colleagues also linked genes that encode variants of the protein (the apoE genes) to varying degrees of risk for Alzheimer's disease. Alison Goate, an Alzheimer's researcher at Washington University in St. Louis, says that while most researchers would agree that the gene known as apoE 4 is "the single most important risk factor" for Alzheimer's disease in the under-70 population, some of Roses's other conclusions are not widely accepted. Most controversial, Goate says, is a theory of Roses and his Duke colleague Warren Strittmatter that "good" versions of the apoE gene (E2 and E3) produce a protein that helps maintain healthy nerve cells, while the "bad" variant (E4) fails to do so, leading to Alzheimer's disease (*Science*, 19 November 1993, p. 1210). Because some Alzheimer's patients do not have the apoE 4 gene, and some people who have the gene do not have the disease, many researchers doubt that a test for apoE 4 would have value in predicting whether a healthy person will get the disease.

While Roses may seem an iconoclast to some, his colleague Peter St. George-Hyslop of the University of Toronto says he's really "not all that outrageous … he likes to play that angle." Goate agrees: "He thrives on controversy." As for Roses's move to Glaxo, St. George-Hyslop comments: "It's good for them, bad for academic science."

–Eliot Marshall