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Kidney stones from bacteria?

HUMAN GENOME PROJECT

A Planned Boost for Genome Sequencing, But the Plan Is in Flux

The National Human Genome Research Institute (NHGRI) last week awarded $60.5 million to seven centers across the United States to scale up their efforts to sequence the human genome. The awards should enable the centers to crank out 117 million bases next year—almost double the total produced so far by all U.S. groups combined. But exactly what the centers will do with the money isn't clear, for NHGRI has asked them to spend the next 2 months evaluating a proposal for a radical change in the plan to sequence all 3 billion base pairs that make up our genetic code.

Until now, the Human Genome Project has been marching methodically toward producing a highly accurate sequence of the entire genome by 2005. For the past 2 years, eight groups in the United States have been honing their techniques and procedures, and last week's awards were originally designed to permit the best of them to start churning out sequence in earnest. Next year, according to the plan, the field would be narrowed to perhaps five groups that would spearhead the final assault on the genetic code. At the same time, Britain's Wellcome Trust has been funding a program at the Sanger Centre near Cambridge, U.K., that would complete one-third of the genome; the NHGRI grantees are expected to sequence about 60%. But now, NHGRI is considering backing a crash effort to create a "rough draft" of the genome by 2001, with the final, detailed blueprint completed perhaps 4 years later. "We're in a period of ferment," says Eric Lander, who heads the sequencing effort at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. "We know [the sponsors] are entertaining all sorts of changes."

The ferment began in May, when J. Craig Venter, president of The Institute for Genomic Research (TIGR) in Rockville, Maryland, stunned the genome community by announcing that he will team up with Perkin-Elmer Corp. in Norwalk, Connecticut, to launch a private effort to sequence all the important parts of the genome in 3 years (*Science*, 15 May, p. 994). Venter insists his results will be about as complete and accurate as those the government-funded program will produce, but many fellow sequencers are not convinced. They also worry that the effort could lock up large amounts of genetic data in proprietary claims. That concern prompted leading genome researchers to call on NHGRI last month to consider ways to generate sequence faster. Thus was born the idea of producing a rough draft, which would help pinpoint genes and provide important information on most of the coding regions, followed later by a rigorous, completed genome.

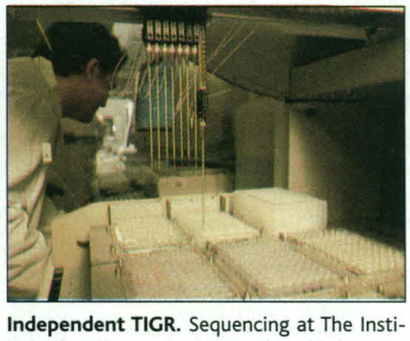
THIRD-YEAR FUNDING

Investigator	Award ($ millions)	Sequencing Goals
Glenn Evans University of Texas Southwestern Medical Center, Dallas, TX	5.04	10
Richard Gibbs Baylor College of Medicine, Houston, TX	8.0	18
Eric Lander Whitehead Institute/MIT, Cambridge, MA	8.2	13
Richard Myers Stanford University, Palo Alto, CA	3.0	4.5
Maynard Olson University of Washington, Seattle, WA	7.5	7.4
Bruce Roe University of Oklahoma, Norman, OK	2.0	4.0
Robert Waterston Washington University, St. Louis, MO	26.8	60
TOTAL	$60.54	116.9 Mb

That approach, however, would require a shift throughout the program from a slow and narrow analytical style to a broader—but riskier—attack. So far, the U.S. centers and the Sanger Centre have been advancing clone by clone—completely sequencing DNA in about 150,000-base chunks, the amount contained in the bacterial clones used to replicate human DNA. Researchers cut each chunk into many smaller, overlapping bits, which are sequenced and then pieced together by computer programs and by experts called finishers. Venter, in contrast, plans to chop the entire genome into small bits, sequence them with a new generation of Perkin-Elmer machines, and use supercomputers to fit the data together—an approach called whole-genome shotgun sequencing.

The NHGRI-funded centers are not planning to try whole-genome shotgunning, but they are looking at ways to speed up their processes. One possibility is not to wait until one chunk of DNA is finished before going on to sequence the next. "Ideally the [sequencing and finishing] would ramp up equally," says Richard Gibbs, who runs the sequencing center at Baylor College of Medicine in Houston. But this summer, he and others plan to uncouple the two processes. In this way they will determine just how difficult it is to generate data and finish the sequence independently.

Other awardees are looking to reduce the amount of redundant data needed for each piece of DNA sequenced. Currently, most bases are sequenced about 10 times in overlapping stretches of DNA. The redundancy helps in piecing the stretches together, and it reduces errors by pinpointing aberrant sequences. Bruce Roe, a biochemist who directs the sequencing center at the University of Oklahoma, Norman, among others, is now evaluating how well his team can piece together sequence where each base is represented only two, four, or six times.



SAM KITTNER

Independent TIGR. Sequencing at The Institute for Genomic Research, which is no longer participating in the NHGRI project.

At the University of Texas Southwestern Medical Center at Dallas, human geneticist Glenn Evans is investigating just how useful various rough drafts would be. "The issue of completeness and utility has never been determined," says Richard McCombie, a sequencer at Cold Spring Harbor Laboratory in New York. "We don't know anything about intermediate sequencing products," notes Jane Peterson, an NHGRI cell biologist who oversees the human genome sequencing effort. "We have to be sure it will be useful." And the first requirement, adds Lander, is that a draft "can't impede our ability to finish."

In early September, NHGRI will evaluate the results of these efforts and decide whether to proceed with its original plan—to produce a detailed sequence over the next 6 years—or shift gears to focus on an interim rough draft. The awards announced last week (see table) are based on the original plan. They assume that the seven centers—which include all those that took part in earlier phases, except for TIGR—will be generating 117 million bases of detailed, finished sequence. If the program is refocused, next year's sequence output should be considerably higher.

That possibility pleases Evans. His team was dismayed by the prospect of being beaten to the complete genome by Venter, and he says doing a rough draft would be "a legitimate way of not being scooped." And, he adds, "it's politically the right thing to do."

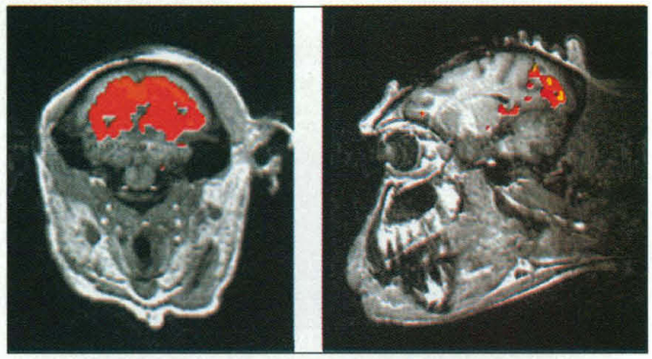
–ELIZABETH PENNISI

NEUROSCIENCE

First Images Show Monkey Brains at Work

Monkey brains have gotten plenty of close scrutiny from researchers studying functions such as perception and memory. But monkey researchers have been unable to use one promising technique: functional magnetic resonance imaging (fMRI), which maps out active brain areas and has revolutionized the study of human brain function. The problem is convincing a monkey to sit perfectly still and perform a thought task inside the claustrophobic banging magnet that creates the magnetic resonance images. Now Tom Albright and his colleagues at the Salk Institute and the University of California, San Diego, have overcome the difficulties. In the June issue of *Neuron*, they have published the first fMR images of activity in a monkey's brain. A second team, headed by Richard Andersen at the California Institute of Technology (Caltech) in Pasadena, has a similar study coming out next week in *NeuroReport*.

These successes, achieved by patiently training the monkey and designing a special seat to restrain it in the magnet, could ultimately help neuroscientists get more out of human fMR images. This noninvasive technique, based on the magnetic signal of oxygen in the blood, records the increases in blood flow that result from changes in neural activity. But what individual neurons are doing in the areas that light up on an fMR image is open to interpretation, because researchers can't stick electrodes into the brains of healthy humans. "Monkey fMRI will allow us to test our interpretations," says neuroscientist Robert Desimone, who directs intramural programs at the National Institute of Mental Health.



L. STEFANACCI *ET AL., NEURON*

Mind of a monkey. The colored patches show activity detected by functional magnetic resonance imaging in the visual areas of the brain of a rhesus monkey as it watched a children's cartoon.

The technique should also benefit traditional electrode studies of monkey brain activity. "Say I am interested in a perceptual phenomenon, but I don't have much evidence about the part of the brain that underlies it," says Albright. "fMRI gives me a way of identifying the relevant parts of the brain, which will then guide my microelectrode studies."

The first monkey fMR images, which show activation of the visual system as the animal watched a children's cartoon, don't offer any new scientific insights—just a proof of principle. To make them, both Albright's and Andersen's groups designed chairlike apparatuses made of nonmagnetic materials that hold the monkey still inside the magnet, in variations of a position Andersen describes as "sphinxlike," on haunches and elbows and looking forward, down the length of the magnet. "We worried that it would be difficult to get the monkey to cooperate," says Albright, but they found that by rewarding the monkey with juice, they were able to train it to relax in the magnet.

Both groups worked with ordinary hospital MRI machines—horizontal magnets designed to accommodate a prone human. But several labs, including those of Nikos Logothetis at the Max Planck Institute in Tübingen, Germany, and Carl Olson at Carnegie Mellon University in Pittsburgh, are working with manufacturers to develop a new generation of MRI machines specifically for monkey research. The magnets are vertical, allowing the monkey to sit upright, and have greater magnetic fields, which will increase the resolution of the images, says Andersen, who hopes to have such a facility at Caltech within 2 years.

In the meantime, Albright's and Andersen's teams are using the hospital magnets to test the relation of fMR images to neural activity in monkey brains and look for new brain areas to explore with electrodes. Eventually, Albright says, the researchers will need the better resolution—and the additional research time—available with the dedicated machines. But for now, he says, "the important thing was to show we could do it."

–MARCIA BARINAGA

DRUG DEVELOPMENT

Small Molecule Fills Hormone's Shoes

As diabetics who must inject themselves daily with insulin know only too well, a major disadvantage of protein drugs is that they can't be taken orally. Drug companies would love to find small compounds that mimic the effects of these drugs yet evade breakdown in the digestive tract. But for many protein drugs—including insulin and other hormones known as cytokines—that has seemed a forlorn hope. These proteins stick snugly to large surfaces on their receptors, and small chemicals—which might be just 1/50 of a protein's size—seemed too puny to turn on such receptors. "People didn't feel that a