# Japan Centers In on Genome Work

From sequencing to large-scale NMR spectroscopy, genomic research wins a big boost in Japan's new budget. But some worry that its priorities are skewed

TOKYO—After years of lobbying for increased support, Japanese genome scientists stand on the threshold of a major increase in funding. Despite frantic efforts to tighten its belt, the government has proposed a doubling of spending on genome-related research in 1998. The increases are spread across agencies and fields, and include one program that researchers see as breaking new ground in genome-related work.

The centerpiece of this new program is a proposed large-scale nuclear magnetic resonance (NMR) imaging center to study protein structure, which scientists both here and abroad believe will be the next important step in genome work. "It will be on a grander scale [than] any NMR centers that we know of," says Kurt Wüthrich, chair of the department of biology at the Swiss Federal Institute of Technology (ETH) in Zurich. Adds Gaetano Montelione of Rutgers University's Center for Advanced Biotechnology and Medicine in Piscataway, New Jersey, "The structural analysis component [of Japan's plans] gives them a chance to leapfrog" to the forefront of genome efforts. Such a major effort "will be crucial ... to complement other methods of determining gene and protein function," says Montelione, who is also studying how to scale up NMR techniques for structural biology.

The center's promoters plan to open the facility to research groups from around the world. "It's one way Japan can make an international contribution" to genome efforts, says biophysicist Akiyoshi Wada, director of the private Sagami Chemical Research Center, who was formerly at the University of Tokyo.

Even that contribution, however, may not be enough to allay concerns that Japan is not doing enough to advance human genome sequencing efforts around the world. Although Japan is setting the pace in sequencing the rice genome (see sidebar on p. 1702), its human sequencing efforts are modest despite government plans to add a sequencing program to ongoing efforts. Molecular biologist Yusuke Nakamura, director of the University of Tokyo's Human Genome Center, finds it odd that the government would fund the NMR center while slighting the sequencing work he thinks should come first. "This research has to be done step by step," he says. "But in Japan, some steps are being omitted."

### Structural solutions

The NMR center would be one of three components of a new Genetics Frontier Research Center at the Institute of Physical and Chemical Research (RIKEN) near Tokyo. Sponsored by the Science and Technology Agency (STA), the new center is expected to get $33.3 million, or more than one-fifth of the $149 million in genetics-related research spending proposed for next year. An enhanced human genome sequencing center will complement the NMR work. "Japan doesn't yet have a high-throughput [sequencing] center," says Yoshiyuki Sakaki, a molecular biologist at the University of Tokyo's Human Genome Center, who will move to RIKEN to head this part of the program.

**BIG BOOST FOR GENOME RESEARCH**

| Agency | 1998 Budget ($ million) | % Change Over 1997 |
|---|---|---|
| **Science and Technology Agency (STA)** | $57.7 | +71 |
| Genetic Frontier Research Center | $33.3 | +400* |
| Gene function database development | $12.2 | –7 |
| Promoting use of research results | $10.6 | NA |
| Other programs | $1.6 | –0.1 |
| **Monbusho (Education/Science Ministry)** | $26.6** | +31** |
| University of Tokyo Human Genome Center | $13.7 | +97 |
| National Institute of Genetics database | $12.9 | –3 |
| **Ministry of Health and Welfare** | $21.1 | +69 |
| Gene therapy research | $21.1 | +69 |
| **Ministry of Agriculture, Forestry, and Fisheries** | $24.2 | +184 |
| Rice genome sequencing, functional analysis | $13.2 | +429 |
| Other programs | $11.0 | +82 |
| **Ministry of International Trade and Industry** | $19.3 | +275 |
| Analysis of industrially useful microorganisms | $2.65 | +16 |
| Genome informatics technology | $12.7 | +533 |
| Other programs | $4 | +53 |

* Includes all programs to be bundled into the new center. ** Depends on 1998 grant awards in two programs. Existing programs disbursed $13.2 million to genome-related research.

SOURCE: JAPANESE GOVERNMENT

Another part of the frontier program aims to sequence mouse cDNA completely, both for the mouse's value as an experimental animal and for studying the function of genes common to both mice and humans. The work will be led by Yoshihide Hayashizaki, chief scientist of RIKEN's Genome Science Laboratory, who is developing new sequencing reagents and techniques to increase sequencing speed and automation dramatically. His techniques also allow cloning of full-length cDNA—the DNA expressed to make a protein—instead of the fragments that typically result from other methods. The cDNA would be used to synthesize proteins, and the protein structure would then be determined by NMR spectroscopy or x-ray crystallography.

The NMR center would be the key to breaking new ground in genome studies. Wüthrich, who is so intrigued with the project that he has signed on as an adviser, explains that sequence data can provide only limited information. In some cases, protein structure and function can be predicted based on similarities with known gene sequence data. But the human genome program, he says, "will lead to the discovery of a very large number of unknown proteins, and to make sense of this information the three-dimensional structure will have to be studied." Structural biology groups are already lined up to use Japan's new SPring 8 synchrotron in Harima, west of Osaka, for crystallography.

Shigeyuki Yokoyama, a biophysicist who holds posts at both RIKEN's Cellular Signaling Laboratory and at the University of Tokyo, says that the scale of the proposed center makes it special. Most labs have only a few of the expensive NMR machines, he says, hardly enough to tackle the 100,000 human proteins arranged in some 1000 structural families. The RIKEN concept is to gather enough machines, 10 in the first stage alone and more later, and a cadre of engineers and technicians to run them.

In addition to its core research, Yokoyama says the center would focus on the development of a new generation of NMR spectrometers using high-temperature superconducting magnets for greater sensitivity. With a large number of advanced NMR spectrometers, Yokoyama says the facility

## How Genome Research Rose to the Top

Japan's national finances are in dire shape. The government has vowed to cut overall spending next year, even though the overall research budget will inch up by 1.4%. So how did genome-related work get earmarked for a doubling? The big increase reflects a confluence of factors, notably a growing public understanding of the value of genome work and a feeling that, after a long wait, it was genome researchers' turn.

"Over recent years, each ministry has devoted more and more of its budget to genome projects as a consensus on the importance of genome work has strengthened," says Kazuo Katao, director of the biochemical industry bureau at the Ministry of International Trade and Industry. Kiyoaki Maruyama, director of research and development for the Ministry of Agriculture, Forestry, and Fisheries, recalls that the small band of scientists and officials in the late 1980s who wanted $2.5 million a year to start mapping the rice genome faced an uphill battle convincing colleagues of the value of the work. But now, a $13.2 million request to move on to large-scale sequencing wins applause because "the value of the work is well understood," he says.

For other programs, it was a matter of waiting their turn. Two of the three projects bundled into the Institute of Physical and Chemical Research's (RIKEN's) proposed Genetics Frontier Research Center—a program to sequence mouse cDNA and a new nuclear magnetic resonance spectroscopy center—had been proposed as separate projects a year ago. But the priority last year at the Science and Technology Agency (STA) and at RIKEN was getting a new neuroscience center off the ground (*Science*, 14 March, p. 1562). This year, RIKEN officials bundled the two programs, added a human genome sequencing center—something the STA had long wanted—and secured backing for the package. Also, in STA's case, significant cuts in nuclear power research freed up funds.

D. NORMILE

**Timely advice.** Mori and science council gave big boost to life sciences.

Another critical factor was an official stamp of approval from the Council for Science and Technology. Chaired by the prime minister, the council is the nation's highest science advisory body. In mid-1996, the council decided to draw up a Basic Plan for Research and Development on Life Science, for no particular reason other than that "the council had never considered life sciences before," says council member Wataru Mori, a pathologist and former president of the University of Tokyo. The council produced a report last August emphasizing the importance of basic research on the functions and structures of genes and proteins as the foundation for progress in all of life science.

Mori says the council's deliberations were not part of a scheme to pave the way for a dramatic increase in funding for life science research. But there is a telling precedent. In mid-1996, the council produced a report on the importance of neuroscience, and the 1997 budget included funding for a new Brain Science Institute. And government officials admit that the genome report helped their case. "If our requests are in line with a report like this, the Ministry of Finance can't be too critical," says Maruyama. –D.N.

would usher in a new era in genome research: "We can combine the structural biology as a part of genome research."

### Gold diggers or good science?

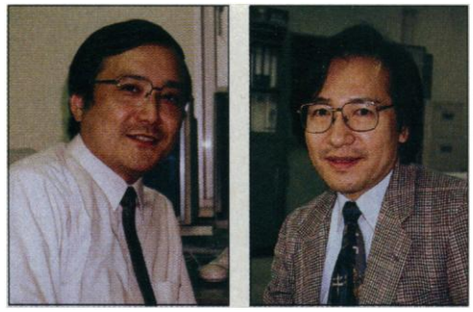
The novel approach has drawn some internal criticism as well as international praise. Tokyo's Nakamura and others would like to redirect the resources for the cDNA and NMR efforts into human genome sequencing. Nakamura says that even with the sequencing component of the RIKEN plan, Japan's contribution to the international sequencing effort will be embarrassingly small.

Nakamura's assessment gets some support from overseas colleagues. "My take [on the plans] is that they are looking toward the future without contributing significantly to the initial sequence data collection phase," says Bruce Roe, who heads a sequencing effort at the University of Oklahoma, Norman. "This smacks of what most [countries] want to do, which is to mine the data," he adds.

Whether the RIKEN program works as planned, Nakamura believes that it will not strengthen the infrastructure needed to pursue the medically important research that builds on the sequencing data. "I am a little afraid about the future of medical research in Japan," he says.

In addition to questioning governmental priorities, Nakamura also thinks scarce resources are being used inefficiently. He notes that most of the additional $6.8 million headed for the university's Human Genome Center next year will go for supercomputing. Meanwhile, a tight budget lets his group run only a few of its 15 sequencers.

For Nakamura, the heart of the problem is the lack of a national strategy for the human genome project. He would prefer to see the government support one or two large-scale sequencing centers, perhaps like Britain's Sanger Centre, that would focus on human genome sequencing and work in cooperation with researchers hunting for disease genes. He feels that the move to structural biology, while important, would benefit by waiting for less expensive, more sensitive NMR equipment.



PHOTOS: D. NORMILE

**At the edge.** Hayashizaki *(left)* and Yokoyama will lead key parts of RIKEN's new genetics center.

The issues raised by Nakamura and others caught the attention of Koji Omi, a Diet member and director-general of the Economic Planning Agency. Omi was one of the driving forces behind the 1995 passage of a Basic Law for Science and Technology, which set the stage for a subsequent plan to boost government spending on research significantly. This fall, Omi reportedly questioned officials of both RIKEN and STA about the feasibility of Hayashizaki's new sequencing technologies and the emphasis on NMR facilities at the expense of sequencing. Omi was not available for comment, but an aide said he was simply trying to understand the program better. In any event, RIKEN and STA officials are confident their plans will be adopted.

Many of those pushing the RIKEN plan agree that the government should also be putting more resources into the university-based genome efforts. But thickets of regulations and red tape make it difficult for universities to hire technicians or assemble teams of scientists. Even Nakamura agrees that Japan's universities are not well-suited for large-scale sequencing efforts.

For political reasons, STA officials say that a grander vision was needed to sell the project to government officials. "It would have been difficult to get the money for a center for sequencing only," says Yasuhiro Itakura, deputy director of STA's life sciences division. At the same time, RIKEN officials acknowledge that the institute can't afford another costly failure after a previous scheme to automate genome

## Rice Genome Races Ahead

While government officials are struggling to reshape Japan's human genome effort, the country's Rice Genome Research Program (RGP) is moving forward with alacrity. Program scientists have put together highly detailed genetic and physical maps, and a large library of cDNA clones, reaching the major goals of the first 5-year phase of the program on schedule and within budget. The work, which includes 2400 DNA markers on a genetic map, has earned plaudits from plant geneticists around the world.

"The [RGP] project has been acclaimed, and rightly so, for its technical contributions," says Susan McCouch, a Cornell University geneticist who works on rice. The program is also getting a vote of confidence from the Japanese government in the form of a proposed 429% increase in funding. The growth could help offset a drop in contributions from the Japanese Racing Association—a quasi-public entity that runs betting operations at the country's horse-racing tracks and is required to donate a portion of its proceeds to agricultural research—that once matched what the government spent but which have been hurt by a sluggish economy.

Whatever the total, the money will support efforts to sequence all 450 million base pairs on the plant's 12 chromosomes and to expand efforts to identify genetic markers common to other cereals. Such a concerted effort has helped the country overcome a fast start by McCouch and her colleagues at Cornell, who published a basic genetic map in 1988. "The U.S. agricultural research establishment is deep; Japan's is shallow," says Naoki Katsura, head of research planning for the National Institute of Agrobiological Resources (NIAR). "So we recognized the merits of concentration."

The logical choice was rice, not only because it has the smallest genome of any of the major cereals, but also because of its importance as a crop and as a cultural icon for Asia. The ministry and its researchers also concentrated resources in one location within NIAR's Tsukuba campus, assembling a team that has grown to 50 scientists.

A similar strategy for the second phase of the project—doubling the number of scientists and hiring more technicians—will also extend collaborations beyond current efforts with the John Innes Centre in Norwich, U.K., to identify markers common to rice and wheat, and scientific exchanges with the International Rice Research Institute in Los Baños in the Philippines. Katsura says he would also welcome help on the large-scale sequencing to shorten what otherwise might be a decade-long effort. **–D.N.**

sequencing was scrapped in the early 1990s. Yokoyama thinks the key to continued government support for genome work is the reaction of the international community. "If this effort is appreciated by other countries, I think [the Japanese government] will expand its support," he says. But if the project is judged solely on its contribution to sequencing, he says, Japan's genome efforts could be in trouble.

Despite the risks, Sagami's Wada is glad the country has decided to chart its own course. And he says he's "very confident" that Japanese researchers will contribute to the global quest to decipher the human genome.

**–Dennis Normile**

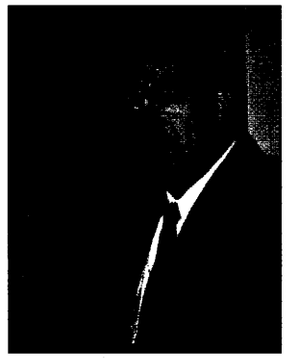
NATIONAL LABS

# SUNY-Battelle Team to Run Brookhaven

Six months of uncertainty at Brookhaven National Laboratory ended last week, when Department of Energy (DOE) managers chose a new contractor to operate the troubled facility in Upton, New York. The winning team, which takes over in January, is made up of the State University of New York (SUNY), Stony Brook, and Battelle Memorial Institute. It now faces the challenge of mending fences with the lab's neighbors and resolving the fate of a major research reactor that local groups and New York politicians want to close.

The new director, former Stony Brook President John Marburger, promises to make major changes to clean up environmental problems and ease the concerns of the surrounding Long Island population. "Job one is to establish contact with our community," he said on 25 November. He also pledged to make "major reassignments" within the 3200-member staff to ensure that Brookhaven abides by environmental regulations while producing quality science. Marburger, a physicist, is a former chair of Universities Research Association Inc., a consortium that operates DOE's Fermi National Accelerator Laboratory, the country's most powerful accelerator.

DOE Secretary Federico Peña fired Brookhaven's current contractor, Associated Universities Inc. (AUI), in May, following revelations of a long-standing tritium leak at the High-Flux Beam Reactor (HFBR), which is shut down for repairs (*Science*, 9 May, p. 890). In the competition that followed, the Stony Brook– and Columbus, Ohio–based Battelle beat out another group led by Westinghouse and IIT Research Institute of Chicago for the $2 billion, 5-year contract to operate the $400-million-a-year lab. The winning factors, DOE sources say, were Stony Brook's proximity to the lab and Battelle's experience in managing large organizations like Pacific Northwest Laboratory in Richland, Washington, next door to the polluted Hanford site used to store waste from nuclear weapons production. DOE says the new contract's higher annual fee—$1 million more than the $4.2 million paid to AUI—reflects the added cost of ensuring environmental safety and restoring public confidence in the lab.



R. STOUTENBURGH/BROOKHAVEN NATIONAL LAB

**Job challenge.** Marburger expects a "difficult" year at Brookhaven.

The new team, called Brookhaven Science Associates, will have a 16-member board, including representatives from the six northeastern universities who make up AUI. But the majority of members will be Stony Brook and Battelle managers, Marburger said. Although DOE told bidders to rule out any layoffs or dismissals, Marburger says "there will be a lot of change in the functions people perform."

One of the most pressing issues for the new operator is the fate of the HFBR. Many neutron scientists are eager for it to come back online, but Senator Al D'Amato (R–NY) and Representative Michael Forbes (R–NY) say it's an environmental hazard that should be closed permanently. Peña is expected to decide by early spring, but even if he sides with the scientists, an environmental impact review will keep the HFBR shut until 1999. That is also the starting date for Brookhaven's newest facility, the Relativistic Heavy-Ion Collider.

Given those problems, Marburger says he's prepared for some long days on the job. "I don't have any illusions," he told reporters. "The next year will probably be a difficult one."

**–Andrew Lawler**