Consensus Elusive on Japan's Genome Plans

Initial goals for automating sequencing project have proved overoptimistic; researchers debate merits of broader program

Osaka

A COUPLE OF YEARS AGO, when American scientists were debating whether to launch a multimillion dollar effort to map and sequence the human genome, there was a lot of talk that Japan was already forging ahead in some of the key technologies. A Japanese government project had been running since 1981 with the aim of developing an automated process capable of sequencing more DNA in a single day than is now sequenced worldwide in a year. Fear of another Japanese technological triumph was one factor in getting the U.S. genome project off the ground.

The goals initially set for Japan's project have proved elusive, however, and they have recently been considerably scaled back. Moreover, there appears to be no consensus here about whether Japan should pursue a more vigorous effort, or what the country's role should be in an international genome project.

"The debate about the value of a sequencing project is just now coming to Japan," says Kenichi Matsubara, director of the Institute for Molecular and Cellular Biology at Osaka University and a strong proponent of a sequencing project. Michio Okamoto, a physician and a senior member of the Prime Minister's Council for Science and Technology, said in an interview, "Human sequencing is a very important subject. But in Japan we haven't reached concrete ideas [about sequencing]. We don't have definite ideas on funding and so on."

A report issued in January by an advisory group to the Ministry of Education, Science, and Culture (Monbusho) endorsed the concept of sequencing the human genome and argued for international collaboration. Last year, the Science and Technology Agency issued a similar statement. But neither agency has offered specific proposals.

While the United States plans on spending about $50 million this fiscal year on sequencing, Japan is spending far less, although it is hard to say exactly how much. The automation project, for example, is budgeted for about 200 million yen, or about $1.6 million, for Japan's fiscal year 1989, which begins on 1 April. Several new projects related to sequencing were begun last year, but they still add up to a modest effort relative to that of the United States.

Japan's efforts have been hampered in part by a lack of good molecular biologists, according to Matsubara. Japanese biologists are also worried that a major commitment by the government to decipher the human genetic code will divert money from their individual work, echoing a concern that has been voiced by some American biologists.

Matsubara, who is a member of the International Human Genome Organization, or HUGO as it is known, says that the idea of a human genome sequencing project "causes an allergic response among biologists" because they fear loss of funding. "They are also afraid of a big project," he says, "because they have an image that it will involve just sequencing and that young people will be used as part of the machine to do the sequencing. I try to tell them that [a human genome project] is an attempt to introduce new biology."

Marjorie Sun

Akiyoshi Wada. *His initial goal of developing technology to sequence 1 million bases a day has been cut back to 100,000.*

Meanwhile, the government's biggest effort related to sequencing—the project aimed at developing high-speed automatic sequencing technology—is struggling along. The Science and Technology Agency initiated the project in 1981, selecting Akiyoshi Wada, a biophysicist at Tokyo University who will become dean of the Faculty of Science next month, to conceptualize and direct the effort.

Wada's ultimate aim is to make the decoding process an assembly line operation. A snip of DNA would be inserted into an automated system that links a variety of different machines to perform the repetitive, complicated procedures involved. At the end of the line, the system would print out the string of bases of the deciphered gene. Operating the process would require a minimal amount of scientific input, which would free up scientists' time for more creative activity, Wada says.

Wada recruited Seiko, Fuji Film, Hitachi Limited, and Mitsui Knowledge Industry Company to bring their technological and manufacturing expertise to bear on the development of prototype machines. His original goal was to "supersequence" an average of 1 million bases a day. The current rate of production worldwide is 1 million bases annually. Eight years and almost $13 million later, the machinery and technology developed can sequence an average of 10,000 finished bases a day. Sequencers developed in the United States have about the same capability.

Biologists criticize Wada for tailoring new machinery and robotics around existing biochemical techniques. They believe the project should have concentrated first on improving the methodology and then building machines based on new techniques. "It took 4 years to construct the machines. But in those 4 years, the techniques changed," says Matsubara.

The project has also been hampered because the interest of a couple of key corporate participants has waned or run out. Seiko, fearing damage to its reputation for producing reliable products, has decided that its sequencing machine is not good enough to market abroad, Wada says. The company markets a small sequencer only in Japan. (Hitachi also has a sequencer that is being used in the project.)

Fuji Film, which developed special electrophoresis gels for sequencing, has dropped out of the project altogether. The gels were expensive to make and so fragile that overseas shipment was virtually impossible, which limited the commercial value of the product to Fuji, according to Wada.

Eiichi Soeda, a scientist at the Riken Laboratories in Tsukuba City who has collaborated heavily with Wada in testing the system, says the goal has been lowered to

sequencing 100,000 bases a day, which he hopes to achieve in 3 years. Although the project has fallen far short of its initial aims, Soeda, who is still upbeat, says, "I'm happy with the progress so far. Three years ago, people said it's crazy to try to automate."

But Wada says with frustration, "I'm stressing the need for a huge system, but there is no need for it right now." The participating companies "are content to build small machines for small labs, but they have no interest in building huge machines until the market becomes confident."

While the automation project continues, various government agencies in the past year or so have undertaken some interesting new projects related to sequencing. Monbusho is sponsoring an effort to sequence *Escherichia coli*. It is a huge objective, but actual funding for the project is modest, according to Maynard Olson of Washington University, who recently returned from Japan where he attended a meeting on genome sequencing. Olson himself is collaborating with Riken Laboratories, which are supported by the Science and Technology Agency, to sequence a yeast chromosome. The government is also spending a small amount of money to begin mapping and sequencing human chromosome 21, Olson says.

Some scientists advocate linking a human genome project with the Human Frontiers Science Program, an international collaborative effort in basic science proposed by Yasuhiro Nakasone while he was Prime Minister. The program is now just getting started. As originally conceived, the Human Frontiers program would have included work in sequencing. But over the years, the focus has shifted to brain science and other areas of molecular biology. Okamoto, who played a leading role in developing the Human Frontiers concept, is among those who would like to see sequencing projects included. "With the start of the Human Frontier Science program," he says, "the next question is how we will tackle the sequencing issue."

But Wada argues that the two projects should be dealt with separately. He says that the Human Frontiers program "is like a newborn baby; it's very fragile. The newborn baby doesn't have the capacity to handle such a big project" as sequencing the genome.

In a society where consensus must be reached before a policy is implemented, there is too much varying opinion among prominent scientists to expect any major new initiatives by Japan in sequencing soon. Matsubara says, "Maybe 2 years from now, we'll achieve some structure" for pursuing a bigger effort to sequence the human genome. ■ MARJORIE SUN

Britain Launches Genome Program

London

Britain's Medical Research Council has announced plans to establish a major new computerized database for storing and distributing data on the structure and function of the human genome. To be located at the MRC's Clinical Research Center at Northwick Park in northwest London, it will be part of a new human genome resource center that will conduct some mapping and sequencing itself and support and coordinate efforts in other laboratories throughout the United Kingdom.

"You cannot have a successful network without a hub, just the spokes," says Sydney Brenner of the MRC's Molecular Genetics Unit at Cambridge, who is one of the chief architects of the British program. It is also hoped that the center will eventually become one of the main—if not the main—nodes in Europe for genome mapping and sequencing projects, and would link up with comparable databases in Japan and the United States. "I think that when the dust settles, there will be four or five such centers throughout the world, serving different time zones, and all connected to one another," says Brenner.

The MRC currently spends about $15 million a year on genetic mapping, with medical charities such as the Imperial Cancer Research Fund (ICRF) spending a roughly comparable sum. Funding for the new resource center will come out of an additional $19 million that the MRC is planning to spend over the next 3 years for research and development in this field.

The scientific content of the genome mapping program will be determined by a program committee. This will invite grant applications in specified topics that are considered directly relevant to the overall objectives of the resource center and its mapping program.

A scientific advisory board will be responsible for maintaining the balance of the research carried out. "The whole program will be very closely monitored, and we will be able to say if we feel there are too many grants going into one area and not enough into another," says board member Malcolm Ferguson-Smith, professor of pathology at the University of Cambridge. Overall strategy will be determined by a top-level committee consisting of representatives of various government departments as well as the ICRF, which has built up considerable experience in mapping techniques and the development of DNA probes.

The scientific strategy to be followed will initially be to construct a genetic, rather than a physical, map of the genome, concentrating on the location of identified genes. This strategy has been pioneered by Brenner at Cambridge, and some of the research that has been carried out in Cambridge will be transferred to the new center.

Brenner says he is keen that Britain's program be based on practical achievements and that it produce early results of value to researchers working on specific diseases. "Our first step will be to bring together detailed information on about 10% of the genome, working with about 100 bits of cloned DNA, and sending them out to various groups," he says.

"We are building a structure bottom up," says Brenner. "If in the next 2 or 3 years we have established a center in the U.K. which has already been of value to our research community, then we will be well placed to play an active role in international efforts."

The MRC has, in fact, already made some moves that could put London at the center of international genome mapping. It has offered to provide office space and administrative assistance for the European office of the Human Genome Organization (HUGO), a loose-knit group of researchers involved with gene mapping and sequencing, and has also said that it would be prepared to make similar facilities available in London for the nongovernmental organization the Japanese government is hoping to set up to run its Human Frontiers Science Program.

It remains uncertain whether there will be any direct relationship between Human Frontiers and genome mapping/sequencing activities, but MRC officials argue that it might be possible to share some administrative and operating costs either with HUGO or with the British genome program (or possibly even with both). If this were to happen, a single individual might be named to run two (or three) of these operations. One leading candidate for such a position is said to be John Tooze, currently executive secretary of the European Molecular Biology Organization in Heidelberg. ■ DAVID DICKSON