'Big science' protein project under fire

TOKYO

It was to have been a giant step towards understanding the many different ways in which a protein can fold. That knowledge would enable one to predict the characteristic structure of any given protein from its gene sequence — a critical tool for understanding how proteins interact and for developing effective drugs.

But Japan's ambitious Protein 3000 project will end its five-year term next March amid criticism that, despite looking set to meet its goal of solving 3,000 structures, the information gained is of limited use, and its high-throughput approach might even be depriving the field of valuable research skills. Recent science-ministry budget requests show that protein research in Japan will change dramatically, focusing on new analysis methods and on proteins related to specific diseases. The shift means an uncertain fate for the huge nuclear magnetic resonance (NMR) facility that has been the backbone of the project.

Protein structures are mainly determined by two methods — NMR and X-ray crystallography. NMR detects the magnetic properties of the atoms in proteins in solution to identify how they are arranged. X-ray crystallography requires that proteins first be crystallized. But many biologically important proteins are too big for NMR and impossible to crystallize.

Instead, the five-year project aimed to develop a 'reference library' of representative protein folds. Scientists could then translate information about the amino-acid building-blocks into predictions about overall structure, even of larger molecules. The project has received roughly ¥8 billion (US$70 million) per year since April 2002. Half of that money went to the RIKEN research institute to solve 2,500 structures using its NMR facility in Yokohama and its X-ray beamlines at the SPring-8 synchrotron radiation facility in Harima. The other half went to labs targeting specific proteins.

The project has, in quantitative terms, sailed along. Japan has an impressive 40 NMR machines, and Shigeyuki Yokoyama, who heads the NMR facility and is overall director of the project, says that by March this year the two RIKEN facilities had produced nearly 1,600 structures, with the project as a whole set to meet its goal of 3,000 by next March. "In this sense it is a great success," says Kurt Wüthrich of ETH Zurich, who won the 2002 Nobel chemistry prize for developing NMR to determine protein structures.

RIKEN YOKOHAMA INST.

Protein-structure work performed at the RIKEN NMR facility in Yokohama has not impressed everyone.

But big numbers aren't enough, say vocal critics in Japan. "A lot of it is junk," says Masatsune Kainosho of Tokyo Metropolitan University, reflecting the sentiment of many protein researchers contacted by *Nature*. He says a lot of the structures solved so far are similar, and relatively easy: "They've gone after a lot of low-hanging fruit." The criticism is compounded by a shifting benchmark. Japan's contribution of 3,000 protein structures was supposed to form a third of about 10,000 protein folds thought to exist. That number has now jumped to 16,000 by Yokoyama's estimation and may be 30,000 according to others.

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Several researchers have also expressed concern that the factory approach at the NMR facility has deprived young researchers there of the skills necessary to solve more complicated and important scientific riddles. It might have "destroyed the next generation", says one.

Wüthrich, who helped plan the NMR centre in 1998 and was a science adviser in 2000–04, agrees that the facility is a wasted opportunity. "A centre of that size should contribute to methodology, but there has been nothing," he says. "It became a one-man show with 40 NMR machines — there is no knowledge."

Yokoyama defends his project, pointing out that Protein 3000 has cracked the structure of many signal-transduction proteins involved in disease. Supporters on the project add that it is too early to judge the value of the structures. Yokoyama points to a long list of publications and patents related to the project, but admits: "We were too busy solving structures, and didn't have time to advertise the function."

Meanwhile, budget requests from the science ministry last month show a shift away from high-throughput methods, reflecting a change of policy. From next April, ¥5 billion has been requested to develop new methods for analysing and manipulating proteins, as well as new information technologies to present and disseminate the collected data. Another ¥2.4 billion has been requested to analyse specific disease-related proteins.

Feasibility studies on candidate projects for next year will start next month, and will include a study led by Kainosho on a new method to apply NMR to larger proteins (see *Nature* **400**, 52–57; 2006) and an exploration, led by the High Energy Accelerator Research Organization, of a microfocus X-ray beam that allows the analysis of smaller crystals.

Yokoyama had hoped to continue at full speed, but now expects to lose as much as half of his previous budget for the NMR facility. "It's a very difficult situation for me and for the people working on the project," he says. To help keep his scientists busy, Yokoyama says he will seek new users from industry and from other countries. He is also working with scientists in Korea to make the NMR machines available to Asian countries that would otherwise have no access to such cutting-edge technology. ■

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