JAPAN BUDGET

Winners, Losers Abound As Reforms Kick In

TOKYO—Next spring, Japan hopes to finish building the Earth Simulator, a mammoth supercomputer capable of modeling global climate change in unprecedented detail. But researchers may not be able to run it full-time because of budget cuts to the three agencies funding it.

That mixed message was repeated last week to scientists in many disciplines as Japanese ministries unveiled their budget requests for the next fiscal year. Although overall spending for science will rise about 5%, the increases are concentrated in a handful of areas deemed economically important and offset by cuts in other fields.

The crunch is especially severe for research organizations that fall into a special class of public corporations, such as the trio funding the Earth Simulator, which the current Japanese administration has called wasteful and in need of major restructuring.

"It would be awful, but Japanese science could die because of these reforms," says Shun-ichi Kobayashi, president of the Institute of Physical and Chemical Research (RIKEN) near Tokyo, another of the affected bodies.

The budget requests, for the year beginning 1 April 2002, reward projects deemed likely to strengthen industrial competitiveness, invigorate the economy, and promote a high quality of life. That includes a 62% jump in the life sciences within the Ministry of Education, Science, Technology, Sports, and Culture to study the structure and function of proteins, a 49% rise in spending on nanotechnology and advanced materials, and a 12% boost for information technologies.

But the flipside is equally dramatic. "Where is the money coming from to fund those increases?" asks Norio Kaifu, director-general of the National Astronomical Observatory of Japan (NAOJ) in Mitaka. "From other fields," he says, including an estimated 10% cut at NAOJ and cuts in space sciences and astronomy, ocean research, and atomic energy at the education ministry (see table).

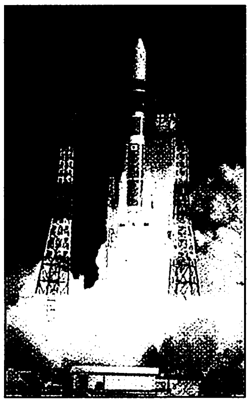
The proposed budget cuts may be just the opening shots for institutes such as RIKEN, the Japan Marine Science and Technology Center (JAMSTEC), and the Japan Atomic Energy Research Institute (JAERI). They have the misfortune of being part of a group of 163 special public corporations—which perform functions ranging from building toll roads to running Japan's public broadcasting system—that Prime Minister Junichiro Koizumi has declared must be either privatized or dismantled.

Who's Up, Who's Down...

... By field*	2002 request (in millions)	% Change
Life sciences	$758	+62%
Information technology	$798	+12%
Environmental studies	$543	+14%
Nanotechnology, materials	$269	+49%
Space and astronomy	$129	–3%
Ocean science	$302	–6%
Atomic energy	$216	–6%
... By institute		
Japan Atomic Energy Research Institute	$862	–10%
Institute of Physical and Chemical Research (RIKEN)	$667	–9%
National Space Development Agency	$1200	–5%
Japan Marine Science and Technology Center	$325	+1%

* Funded by the Ministry of Education, Science, Technology, Sports, and Culture.

Wrong direction. Space science takes a hit despite successful H-2A rocket launch (*below*) last month.



CREDITS: (TOP TO BOTTOM) SOURCE: MINISTRY OF EDUCATION, SCIENCE, AND TECHNOLOGY; NATIONAL SPACE DEVELOPMENT AGENCY

On 10 August, a task force issued a string of recommendations for these agencies. Although their fates may not be settled for years, the administration has pledged to start by slicing $8 billion next year from the $44 billion these agencies now receive.

Unhappily for climate modelers, the new supercomputer is part of the Earth Simulator Research and Development Center, which is jointly supported by three of these agencies: JAERI, JAMSTEC, and NASDA, Japan's space agency. "I'm very worried about the effect of this on our research program," says Taroh Matsuno, director-general of the Frontier Research System for Global Change.

The center is scrambling to find other potential users of the computer who might be able to contribute to its operating costs. JAMSTEC is also facing a 10% cut in the construction budget for its large ocean-drilling research vessel. "It means we'll have to push back completion of the ship by a year," says Takeo Tanaka, head of JAMSTEC's ocean-drilling program office, delaying its first scientific cruise until 2007 at the earliest.

Some ministries have already accepted the task force's recommendations. Last week, the education ministry announced that by 2003 it would merge NASDA, which is responsible for launching weather and communications satellites and for Japan's contribution to the international space station, with two other agencies: the Institute of Space and Aeronautical Science (ISAS), which focuses on space science, and the National Aerospace Laboratory, which conducts research into fluid dynamics and other more technological problems.

Although ISAS researchers fear that the merger will shortchange space science, ISAS director-general Hiroki Matsuo says the move is unavoidable: "We just have to try to make this merger work as well as possible."

Other proposals, however, are expected to generate fierce opposition. One involves merging JAERI, which heads Japan's efforts on the International Thermonuclear Experimental Reactor, with the National Institute of Fusion Science (NIFS), which operates the Large Helical Device near Nagoya. NIFS's budget for next year was cut by 27%, and Osamu Motojima, who heads the helical device project, fears that a merger could wipe out his project's alternative approach to fusion. —DENNIS NORMILE

With reporting by Charles Whipple in Tokyo.

CELL BIOLOGY

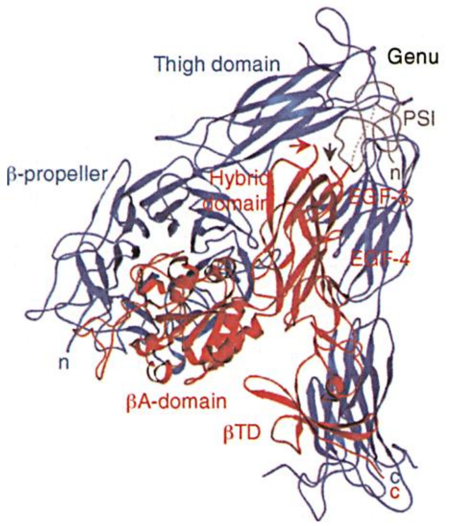
Integrin Crystal Structure Solved

For crystallographers, some of the more challenging proteins are those found on cell membranes. Often large and insoluble, membrane proteins are difficult to induce to form crystals. Even when that can be done, researchers run the risk that their manipulations so distort the structure that it doesn't reflect the natural molecule.

Now, a team of structural biologists at Harvard's Massachusetts General Hospital in Boston has overcome those obstacles to bag one of the most important membrane proteins yet. In work published online this week by *Science* (www.sciencexpress.org), Mass General's M. Amin Arnaout and colleagues have determined, for the first time, the crystal structure of one of the many integrin proteins.

These important denizens of the cell membrane control many cellular activities, including proliferation and migration. For example, the integrin studied by the Arnaout group, which is designated αVβ3, is believed to play a major role in tumor growth, bone maintenance, and inflammation. What's more, some infamous viruses, including the culprits in AIDS and foot-and-mouth disease, use the integrin as a port of entry into the cells they infect.

Now that they have the structure, researchers should get a better picture of just how the integrin engages in those activities, and that insight may spur the design of new drugs to combat diseases. "It's definitely one of those spectacular results that will change a field," says structural biologist Dan Leahy of Johns Hopkins University School of Medicine.



First look. This ribbon drawing shows the overall structure of the integrin and its various domains.

CREDIT: J.-P. XIONG ET AL.

Like all integrins, αVβ3 includes two distinct protein subunits encoded by two different genes. It's large, containing roughly 2000 amino acids, and flexible—a disadvantage when it comes to producing the highly ordered crystals needed for x-ray crystallography. Indeed, Arnaout had to cajole Jian-Ping Xiong, the paper's first author and a postdoctoral fellow at Mass General at the time, to participate in the project. Xiong feared squandering precious fellowship time on what he viewed as a hopeless task.

Researchers at Merck KGaA in Darmstadt, Germany, provided purified protein for Arnaout's team to crystallize but, says Arnaout, Merck wanted no part in funding a project that seemed so unlikely to bear fruit.

Despite the doubts and frustrations, scientists worldwide have hotly pursued αVβ3's structure for years, holding their cards tightly to their chests to avoid alerting the competition to what they were doing. As recently as last February, most scientists attending an integrin conference in Ventura, California, presumed that it would be years before an integrin crystal structure was complete. At the time, Arnaout gave no hint to the contrary.

To make the integrin soluble—a prerequisite to crystallization—scientists at Merck KGaA truncated the tiny segments that anchor it to the cell membrane and allow it to transmit signals into and out of the cell. Once the Merck group provided enough protein, the Arnaout team spent more than 3 years tinkering with conditions before they could produce crystals worthy of study. Their x-ray analysis, conducted at Argonne National Laboratory in Argonne, Illinois, revealed a structure that was partly expected, but it also contained a few bombshells.

The integrin includes 12 distinct regions, or "domains," four in the α protein subunit and eight in the β protein subunit. They are arranged in a molecule with an oval head and two tails.

Previous work by Arnaout's group and others, including Harvard pathologist Timothy Springer, suggested that some of these domains might exist. Springer's prediction several years ago that part of the protein would be shaped like a propeller has held true. A couple of domains, though, are new.

A hybrid domain combines portions of known structures, and a domain tacked onto the end of one tail is folded in a novel pattern. But perhaps the biggest surprise was the finding that the two tails, which appeared to extend stiffly from the head section in earlier electron micrograph images, are folded sharply in on themselves. The researchers don't yet know whether that bending occurs naturally; it could be an artifact of the preparation or of crystallization procedures.

Most intriguing, though, the shape might help cell biologists understand how the integrin transmits its signals. The Mass General group argues that it has crystallized the protein in its "on" structure, but left unanswered is how that differs from the inactive form and how the protein might pass signals to the cell with which it's connected.

Pharmaceutical companies, meanwhile, are expected to use the αVβ3 structure to guide the development of new drugs aimed at the protein. Compounds that block the

ScienceScope

More Censure for Hopkins Johns Hopkins University's process for reviewing studies of human subjects is "grossly inadequate," and "it is critical that the culture of the institution change." That stark assessment comes from an outside panel tasked with probing the death of a volunteer in an asthma study last spring.

The conclusions of the five-member panel—led by Samuel Hellman, dean emeritus of the University of Chicago's medical school—are similar to those of an internal review and the federal Office for Human Research Protections, which found problems with informed consent procedures and university oversight (*Science*, 27 July, p. 587). In its 8 August report, the panel also found "possible subtle coercion" of staff to volunteer for studies. But Hellman is "optimistic" that Hopkins can correct course in light of many reforms now under way.

Want to Be a Millionaire? Maybe money can't buy happiness. But the Howard Hughes Medical Institute (HHMI) is hoping that it can buy a better science education for thousands of U.S. undergraduates. The Bethesda, Maryland–based philanthropy last week announced plans to give $1 million over 4 years to each of 20 faculty selected from 84 top research universities.

"It's a grand experiment," says molecular biologist Edward Cox, who runs a Hughes-funded summer research program for undergraduates at Princeton University. Cox says that the challenge for Hughes is "finding people with the right blend of an active research program and high-quality teaching skills." The first grants will be awarded in August 2002.

Cluck, cluck China, the United Kingdom, and other nations say the chicken should be the next vertebrate fed to the genome sequencers. Researchers attending the 10th International Strategy Meeting on Human Genome Sequencing last week in Hangzhou, China, agreed that sequencing the chicken could not only help agriculture, but also "medicine, [as it] helps us to understand humans [and] developmental embryology," said sequencing guru Eric Lander of the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts. The Beijing Genomics Institute may take the lead on the project, but poultry genome planners must still decide on which chicken variety to work on and how to raise the $35 million needed to start. Lander says those decisions could come within 6 months.

Contributors: Jocelyn Kaiser, Jeffrey Mervis, Yang Jianxiang

protein might, for example, inhibit uptake into cells of the AIDS virus or prevent the cell migrations needed to build the new blood vessels required for tumor growth. "These are targets that [companies] have identified for a while, and they have been playing with them, but without any structural basis," says Arnaout.

Indeed, researchers say that the $\alpha V\beta 3$ structure is sure to inject new energy into the integrin field. "In a lot of ways, it's really just a starting point," says cell biologist Jeffrey W. Smith of the Burnham Institute in La Jolla, California. But, he adds, "it changes the level of research that we can do."

–JENNIFER COUZIN

Jennifer Couzin is a writer in San Francisco.

ELECTRONICS

Organic Device Bids to Make Memory Cheaper

CHICAGO—Beware, silicon engineers: Organics are at the gate. Researchers have already turned electrically conducting organic compounds into light-emitting displays and flexible circuits (*Science*, 12 June 1998, p. 1691; 21 January 2000, p. 415). Now they're laying claim to one of silicon's remaining strongholds: memory. Last week, materials chemist Yang Yang of the University of California, Los Angeles (UCLA), told the American Chemical Society* that his group has devised an organic-based digital memory.

New trick. Conducting organic materials similar to this light-emitting diode can store data.

The new devices work similarly to flash memory, a relatively expensive silicon-based technology that retains its data even when power to a device is turned off. An organic version has the potential to be much cheaper because it could be far simpler to produce, says Edwin Chandross, an organic-electronics expert who runs a consulting firm in Murray Hill, New Jersey. "It's impressive," Chandross says of the new work. "A lot of people have been talking about trying to do this."

Talk hasn't gotten them very far. No one has yet found a way to make an organic device that has two stable states, which can encode the 0's and 1's of computer lingo.

Yang's group was struggling with this problem as well. The researchers first tried to make organic memory devices by putting a layer of conducting organic molecules between two electrodes and applying a voltage. That caused the conductivity of the organic material to rise, a signal that potentially could encode bits of information. But it dropped again when the voltage was turned off, so the chance to store information was lost.

On a hunch, one of Yang's postdocs, Liping Ma, suggested following the lead of compact-flash devices, in which tiny strips of metal act like batteries to store electronic charges. Yang gave him the green light, and Ma sandwiched a thin metal layer between layers of conducting organic molecules. To their surprise, it worked splendidly. The device could not only write and read bits of data but erase and rewrite them as well.

To write a bit of data, Yang's team simply applies a potential of 3 volts between a pair of electrodes bracketing the organic-metal-organic sandwich. The voltage makes the material between the electrodes more conductive, a quality it retains even when the voltage is turned off. That high-conductivity state acts as the 1. To read the bit, the UCLA team applies a second voltage of 1 volt. The highly conductive material produces a rush of electrons between the electrodes, signaling that the device is in the 1 state. Applying a third voltage of –0.5 volt returns the cell to its original low-conductivity state, a 0, which the team can read by applying another voltage of 1 volt.

Yang says his team has run through this write-read-erase cycle about 1 million times without seeing any signs of degradation. That track record leaves other researchers both impressed and scratching their heads, because just what causes the material in the device to change its conductivity when different voltages are applied remains a mystery. "It's intriguing," says Alan Heeger, a physicist at UC Santa Barbara, who won the Nobel Prize in chemistry last year for his work on conducting polymers. "I'd like to know what is going on."

In earlier devices that claimed similar properties, it turned out that metal from the electrodes was migrating into the organic layers and giving rise to some of the effect. Although such devices seemed to work for a short while, they were difficult to reproduce and eventually stopped working when the small metal fragments broke down, Yang says.

To test whether similar metal reactions were behind the properties of the new device, the UCLA team replaced its aluminum metal layer with layers of less reactive silver, copper, or gold. All worked similarly to the aluminum, Yang says. "It was the right experiment to run," Chandross notes; gold, in particular, is fairly inert and shouldn't react as aluminum does.

Whatever causes the change in conductivity, organic memory devices could move into applications quickly, Chandross and others say. Manufacturers can make the devices simply by evaporating different materials through a mask in a vacuum. UCLA has granted an exclusive license to a Boston-based start-up company interested in commercializing the technology. If the effort flies, it could result in ultracheap flash memory–based computers that turn on instantly, without the minutes-long boot-up that a standard computer needs to reload its working memory with data that get lost whenever the power goes off.

No doubt silicon is safe for a while. But it may soon be under siege.

–ROBERT F. SERVICE

* 222nd ACS Annual Meeting, 26–30 August.

NEUROSCIENCE

New Route to Big Brains

Never mind the bipedal posture, relative lack of fur, or opposable thumbs. What really sets humans apart from other animals is our oversized brain. But building a bigger brain is an evolutionary challenge. In addition to all the extra neurons and other brain cells that have to develop, somehow all those cells have to be wired together correctly. Now, researchers report that in humans—but apparently not in other species—some neurons in the developing brain travel along an unexpected route. This detour allows them to link to and serve the most overgrown and recently evolved parts of the human brain—those involved in higher functions such as memory and problem solving.

"The exciting point here," comments developmental neurobiologist Gord Fishell of New York University, is that the study identifies a "fundamental difference in the way human brains develop." Neuroscientists still don't understand, he says, "what it is about the human brain that allows it to become more complex than [in other] primates." The newfound pathway, which is described in the September issue of *Nature*

CREDIT: YANG YANG/UCLA