an ever-increasing number of successful competing grant applications," Lenfant wrote. At the same time, he noted that the average grant has gotten bigger.

At the $3.74 billion NCI—the largest member of the NIH family—Klausner notes that the cost of grants has risen faster than the institute's budget in recent years, steadily eating into the pool of money available for new projects. The amount of money for new initiatives is shrinking fast, from $262 million in 2000 to $176 million this year, with a continued drop forecast for 2002. "Next year will be the most difficult by far," predicts Klausner.

In response, NCI is capping the increases that can be requested by investigators seeking renewal of their 3- and 4-year awards and ordering a special review for grants larger than $500,000 a year, a category that's growing rapidly. By 2003, however, Klausner predicts that enough existing grants will have expired to ease the transition to slower growth rates.

Although the report of the special post-doubling committee isn't due until fall, the agency's 2002 budget request offers some clues about the strategies it might recommend for spending future budget increases wisely. One is to continue investing heavily in infrastructure. For instance, NIH officials are touting plans to spend tens of millions of dollars over the next few years on high-end equipment—specialized electron microscopes, supercomputers, and other machines costing $500,000 or more. There is also talk of making a dent in an estimated $6 billion backlog in needed construction and renovation projects at universities and research hospitals. Both types of spending are attractive because, unlike grants, they can be paid for in a single budget year.

Last year, similar ideas led Representative David Obey (R–WI), the senior Democrat on the House panel that oversees NIH's budget, to ask whether such spending "really was the way the science is going, or a way to move larger sums of money now that you are getting these increases?" This year, however, there were virtually no such challenges at a House hearing on NIH's infrastructure proposals. And in the Senate, Tom Harkin (D–IA), the new head of the spending panel that oversees NIH's budget, encouraged officials to think about giving more cash to grantees who need bigger labs and better equipment.

Researchers are seconding that idea. Last week, for instance, an advisory group led by William Brody, president of Johns Hopkins University in Baltimore, Maryland, recommended that NIH boost construction and renovation grants to $1 billion a year—from $75 million this year. But Kirschstein deferred the idea until December.

Another issue likely to be aired in committee discussions is the impact of "modular" grants. Under the streamlining policy, a legacy of former director Harold Varmus and implemented in earnest last year, all grants of $250,000 or less have been awarded in increments of $25,000. The idea was to reduce the amount of paperwork for smaller grants. But it has had the unintended side effect of boosting overall spending: Lured by the lack of paperwork, more investigators appear to be requesting funding levels closer to the ceiling, and renewal grant amounts are routinely rounded up.

In his letter, for instance, Lenfant noted that his institute limits renewal grants to a 10% increase, so a $100,000 grantee can ask for up to $110,000 the second time around. Under the modular grant approach, however, the grant is rounded up to $125,000. The development is "one noteworthy cause" of rising grant costs, Lenfant wrote.

Klausner would also like to see peer reviewers take a closer look at the costs of proposed research. The thousands of scientists who review proposals to NIH are currently instructed to focus on scientific merit, and Klausner says that most study sections routinely recommend funding levels very near the investigator's request. But those budgets are "often far in excess of what we can realistically provide," says Klausner. The process of negotiating lower amounts has "become an enormous stress on program staff," he says.

Resolving these issues to everyone's satisfaction, however, still won't solve NIH's budget crunch. Observers say that only a miracle will prevent stagnation and slumps after 2003 in the number of grants, infrastructure spending, and clinical research. Doubling has "given everyone a little something to celebrate," notes one NIH official. But the bill is rapidly coming due.

–DAVID MALAKOFF

THE FUTURE OF NIH

THE WINNERS

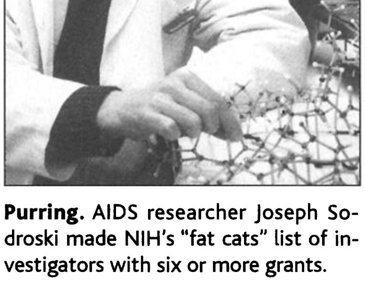
Even in a Time of Plenty, Some Do Better Than Others

"Fat cat" basic researchers, directors of large trials and surveys, and genomics Pooh-Bahs top the list of scientists with the most NIH funding

With a 25-person lab and eight grants from the National Institutes of Health (NIH), virologist Joseph Sodroski of the Dana-Farber Cancer Institute in Boston has a lot going on. "There are people from all over the world here," he says, "and keeping everybody fulfilled and happy is a challenge." And his research keeps sprouting in new directions, from how HIV envelope glycoproteins help the virus enter cells, to their cytopathology, to their possible role in vaccines. Federal funding is the food that nourishes those ideas, so even though his plate is full already, Sodroski says, "if an idea comes along that looks fundable, I'll probably write a grant [proposal]."

That drive netted Sodroski $4 million in NIH funding last year, putting him in the upper echelons of the agency's basic research grantees and at the very top in terms of number of grants. A leading AIDS researcher and skilled proposal writer, Sodroski has benefited from an exploding NIH budget that has allowed the agency to award more and larger grants (see p. 1992). In this time of plenty, NIH grant administrators early this year examined what they call the "fat cats"—principal investigators (PIs) with six or more grants—to make sure that NIH's 27 institutes and centers are not funding duplicative work and PIs aren't overextended. Extramural research chief Wendy Baldwin concluded that "there was nothing to be concerned about" for the 30 or so people on her list.

Science decided to take its own look at the people at the top of the funding heap, examining the total amount of money received and number of grants. Recipients were divided into three groups—those who do mostly basic research, clinical and social science researchers, and genomics centers. The leaders receive $3 million or more a year, eight times what the average investigator receives. At the same time, the portfolios of most of the top investigators include grants shared with other labs. Identifying the top-funded researchers from an NIH list of grants



Purring. AIDS researcher Joseph Sodroski made NIH's "fat cats" list of investigators with six or more grants.

CREDIT: DANA-FARBER CANCER INSTITUTE

awarded in 2000 wasn't an easy task. (Baldwin calls NIH's grant data "a morass.") The totals for individual PIs are the sum of many variables—from their institution's indirect costs and salaries to whether the research involves cells or transgenic mice or primates, or relies on expensive equipment or subcontractors. The tables are also a snapshot for 1 year.

Those on these lists say the money brings plenty of headaches, including 18-hour days writing grant proposals and setting aside time to prepare and host site visits from outside reviewers. Although most pine for more time in the lab, they say they're driven to seek more research funding by a surfeit of ideas, as well as the trend toward big biology. Many also believe that outside collaborations and big labs provide the best training for the next generation of investigators.

Top-Funded Basic Research PIs

Investigator	Institution	Lab staff	Main topic	NIH grants ($M)
1. Stanley Prusiner	UC San Francisco	67	Prion diseases	12.5 (6.6)*
2. Alfred Gilman	U. of Texas SW Med. Center	13	Alliance for Cell Signaling	9.8†
3. Ronald Crystal	Cornell University	46	Gene therapy	6.6
4. George Stamatoyannopoulos	University of Washington	19	Blood disease gene therapy	6.4†
5. Seigo Izumo	Harvard/Beth Is. Deac. Med. Ctr.	25	Cardiovasc. functional genomics	6.1†
5. Ian A. Wilson	Scripps Research Institute	16	Structural genomics initiative	5.6†
6. Rainer Storb	Fred Hutchinson Cancer Res. Ctr.	30	Bone marrow transplants	5.4
7. Richard Boucher	University of North Carolina	NA	Cystic fibrosis gene therapy	5.1
9. Paul Greengard	Rockefeller University	40	Signal transduction	5.0
10. Michael Gimbrone	Harvard/B&W's Hospital	17	Vascular endothelium	4.9

* Larger figure includes a contract to develop a prion assay.
† Had significantly lower funding in 1999.
Notes: Grants for several PIs include some translational and clinical research. Includes all fiscal year 2000 awards, including indirect costs, except training and conference grants. Some grants include forward year funding. Excludes one PI with a structural genomics initiative award but no other NIH support. Lab staff includes administrative staff.

At the top of basic research money winners (above) is prion researcher Stanley Prusiner of the University of California, San Francisco (whose work involves costly biosafety facilities for mice). He's a Nobel Prize winner, as are two others in the top 10 (cell biologist Alfred Gilman of the University of Texas Southwestern Medical Center in Dallas and neurobiologist Paul Greengard of Rockefeller University in New York City). Other ranking investigators include pioneers in their field, such as gene therapy researcher Ron Crystal, who ran the biggest lab at NIH before moving to Weill Medical College of Cornell University in New York City in 1993.

Greengard says he's ambivalent about the honor: "I've thought for a long time that there is an ideal limit on lab size." But he says it's hard to turn down the constant influx of talented young scientists interested in working with him and the "exciting ideas" that come along. As a result, his group now numbers some 40 people, up from about 30 a decade ago. "I'd much rather have a smaller lab, but I don't have the willpower" to say no, he confesses.

Other top-funded scientists don't necessarily maintain big labs. Instead, they owe their lofty rank to being a PI on a center grant, or more often program grants—called P01s—that are equivalent to several R01s split among various labs. They are attracted to these grants because they allow for interdisciplinary and collaborative science that can't be done on an R01.

Michael Gimbrone of Harvard Medical School in Boston, who for 23 years has done pioneering work on atherosclerosis with a team ranging from engineers to molecular biologists, says that the combined brainpower on a grant that involves about five other labs creates "a SWAT team" for solving problems. Rainer Storb, head of transplantation biology at the Fred Hutchinson Cancer Research Center in Seattle, says he's been driven to grow lately by promising discoveries such as a new technique that allows bone marrow transplants to be used on more patients. "Working as a group [of 125 basic and clini-

Top-Funded Clinical, Social Science PIs
(Investigator-initiated grants, centers only)

Investigator	Institution	No. of Grants	Main Topic	NIH Grants ($M)
1. Donald Morton	John Wayne Cancer Institute	3	Cancer vaccine, surgery trials	11.9
2. J. Richard Udry	U. of North Carolina	1	Adolescent health survey	8.4
3. David Alberts	U. of Arizona	2	Cancer prevention trials	6.3
4. Thomas Coates	UC San Francisco	3	AIDS behavioral prevention	5.8
5. Fred. Appelbaum	Fred Hutchinson Cancer Res. Ctr.	1	Adult leukemia research	5.7
6. Igor Grant	UC San Diego	4	AIDS neurology, tissue bank	5.2
7. Kenneth Manton	Duke University	5	Demographics of aging	5.1
8. Walter Willett	Harvard University	3	Diet and disease risk	5.1
9. Robert Hobson	U. of Med/Dent New Jersey	1	Vascular surgery trial	5.1
10. Carl Grunfeld	UC San Francisco	1	HIV and metabolism	4.7

Notes: Grants are for fiscal year 2000 and include indirect costs. Grants include P01s, R01s, R24, R37, and P50s. Analysis did not include the following grant types: N, U01, U10, U45, UC1, U19, C06, M01, P30, P51, training, and conference grants.

"I'm just euphoric that my scientific peers have given me the opportunity," says Donald Morton (left), a cancer researcher at the John Wayne Cancer Institute in Santa Monica, California, who tops *Science*'s list of the best funded clinical researchers. Morton manages $12 million worth of trials, including $7.8 million for a cancer vaccine that he's worked on since the 1960s.

This ranking includes only investigator-initiated clinical projects and centers. It leaves out some larger trials, including AIDS drug trials, that are instigated by NIH, as well as cooperative cancer centers. Other top-funded principal investigators (PIs) include bench-to-bedside research on leukemia treatments by Frederick Appelbaum of the Fred Hutchinson Cancer Research Center in Seattle and work by psychologist Thomas Coates of the University of California, San Francisco, on promoting behaviors that prevent AIDS. Also on the list is a teenage health study, which PI Richard Udry of the University of North Carolina, Chapel Hill, calls "one of the most expensive and complicated surveys ever done." The results will provide social and biological data for countless researchers.

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Top-Funded Genomics PIs

Investigator	Institution	NIH grants ($M)
1. Eric Lander	Whitehead Institute	65.3
2. Robert Waterston	Washington University	44.6
3. Richard Gibbs	Baylor College of Medicine	23.8
4. Gerald Rubin	UC Berkeley	14.1
5. Ronald Davis	Stanford University	9.4

Notes: Includes all grants for fiscal year 2000, including indirect costs, except training and conference grants. Includes sequencing of the genomes of human, mouse, and other organisms.

The NIH grants for the major publicly funded genome sequencing labs are way off the charts, reflecting the biggest of big biology—and the race to sequence the human genome that ended last year. Topping this list of five is Eric Lander's Whitehead Institute in Cambridge, Massachusetts, which got a whopping $65 million in 2000. (The sprint to the finish swelled his total, which stood at $13 million in 1995.) "That is truly production"—reagents and automated equipment, not so much people—says Jane Peterson, a grants administrator at the National Human Genome Research Institute. Lander (above) says his high-volume operation is nevertheless an exhilarating scientific endeavor involving 20 senior researchers: "It has the spirit of a fun 20-person lab."

Peterson says the "hallmarks" of these investigators are hiring "good lieutenants" and "an ability to manage a big production facility. It's not something you learn in graduate school." Although the human genome grants will wind down when finishing steps are completed in 2003, demand for sequencing other organisms and comparative genomics will keep these labs busy (*Science*, 16 February, p. 1204).

cal people] has given us an enormous amount of strength," Storb says. "Without that you can't push this very complex field ahead at the breathtaking pace we have."

These researchers share a belief that big programs are a good way of doing science and training scientists. Gene therapy researcher George Stamatoyannopoulos of the University of Washington, Seattle, for example, has only 19 people in his lab. But his two P01s allow him to jump-start the careers of young researchers who don't have enough publications to compete on their own by essentially giving them their own R01. A few years after becoming part of the program grant, he says, these young scientists "are all extremely well funded."

Others on the list head brand-new collaborations involving multiple institutions. They include Ian Wilson of the Scripps Research Institute in La Jolla, California, who last year got a large grant for a structural genomics initiative, and Seigo Izumo of Harvard's Beth Israel Deaconess Medical Center, whose collaborative grant for cardiovascular functional genomics "is not something a traditional lab can do." NIH officials see these consortia as the wave of the future: Gilman received $8.8 million last year for a cell-signaling alliance shared among 20 institutions in what's called a "glue grant," the first of many from NIH.

What does it take to get these large, shared grants? A critical mass of talented investigators and strong institutional support are essential, researchers say. "You've also got to set up some management structure," Wilson says. In his lab, that means putting Ph.D.s who would otherwise gravitate to biotech companies in charge of areas such as computing, x-rays, and cloning.

Not every researcher wants to join collaborations, however. *Science* found that basic PIs with many grants (below) tend to run large, self-contained labs. The predilection for multiple grants, they say, stems in part from hard times at NIH in the early 1990s. Tight budgets often led institutes to cut the size of a grant sent in for renewal, forcing investigators to apply for a second R01 to cover their costs. Scripps virologist Michael Oldstone admits that the system was inefficient. "I'd rather have half as many grants and the same amount of money for research," he says.

But PIs who pile up the R01s have their reasons. "I think it's a good thing that it's not one big hunk but that I competed for these grants six times," says human geneticist Aravinda Chakravarti of Johns Hopkins University in Baltimore. And some don't see a need to limit the number of grants going to a single lab. Bigger labs "are the main source of training for the future," says Sodroski. "I'm not sure [funding] more investigators is better." The rapid growth in NIH's budget has improved everyone's chances of getting money, he adds. "So what's the big deal?"

Of course, those at the top say that not everybody wants or should try to be a rainmaker. "I think it's a choice. It would be a terrible thing if we say simply that having more money [means you are] more successful," says Chakravarti. Baldwin agrees that there are "lots of different ways to measure success," including the ability to sustain funding.

In that arena, the apparent winner is Harold Scheraga, a protein chemist at Cornell. He's just sent off a renewal for an R01 he's had for 45 years—one that has provided data for more than 1000 papers. At the age of 79, Scheraga, who has a 20-person lab, brought in $717,000 last year from NIH for his university.

Scheraga has embraced many new ideas and technologies over his career. But he hasn't changed his mind about the value of being an independent investigator, in no small part because he can stay in closer contact with the work. "I have a wide range of expertise in my lab," he says. And as for grant size, he says, "I just ask for what I need."

–JOCELYN KAISER

Top-Funded PIs With Six or More Grants

Investigator	Institution	No. of Grants	Lab staff	Main Topic	NIH Grants ($M)
1. Ronald Crystal	Cornell University	6	46	Gene therapy	6.6
2. Mary Jane Rotheram-Borus	UCLA	6	*	AIDS education, interventions	5.7†
3. Kenneth Manton	Duke University	6	*	Demographics of aging	5.5†
4. Xiping Xu	Harvard University	8	30	Genetic, environmental epidemiology	4.2
5. Joseph Sodroski	Dana-Farber Cancer Inst.	8	25	HIV glycoproteins	4.1
6. Aravinda Chakravarti	Johns Hopkins University	6	30	Human disease genetics	3.7
7. Bruce Walker	Harvard University	6	34	Immune response to HIV	3.4
8. Irving Weissman	Stanford University	8	40	Hematopoietic stem cells	3.0
9. Daniel Tenen	Harvard University	7	19	Blood development and leukemia	3.0
10. Michael Oldstone	Scripps Research Institute	7	15	Virus immunobiology	3.0

* Not applicable for clinical and social science researchers. † Clinical totals are lower because certain grants were excluded.
Notes: Analysis based on all fiscal year 2000 awards, including indirect costs, except N awards and grants for conferences, training, teaching, and small business. (Supplements were not counted in grant number.) *Science* found a total of 15 PIs with six or more grants using these criteria. Lab staff includes administrative staff.

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