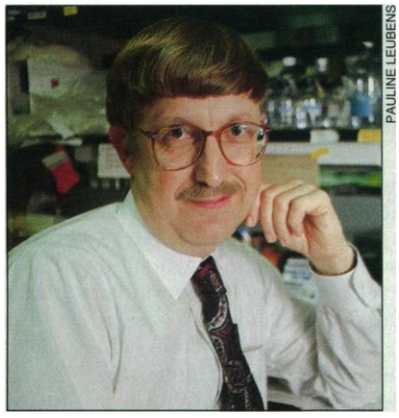
Genome Project Plans Described

Incoming director Francis Collins says the extramural program will stay focused on mapping and sequencing while his new lab at NIH will take a more medical tack

It took almost a year, but the U.S. genome research community finally has a new leader: Molecular geneticist Francis Collins arrived last week at the Bethesda campus of the National Institutes of Health (NIH), ready to get down to the business of running the National Center for Human Genome Research (NCHGR), which is budgeted at $106 million for fiscal year 1993. As part of the package that helped lure him from the University of Michigan, where his achievements include co-discovery of the cystic fibrosis and neurofibromatosis genes, Collins will not only run the extramural component of the project, but will also set up the first-ever intramural NCHGR lab at NIH, stocked with his "dream team" of 20 or so gene researchers who hope to be funded to the tune of roughly $25 million in FY 94. But while Collins' new job comes with its share of promise and opportunities, he's also inherited some major challenges.



PAULINE LEUBENS

On board. Francis Collins has just taken charge of NIH's genome effort.

From the very beginning of the genome project, many in the biomedical community have been fearful that funding for the "big science" program, which carries an estimated price tag of $3 billion over 15 years, would come at the expense of their research. Those fears are not assuaged by the Clinton Administration's new budget, which shows the NCHGR as one of the very few NIH programs scheduled for an increase in FY 94 (*Science*, 2 April, p. 24). Then there's the thorny issue of when—or if—to seek patents on genes. And, of course, there's the intriguing question of what Collins plans to do with his new lab at NIH.

To give the community an early idea of what he's planning, Collins granted *Science* an interview a week before a press conference scheduled for 7 April. To allay fears that the genome project will succeed only at the expense of other research, Collins said he will use his office to argue for funding not just for the project itself but for biomedical research generally. He will also put high emphasis on the ethical, legal, and social implications of the widespread availability of genetic information. Next, he promised no major changes in the extramural segment of the genome project. He also pledged to keep it out of head-to-head competition with research funded by other institutes. His intramural program will take a much more disease-oriented tack than the extramural program, however.

Originally, Collins thought he might create an intramural program at NIH that focused on mapping and sequencing, much as the 10 or so extramural genome centers located at major universities around the country do. But he says he changed his mind because he thought that a more disease-oriented approach would fit in better at NIH, where the forté is in marrying basic research with its clinical applications. In his own case, this would mean continuing his collaboration with geneticist Mary-Claire King of the University of California, Berkeley, to hunt down the breast cancer susceptibility gene, as well as searching for other disease genes. In addition, his dream team will work on developing diagnostic methods and therapies for genetic diseases.

Recruitment under way

To these ends, Collins will bring much of his current research group from Michigan to NIH, while also recruiting about 10 scientists, many of them senior researchers, from other institutions. (He declined to name them because the negotiations are not yet complete.) What would make top researchers come to NIH when many are leaving government service because of low pay and poor morale? Reminded that prominent gene therapy pioneers French Anderson, Ronald Crystal, and Arthur Nienhuis have all left recently, Collins concedes that he can't out-compete the leading academic and industrial labs on salary for senior scientists but insists that he can compete on "scientific excitement," the opportunity to use such facilities such as the NIH clinical center, and the chance to tackle problems, such as the genetics of complex common diseases, not readily possible elsewhere.

As for the extramural portion of the genome project, Collins says, it needs no major changes because former head James D. Watson and his staff got the program under way in "a remarkably rapid and effective way." As before, the extramural effort will focus on building what Collins calls the "infrastructure"—the detailed physical and genetic maps of the human genome as well as, ultimately, its complete base-by-base sequence. There will be no extramural support, he says, for disease-gene hunting for its own sake or for gene therapy research, activities that are currently supported by other institutes. "I don't want in any way to become competitive with those very successful efforts," he says.

But while the extramural program doesn't need major changes, it does need what Collins calls "fine-tuning." The first 5-year plan for the genome project was originally drawn up in 1989. So Collins argues that now is an appropriate time "to stand back and look at those 5-year goals and ask the question whether we have got it just right or whether we ought to tilt a little bit in one direction or another." And there's already an answer to the question: Collins, in consultation with the genome center directors and other researchers, has concluded that three main areas need some adjustment.

Current genome maps, for example, primarily show the location of "markers," variable DNA sequences that can serve as landmarks for finding genes of interest, but not of most genes themselves. But knowing the gene locations on the physical map would provide useful information about the context in which the genes are acting as well as additional landmarks that can aid researchers on the often difficult final searches for important disease genes. So, in the future, Collins says, more emphasis will be placed on identifying genes and their precise locations on the physical map—a task that's easier today than it was 5 years ago.

Collins also thinks that more attention should be paid to "outreach"—making the fruits of the genome project more accessible to other researchers. To accomplish this, researchers submitting grant applications for genome centers will be asked to put more emphasis on outreach programs—for example, providing lab space for outside collaborators and setting up systems for sharing reagents and other resources, as well as data.

And last, Collins says, more needs to be

done to develop new technologies for constructing the physical map and determining the sequence of all the nucleotides in the DNA of the human genome. The latter may be a particular concern since the human genome is estimated to contain 3 billion nucleotides, raising questions about whether sequencing methods will be up to the formidable job of determining their exact order. To bolster research in this area, Collins will seek additional funds for people with novel ideas. Sequencing by mass spectrometry and DNA hybridization are among the technologies that deserve a deeper look, he notes.

The political challenges

Of course, the new genome head will face political as well as scientific challenges. And the project has had its share of high-profile political problems. Take the patent controversy that became one of many sore points between Watson and his boss, NIH Director Bernadine Healy. The trouble started when NIH filed for patents first on hundreds and then on thousands of gene fragments identified by former NIH researcher Craig Venter. Watson, like many other biomedical researchers, strongly disagreed with the filing and subsequently departed from the project.

Collins takes a middle-of-the-road approach to this issue. The original application was turned down, and he has no objection to NIH appealing that decision: "Having gone this far, it would be unfortunate to just let the issue lie there unresolved." But he hopes that when a definitive resolution comes, it will hold that what he calls these "snippets of sequence with no known biological function" are not patentable. He does not object, however, to the idea of obtaining patents on full-length genes with known biological functions and thinks that the genome project ought to be a plus for the biotech industry.

And last, but definitely not least, there are the politics of funding. Even though the intramural program fared well in the Clinton Administration's first budget, the extramural program suffered the same fate as other NIH units, and Collins says, "we are getting into a crunch." The original intention was eventually to ramp up the annual NIH genome budget to $173 million, but the scheduled increases have plateaued prematurely. The budget for the FY 93 was supposed to be $146 million, but it is $106 million. That's scheduled to rise to $135 million in FY 94, but almost all the increase is for starting the intramural program. "This truncation of the ramp-up is going to create some difficulty for technology development and sequencing," says Collins, noting that these are already underfunded. Collins will try to make the case that more funding for technology development will save money in the long run by making mapping and sequencing easier—and therefore cheaper. But whether he will prevail in the current climate of budget cutbacks remains to be seen.

–Jean Marx

FEDERAL BUDGET

Clinton Asks for a Greener DOE

In an ordinary budget year, agencies marshall funding plans and release them in a package. But in this disheveled year, with the government still reeling from the change of administrations, funding plans aren't released—they dribble out. Last week, the National Science Foundation informed Congress that President Clinton would favor the agency with a big increase in his 1994 request, while the National Institutes of Health (NIH) found out he would not do the same for NIH. This week's budget preview comes from the Department of Energy (DOE), whose fortunes appear to lie somewhere between those of the other two scientific players.

When Clinton makes his formal budget request this week, he will ask Congress for a 7.2% rise (to $4.75 billion) in DOE's general science and energy supply research programs. Reflecting Clinton's—or perhaps Vice President Al Gore's—green streak, the big winners are solar and other renewable energy sources (up 27% to $327 million) and biological and environmental research (up 17% to $416 million). Losers include some accounts that were expected to suffer—such as nuclear energy research, whose $345 million 1993 budget is to be cut almost in half—as well as some that were not, including basic energy sciences, which would drop 7% from its $861 million 1993 budget. This means that the defense labs will shrink, a blow only somewhat softened by a 68% ($624 million) increase in lab technology transfer programs.

In basic research, most of what appears to be a healthy increase is eaten up by new construction, leaving core science programs with little more than a cost-of-living rise of about 3%. Clinton's 1994 request will include $20 million to start work on the Tokamak Physics Experiment at Princeton, $26 million to kick off an Advanced Neutron Source at Oak Ridge National Laboratory, and $36 million to establish a "B-factory"—an accelerator to produce a high-intensity beam of particles known as B mesons—at either the Stanford Linear Accelerator Center (SLAC) or Cornell University.

DEPARTMENT OF ENERGY

Selected Research Programs	Appropriated 1993	Request 1994	Percent Change
	(million dollars)		
Solar and Other Renewables	257	327	27.1
Nuclear Energy	345	184	-46.8
Biological and Environmental	357	416	16.6
Fusion Energy	340	348	2.3
Basic Energy Science	760	861	-6.8
High-Energy Physics	613	628	2.3
Nuclear Physics	309	322	4.3
SSC	517	640	23.8
Total, General Science & Energy Supply R&D *	4434	4754	7.2

*Total includes selected categories and other programs not listed.

In this era of budget pinches nothing happens without a tradeoff, however, and the tradeoff for this growth is that some other projects would slow. Fermilab, which wanted $100 million for work on its Main Injector upgrade, may have to settle for the $25 million in Clinton's 1994 request. The Superconducting Super Collider would have to wait an extra 3 years to power up its first beam under Clinton's plan (assuming Congress does not kill the machine outright). Construction would also slow on the Relativistic Heavy Ion Collider now under way at Brookhaven National Laboratory.

Other labs have it even worse. Los Alamos National Laboratory's venerable Meson Physics Facility (LAMPF) is slated for elimination, with just $1.5 million of close-out costs in the budget. But LAMPF's 800-strong user community isn't rolling over. They've started a letter-writing campaign to get 2 more years out of the machine to complete experiments that have been in the pipeline for years.

Clinton's budget is likely to change considerably before it gets out of Congress this fall. The numbers aren't likely to go much higher, and at the end of the appropriations process, when money gets tight, some projects are likely to get cut. One candidate likely to go this year, say insiders in the budget game, is Clinton's B-factory request. But it's still early in the year, and there's a lot of politics to be played between now and the time when the winners are separated from the losers.

–Christopher Anderson