Agencies Vie over Human Genome Project

Faced with a project of unprecedented scale and cost in biology, researchers and bureaucrats are beginning to come to terms with the organization and funding of the human genome sequencing project

This is the second of two articles addressing current developments in the human genome project. The first, published last week, covered issues of access to the mapping and sequence data.

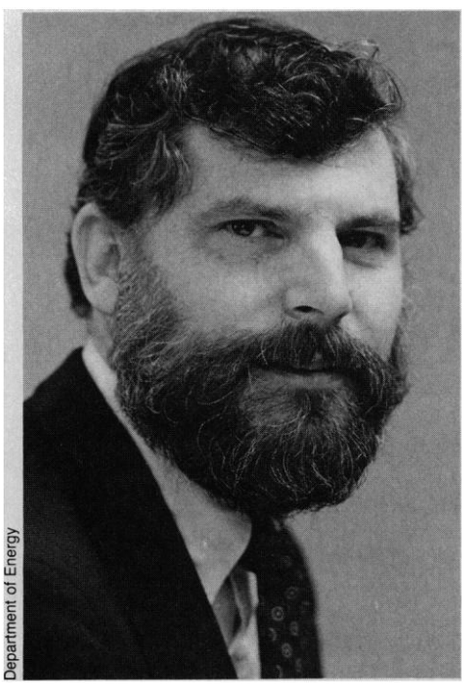
EVER since the proposal to map and sequence the human genome gained momentum 18 months ago, there has been uncertainty—and some unease—among biologists about how such a project might be organized and funded. The nature of the project is something new in biological science: it might take a decade or more to complete and consume as much as $1 billion; it therefore qualifies as Big Science.

The Department of Energy (DOE), which initiated the proposal and has a track record in successfully implementing projects of this magnitude, is keen to continue to promote it. The National Institutes of Health (NIH), into whose research orbit the scientific and biomedical aspects of the project naturally fall, is eager to exert some influence over the project but is awed by its scale and nervous about diverting funds from other areas of its research.

Something of an interagency rivalry has ensued, which, among other things, has served to illuminate the scope and complexity of the challenge. And, in addition to the scientific advisory committees established by DOE and NIH, three other major national committees are due to report on the organization and funding of the genome project. In spite of the potential for confusion, some broad agreements are now emerging. As David Kingsbury of the National Science Foundation (NSF) notes, "We are all talking to each other."

Numerous workshops over the past year have brought consensus on broad outlines of the project, if not on precisely how to get there. The general view seems to be to begin by developing a physical map of the genome—an ordered set of DNA fragments—and then locate genes on it. A massive sequencing effort, which would entail working out the exact nucleotide sequence of the 3 billion base pairs of the human genome, would be delayed until automated technologies can make it both cheaper and faster.

Beyond that, numerous questions are still unresolved: Should the genome project be undertaken as a large, centralized effort, and, if so, which agency should lead it? How targeted should it be? Is the focus on the human genome or on complex genomes in general? How much work should be done in large centers and how much through investigator-initiated grants? Is a scientific advisory body needed to set scientific priorities?



David Kingsbury *of NSF thinks his new subcommittee on the Domestic Policy Council is all that's needed to coordinate federal genome efforts.*

At this stage, efforts to establish a formal interagency effort are clearly on hold, and each agency is going its separate way. Both DOE and NIH would like to keep it this way, with increased communication but no formal ties. What is not clear, however, is whether they will be allowed to do so. New players are entering the scene, with different ideas about how to proceed.

Congress, which sees this project as a tool to boost competitiveness, is keenly interested. It is also leery of investing substantial sums of money in an uncoordinated and potentially duplicative effort. Both the National Research Council (NRC) and the Office of Technology Assessment (OTA) are studying the genome initiative and will issue reports in the coming months. The NRC report, due out in the fall, is expected to call for a highly coordinated effort and recommend establishment of an advisory body outside of government. The OTA report, due out in the spring, will also discuss issues of coordination. A new subcommittee on the human genome has been established within the Biotechnology Science Coordinating Committee (BSCC), the group that oversees biotechnology for President Reagan's Domestic Policy Council. Many scientists involved in the effort believe that it cannot succeed without a targeted program and a lead agency. James Watson of Cold Spring Harbor, for one, hopes to establish a committee of distinguished scientists to advise agencies on how to proceed.

As these discussions continue, DOE is pursuing the project aggressively, if perhaps more diplomatically, than in the beginning. It has launched a highly targeted new program and has requested $12 million for fiscal year 1988 to begin work. Charles DeLisi, director of the DOE's Office of Health and Environmental Research (OHER), says the department is planning to develop the biological, mathematical, and engineering tools necessary to characterize the human genome. Big-budget technology development effort is DOE's métier, he says.

Moreover, an April report by a subcommittee of DOE's Health and Environmental Research Advisory Committee pushes for a far more aggressive program. Urging DOE to undertake a "major new initiative" to order and sequence the human genome, the subcommittee calls for increasing the budget to $40 million for fiscal year 1989, with steady increases over a 5-year period to $200 million a year.

The report also unabashedly asserts that "DOE can and should organize and administer this initiative." While encouraging cooperation among all the organizations involved, national and international, it also says that DOE "should not delay implementation of its plan or defer to some other organization."

David Smith, who runs the human genome project at OHER, says the department is now crafting a response to the subcommittee. While generally endorsing

the tenor of the report, he says its goals are too ambitious and hints that the budget figures may be too high. "We agree with the general idea to undertake an initiative to pursue this vigorously," he says, "but not as broadly as they outline, at least in the beginning. . . . Their proposal includes all of human genetics, and that's not what we think DOE should be doing. We're better at creating a tool and technologies that will allow characterization at the molecular level, but not necessarily doing all the characterization." And in a nod to NIH he added, "We think that belongs in the medical biological community, and that's in Bethesda."

Smith declined to say whether DOE would up the ante to $40 million next fiscal year, as the subcommittee recommended. "Let's just say it's a nice number. We could certainly make use of tens of millions."

DeLisi emphasizes that DOE's role is not to do the pure science, which falls to NIH, but to develop a tool to make it possible. Although DOE's recent report states that the department's long-term goal should be to obtain a base sequence of the human genome, DeLisi says that the agency is "not committed" to that yet. In his view, "having the capability to sequence is more important than having the sequence itself."

Confusion over DOE's plans might have created some interagency tension in the beginning, but that has changed now. "We each have a role to play," says DeLisi. "The bottom line with NIH is that we are in very, very good shape. We are complementary, not competing."

The exact shape that DOE's program will take over the coming months is somewhat unclear, however. Alvin Trivelpiece, former director of the Office of Energy Research and a strong supporter of the effort, left DOE in April to become executive officer of AAAS. And DeLisi, who first came up with the genome project idea and has shepherded it through DOE, is leaving for Mount Sinai School of Medicine, New York, where he will chair the biomathematics department. He expects his departure to have little effect on the program, which "now has a life of its own," he says. "This project is going. There is no doubt about it."

In contrast to DOE, NIH seems very much the reluctant bride, unenthusiastic about an all-out effort yet unwilling to turn the project over to DOE. According to Ruth Kirschstein of NIH, the agency has decided that the best approach is to continue its substantial support of investigator-initiated research in genetics. NIH is already spending $300 million on research related to mapping and sequencing—$100 million on the human genome, she says, and $200 million on other complex organisms.

NIH recently issued two new program announcements "encouraging research" in new mapping and sequencing strategies and in the development of data management systems. But it set aside no new money for these programs and created no new study sections to review the proposals. "It's not exactly business as usual," Kirschstein says, "but it is not highly targeted either. It is something in-between. We see no need for a targeted program." This does not reflect a lack of commitment, she stresses, just a different assessment of the best way to get the job done.

Rachel Levinson in the NIH director's office admits that while this may look like lukewarm support, it is not. "The money we are putting into it proves it [our commitment]. We don't have to have a concerted effort because it is not new. Every institute has work related to mapping and sequencing."

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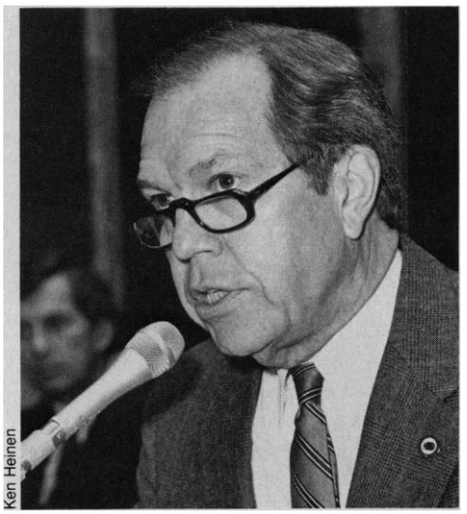
Rubbish, say others, if not in those words. "Our feeling is that NIH's $300 million should not be confused with the genome initiative," says DOE's Smith. "Most of that $300 million is going to very different things than a focused effort to develop a physical map. In the end, of course, investigator-initiated research can get us there. But if we set this up as a national goal to develop this resource, there are quicker ways to get there."

Referring to NIH's statement on funding, Leroy Hood of the California Institute of Technology says, "That confirms it as lukewarm. We all agree this project will require a new approach and new money—for NIH to say they are already spending $300 million means they see it as more of the same."

NIH's apparent coolness to the project can be traced to several concerns. NIH has long been the bastion of support for investigator-initiated research. The genome project would catapult the institute into the world of Big Science. And, with such a hefty component of technology development, the project falls outside the realm of pure science that NIH typically supports. The genome project "would require a change in NIH's philosophical outlook and in approach to scientific funding," observes George Cahill of the Howard Hughes Medical Institute.


Ken Heinen

NIH director James Wyngaarden. *NIH sees no need for a targeted program to map and sequence the human genome at this time.*

And perhaps most important, NIH is worried that a project of this magnitude may drain money away from other areas. "We don't think it would be appropriate to have a specifically targeted program that would compete with all the extraordinarily important programs NIH funds," says Kirschstein. "Before we would target the human genome specifically, we would have to be assured that this would not take money away from other areas."

Yet at the same time, NIH seems unwilling to let DOE assume the lead for a project that falls so squarely within its mandate of human health. "Given the amount of money NIH is spending in biomedicine in general and on work related to the genome in particular, whether or not we are called the lead agency, we are a very substantial leader," says Kirschstein.

A number of biologists seem caught in the middle: They would prefer NIH to take the lead, but they also want the project to be done reasonably quickly and without damage to other areas of biological research. And that may mean tossing their hats in with DOE.

"Who should be the lead agency is up in the air," says Hood. "It's a bit of a paradox. DOE would like to do it and they are very committed. But NIH has a better track record for peer review and spending large sums of money for biological research. We all agreed that DOE could play a major role," he notes, referring to the DOE subcommittee. "The question turns on peer

review and whether money can be disbursed to external groups effectively."

For its part, DOE is doing all it can to assuage those doubts. The subcommittee report recommended enhanced peer review, and the department has endorsed it wholeheartedly. All proposals on the genome will be peer reviewed, says DeLisi, whether they come from the national laboratories or from the universities—a departure from DOE's normal procedures.

Kingsbury of NSF says that no lead agency is necessary as long as the project is well coordinated. "DOE will run its own research program, and NIH will run its own," he says, echoing the sentiments of officials of both agencies. And in terms of coordination, Kingsbury thinks his BSCC subcommittee on the human genome can serve that function. The subcommittee was created in response to congressional interest and queries from cabinet members. "Congress was clearly wondering, is this another superconducting supercollider? Is there a potential problem between NIH and DOE?"

The BSCC subcommittee, which met first in May, is composed of senior staff of NIH, DOE, NSF, and the Food and Drug Administration. The U.S. Department of Agriculture and the Environmental Protection Agency are "interested, smaller players," Kingsbury says. The subcommittee has a rotating chair, shared by NIH and DOE, which to date has been occupied by NIH director James Wyngaarden.

The subcommittee's first task, which is well under way, is to compile a report on existing and planned activities in the federal agencies and the nonprofit sector, including the various foundations devoted to specific diseases, such as cystic fibrosis and Alzheimer's. The subcommittee will then decide whether these efforts need to be coordinated, and, if so, who should do it, and how, Kingsbury says. But the answer seems to be a foregone conclusion. Indeed, the subcommittee's aim seems to be to ward off congressional interference, such as the creation of an oversight committee or advisory board. "At the working group, we already have a mechanism for exchanging information—we have the right people, at the right level," says Kingsbury.

"Scientific interests go across agencies and political boundaries," comments Levinson of NIH, who is also executive secretary of the BSCC subcommittee. "When politicians try to step in and say this is what DOE and NIH should be doing, it's not that clear-cut. It is important for some oversight to take place, and that is the purpose of this group. We will not recommend that some other coordinating group be over us."

DeLisi agrees. "What is developing is a mechanism to ensure that there is no needless duplication of effort and that information flows freely. We don't need more. We all hope the Domestic Policy Council's subcommittee will continue in the coordination function."

DeLisi and Kirschstein say they are continuing their discussions. For instance, NIH and DOE may jointly fund a multicenter effort in California to develop sequencing technologies, says DeLisi. And to improve coordination further, an NIH staff person will be joining DeLisi's staff in September.

Others are less sanguine about the prospects of coordination falling to the Domestic Policy Council. "I don't think the coordination should be done by bureaucrats," says Watson. "It must be done by scientists. You can't build a bridge without calling in the engineers." He is planning a meeting this fall to discuss establishing an advisory group of scientists. "All I am proposing is that we should get together. When physicists want to build an accelerator, they get together. I would be happy to help such a group come into existence. It would include people like Victor McKusick, Frank Ruddle, Lee Hood, Thomas Caskey—everyone on the three [NRC, OTA, and DOE] committees."

As Watson sees it, the group would advise on a range of questions, from scientific priorities to who should be the lead agency and how the program should be implemented. And he suspects, given the stature of the group he has in mind, the government would be compelled to listen to their advice. He is emphatic on one question: "It is not possible to do the project without a lead agency. There is only one genome."

Meanwhile, several bills are in the works in Congress that may appoint one agency or the other the lead, or at least create a coordinating body. Senator Pete Domenici (R–NM), for example, has introduced a bill as part of a larger national laboratories bill that would create a national policy board on the human genome within the White House Office of Science and Technology Policy. This board would essentially be a transplanted version of the BSCC subcommittee, cochaired by DOE and NIH.

Domenici's bill also calls for placing the day-to-day management of the project in the hands of a consortium of representatives from the national labs, universities, and industry. The goal is to ensure that the fruits of the project are transferred rapidly to industry, according to administrative assistant Paul Gilman. "If the project is going to be done with maximum effect in the minimum amount of time, it will have to be more coordinated."

"I think it's great," says DeLisi. "I am glad Congress is interested. It will be a great stimulus to the nation."

Meanwhile, Congress has already taken some action, with the House Appropriations Committee having voted $12.7 million for a new "Institute for Genomic Studies" at Mount Sinai School of Medicine. The new facility will conduct research "into genetic components of chronic disease," notes the bill, and thereby "contribute to the Department of Energy's Human Genome program." The initiative, which was engineered by the Washington lobbying firm Cassidy and Associates, has yet to pass muster with the Senate.

The major issues may be sorted out next year in Congress. Meanwhile, opinion is divided on whether DOE and NIH have indeed resolved their differences or simply moved their fight inside, away from the public gaze. At this stage, when DOE's budget request is only $12 million for fiscal year 1988, there is not much to fight over. But if DOE does request $40 million for fiscal year 1989, as its advisory committee recommended, Robert Cook-Deegan, an analyst at the OTA speculates, "that might begin to get NIH nervous." ■

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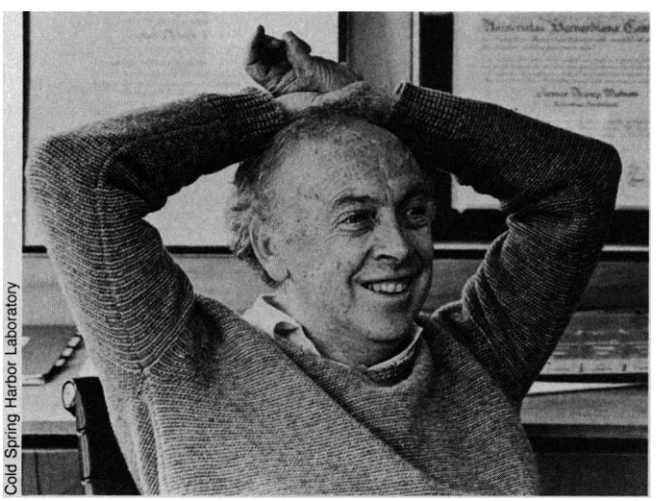

Cold Spring Harbor Laboratory

James Watson

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