The Genome Project: Life After Watson

The Nobelist's abrupt departure from a project he has personified for 3 years leaves researchers wondering what kind of a leader the effort needs now

On 7 May 1991, James D. Watson stood in front of a hostile crowd at a packed auditorium in Dallas, Texas. The occasion was the annual meeting of the American Society of Microbiologists, and Watson had been invited to give a talk about the human genome program. Many of the microbiologists were skeptical about the effort: They saw it as an expensive boondoggle, soaking up research dollars at a time when resources were particularly scarce. Watson gave what had become his standard stump speech, explaining the importance of the project to the future of biomedical research. But he reassured the skeptics that the Human Genome Project would not be a blind, brute-force effort to sequence all 3 billion bases in the human genome, no matter what the cost. And he patiently answered questions about why the time was right to start such a large undertaking.

"He disarmed them," says Stanford geneticist David Botstein, who was at the meeting. Although Watson was delivering a message that many in the audience didn't want to hear, Botstein says they listened—and were persuaded largely because Watson is a hero to many of them. Afterward, as Botstein describes it, the microbiologists crowded around Watson "almost as if he were a rock star," anxious to have a word with the man who helped launch a new age of biology.

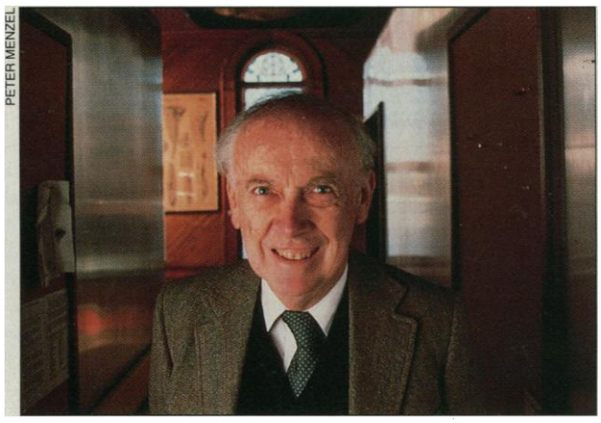
No, James Watson did not singlehandedly launch the human genome program, but, probably more than anyone else could, the 64-year-old Nobelist gave it instant credibility—both among scientists and the public. Not only was he the program's staunchest cheerleader, but Watson's fans say that, as head of the National Institutes of Health's National (NIH) Center for Human Genome Research, he played a critical role in holding together an often fractious amalgamation of researchers, bureaucrats, politicians, and foreign partners that made the project go.

But, famed for his blunt style, Watson has not always been the smoothest operator. He's had legendary run-ins with key researchers and government officials—including NIH Director Bernadine Healy, which led to his abrupt resignation last month. "He was intemperate from time to time in the way he spoke publicly about the project in relationship to his opponents and to the contributions of the Japanese," says one academic who has studied the genome program's origins.

Watson's abrasive management style has left the project with a clear direction, momentum, and a substantial budget. But the project's future is still far from assured.

A tough balancing act

Whoever follows Watson—and several names are already beginning to surface—will still have to contend with the project's influential critics. People like Harvard microbiologist Bernard Davis remain concerned about how useful a complete sequence of the human genome will be. They also worry that the effort has been oversold: Congress and the public may have been led to expect a cure for all genetic diseases once the sequence is known, an expectation researchers obviously will not be able to meet. And, with a budget now running at $164 million a year—split between NIH ($104.9 million) and the Department of Energy (DOE) ($59 million)—it has become highly visible on Capitol Hill. Unless Congress can be assured that the program is in good hands, friends of the program such as Norton Zinder of Rockefeller University worry that the political support the effort has enjoyed until now could dissipate in these tough fiscal times.



PETER MENZEL

Blunt operator. Watson shaped the project's public image and its scientific content.

If the critics outside the program can be satisfied—no small task—that still leaves the critics inside the program. Watson is widely credited with shaping the effort scientifically—sometimes over the opposition of researchers who want to see a different emphasis and others who argue that it should support far more investigator-initiated research.

The course of the project was formally charted at a joint meeting between DOE, NIH, and extramural scientists in 1989. By 1995, it was expected to accomplish several discrete goals:

- a high-resolution genetic map of the human genome;
- a complete physical map of certain model organisms and a start on physical maps of human chromosomes;
- the development of new technologies to increase the efficiency and accuracy of mapping and sequencing and to lower the costs.

Watson was a strong advocate of the need to create a physical map of the genome so that researchers could go directly to the appropriate spot on a chromosome when they found an interesting gene. "If you don't have a physical map, you're going to run up against a problem," says Watson. Initially, critics thought Watson was trying to commit enormous resources to what many thought would be a trivial task. "A lot of people in the nonmapping community thought that it was a no-brainer," says medical geneticist David Cox of the University of California at San Francisco (UCSF). But, says Cox, "people involved with mapping realized that this was a nontrivial exercise," and he says that without a strong commitment from Watson, physical mapping would have gone nowhere. Now Cox predicts it is about to take off.

Watson was also convinced that model organisms would play a crucial role in the genome project, another area that is currently paying significant dividends. A collaboration between John Sulston and Alan Coulson of the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England, and Robert Waterston of Washington University in St. Louis has completed a physical map of the nematode *Caenorhabditis elegans*, and a sequencing effort is likely to be scaled up soon (see sidebar, p. 958).

Progress toward the third goal—the development of new sequencing technologies—has been more disappointing. Caltech's Leroy Hood argues that Watson did not devote adequate resources to new technology development in the genome centers he established. "I would argue that half the funds that a center gets should be put into technology

development," he says. Although there are some promising approaches, such as using mass spectrometry and a DNA "chip" (*Science*, 27 September 1991, p. 1489) to determine sequences, there have been no "breakthroughs" on the sequencing front that will speed things up (or lower the cost) in a way that would make starting a large-scale sequencing program practical.

But, Hood adds, even "if I gave you tomorrow a DNA sequencer that could do 50 times the throughput of sequencing, in many ways it wouldn't do you any good. The front end of producing the fragments for sequencing, and the back end of the computational tasks have to be matched," he says. "So there's this enormous task of systems integration which has largely been ignored."

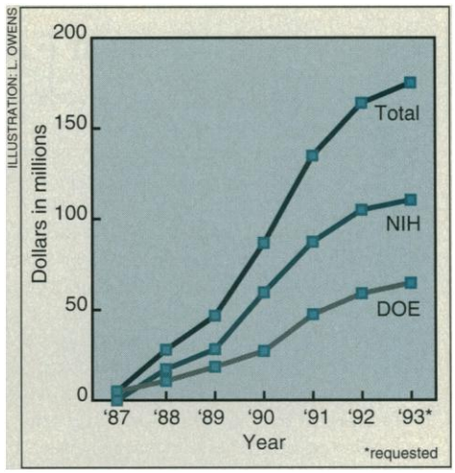
Big vs. small science

Hood's complaint lies at the core of the debate that the next director will have to resolve: how to balance small science that usually fosters innovation with the larger infrastructure needed to complete the genome project. The European Community has proceeded with a kind of "cottage industry" approach to the yeast genome (*Science*, 8 May, p. 730), but even proponents of that scheme admit it is not the most efficient way of getting the job done. So Watson, along with DOE, decided to establish larger centers.

There are now seven NIH-supported centers scattered around the country, and they account for about one-quarter of the NIH genome budget. Their share of the project is expected to grow, and that, says UCSF molecular biologist Bruce Alberts, is bound to cause political problems: "They are going to need more support than they have, and more support than the community would like, because it's the kind of support that most of us never get." Maynard Olson, a physical mapper at Washington University, agrees. Olson, who will leave St. Louis next fall to join a large genome effort being organized by Hood at the University of Washington in Seattle, says there is a reticence to move away from investigator-initiated projects: "There are many people in the American scientific community who will support small mediocrity before they will even consider the possibility that there can be some large excellence."

But in the minds of many, the move toward big genome centers is keeping people away from the genome project. Craig Venter, a sequencer at the National Institute of Neurological Disorders and Stroke, is a proponent of a distributed structure for the program. Venter, who caused a stir by applying for a patent on several thousand gene fragments without knowing the biological function of the proteins the genes coded for, says bigger isn't better: "People were told, 'If it isn't going to be large scale, don't apply here. If you're not going to sequence 2 million bases, don't send in an application because it will get turned down,'" says Venter. "As a result, nobody has sequenced 2 million of anything."

Stanford geneticist Paul Berg, who chairs the NIH Program Advisory Committee on the Human Genome, agrees that the next director should listen to what smaller labs say they can do for the genome project. Berg argues that more of the budget should be spent on pursuing the interesting biology that is discovered as scientists work on maps and sequences—a belief that put him at odds with Watson. "Clearly, Jim and I differ in that way. Jim says if you want to get the genome project done, you've got to keep people's nose to the grindstone, and not let them go off on tangents to satisfy their curiosity," he says. "I think that to maintain interest and excitement about the program, we have to link it to [gene] function in some way."



Reaching a plateau. Federal funding for the genome project, split between NIH and DOE, has begun to level off.

"Paul Berg has never really understood the point of the thing," says Watson, betraying the blunt style that some find off-putting. "He thinks we should be spending some of our money on gene function. I don't think so. We're there as a resource for other people. So if you want to study your gene, that part of the chromosome is already at hand, and you don't have to isolate it yourself."

Wanted: working scientist

What kind of leader would be able to satisfy all the constituencies that make up the ge-

A Standing Ovation From the Troops

James Watson may have rubbed some researchers the wrong way with his blunt, abrasive style during his 3-year reign as head of the Human Genome Project at the National Institutes of Health. But, to judge by the reception he received last week from more than 450 scientists gathered at the Cold Spring Harbor Laboratory for the annual genome mapping and sequencing meeting, his leadership will be fondly remembered. In what was clearly a bittersweet moment for all concerned, Watson made a brief appearance before the overflowing crowd, which gave him a standing ovation.

"I had wanted to quit—but not necessarily the way I did," said Watson, in an obvious dig at NIH Director Bernadine Healy, who Watson says forced him out—a charge Healy roundly denies (*Science*, 17 April, p. 301).

Then Watson had a few words of advice for his successor: Whoever takes the job must be willing to fight for more money amid a chorus of demands for more support from other areas of biology, he said, adding in vintage Watson style: "All science isn't equally interesting. Getting the human genes and the other genomes is the most important thing in biology."

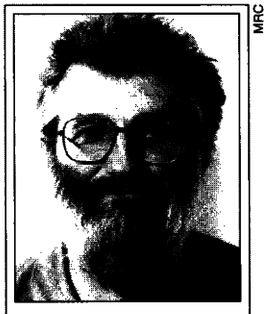
That kind of passion is just what the project will need in its new leader, says Maynard Olson, a physical mapper who will join the University of Washington this summer—and Olson should know: just last week he was appointed by Healy along with 13 other top scientists to act as a search committee (see accompanying story).

Watson, in any case, is convinced that he's handing the project over in good shape, a conclusion he said is evident from last week's meeting—with its 350 talks and posters. Even though large-scale sequencing still lags behind expectations, mapping is clearly going full tilt, and some notable advances were reported, including an all-but-complete map of the Y chromosome, done by David Page's group at the Whitehead Institute; the mega-YACS, or yeast artificial chromosomes, developed at the Centre d'Etude du Polymorphisme Humaine in Paris (without NIH funding), which promise to speed genome mapping worldwide; and the extensive maps of the mouse genome developed by Eric Lander's genome center at the Massachusetts Institute of Technology. "It has been an American success and an international success, and I am very pleased," said Watson.

–Leslie Roberts

Britain Plans Large-Scale Sequencing Center

LONDON—While U.S. researchers debate the future of the genome project without James Watson, the Wellcome Trust—Britain's largest medical research charity—is laying plans for a bold step into large-scale gene sequencing. Last week, the trust announced that it has asked geneticist John Sulston, a senior researcher at the Laboratory of Molecular Biology (LMB) in Cambridge, to submit a proposal for a new multimillion-dollar center for human gene sequencing. Why Sulston? He's been using the latest automated gene sequencing technology to tackle the genome of the nematode *Caenorhabditis elegans*. And now that the nematode project has shown the potential of this production-line approach, the Wellcome Trust sees the chance to turn Britain into a major player in human genome sequencing.


MRC

John Sulston

Sulston declines to discuss the details of the plan until he has completed his proposal, saying only that the center would be built around a team of about 30 people working on a scaled-up version of the *C. elegans* project. They would churn out about five megabases of completed nematode sequence a year—about five times the present output of Sulston's group at LMB. The center's human gene sequencing effort could start off at about the same level, says LMB director Aaron Klug, who has been involved in discussions with Wellcome Trust officials. Over time, this could be ramped up substantially, he adds, prognosticating that "this technology could be and should be applied to the human genome on a massive scale."

To broaden the center's outlook, Sulston hopes that he will pull in gene mapping groups, and he intends to expand his group's existing work on genome databases, making his proposed center one of "the largest [genome] facilities in the world." If all goes well, the center could open—initially in rented accommodations in Cambridge—by the end of the year.

Sulston's decision to concentrate on launching a genome center in Cambridge kills speculation that he and his collaborator on the nematode project—Robert Waterston, from Washington University in St. Louis—will join a commercial sequencing company in Seattle. Before resigning, Watson had gotten into a bitter tussle with entrepreneur Frederick Bourke, who planned to set up the company with advice from gene sequencing pioneer Leroy Hood, who moves to the University of Washington in Seattle later this year (*Science*, 7 February, p. 677). Watson violently opposed the idea of moving the nematode project—one of the few truly international collaborations in genome research—into the private sector. Now Waterston says that discussions with Bourke had broken down in any case: Bourke's interest was in commercial contract sequencing and applying the technology to medical diagnostics, rather than the "pure genomic sequencing" that he and Sulston want to pursue.

This should be welcome news to the wider genome community, which seems to agree that there is a demand for the type of center that Sulston is planning. Doug Higgs, from the Institute of Molecular Medicine in Oxford, for instance, wants to sequence the end of chromosome 16, which contains the alpha-globin gene cluster. "I'm not really interested in the technology and the handle turning," he says, so if Sulston's planned center could do the job, that would be ideal.

The proposal also comes just as Sulston's employer, the UK Medical Research Council (MRC), is due to launch a far-reaching review of the British genome project, which will be 3 years old this summer. The MRC hasn't yet funded large-scale human gene sequencing but views the *C. elegans* work as a pilot project to reduce costs and refine the technology. If the Wellcome Trust does decide to back Sulston with a multimillion-dollar budget for human gene sequencing, however, this is bound to color the MRC's plans. The MRC is already bidding for government funds to expand Sulston's *C. elegans* work and is now setting up a joint working party with the Wellcome Trust to discuss Sulston's proposal.

Whether Sulston's center will be among the leaders in the race toward production-scale human gene sequencing now lies in the hands of referees and the Wellcome Trustees, who will reach a decision later this summer. But, given that the trust has taken the unusual step of making a public announcement about the project even before receiving a formal proposal, the betting is that Sulston can trust he's about to get a warm welcome.

–Peter Aldhous

nome project? In addition to coping with the varying interests within the U.S. scientific community, the new director will have to be willing to play the role of diplomat. He or she will not only have to keep enthusiasm—and funding—for the project high, in this country and abroad, but will have to try to prevent any country, including the United States, from becoming excessively proprietary about the work its scientists are doing. "That's part of the reason why somebody like Watson is so essential, says Alberts. The new director should be "somebody with credibility who knows what's going on and can give people confidence that this is quality stuff."

Last week, three of the major players in the project flew to Washington for a private talk with NIH Director Healy—who will choose Watson's replacement—to discuss where the project is headed and who might lead it there. Healy doesn't want to second-guess her search committee, but, according to one of the scientists, everyone, including Healy, seemed to agree that rather than a senior statesman, the new head should be a practicing genome researcher who can command the respect of the scientific community. Moreover, the scientists said they wanted someone firmly grounded in medicine who can understand—and, more important, convey—just what this vast project means for human health. Some of the names being discussed at a meeting of genome researchers held last week at the Cold Spring Harbor Laboratory included UCSF's David Cox, Nancy Wexler of Columbia University, and, most frequently, Francis Collins of the University of Michigan.

Whether one of these three—or anyone else—would take the job, should NIH come calling, is another matter. But already, discussions are under way about setting up an intramural genome program that would allow the new director to continue his or her research, at least part time, at NIH.

NIH announced last week that Ruth Kirschstein, director, National Institute of General Medical Sciences, and George Vande Woude, director, Advanced Biosciences Laboratories Basic Research Program, will co-chair a search committee to find Watson's replacement. Acting director Michael Gottesman says Healy told him to be prepared to stay in that capacity for at least 6 months. The program's momentum should carry it along for that duration without difficulty, but if by the new year the interregnum has not ended, the babble of differing opinions about how to proceed may reach a deafening roar, and make leading the genome chorus a nearly impossible task.

–Joseph Palca

With reporting from Leslie Roberts at Cold Spring Harbor.