

Watson resigns, genome project open to change

- Will leave immediately, acting head named
- Smaller centres, more research anticipated

Washington

JAMES Watson, who officially resigned last week as director of the \$3,000 million US human genome project, was probably the only person who could have brought the effort so far in its first three years. But now that the once-controversial project is on its feet, many researchers are hoping for a change of pace.

Advocates of cDNA sequencing, small genome centres and more research on the way genes function — all of whom struggled for funding under Watson's vision of a high-technology genome effort with an emphasis on mapping large stretches of DNA in the human genome and other model species — are likely to see their fortunes brighten under new leadership. And other researchers are hoping that a change at the top may mean an end to the 'old boys' genome network' that they believe has kept the Center for Human Genome Research at the National Institutes of Health (NIH), which Watson directed, from evolving as quickly as similar efforts in other countries and even within the US Department of Energy (DOE), which shares responsibility for the project.

Watson departed in the wake of concern over possible conflict of interest in his holdings of various biotechnology stocks and an increasingly visible dispute with Bernadine Healy, the NIH director. His stepping down is seen as the loss of an able genome advocate and a harbinger of difficult political times. Genome researchers have expressed nearly uniform sadness over the circumstances and haste of his departure. They also credited Watson for giving the project shape in its early years, and leading it through initial congressional opposition.

But it was the timing of Watson's decision that concerns researchers most. He had been expected to leave soon anyway, says Norton Zinder, a Rockefeller University geneticist and former chair of Watson's genome advisory panel. But Zinder and other associates had recommended a graceful departure towards the end of the year, after seeing through this year's congressional budget process. Almost any arrangement, in fact, would have been better than what actually happened: a tumultuous resignation coming just days after the first congressional hearing on the project's proposed 1993 budget.

If the project can survive this year's budget cycle, however, it may emerge reinvigorated. Watson formed a working

enterprise out of what was only an idea four years ago, but "he never planned to stick around to micromanage the genome project," says Zinder. But, over the past year, some researchers were concerned that that was just what was happening. Watson was more of a genetic visionary than a practising researcher or manager, and his strength, both at the genome project and as director of the Cold Spring Harbor Laboratory on Long Island, New York, was not in day-to-day operations.



Watson's departure may make a place in the genome project for cDNA and its chief advocate, Craig Venter (at right, with NIH's Mark Adams)

His clash with Healy over cDNA patents last year was only the most apparent of his legendary disagreements with members of the genome community. He also opposed cDNA sequencing itself, arguing against churning out portions of expressed genes without knowing their function. And his determination to focus on obtaining a physical map of the entire genome assumed that gene sequencing technology would see great improvement over the past few years, something that has not happened.

"According to his text, we'd get revolutionary improvements in the technology, and that has not materialized," says Paul Berg, director of the Stanford University Beckman Center and current chair of the genome project's advisory committee. Sequencing cDNAs offered a cheap and easy way to find expressed genes that could be used as markers in genetic mapping, and an alternative to the straight-ahead, sequence-to-the-end approach that Watson advocated as the eventual goal.

But Watson disapproved of cDNA sequencing as being insufficiently rigorous,

and he fought its leading proponent, J. Craig Venter of the NIH. Since then, the DOE (which supports about a third of the US genome project), France, the United Kingdom and Japan have all embraced cDNA sequencing. Only NIH have resisted.

Now, says Berg, "I think that there will be a much more receptive atmosphere to cDNA work." In his effort to give the genome project direction and momentum in the face of early opposition, Watson "may have focused too narrowly", Berg says. "He wanted to keep people's noses to the grindstone. And we might not have been so far along today, if it were not for his single-mindedness and doggedness." Berg predicts that the genome project will in future be more tolerant of other approaches, including more studies of gene function and biology.

Small genome centres may also come into favour. Several teams in Europe that are studying the yeast chromosome have shown that a dozen researchers with an automated gene sequencer, if they collaborate will similar teams, can be as productive as a large group, says Venter. "Originally, it seemed like exactly the wrong approach — exactly the opposite of the high-tech strategy" that Watson advocated, he says. But once the small teams learned to work with each other, they were able to move on to different projects with a flexibility that large laboratories can only hope for.

NIH are deciding how large to make the next set of genome centres. Many researchers argue for a balance between large and small laboratories, rather than a focus on laboratories with a 'critical mass' of researchers, about 20 PhDs, such as is headed by Eric Lander at the Whitehead Institute of Biomedical Research in Cambridge, Massachusetts.

In his resignation letter, Watson promised to continue to support the project enthusiastically, and to advise NIH informally. But his resignation takes effect immediately, and last week Healy appointed Michael Gottesman, currently chief of the Laboratory of Cell Biology at the National Cancer Institute, to be acting head of the National Center for Human Genome Research.

Healy also announced that the search for a permanent director would begin immediately. Although several prominent researchers (including Victor McKusick, a geneticist at Johns Hopkins University) have been mentioned in the past as possible replacements for Watson, the likeliest candidate right now is Daniel Nathans. He is a Nobel Laureate like Watson and, like McKusick, a Johns Hopkins geneticist, as well as being a member of the President's Council of Advisors on Science and Technology, on which Healy served before becoming director of NIH.

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