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A new view of the mantle

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Angiostatin's target

HUMAN GENOME

Academic Sequencers Challenge Celera in a Sprint to the Finish

The Human Genome Project has just entered warp speed. Several large grants announced this week by the U.S. government and the Wellcome Trust, a U.K. charity, may make it possible for researchers to determine the order of the 3 billion bases in the human genetic code much earlier than expected—by the spring of 2000.

A year ago, even the most optimistic project leaders were predicting that the human genome would not be sequenced before 2005. Then, boosted by some early successes and prodded by a private competitor, they announced last October that they could deliver a "rough draft" by the end of 2001. Now, they've advanced that date by 18 months. "Every time we talk, we move [the deadline] up," says Robert Waterston, director of the sequencing center at Washington University in St. Louis.

Finalists. NHGRI announced $81.6 million in grants to sequencing teams led by (*from left*) Robert Waterston, Richard Gibbs, and Eric Lander.

The money for this accelerated schedule comes largely from the National Human Genome Research Institute (NHGRI). On 15 March, it announced that it had selected three major centers to do high-volume human DNA sequencing, awarding them $81.6 million over the next 10 months. NHGRI also expects to provide them with comparable support over the following 4 years. The winners include Waterston's group at Washington University ($33.3 million), Richard Gibbs's team at Baylor College of Medicine in Houston ($13.4 million), and Eric Lander's team at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts ($34.9 million).

At the same time, the Wellcome Trust upped this year's support of the human genome sequencing effort by the Sanger Centre in Cambridge, England, from $57 million to $77 million. These four, together with the U.S. Department of Energy's (DOE's) Joint Genome Institute, have promised to sequence at least 90% of the human genome with fivefold coverage by March 2000. After that, they plan to spend 2 or 3 years combing through the data and creating an accurate version of the whole genome.

The new agenda, announced by Francis Collins of NHGRI and Michael Morgan of the Wellcome Trust, has been greeted with both joy and dismay. Many researchers are delighted that human sequence data will be made available to the public more rapidly. But some fear that the smaller sequencing centers, left out of this round of competition, may become obsolete. Some international partners in the effort were upset, as well.

Neither German nor Japanese groups were involved in setting this new deadline. "The policy was not agreed upon in the same international spirit as had [been cultivated] in the past," says Andre Rosenthal, who heads the Institute of Molecular Biology in Jena, Germany, and hopes that his group will do about 7% of the human genome. Rosenthal is determined to have Germany contribute its share—as long as funding holds out—but "this announcement gives the impression that [we're] not needed," he complains.

For some researchers, however, the new sequencing target seems like a natural outgrowth of experiments that began several years ago. In 1996, NHGRI began funding labs to assess the feasibility of doing high-speed sequencing. "The problems that everyone thought were limiting 3 years ago have all been solved," says Lander, who ran one of the pilot projects. As a result, "we have a rock-solid way to sequence the genome accurately." At the same time, increasing amounts of human data from the pilot projects, along with the complete sequences of organisms such as yeast and nematode, "created a real enthusiasm for more [DNA sequence]," Waterston says.

Despite such enthusiasm, some researchers continue to worry that too fast a pace might degrade the quality of data. Those qualms were debated intensely within the genome community—until May 1998. That's when sequencing maverick J. Craig Venter announced that he was teaming up with the Perkin-Elmer Corp. of Norwalk, Connecticut, to sequence the human genome by 2001. Academic researchers became concerned that Venter's new company, Celera Genomics of Rockville, Maryland, might patent the human genetic code, and the Human Genome Project participants responded by stepping up their own efforts. "Our community must compete with or beat Venter's efforts," says Yoshiyuki Sakaki, a molecular biologist and sequencer at Tokyo's Institute of Medical Science.

Morgan and Collins decided that the best way for nonprofit institutions to keep up was to scale up, concentrating resources in the most efficient centers. And the three groups that won NHGRI's big awards have already hunkered down to work with the DOE and Sanger Centre. Every Friday they get together by conference calls for a group lab meeting. They share opinions about capillary automated sequencers and efficient management. The pressure has created "a sense of needing to work together to get the job done," says Waterston.

His crew, for example, is fingerprinting two sets of clones so that the pieces of DNA they contain can be used more efficiently. In this way, the Human Genome Project participants will be using familiar processes, tracking the location of each clone along the genome. "That will be of great assistance," says Collins, avoiding the time-consuming step of making detailed, sequence-ready maps. But this approach contrasts with the "shotgun" random sequencing of the whole genome being undertaken by Celera.

As these high-production labs step out, they could be leaving behind some of the field's pioneers—like Bruce Roe of the University of Oklahoma, Norman, and Glen

CREDITS: (LEFT TO RIGHT) WASHINGTON UNIVERSITY SCHOOL OF MEDICINE; L. L. GORRELL/BCM/HGSC; SAM KITTNER

Evans of the University of Texas Southwestern Medical Center at Dallas. Both had genome center grants before NHGRI's pilot projects began in 1996. And they worked hard last year, with half a dozen others, to meet NHGRI requirements that each center should complete 7.5 megabases of finished sequence data. But last fall, the NHGRI advisory council decided to rank the competitors for new grants in two groups: those that had at least 15 megabases of sequence under their belt, and those that did not. That put some—including Evans and Roe—in the second tier, still awaiting funding. Although Evans applauds NHGRI's fast-paced approach, he also feels a bit left out in the cold. "It's kind of upsetting for all of us," he says.

When the deadline for completing the human genome rolls around next year, some researchers fear that interest in closing gaps in the data and removing errors will fade. Evans, for example, worries that a highly accurate, complete version of the genome may never be done. But Collins thinks these worries are not justified. "We didn't intend to pull the plug on the other centers," he says, although he does not know how much money will be available for them. And he insists that next year's draft genome is on "a direct path" to the goal of producing a polished, error-free version. Morgan agrees: "We are determined to finish," he says. **–ELIZABETH PENNISI**

With reporting by Dennis Normile.

EVOLUTION

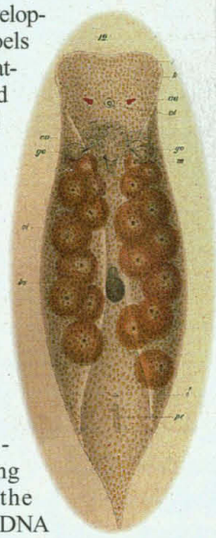
From a Flatworm, New Clues on Animal Origins

One of nature's more enduring mysteries has been how millipedes, mollusks, snakes, and butterflies came to be. The fossil record shows an eruption of diversity of such groups—all of which have bilaterally symmetrical bodies—during the Cambrian explosion, some 530 million years ago. But fossils of the very first such creatures have been scarce. Now, a living creature, a humble flatworm, may provide some key clues.

As Jaume Baguñà, a geneticist at the University of Barcelona in Spain, and his colleagues report on page 1919, tiny marine worms called acoels may be one of the closest living representatives of the first bilaterally symmetrical organisms on Earth. Acoels are usually grouped with Platyhelminthes, a group that includes such unpleasant parasites as tapeworms and liver flukes, and whose position in the tree of life has been subject to debate. But using DNA analyses, Baguñà's team concludes not only that the acoels don't belong with other flatworms, but that they alone represent a living relic of the transition between radially symmetrical animals such as jellyfish and more complex bilateral organisms such as vertebrates and arthropods.

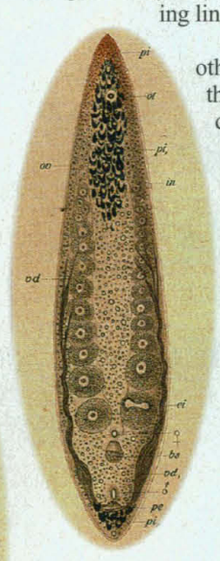
Putting acoels in this key position "is going to stimulate a lot of research," predicts Julian Smith III, an invertebrate zoologist at Winthrop University in Rock Hill, South Carolina. The results are "quite exciting," agrees David Jablonski, a paleontologist at the University of Chicago. "We might have one bilateral survivor from before the Cambrian explosion giving us a living window on early metazoan life."

Baguñà and Timothy Littlewood, a molecular biologist at The Natural History Museum in London, decided to use molecular studies to evaluate the acoel's placement on the tree of life because anatomical data—including simpler brains, kinked cilia, and a different pattern of development—suggest that acoels may differ from other flatworms. The pair obtained DNA from 18 acoel species from around the world and sequenced the gene for the 18*S* ribosomal RNA subunit from each. They then compared these data to the same genes from other platyhelminths and from both simpler and more complex organisms.



The team first removed 16 fast-evolving acoel species from the analysis, because their DNA sequences were so different from those of simpler organisms that the phylogenetic analyses would be suspect. When they used only the two slow-evolving species to represent the group, "the acoels dropped out completely from the rest of the platyhelminths," notes Mark Martindale, a developmental biologist from the University of Hawaii, Honolulu. The worms ended up branching off from an ancestral animal after the radial jellyfish and their cousins, but before the three major bilateral groups, today encompassing vertebrates, mollusks, and arthropods, began to diverge. By moving into this prime spot on the animal tree of life—close to the first bilateral animal—the acoels and their idiosyncrasies take on new meaning for evolutionary biologists, offering a living link between primitive and more complex animals, says Martindale.

For example, primitive, radially symmetrical animals have just two types of cells, ectoderm and endoderm, whereas all bilateral animals, including acoels, also have mesoderm. Most of those with three layers have a distinct gut lined with mesoderm, but acoels have mesoderm but no true gut. "They may be some sort of 'missing link,' " says Littlewood.



Living relics. Acoel flatworms, shown in 19th century drawings.

Acoels also differ from other bilateral animals in the way their cells divide during development. During the early cell divisions (called cleavage) of related bilateral animals, the fertilized egg forms two, then four cells. Then each of those cells gives rise to many small cells, explains Martindale. But the acoel egg divides once, and the two resulting cells immediately generate many small cells. "They have a spiral cleavage pattern that's different," and may have evolved separately from the pattern seen in most bilateral organisms, says Martindale. That suggests that acoels branched off from all other bilateral animals very early indeed, and that their cleavage pattern represents an early experiment in the evolution of body form. The acoels would therefore possess many of the same genes as the earliest bilateral animal. "It's beginning to look like we are looking at something close to the fuse for the Cambrian explosion," Jablonski suggests.

If so, then acoel biology may offer clues as to which traits evolved first in evolutionary history. Acoels go directly from egg to the adult form, skipping the larval stage seen in many more complex organisms, including some platyhelminths. That suggests that larvae evolved later in the tree of life.

For all these reasons and more, acoels

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