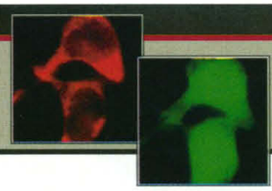

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HUMAN GENOME

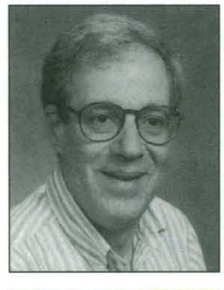
Team Wrapping Up Sequence of First Human Chromosome

TOKYO—While the Human Genome Project races to finish a rough draft of the 3 billion bases in our DNA by next March, three sequencing teams are about to reach a different, potentially more significant milestone: a final draft of the first human chromosome. Sometime within the next week or two, the international consortium sequencing chromosome 22 will conclude that it has done everything possible to complete the sequence. As the team approaches that landmark, it is also setting precedents for those whose work on the rest of the human genome is scheduled to be finished by 2003, including a definition of what constitutes success.

The official announcement about chromosome 22 is not expected until early November, timing that coincides with both a conference in Tokyo and publication in a peer-reviewed journal. The scientists involved—from the Sanger Centre near Cambridge, United Kingdom; the University of Oklahoma, Norman; and Keio University School of Medicine in Tokyo—say theirs has been a model of international cooperation. "A lot of people have put a lot of blood, sweat, and tears into this," says Oklahoma's Bruce Roe. "This has been international cooperation at its finest."

Chromosome 22 will be the first across the finishing line primarily because, at roughly 53 megabases (53 million base pairs), it is the second-shortest chromosome. (Chromosome 21 is slightly shorter, but its sequencing is progressing more slowly.) Another factor has been the right mix of partners. The Sanger Centre, which can churn out a lot of sequence data in a short time, took on the seemingly straightforward half of the chromosome, while the two smaller groups tackled regions, such as those with numerous repeats and few genes, that could have slowed down the Sanger team.

Although part of the international Human Genome Project, the chromosome 22 consortium had enough of a head start over other groups that it was unaffected by the project's decision last year to concentrate on a rough draft first. Before human genome sequencing efforts were launched in earnest, chromosome 22 had already been the focus of a fair amount of mapping and even some sequencing work. Ian Dunham, who now heads Sanger's chromosome 22 group, was part of a team at Guy's Hospital in London that in the early 1990s used chromosome 22 to develop sequencing tools and techniques. By 1995 the team had moved to the Sanger Centre and completed a map of the chromosome.



No Catch-22. Nine small gaps won't prevent three teams (led by, from top, Keio's Shimizu, Oklahoma's Roe, and Sanger's Dunham) from soon declaring that they have sequenced chromosome 22.

At roughly the same time, a group at Keio led by Nobuyoshi Shimizu had completed what was then the largest complete human contig, a map depicting the relative order of a linked library of small overlapping clones. The contig covered a 1.02-megabase stretch of chromosome 22 containing the immunoglobulin-λ gene cluster, which is involved in human immune response. In late 1995, Shimizu set up a sequencing effort for that region and for another region implicated in cat eye syndrome, which can result in congenital heart defects and mental retardation. And the Oklahoma lab got involved in sequencing chromosome 22 when one of Roe's graduate students, Stephanie Chissoe, sequenced a 152,000-base stretch of DNA that included the *Bcr* gene, which has been implicated in certain forms of leukemia.

From those humble beginnings, says Dunham, the chromosome 22 consortium "just sort of evolved," with the trio finally deciding to tackle the entire chromosome. "We got together and divided it up into regions that we had reagents for," Roe recalls. The effort also included other labs in Europe, North America, and Japan that helped map the chromosome and provided clones, reagents, and other material for the sequencers.

The sequence actually covers only the lower arm, the so-called q region, of the chromosome. It's roughly 32 megabases long and contains almost all of the chromosome's genes. The upper arm, called the p region, was ignored because it doesn't seem to code for proteins. The consortium also skipped the telomere—the tail end of the arm—and most of the centromere—the "waist" of the chromosome that separates the two arms. These two regions contain few genes and are very difficult to sequence.

The last bits of sequence were the most difficult. "We decided we were almost finished [last spring]," says Shimizu, "but then it took 6 months to actually finish." For reasons that are not completely understood, the bacterial clones that researchers depend on to produce the DNA needed for actual sequencing don't retain certain human sequences. This led to an exhaustive and frustrating search through clone libraries in hope of finding a clone that would cover a particular gap.

The group succeeded in filling some of the gaps, but nine small gaps remain that Dunham says "seem to be unclonable" (see chart). "I'll be happy when we put the whole thing to bed," says Roe, "but I wish we had [my] two gaps closed. We really want to get it done, done, done."

CREDITS: (CLOCKWISE FROM TOP RIGHT) DENNIS NORMILE; OKLAHOMA UNIVERSITY COMMUNICATION SERVICES; ROB HARPER/EBI; ILLUSTRATION: CARIN CAIN

The consortium's experience with chromosome 22 has helped the leaders of the Human Genome Project decide on a definition of "finished" that likely will be applied to sequencing of the remaining human chromosomes. Earlier this month, at a meeting in Cambridge of the international partners involved in this massive effort, the partners reached a consensus on what's needed. The three major criteria are: More than 95% of the chromosome must have been sequenced; the number, location, and size of remaining gaps must be pinned down; and individual gaps must be shorter than about 150,000 bases.

Dunham says the criteria may never be "written in stone," but the chromosome 22 consortium is already well within these criteria if the sequence data "in the pipeline" count, along with what has been posted in databases. What remains, he says, is to "check everything" and make sure that the entire sequence is correctly labeled and deposited in a public database. Completion of that task will be a signal to pop the champagne corks. But the celebration will be brief. "Mapping and sequencing has already taught us a lot about the nature of the genome," Shimizu says. The next step, he says, will be to clarify the biological significance of it all. And that work has barely begun.

–DENNIS NORMILE AND ELIZABETH PENNISI

SCIENCE PUBLISHING

Turnover at the Top at *Cell* and *NEJM*

Earlier this year, *Cell* and *The New England Journal of Medicine* went through abrupt transitions as *Cell* changed owners and the *NEJM*'s editor was forced out. Now, the management of both journals is changing again.

Cell Editor Steps Down

Benjamin Lewin, the editor of *Cell* and its sister journal *Molecular Cell*, announced to his staff and editorial board last week that he plans to retire on 1 October. His sudden departure represents "a big loss for *Cell*," says cell biologist Tony Hunter of the Salk Institute for Biological Studies in La Jolla, California.

After Lewin founded *Cell* in 1974, it quickly became a premier journal of molecular and cell biology. Scientists attribute the journal's success largely to Lewin's depth of scientific knowledge and his hands-on management style. "It will be very different without Benjamin there," says Hunter, who has been on the journal's editorial board since 1980. "He was always there to talk with you about your paper or someone else's. This was in contrast to most other journals."

Lewin sold the journal, along with its three sister journals—*Neuron*, *Immunity*, and *Molecular Cell*—to Dutch science-publishing giant Elsevier Science in April, for an amount rumored to be close to $100 million. Insiders wondered how long Lewin would stay on, although Elsevier had announced that he would remain editor for 5 years. When reached by *Science*, Lewin declined to comment.

Some close to the journal fear that Lewin's departure, combined with Elsevier's takeover, will trigger an exodus of staff. But Deputy Editor Vivian Siegel will stay on at the helm, and editorial board member Ira Herskowitz of the University of California, San Francisco, expresses "absolute faith" in her. Siegel, he says, shares Lewin's engaged management style, but he expects *Cell* to "evolve in some manner. She is not a clone of Ben."

–MARCIA BARINAGA

NEJM Publisher Resigns

The publisher of *The New England Journal of Medicine*, Joel Baron, quit his job less than 2 months after former Editor-in-Chief Jerome Kassirer was forced out. In a 13 September letter to colleagues, Baron said that after an expansionary push in which the journal's owner, the Massachusetts Medical Society, launched several new publications, he was ready to move on.

Under Baron's 2-year tenure, the society has started up new publications such as *Heartwatch*, a consumer newsletter, and acquired *Hippocrates*, a journal for physicians. It has also been looking into lucrative arrangements with commercial publishing enterprises. Now that things have quieted down, Baron, who calls himself a "strategist" rather than an "implementation" person, said in the letter, "I think I will be able to make a bigger contribution elsewhere." (Baron couldn't be reached for comment.)

Some observers suspect that in the turmoil following Kassirer's dismissal, Baron no longer had a free hand to do what he was hired to do. Kassirer was pushed out because of "differences of opinion" with the medical society over activities that he claimed would compromise the journal's good name (*Science*, 30 July, p. 648). "There's been enough concern expressed by editors of the journal and the academic community" over the new publications initiatives that management may have decided to shelve its plans for the present, says *NEJM* Associate Editor Morton Swartz, former chief of infectious disease at Massachusetts General Hospital in Boston.

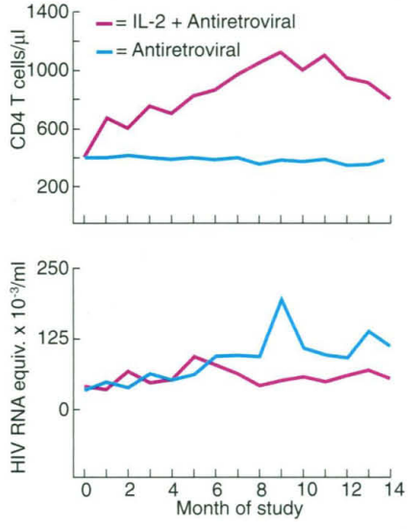
Taking it one departure at a time, the society last week announced the appointment of a search committee, headed by Harvard Medical School professor Ronald A. Arky, chair of the medical society's publications committee, to look for Kassirer's replacement.

–CONSTANCE HOLDEN

AIDS THERAPY

Ambitious Clinical Trial Stirs Debate

The National Institute of Allergy and Infectious Diseases (NIAID) last week decided to fund what will likely be the largest and most expensive trial of an AIDS treatment the institute has ever backed. During the next 5 years, the $43 million study will follow 4000 HIV-infected people who are already taking anti-HIV drugs to see whether adding an immune-



Mixed results. IL-2 treatment raised CD4 levels but had little effect on viral load.