The Great Clone Giveaway

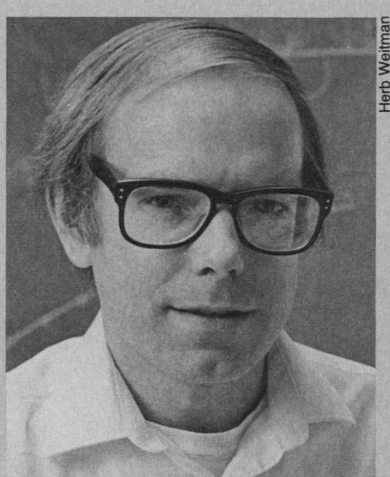
Amid all the complaints about data withheld and clones "lost in the mail," Maynard Olson and his colleagues at the Center for Genetics in Medicine at Washington University stand out as something of an exception. Olson, David Schlessinger, and Buddy Brownstein are in the midst of sending out 60,000 clones—their entire collection of valuable YAC clones—to each of six labs.

It is "incredibly magnanimous," says Glen Evans of the Salk Institute, who is receiving his own set of the YAC clones, which stands for yeast artificial chromosomes. "This is the way we hope others will act," says James Watson, who directs the genome project at the National Institutes of Health, which has been funding Olson's work.

True, there are precedents. But the clone collections that other researchers send out typically take about 2 weeks to make and are then popped in a test tube and into a Federal Express bag. Olson's YAC collection, or library, by contrast, took 2 years to make and characterize. The 60,000 YAC clones are essentially pieces of human DNA contained inside yeast cells. Each YAC clone is stored individually in its own well on a microtiter plate—and there are about 600 of these 96-well microtiter plates. The group is now sending out 40 trays a week to each of six labs—a process that is taking several technicians 15 weeks.

"No one can say we are not sending out our clones," quips Olson.

Why in the world are they doing this? "Anything made with NIH support should be in the public domain," Schlessinger says modestly. But Olson admits it is not entirely altruism. For the past year, the genetics center has been screening its library for anybody who wants a specific bit of DNA and then sending out individual clones, and they have been inundated with such requests. As Francis Collins of the University of Michigan describes it, Olson and his colleagues have been "serving the needs of the entire world." The other groups that are getting the complete library can now help serve those needs.



Herb Weitman

No strings. *Maynard Olson has put no restrictions on use of his clones.*

YACs are pieces of DNA that have been jury-rigged to function as chromosomes inside a yeast cell. This is done by building into a plasmid the key ingredients that make up a chromosome—the telomeres, or ends, the centromere, the replication origin, and so on. A few years ago Olson and postdoc David Burke, who is now at Princeton, realized that, with a few manipulations, they could adapt YACs to serve as cloning vectors. The immense attraction is that YACs can hold huge pieces of foreign DNA, 400,000 or perhaps 1 million bases, as opposed to 40,000 in the most widely used cloning vector to date.

This makes YACs enormously valuable for physical mapping, in which investigators are trying to piece together stretches of the chromosomes in the correct order. Obviously, the bigger the pieces, the easier the puzzle is to put together.

Olson and Burke got the technique to work and then set out to clone the entire human genome, several times over, this way. They finished about a year ago. But were these YACs really the panacea everyone thought they would be, or would the human DNA be scrambled, or would "unclonable" parts of the genome be missing from the library?

"The only way to find out if YAC cloning was any good was to get out clones and give them to people who would give them loving attention," says Olson. So Olson mentioned just a year ago at a meeting at Cold Spring Harbor Laboratory that if investigators would send them probes, the St. Louis group would screen its library to see if they had the corresponding YAC clone. If so, they would send them the clone to use and analyze. Schlessinger describes it as a "fortunate conjunction" of their desire to test the new technology and the desire of the rest of the community to get their hands on these YACs.

Requests began pouring in and "by January, we were getting overwhelmed," says Olson, even with a rapid new screening technique, based on the polymerase chain reaction that Olson and postdoc Eric Green had come up with. At one point they were screening for 85 different investigators, says Olson, who adds: "We have projects of our own we want to do."

By that time as well, any questions about the usefulness of YACs had long since vanished. Though the screening process has turned up some problems, especially "co-cloning" artifacts, in which the YAC contains two unrelated pieces of DNA, YACs are fast becoming indispensable in large-scale mapping.

And that made it imperative that the genetics center continue to make its clones available, says Olson, since "most of the people we work with had no place else to turn." Other YAC libraries, like the promising new one just developed at the Centre d'Etude du Polymorphisme Humain, or CEPH, in Paris were not yet up and running.

That's when Olson and his colleagues decided to send the entire YAC collection to essentially anyone who wanted it, in what they hope will be a one-shot operation. It is going to Tom Caskey at Baylor College of Medicine, Francis Collins at the University of Michigan Medical School, Kay Davies at Oxford University, Glen Evans at the Salk Institute, David Patterson at the Eleanor Roosevelt Institute for Cancer Research in Denver, and Cassandra Smith at the University of California, Berkeley.

What will the recipients do with the YACs? "Anything they damn well want to," says Olson, who feels strongly that no strings should be attached when materials go out to another group.

Already, some groups have made arrangements for secondary transfers. Others plan to set up their own screening operations. Patterson, for one, is going to screen the library for investigators working on chromosome 21 as part of a new collaborative venture (see p. 953). "I expect they will find it is not such a trivial undertaking," says Olson.

And Olson and his colleagues are going to get back to their own work. ■ **Leslie Roberts**