the uses to which his company's Taq is put by individual customers, but he's adamant that his company has been "squeaky clean." Heffernan points out that the Promega catalog contains a disclaimer stating clearly that its Taq is not licensed for PCR. But Agnieszka Junosza-Jankowski, PCR licensing manager at Roche's headquarters in Basel, maintains that the Swiss company will prove that Promega has violated the terms of its license. "They are not enforcing [the] disclaimer in a way that is sufficient for our purposes," she says.

Although Roche has gone after Promega in a U.S. court, insiders speculate that the primary target may be Europe, where Perkin-Elmer now commands less than half of a Taq polymerase market valued at $26 million in 1991 (see table). Analysts say that the aggressive marketing stance taken by alternative Taq suppliers in Europe reflects the fact that the European Patent Office (EPO) hasn't yet issued any patents covering PCR. But that is about to change: Roche got word from EPO in November that its first PCR patent has now been granted and will take effect later this month. Other patents are expected to follow in a matter of months.

So far, Roche has only gone after the suppliers of Taq polymerase, not the scientists who use unlicensed supplies of the enzyme for PCR. And Douglas McQuilkin, vice president for business development with Roche Molecular Systems—a U.S. subsidiary that's handling Roche's PCR business—says his company has no plans at present to target researchers directly. But many researchers in Australia, where Roche's basic PCR patent was granted in April, are complaining that they have already come under heavy pressure to stop buying Taq polymerase from sources other than Perkin-Elmer.

This pressure hasn't come from Roche, but from Perkin-Elmer itself. John Bignall, general manager for Perkin-Elmer in Australia, says the company's policy has merely been "gently to remind users that there are patents that apply to this technology." But staff at leading Australian biomedical research centers say that the clear implication has been that institutes may be prosecuted if they refuse to switch to AmpliTaq. Helen Croll, purchasing officer at the Royal Children's Hospital in Melbourne, says Perkin-Elmer representatives had led her to believe that "the hospital could be involved in unpleasantness" if she continued to order Taq from other suppliers. A 7 April letter from Bignall, addressed to the general manager of Melbourne's Walter and Eliza Hall Institute for Medical Research, made a similar point: "It is our belief that, unless you can obtain a written disclaimer from your alternative supplier, it is your organization that would be in breach of any patents covering the use of the technology."

If Perkin-Elmer adopts the approach it has taken in Australia in other countries, it would risk a backlash from the research community. "That sort of thing doesn't sit well with scientists," says geneticist Norton Zinder of Rockefeller University in New York. "It would be a very bad policy....They would lose the constituency." And that could soon be a major concern for Roche and Perkin-Elmer. For the time being, PCR is the only serious game in town when it comes to rapid and accurate gene amplification, but a rival DNA amplication technique, the ligase chain reaction (*Science*, 26 November 1991, p. 1292), is currently being readied for the market by Abbott Laboratories in Illinois. With alternatives possible, Roche and Perkin-Elmer will have to tread carefully to avoid upsetting the core users of their technology.

–Peter Aldhous

HUMAN GENOME PROJECT

NIH Takes New Tack on Gene Mapping

For several years, the U.S. Human Genome Project has followed a piecemeal approach to genome mapping, dividing the research pie chromosome by chromosome—say, chromosome 5 for one group, 21 for another. Now such strict balkanization is giving way to a more global approach. Leading the way are two NIH-funded centers—a new one headed by Jeffrey Murray at the University of Iowa and an expanded version of Eric Lander's existing center at the Whitehead Institute and the Massachusetts Institute of Technology (MIT). Both are embarking on projects to map the entire genome in one fell swoop.

The chromosome-by-chromosome approach was scientifically and politically attractive, providing a way to divide up the work and the credit. But Daniel Cohen's stunning success at the Centre d'Etude de Polymorphisme Humain (CEPH) in Paris earlier this year in creating giant clones that span the entire human genome prompted considerable rethinking (*Science*, 2 October, p. 28). To at least one prominent U.S. researcher, Cohen's success shows that "the U.S. approach never made any sense at all." Others, though, vehemently disagree.

In the newly expanded Whitehead/MIT center, funded at about $24 million for 5 years, Lander and colleagues from Princeton, the Jackson Laboratory, and CEPH will map both the mouse and human genomes. For the mouse, the first goal is a high-resolution genetic linkage map—essentially an abstract representation of the genome, with DNA markers spread out along the chromosomes. The Whitehead group completed a low-resolution map earlier this year with 1000 of these markers; they now plan to add 5000 more.

At the same time the group will construct physical maps—albeit relatively crude ones—of both human and mouse genomes. Physical maps, which are needed to actually pull out a gene, consist of cloned pieces of DNA with markers in each piece that are used to line them up in the right order. Detailed physical maps of several human chromosomes are already under way, but "this chromosome by chromosome approach has not yet addressed two-thirds of the chromosomes," says Lander.

The building blocks for the human map will be Cohen's megaclones, known as YACs (for yeast artificial chromosomes). Lander and his colleagues, who include Cohen, will try to align the YACs with a new type of marker called a sequence-tagged site, or STS—a short unique stretch of DNA that can be easily detected by PCR. The goal is 10,000 of these markers—roughly one every 300 kilobases—a tall order since fewer than 1000 STSs have been mapped so far. Even that will be an intermediate map, says Lander. While the whole genome approach offers advantages in speed and cost, it can't provide the degree of detail that will ultimately be needed, says Lander. "There is a mistaken perception that it can replace chromosome-specific efforts. It can't."

At the Iowa center, funded at $15 million for 4 years, Murray and his colleagues at the Fox Chase Cancer Center, Harvard, and the Marshfield Medical Research Foundation in Wisconsin are working on a fine-resolution genetic map of the human genome. They will build on the "index" map already being constructed, chromosome by chromosome, by teams around the country. When complete in 1994, the index map will consist of very "informative" or useful markers spaced roughly every 2 million to 5 million bases. Murray and colleagues plan to push the resolution up to about 4000 markers, or one every million bases, which would greatly speed the task of cloning disease genes.

Both Lander and Murray say they are committed to getting their data out to the community promptly. Not only will both publish their PCR primer sequences, which will enable others to synthesize the markers, but both will follow a strategy Lander pioneered at his center. The group contracted with a company to synthesize the primers in bulk and then took only half for their own use. The rest were sold to the mouse community for just a handling charge—$12 for each pair of primers versus $220 to synthesize them from scratch. Says Lander: "It is instant access at affordable prices." The Whitehead investigators have now gone one step further, explicitly agreeing to make data available prior to publication, as soon as it is confirmed, and not to seek patents on the clones, markers, or maps, which they consider basic infrastructure for the scientific community.

–Leslie Roberts