

Antisense patent trial wraps up

Two biotechnology companies — and a host of other companies and research institutions — are awaiting a federal ruling on antisense technology patent rights.

As the hard realities of the business side of biotechnology demand more attention from academic scientists, news of another patent dispute between companies may barely attract interest. But the recently litigated patent infringement trial between Enzo Biochem, Inc., of Farmingdale, New York and Calgene, Inc., of Davis, California, has caught the attention of many researchers who use the controversial technique that both companies claim. And the pending ruling has implications for many companies and research institutions other than the trial's participants.

On the surface, the legal battle is being waged over the ownership of patent rights to an emerging technology known as 'replicative antisense', a technique that can radically alter the cellular expression of specific genes and therefore has strong promise for therapeutic applications. But the core issues are far broader, going to the heart of how science is done in a time of overriding financial and legal interests. The addition of allegations of scientific misconduct to the patent infringement trial indicates just how high the stakes are in this case, which has "all the hot-button sexy issues in contemporary science," according to one trial participant.

Three patents issued to the State University of New York (SUNY), based on work performed by Masayori Inouye and collaborators in the early 1980s and exclusively licensed to Enzo, contain claims that cover the use of replicative antisense technology in all cells, although Calgene holds a patent

claiming the use of the same technology in plant cells.

Replicative antisense involves inserting a gene into the genome in such a way that the RNA transcribed from the gene is opposite, or 'antisense', to the normal, 'sense' RNA. When the cell transcribes both the sense and antisense genes, the antisense RNA can interfere with the translation of the sense RNA by binding to it directly.

Enzo filed suits in Delaware against Calgene in 1993 and 1994, alleging patent infringement for the replicative antisense technique. Calgene countered with a suit seeking a declaration that at least one of the SUNY patents licensed by Enzo was invalid, based in part on prior antisense research performed in the early 1980s at the Fred Hutchinson Cancer Research Center in Seattle by John Izant and the late Harold Weintraub (see obituary). The Delaware actions were consolidated, and the trial began on 4 April, with scheduled completion on or around 21 April. A judgement is not expected for six months to a year.

Many issues in the trial are typical of patent disputes, including questions of prior art, unfair competition, and so forth. But several trial participants from both sides, all of whom spoke on condition of anonymity while the trial was proceeding, expressed dismay with the nasty turn the trial took halfway through the hearings. Calgene claimed that the work of Izant and Weintraub proves prior art, rendering the Enzo-licensed SUNY patents invalid. Enzo countered by claiming scientific miscon-

duct on the part of the Hutchinson Center researchers, bringing forth several witnesses, including Walter Gilbert of Harvard University, to support their allegations that data critical to the antisense work was falsified. The witnesses did not accuse Weintraub of fraud, claiming instead that Izant was solely responsible for the 'cooked data'.

These accusations also form part of the basis of another patent infringement suit filed by Enzo in Seattle earlier this year. This action, still in the early stages, names the Hutchinson Center and Calgene as co-defendants. This second suit was prompted, at least in part, by an announcement made in February by the Hutchinson Center that it had licensed to Calgene the rights to a patent application filed on Izant and Weintraub's work. The suit seeks to prevent the Hutchinson Center from practising techniques claimed under the SUNY patents and, if successful, will have profound effects on the antisense research at the Center. "Enzo is asking the judge to shut down the academic antisense program," said one trial participant on the condition of anonymity. "It's going to affect a lot of places if they get their way on this."

Though the ruling in the Delaware case won't be announced for at least six months, an indication of the outcome may be found in a preliminary finding issued in March by the European Patent Office (EPO). Oppositions brought by Calgene and Unilever in 1993 against a European patent granted to SUNY was denied by the EPO's ruling. The relationship and significance of this preliminary ruling to the Delaware case is difficult to determine. Not surprisingly, Enzo and Calgene representatives see the EPO ruling differently, though neither was willing to comment on anything related to the antisense litigation during the course of the Delaware trial.

The forthcoming opinion in the Delaware case, regardless of its content, will likely affect all future antisense work, especially if the technique fulfils its promise as a successful strategy to treat cancer and other diseases. It also serves to remind researchers that scientific issues aren't the only ones to which they must attend.

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Harold M. Weintraub, 1945–1995

Dr. Harold M. Weintraub, 49, a prominent developmental and molecular biologist, died on 28 March at the Fred Hutchinson Cancer Research Center in Seattle, Washington, of complications from glioblastoma.



"Hal was a mentor to those of us that had the privilege of working with him," said Richard Wagner of Gilead Sciences in Foster City, California, a company Weintraub cofounded. "Among his many attributes, he had uncanny scientific intuition and extraordinary integrity. He's deeply missed." Among Weintraub's many scientific contributions was the development of the RNA antisense technique (see above). He was a faculty member of the Hutchinson Center's Division of Basic Sciences since its founding in 1978. He was also appointed an investigator for the Howard Hughes Medical Institute in 1990. W. Maxwell Cowan, Vice-President and chief scientific officer of the Howard Hughes Medical Institute called Weintraub's early death "a serious loss not only to the Hughes Institute, but to all of science."