Genentech sues to protect clot buster market share

Seeking to protect its position in the $300 million thrombolytic drug market, Genentech (S. San Francisco, CA) has filed a patent infringement suit against Centocor (Malvern, PA). The suit alleges that Centocor's Retavase (reteplase) infringes two newly issued Genentech patents covering Activase (alteplase), a recombinant form of natural tissue plasminogen activator (t-PA). What is odd is that Centocor only recently acquired the product rights to Retavase from Roche (Basel, Switzerland), the majority shareholder of Genentech. The claims of the newly issued patents seem to have been drawn up specifically to challenge Retavase, and may indicate the start of a new series of clot-buster litigations.

The infringement suit was filed on March 17 in the US District Court for the Northern District of California following Centocor's $335 million purchase of Retavase (*Nature Biotechnology* **16**:316, 1998). The opportunity to purchase Retavase arose through the conflict created when Roche acquired Corange, the parent company of Boehringer Mannheim (Mannheim, Germany), which develops and manufactures Retavase. Under the Retavase acquisition agreement, Centocor will assume responsibility for defending the pending patent litigations initiated by Genentech against Mannheim in the United States and Germany. Roche will share in the litigation expenses and, under certain conditions, indemnify Centocor for liabilities relating to the Mannheim litigation.

Natural t-PA (and Activase) contains five protein domains: a finger (F) domain, an epidermal growth (E) domain, a kringle 1 domain, a kringle 2 domain, and a serine protease domain. Retavase is a third-generation variant lacking all but the kringle 2 and the serine protease domains. As a result, Retavase has a longer half-life, binds less fibrin, and is easier to administer than Activase. Nevertheless, a large-scale trial involving over 15,000 patients from 20 countries (*N. Engl. J. Med.* **337**:1118–1123, 1997) concluded that "Reteplase, although easier to administer, did not provide any additional survival benefit in the treatment of acute myocardial infarction." According to industry data, Retavase claimed 12% of the US market in 1997, its first year on the market.

Until now, the fear that Retavase would be held to infringe Genentech's original t-PA patents was questionable: In the late 1980s, Genentech sued The Wellcome Foundation (Beckenham, UK), Genetics Institute (Cambridge, MA), and others over a similar t-PA variant, FE1X, which lacks the F and E regions present in natural t-PA (and Activase). At the district court level, Genentech prevailed; a jury found that while FE1X did not literally infringe Genentech's claims, the variant was similar enough to infringe under the doctrine of equivalence. On appeal, however, the US Court of Appeals for the Federal Circuit held Genentech's t-PA claims were limited to "t-PA produced through recombinant DNA technology but having the same structure as natural t-PA." The court went on to hold that the differences between Genentech's recombinant t-PA and FE1X were too great to support the jury's finding of infringement under the doctrine of equivalence.

Now, however, Genentech is armed with two new patents—US Patent 5,728,565 (the `565 patent) and US Patent 5,728,566 (the `566 patent)—the claims of which appear to have been drafted specifically to cover Retavase. The `565 and `566 patents claim a recombinant protein and a process for preparing a recombinant protein "compris[ing] an amino acid deletion derivative of the [natural t-PA] amino acid sequence. . .which has [t-PA] function, . . .is capable of catalyzing the conversion of plasminogen to plasmin, . . .binds fibrin, and is classified as t-PA based on immunological properties." Various other specific t-PA deletions are also claimed.

The new patents, issued in March, stem from a long line of patents and applications dating back to 1982. As Genentech's litigation against Novo Nordisk (Bagsvaerd, Denmark) illustrates, recently issued patents relying on old parent applications for enablement have their share of invalidity problems (*Nature Biotechnology* **15**:403, 1997). Nevertheless, Genentech is sending a clear message to would-be competitors: Those that want to play in the clot-buster end of the sand box should expect a fight.

Should Genentech prevail against Centocor, more legal battles are on the horizon. A group of second- and third-generation t-PAs are progressing through clinical and preclinical trials (*Nature Biotechnology* **15**:405, 1997). One variant near approval is Bristol-Myers Squibb's (Princeton, NJ) NPA (lanoteplase), made by a variant lacking the F and E regions, and containing several point mutations. If the current phase III trials are successful, expect Genentech to assert its new patents against this variant as well.

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