Fight for reputation
Judah Folkman counter-sued Abbott in the legal battle over kringle 5

Patent disputes have become commonplace in the biotechnology industry, but few have taken on such a personal and bitter tone as the legal battle between Abbott Laboratories and angiogenesis pioneer Judah Folkman. The dispute concerns who discovered the anti-angiogenic potential of a plasminogen fragment and to whom the patent rightfully belongs. Abbott claims in its lawsuit of May 2000 that one of its researchers, Donald Davidson, made the discovery and seeks compensation and damages of US $10 million for ‘unlawful misappropriation of and conspiracy to steal an invention.’ Folkman and his collaborators at Children’s Hospital in Boston, MA and Entremed Inc. in Rockville, MD, to whom the patent is assigned, maintain that this is false. Stepping up the legal battle, they counter-sued Abbott in July for fraud, conspiracy and defamation of character, demanding treble damages.

Folkman and his associates assert that Abbott’s suit is an attempt to intimidate the hospital and its researchers because the drug maker wants to avoid paying royalties on kringle 5, the plasminogen fragment in question. But the stakes are higher than just money. They say that Abbott’s suit represents ‘an inflammatory and vicious’ attempt to damage their collective reputation, and that it could have dire consequences for drug development. ‘A suit such as this threatens to disrupt the long-standing practice of sharing information among scientists,’ he added. Indeed, the tone has grown increasingly bitter. Calling Abbott’s lawsuit ‘egregious, tasteless, and shameful’, John Holaday, EntreMed’s Chairman and Chief Executive Officer, commented, ‘By attempting to intimidate parties in order to obtain the rights to a product it neither discovered, nor owns, Abbott has taken the lowest road […]’. ‘Abbott does not want to comment on the ongoing legal battle at this stage.

Plasminogen contains five distinct regions, each with a characteristic three-dimensional structure resembling the eponymous Danish cookie—hence the name kringle for these domains. A sixth, non-kringle domain is where the protease activity of plasminogen is located. In 1994, Folkman and Michael O’Reilly at Children’s Hospital discovered that angiotatin, a fragment of plasminogen, acts as a promising anti-cancer agent in blocking the growth of blood supplies into growing tumors (O’Reilly et al., 1994). A recombinant version of angiotatin is now in phase I clinical trials in the USA for the treatment of cancer. It does not contain kringle 5 and the protease domain, so the lawsuits between Abbott and Folkman do not affect angiotatin and its clinical development. At stake is the ownership of kringle 5. Folkman’s team found it to be a weak angiogenesis inhibitor, but Abbott improved upon it, and the company wishes to develop it into an anti-cancer drug.

The warring parties dispute a number of key facts and events leading to the filing of Abbott’s suit on kringle 5. The differences start with disputing exactly what Abbott’s researcher Donald Davidson was working on, when he began collaborating with Children’s Hospital in May 1994. According to Abbott’s suit, he focused on tumor inhibition among other things. Davidson then began providing Yihai Cao in Folkman’s lab with research quantities of kringle 1–4 for angiogenesis research. According to Folkman, however, Davidson was an expert in plasminogen and was working on thrombolytics, but had no background in angiogenesis and only learned about kringle 5’s anti-angiogenic potential through Folkman and his colleagues.

Abbott asserts that its version of kringle 5 has greater anti-angiogenic potency than Folkman’s angiotatin

A letter from Davidson’s supervisor, Jack Henkin, sent to Folkman in November 1995, affirms that Davidson was a novice in the field of angiogenesis. Henkin proposed a ‘gentleman’s agreement’ for the research on angiotatin and kringles 1–4 with the understanding that ‘the techniques and knowledge of his (Folkman’s) lab would be readily available to them.’ In return, Henkin proposed sending Davidson and another colleague to Folkman’s angiogenesis lab ‘to learn the methodology and art of your angiogenesis assays.’ He closed the letter stating that if such an arrangement was agreeable, ‘Don’t [s] payback will be to eat from your tree of knowledge and hopefully become our local angiogenesis maven.’
Abbott asserts in the suit that Folkman signed the agreement; however, Folkman maintains that although he signed the agreement, it was ultimately stopped at the hospital’s technology transfer office and never returned to Abbott.

Abbott tried and failed three times to obtain exclusive control of kringle 5, Folkman’s countersuit states. Abbott’s suit claims that Children’s Hospital and Folkman had entered into a written agreement giving Abbott rights to discoveries, in exchange for receiving waste plasminogen samples for research, in November 1995. Children’s Hospital maintains that the document was never signed and returned to Abbott, but that Abbott deleted hand-written criticisms by Children’s Hospital officials, and submitted it as evidence of an agreement. Children’s Hospital’s patent was issued in July 1997, at which time Abbott saw that its efforts to obtain control of kringle 5 would not succeed. A few months later, Abbott contacted Children’s Hospital, demanding all rights to its patent. A year of negotiations left both sides with no agreement, and then after a period of quiet, Abbott filed its suit in May 2000.

Folkman has little to lose in this fight except his reputation — but in science that is nearly everything

In its suit, Abbott maintains that Davidson was the first to discover the anti-angiogenic properties of kringle 5. The company states that Davidson learned that cleaving plasminogen with elastase for long periods yields a novel kringle 5 fragment, with a different sequence. Abbott asserts that this version of kringle 5 has greater anti-angiogenic potency than angiostatin or the other kringle fragments. Furthermore, the lawsuit states that Folkman congratulated Henkin on this discovery, said that he had overlooked kringle 5 and told Henkin to file patents on it.

While Folkman concedes that his group did not see remarkable properties in kringle 5 and is happy to see Abbott develop it into a cancer drug, he says that the company owes Children’s Hospital royalties on the plasminogen fragment. When Cao and others published their article on the anti-proliferative effect of various plasminogen kringle fragments on endothelial cells (Cao et al., 1996, 1997), Abbott never claimed that it represented an invention of Davidson or the company, Folkman said. Abbott realised only later that kringle 5 had anti-angiogenic potential. According to Folkman, Abbott is seeking to invalidate Folkman’s patent on kringles 1–5 because it allegedly discovered kringle 5’s unique properties. Abbott disputes that its involvement was late, and is seeking not only to invalidate Folkman’s patent, but is also alleging that he seeks to appropriate intellectual property that he does not own.

This is not the first time that doubt has been cast on Folkman. In November 1998, a journalist at the Wall Street Journal reported that no lab could verify Folkman’s animal data using endostatin, another anti-angiogenic compound discovered in his lab. Soon after, however, this was shown to be untrue when a number of labs demonstrated that Folkman’s results were correct and reproducible.

Folkman’s lab has discovered five compounds to date, all of which are licensed to biotech companies and none of which Folkman stands to profit from financially. Indeed, Folkman has little to lose in this fight except his reputation—but in science that is nearly everything a researcher can have.

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Abbott, on the other hand, stands to gain considerable financial advantages if it obtains patent rights on kringle 5. With US $5 billion a year in sales, Abbott ranks only 16th of the top 20 international drug companies. While its budget for research and development is less than other drug makers, it does have a reputation for being an aggressive litigator. Abbott waged a costly war to stop Zenith Goldline Pharmaceuticals from marketing a generic version of its US $500 million a year drug Hytrin, which is used to treat non-cancerous growth of the prostate gland. It also faced an antitrust suit for trying to keep this company’s drug off the market in the USA. Compared with its product range, Abbott has only a small anticancer pipeline, but one on which it may be trying to build. Kringle 5 is its first anti-angiogenesis compound and it recently obtained the rights for another anti-cancer compound from Eisai Co. in Japan. Abbott’s strong interest in anti-angiogenic drugs is easily understood given that ~20 other angiogenesis inhibitors are now being tested in phase I and II clinical trials in the USA (http://cancertreats.nci.nih.gov/news/angio/table.html).

Such a change in the company’s research direction may also be seen in its recent hiring of Jeffrey Leiden from Harvard Medical School, for whom it created the new position of chief scientific officer. Soon after, Abbott announced a new management structure and moved Leiden to head the pharmaceutical business. This movement indicates that it could be gearing up to move its drug business ahead swiftly; an anti-angiogenesis compound that is more powerful than angiostatin would certainly bring Abbott good press and could serve as a cornerstone for its revitalised oncology line.

Now it is up to the courts to decide whether Abbott or Children’s Hospital is right. But it will certainly not be the end of lawsuits against scientists in an industry that is increasingly using courts to obtain control over important molecules. And given the publicity surrounding this case, scientists in academia may become less willing to cooperate with Abbott or other drug companies that may question their integrity in seeking profits from shared discoveries.


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