

Burning bridges

A Wisconsin foundation's aggressive approach to patent licensing is damaging its reputation, compromising its own university's research collaborations and stymieing stem cell research.

The Wisconsin Alumni Research Foundation (WARF) is a private, nonprofit organization that supports scientific research at the University of Wisconsin, Madison. Since its 1925 founding, it has contributed >\$750 million to professorships and research grants at the university as well as funded several new buildings and institutes on the Madison campus. Through its technology-transfer role, it has also helped bring to market vitamin D-enriched food to fight rickets, a storage solution for transplant organs, the blood thinner warfarin for use in stroke treatment and key hardware components for Sony's PlayStation 2, to name a few. In short, WARF has built a solid reputation as a pioneer in commercializing university inventions.

Lately, though, that reputation has come under fire because the foundation's licensing practices governing another part of its intellectual property (IP) portfolio—two seminal stem cell patents, one of which is the only patent issued in any nation that claims human embryonic stem (ES) cells *per se*—have been subject to intense and widespread criticism.

Many US-based researchers seeking access to ES cells find WARF's licensing terms too cumbersome, too restrictive of downstream collaborations and too onerous with respect to commercial reach-through rights. It's not only that WARF has gone out of its way to enforce IP licenses in academia (which traditionally has been left to its own devices), but also that it has departed from the convention of making institutions pay a one-time charge, opting instead to charge per cell line, per investigator. If several investigators at an institution are working on several ES cell lines, licensing costs can mount up very fast. Not surprisingly, most academic institutions have resisted WARF's demands on principle. Six months ago, only eight research centers, including the Harvard Stem Cell Institute, had signed up for a license.

Cash-strapped stem cell companies are also balking at WARF's commercial rates, which range from \$75,000 to \$400,000, plus royalties on sales. At the moment, WARF has active licenses with just over a dozen companies. Many others are engaged in protracted negotiations to find common ground or otherwise are simply choosing to infringe WARF's IP. Only companies lucky enough to be located in Wisconsin can take free, nonexclusive licenses—a dispensation negotiated in October by Governor Jim Doyle (Dem.). One firm, Geron, has exclusive commercial rights to heart, nerve and pancreatic cells derived from ES cells.

The patents held by WARF belong to University of Wisconsin-Madison researcher James Thomson, who first derived human ES cell lines in 1998. US Patent No. 5,843,780 claims a purified preparation of primate ES cells and a method for isolating them, whereas US Patent No. 6,200,806 claims a purified preparation of pluripotent human ES cells and their method of derivation. Notably, the latter lays claim to mesodermal, endodermal and ectodermal derivatives of human ES cell lines as 'compositions of matter'—patented substances in themselves,

without reference to the ES cell derivation method. This means that WARF essentially claims ownership rights to all human ES cell and downstream products, regardless of how they are derived.

As various US states ramp up their own stem cell research initiatives, WARF's licensing demands are becoming increasingly problematic. The California Institute for Regenerative Medicine (CIRM), for example—which last month issued interim rules specifying the royalties due from companies that will compete this spring for a share of \$181 million in funding—has raised money by issuing bonds, which will be repaid to state coffers through income from grantees. WARF argues that CIRM is acting like a business and it should therefore share the spoils. In effect, it wants payment twice: first from the Californian research institutions carrying out ES cell research, and then from the agency funding it. Similar initiatives in New Jersey, which in December approved \$270 million in bonds to fund its stem cell efforts, and in Connecticut and Maryland are also in WARF's legal crosshairs.

One approach that has been taken to escape WARF's IP clutches is to challenge the validity of the Thomson patents. In October, the US Patent and Trademark Office accepted a request from a coalition of nonprofit groups in California to reexamine WARF's patents covering primate ES cells and their culturing techniques on the basis that the isolation methods were obvious. With annual earnings >\$50 million, it seems likely that WARF will defend its IP vigorously, no matter what the cost.

Others have opted to circumvent the foundation by carrying out ES cell research offshore, outside the US patents' jurisdiction. WARF patents on ES cells filed in Europe are unlikely to issue because of moral concerns over patenting life. The Hatch-Waxman Act also enables companies to use the research safe harbor codified at 35 USC 271(e)(1) to continue developing ES cell products, even while WARF's IP is in force. Given that the Thomson patents expire in 2015, this may all be moot anyway—a commercial product is unlikely to emerge in the next eight years, especially as no ES cell therapy has yet entered the clinic.

In the end, WARF's restrictive licensing provisions and aggressive reach-through rights are backfiring by giving researchers an incentive to search for loopholes and to invent around the Thomson patents. In its headlong pursuit of as much profit as possible from as many as possible, WARF is not only damaging its own reputation, but also compromising future research collaborations between the University of Wisconsin and other academic institutions. One need look no further than the uphill struggle the National Stem Cell Bank has faced in obtaining ES cell lines from outside entities.

The choice ahead for WARF is simple. License the Thomson patents more broadly, without encumbering clauses and at a price that's cheaper than going to court. Or continue on the present course: bully, litigate, alienate the community and exacerbate an already difficult situation for stem cell research in the United States. 