

Winning the WARF way

The University of Wisconsin earns millions of dollars a year from WARF, its technology licensing operation. Ownership of great patents is a prerequisite but to maximise returns, explains WARF chief Carl Gulbrandsen, flexibility and business skill are also essential

By **Victoria Slind-Flor**

Carl Gulbrandsen was once asked to help the University of Wisconsin shut down its patent-licensing operations. But that was more than 20 years ago.

The attitude at the university has changed dramatically since then and now the 58-year-old Gulbrandsen is at the head of the Wisconsin Alumni Research Foundation (WARF), the non-profit entity providing patenting and licensing services to the University of Wisconsin.

Because WARF controls the patents relating to Dr James Thomson's human embryonic stem cell research, Gulbrandsen may well be leading the most important university technology-licensing centre in the world. The value of these cells is that they have the potential to grow into any kind of human tissue or organ.

Gulbrandsen, who has both a law degree and a PhD in physiology, wrote patent opinions for the university in the 1980s, when he was an associate at the Madison, Wisconsin, firm of Ross & Stevens. At that time, the university and the Internal Revenue Service were locked in a lengthy dispute over WARF's non-profit status. "The IRS was taking the position at the time that transferring technology was nothing more than a business," says Gulbrandsen. "So our managing director wanted to spin off the patent-licensing operation or shut it down."

Eventually a compromise was reached, with WARF reconfigured as a charitable organisation that has, over its life, contributed more than US\$800 million to the University of Wisconsin. Today WARF operates from a 14-floor skyscraper overlooking the entire 41,000-student campus, the adjacent Lake Mendota

and the dome of the state capital building in downtown Madison. And through its subsidiary WiCell Research Institute, WARF has completed 460 licences relating to the human embryonic stem cells.

Built on rat poison

To take an historical view, one could say that Gulbrandsen, whose official title is managing director of WARF, works in the house that rat poison built. Or that he rests on the firm foundation of Vitamin D. Early-day researchers at the University of Wisconsin discovered the anti-coagulant properties of spoiled clover hay. From that discovery came Warfarin, a powerful rat poison, and coumarin, a blood thinner marketed as Coumadin and still widely used by cardiac patients around the world.

The vitamin D connection comes by way of biochemistry Professor Harry Steenbock, who, in 1923, discovered a cure for rickets by irradiating food with ultraviolet light to increase the vitamin D content. WARF was formed in 1925, largely to manage the initial revenues from Steenbock's patents. And even today, WARF is administering a large vitamin D-related patent portfolio. Current vitamin D research is led by Dr Hector DeLuca, who has found ways to use the vitamin to stem a variety of bone and auto-immune disorders.

WARF, as one of the very first university technology-transfer offices, became a model and consultant to others following the 1980 passage of the Bayh-Dole Act, which gave US universities the right to control inventions, even if the research that yielded those inventions was funded by the federal government.

The Northbrook, Illinois-based Association of University Technology Managers, which tracks university technology licensing activities, reported in its Fiscal Year 2003

survey that 7,921 US patent applications were filed and 3,933 US patents issued that year to its member institutions. Additionally, 4,516 new licences and options were executed and 374 new companies formed using university-invented technology. University licensing income in Fiscal Year 2003 was US\$1.3 billion and running royalties brought in another US\$1.125 billion.

While the Thomson stem-cell patents are what currently grab the headlines, WARF actually patents and licenses a wide range of university-developed technologies. They include a new variety of ultra-red cranberries, a method of producing DNA array chips, a technique for coating pills to mask disagreeable tastes, a process of using magnetic resonance imaging to measure the flow of bodily fluids and, in a nod to Wisconsin's famous dairy industry, even a laser cheese slicer.

All in all, in its 80-year life, WARF has obtained nearly 1,550 US patents for University of Wisconsin faculty and staff, completed nearly 1,400 licensing agreements worldwide and is currently managing 720 pending and 880 issued US patents. Today WARF has equity in 30 companies spun off from university-created technology and is offering 3,800 different technologies to would-be licensees.

Wisconsin spin-off companies include Cambria Biosciences of Woburn, Massachusetts, a drug-discovery company focused on neurodegenerative disease; hometown Virent Energy Systems Inc, which produces hydrogen from biomass feedstocks; and Platypus Technologies LLC, a producer of nanotechnologies for life sciences.

The Thomson gift

But the crown jewels are clearly the Thomson patents. The '780 US patent issued in 1998, and the '806 in 2001. Both are captioned "Primate Embryonic Stem Cells" but there is no doubt that the primate of interest is the human being.

WiCell Research Institute, which is run by Thomson, is a separate private non-profit entity, established in 1999 because of a ban on the use of federal funds for human embryonic stem cell research. President George W Bush lifted that ban in 2001 for certain existing stem cell lines, including WARF's. But before that change in the political climate, much of Wi-Cell's funding came from Geron Corporation of Menlo Park, California. In return, Geron has exclusive licences to a limited number of stem cell-related therapeutic and diagnostic products.

In 2001, the two companies went to court seeking clarification of their complex licensing agreement. Specific terms of the settlement that came six months later remain confidential, but it is known that Geron gave up some broad rights to commercialise human embryonic stem cells, but retained exclusive rights to cardiac, nerve and pancreatic cells under the licence.

Gulbrandsen is sensitive about accusations that Wisconsin will use its stem-cell patents to extract a significant toll from others who want to do research in that area: "People criticise us a lot but I think they should be very happy that WARF was here, that we took the technology, patented it and carried out the programme we have. If we hadn't, this technology would be owned by a government agency that would be ambivalent about moving this technology forward, or by a private industry that would not have been eager to share."

The intent is to license the technology in a similar way to Stanford University's licensing of the famed Cohen-Boyer patent for uses of recombinant DNA. That technology is widely credited with giving rise to the modern biotech industry. The Cohen-Boyer patent, which expired in 1997, was licensed at what were generally considered reasonable rates to more than 400 companies and generated US\$225 million in licensing revenues over its life.

Gulbrandsen says the stem cell technology deriving from Thomson's research "is a gift that Wisconsin is giving to the rest of the world. We have not tried to sit on this technology". He complains that he's heard people say "if I get WiCell cells, it's like I'm working for them". But nothing could be further from the truth, he claims: "They can publish what they discover. They can patent what they discover. They don't even have to let us know they've filed the patents."

And Gulbrandsen insists that the licences with Geron will not hold up or impede others' research. "Geron has no rights to those scientists to whom we provide materials," he says. "There's no grant-back to Geron."

The only downside has been the Wisconsin's conservative politicians' distaste for stem-cell research. Earlier this year, the lower house of the state legislature approved a ban on both reproductive cloning – which could potentially create a baby – and therapeutic cloning, which relates to specific medical conditions, organs or systems. The state senate is set to take up the measure shortly.

"We live in a very unfriendly state for doing this research," Gulbrandsen claims, noting that California, by contrast, has allotted US\$3



Carl Gulbrandsen, WARF MD

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Stem cells for industry

Wisconsin stem cells are the gold standard. University of Wisconsin researcher James Thomson was the first to derive human embryonic stem cells, and his results were published in *Science* (November 1998). Since then, researchers have been using the cells in their own research. Because licensing for commercialisation is different to academic research agreements, WiCell Research Institute – a WARF subsidiary – provides a number of questions and answers on its website to assist potential licensees. Some of these are reproduced below.

How do I know whether I need an industry research licence and material transfer agreement?

If you are working at or for a for-profit company, you will need to enter into an industry research licence. If you are an academic researcher whose research is sponsored by a for-profit company, your sponsor will likely need to enter into an industry research licence.

What is the process for entering into an industry research licence and material transfer agreement?

The first step is to contact the licensing staff at the WARF. They will explain the agreement to you and talk to you about your plans for using the stem cells. They will also discuss the basic fees – a licence fee and an annual maintenance fee, which are based on the size of your company.

What do the industry research licence and material transfer agreement allow my company to do?

The agreement allows for internal research as well as access to human and non-human primate stem cell lines. Under this agreement, your researchers will be allowed to conduct internal research, including the differentiation to any cell types as well as derivation of new lines. This agreement also defines the parameters for commercialisation of products, but a separate industry commercial licence agreement must be negotiated before product development or commercialisation occurs.

Can I purchase stem cells from other sources?

There are other sources of stem cells, but you must still enter into an agreement with WARF to use the cells in commercial research under WARF's patent rights.

How are commercialisation rights determined and which rights would be available to my company?

Stem cell commercialisation rights are defined by cell type (cardiomyocytes, for example) and application (screening, for example). All fields are available except heart, neural and pancreatic cells for cell therapy and diagnostic applications.

Are there any restrictions on research that can be conducted with stem cells?

Yes, as detailed in the agreements under which cells are provided, restrictions include the following: the transferee warrants that the materials must be used in compliance with any and all applicable governmental rules and regulations relating to the handling or use of such materials. Transferee further warrants that three experiments that will not be performed with materials are: (I) intermixing of materials with an intact embryo, either human or nonhuman; (II) implanting materials or products of materials in a uterus; and (III) attempting to make whole embryos by any method. Further, transferee acknowledges that the materials have not been prepared using protocols appropriate for therapeutic use and transferee agrees not to use the materials for therapeutic or diagnostic purposes. Introduction of materials or derivatives of the materials into human beings requires approval of the appropriate review board at transferee's/s' institution. Recipients are required to adhere to all local laws regarding the import of this material and any restrictions to research.

Does WiCell provide financial support for stem cell investigators.

No. WiCell's mission is to distribute cells to academic researchers worldwide and to engage in research using scientists at the University of Wisconsin-Madison. The cells are supplied at a price below our costs.

Source: WiCell Research Institute website
<http://www.wicell.org/forindustry/index.jsp?catid=20&printable=1>

billion for similar research. He says that 69% of Wisconsin's voters support stem cell research, but "we have a legislature that can at times be fairly outrageous". However, Wisconsin's Democratic Governor Jim Doyle has said that if the ban passes, he will veto the measure.

Selling hard

WARF has had a California office up and running for three years, although Gulbrandsen says it is not related to that state's stem cell initiative. The WARF office, which is in San Diego, is a sales office, opened to promote the licensing of Wisconsin-developed biotech research tools. "We have a large portfolio of research tools but nobody is going to pay a lot of money for them," says Gulbrandsen. "So if we want to get a return on them, we need to supply them to a lot of companies."

Gulbrandsen's use of the term "sales office" to describe the outpost of a university licensing office is surprising. Many in industry criticise university technology-transfer offices as bureaucratic fiefdoms more interested in tidy paperwork than in doing deals.

But that is definitely not WARF's orientation. "We've moved very hard at moving the ball forward," Gulbrandsen says. He has commissioned a customer survey and established target markets. "We find out their needs and try to build relationships. We want to treat them as partners." His staff attend professional meetings in the various scientific disciplines and take a day before and a day after each meeting to make sales calls on local companies. "We're out knocking on the door," Gulbrandsen says.

Today WARF has 48 employees, including six lawyers, all of whom also have scientific training. Michael Falk, who has a degree in microbiology in addition to his law degree, is the director of intellectual property. Craig Christianson, director of licensing, is a lawyer with an undergraduate degree in electrical and computer engineering and a master's degree in biotechnology. General counsel Elizabeth Donley has two master's degrees, one in finance and the other in bacteriology. Associate general counsel Dave Kettner received an undergraduate degree in genetics and cellular biology before he went to law school.

Other universities' technology-transfer offices are often thwarted by bureaucratic regulations, inefficiencies and insufficient resources, says Gulbrandsen: "Most technology-transfer offices are integrated into the university. They have to get in line behind everyone else in getting their needs taken care of. If you want a contract at most

universities, it has to be reviewed by administrative legal services that are responsible for everything else.”

But WARF is separate from the university, with an integrated legal staff and a great deal of authority given directly to licensing managers. “We can get a deal done in days or weeks that would otherwise take years to do,” Gulbrandsen claims.

Gulbrandsen says one problem with many other universities’ tech-transfer problems is that the staff lack the background for the job: “They may have been the assistant dean of something who all of a sudden gets moved into the licensing office. They’re scared about doing the wrong kind of deal, of giving the crown jewels away.” WARF tries to stave off this problem by hiring licensing managers from outside industry rather than from within the university. For example, senior IP manager Marnie Mott is a biological systems engineer who designed digital test instruments and designed and sold agricultural structures before she came to WARF. And licensing manager John Hardiman is a chemical engineer with 20 years’ experience in the oil-refining industry.

Because WARF has so many lawyers in-house, Gulbrandsen says, its licensing managers are freed up to do what they are really paid for: “Selling and getting the deal done.” And he does not have to get permission from the university’s legal office to hire outside counsel when necessary. At some other state universities, the state’s attorney general must be consulted before outside counsel can be hired. This is not the case with WARF: when it was time to prosecute the Thomson stemcell patents, Gulbrandsen was able to bring in experienced biotech patent counsel Nicholas Seay, a partner in the Madison office of Milwaukee’s Quarles & Brady.

One of WARF’s spin-off partners is NimbleGen Systems Inc, which produces micro-array products under an exclusive licence from the university. WARF established an office in Reykjavik, Iceland, solely to service NimbelGen’s gene-chip manufacturing facility.

Gulbrandsen would like to see many more spin-offs, but he acknowledges that today it is difficult to find investors who want to take a licence for and spin off a company around early-stage technology. “We have the valley of death that everyone talks about,” he says, referring to the reluctance of investors to fund a company based on early-stage medical or drug technology.

On the other hand, many companies have shut down their R&D divisions, and are coming to the university seeking products for

their pipeline. The challenge, says Gulbrandsen, is to convince those companies they need to make investments in early-stage technology, to remove it from that so-called valley of death.

Gulbrandsen says WARF established the California and Iceland offices because of the need for aggressive marketing. “The market itself has changed, and WARF has had to re-invent itself,” he says. He notes that 15 years ago, it would have been easy for WARF to license something right off the lab bench. “But that’s just not possible today.” Changing approaches to changing times: it is a lesson WARF could teach other university technology licensing operations, wherever in the world they are. ■

WARF’s royalty sharing programme

WARF shares the royalty revenue generated by a licensed technology with the technology’s inventor(s) or author(s); the inventors’ laboratories; the inventors’ academic departments; and the UW-Madison Graduate School. The following is a general description of how royalties are divided among these entities.

Inventors’ share

The inventors receive 20% of the gross royalty revenue generated by a licensed invention. Payments are made to the inventors in the month following the receipt of the royalty payment.

WARF’s annual grant to the UW-Madison

After paying the inventors’ share, WARF deducts its operating expenses from its two sources of revenue: royalties on licensed inventions and WARF’s endowment. The net income from these sources is then used to fund WARF’s annual grant, or gift, to the UW-Madison.

WARF’s grant to the university is unrestricted, meaning the university can spend as it sees fit. The following is a general description of how different portions of the grant are allocated.

Lab share of the annual grant

Of the first US\$100,000 generated by each licence agreement, the inventors’ laboratories receive a grant equalling 70% of the gross royalties. For example, if an agreement generated US\$50,000 in royalty revenue over its lifetime, the inventors’ laboratories would receive 70% of US\$50,000, or US\$35,000.

Department share of the annual grant

The inventors’ academic departments receive a grant equalling 15% of the gross royalties generated by the inventors’ licensed technology.

Graduate school share

After the laboratory and department shares have been allocated, the remainder of WARF’s annual grant is given to the UW-Madison Graduate School. The Graduate School uses this money to support a variety of projects and programmes each year.

Source: Wisconsin Alumni Research Foundation website (<http://www.warf.ws/inventors/index.jsp?cid=14&scid=40>)

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