SPECIAL REPORT

The winding road from ideas to income

Huge numbers of offices have been established over the past 30 years to help university researchers take their discoveries from the lab to the clinic. **Meredith Wadman** assesses their success.

It looks as though Phillip Robinson may achieve something most researchers don't dare to dream of — seeing his past decades' bench slog translate into a commercially available drug to treat conditions such as epilepsy. It's early days, but companies are already contacting the neurobiologist, declaring their interest in taking his products into the clinic.

Robinson, based at the Children's Medical Research Institute in Sydney, Australia, works with dynamin, a brain protein that is important for maintaining synaptic transmission. Over the past ten years, his group has developed dozens of dynamin inhibitors while looking for much-needed alternatives to treat epilepsy and perhaps cancer (V. Anggono *et al. Nature Neurosci.* **9,** 752–760; 2006).

Finding the drug candidates was only part of the battle, he says. The university technology transfer offices (TTOs) they approached were "hopeless", says Robinson. One of them "just showed no interest", he recalls. Another "helped us find patent attorneys and helped us write patents. But then they don't do anything. When you contact them, they say: 'have you commercialized it yet?' There was no understanding that we are scientists. This is not what we do."

But Robinson's complaints are not unique. A multi-continental chorus of academic researchers argues that the plethora of TTOs that have sprung up over recent decades are at best a mixed blessing to researchers in the life sciences.

Robinson got lucky with BioLink, a company established by the government of New South Wales in 2005 to commercialize preclinical discoveries in the life sciences. BioLink located an animal-model screening programme at the US National Institutes of Health (NIH) in which Robinson's group became the first Australian participants. That landed them, at no charge, with US$500,000-worth of screening services, allowing them to narrow down which of their many drug candidates were likely to be effective in epilepsy.

Pathology data from animal trials were needed next, Paul Field, BioLink's head, told Robinson. Field's team found five companies that could do the work, then the cheapest of those, which recently produced the animal data.

Today, says Robinson: "We feel we've got the upper hand. We're not going to take the first deal we find. Now we have the companies contacting us."

The difference between BioLink and the other TTOs he experienced is simple, he says: "BioLink works with its clients to help and advise how to take the idea forward." TTOs, he adds, "might help you get a patent. But that's the extent of what they're good at. That's not facilitating commercialization at all, or translation."

"We're definitely helping the academic researchers who want to be helped," counters Andy Sierakowski, director of the TTO at the University of Western Australia in Crowley and chair of Knowledge Commercialisation Australasia, an association of 28 TTOs from universities in Australia and New Zealand.

Sierakowski cautions that academics such as Robinson may be expecting too much of TTOs. "They can only do the [licensing] deal itself," he contends. "There's no way a TTO should think it's got all the knowledge. If you can get additional get help from BioLink, do it."

Chorus of complaints

Even scientists with an enviable track record are critical of TTOs. Mike Clark, an immunologist at the University of Cambridge , UK, says that his several successes in translating medications to the marketplace "have been despite TTOs, and mainly because of the dogged determination of a large group of scientists who kept on plugging forwards when things looked difficult both scientifically and business-wise". Clark is one of the scientists behind the discovery of Campath (alemtuzumab), a humanized monoclonal antibody made by Genzyme in Cambridge, UK, for patients with a hard-to-treat type of chronic leukaemia (L. Riechmann, M. Clark, H. Waldmann, G. Winter *Nature* **332,** 323–327; 1998).

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The list of complaints about TTOs is long and diverse. Critics say that they tend to overvalue their intellectual property, leading companies to walk away from potential deals. Others complain that they hoard inventions — even those of dubious commercial merit — with the result that many gather dust in TTO files rather than being built on by companies that might transform them into useful products. This is a particular problem in the United States, where a 'first to invent' rule exists, rather than the 'first to file' rule elsewhere. If a US researcher can document that he or she was the first to invent something, even if no patent application was filed at the time, then his or her application will trump that of a competitor who develops it later on.

There are also problems with small staffs — the median size of a US TTO is six employees, and many others around the world are smaller. The TTOs are being stretched too thinly, and lack expertise in the huge range of fields from which inventions may issue. Attrition of highly qualified staff is also a problem for some. "Most people who are any good are going to get better offers from industry, or end up working for a top venture capital firm," says Clark.

Others charge that universities are showing an unseemly keenness to capitalize on inventions through their TTOs, blurring what should be a clear line between public institutions and commercial enterprises. Occasionally, this has caused students and postdocs to be pushed in commercial directions, against their better interests. "Phenomenal amounts of money have been made by a very small number of institutions. That's really what these offices are set up for. Every tech-transfer person in the country wants to land the next Gatorade, the next Taxol, the next Cisplatin," says John Frangioni, who works on *in vivo* cancer detection at Beth Israel Deaconness Medical Center in Boston, Massachusetts. Frangioni has filed some 50 invention disclosures with his TTO; of these, five have been patented, three licensed and 12 patents are pending.

TTO managers dispute this charge of money-grabbing, pointing out that some TTOs lose more money than they make for their institutions, and that windfall deals are rarities. They say that their work is about translating the science into new therapies, not about making money. Sierakowski points out that globally, almost all major universities have between 1% and 5% of their research budgets returned via TTOs in royalties and cash from selling their original interests. "This is not big money."

Jon Soderstrom, managing director of the TTO at Yale University in New Haven, Connecticut, and president of the Association of University Technology Managers (AUTM), the trade group for TTOs in the United States,

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SWAPPING FUTURE ROYALTIES FOR CASH: RECENT US MEGA-DEALS

Inventing institution	Invention	What it does	Company licensed to develop invention	Amount (US$) royalty rights were sold for
Northwestern University	Lyrica (pregabalin)	Anti-convulsant and pain reliever	Pfizer	$700 million (to Royalty Pharma)
New York University	Remicade (infliximab)	Anti-inflammatory to treat autoimmune diseases	Centocor (later acquired by Johnson & Johnson)	$650 million (to Royalty Pharma)
Emory University	Emtriva (emtricitabine)	Reverse transcriptase inhibitor to treat HIV	Triangle Pharmaceuticals (later acquired by Gilead Sciences)	$525 million (to Gilead Sciences & Royalty Pharma)
Memorial Sloan-Kettering Cancer Center	Neupogen (filgrastim) and Neulasta (PEG-filgrastim)	Stimulates production of white blood cells	Amgen	$263 million (to Royalty Pharma)
Yale University	Zerit (stavudine)	Reverse transcriptase inhibitor to treat HIV	Bristol-Myers Squibb	$115 million (to Bristol-Myers Squibb)
The Wistar Institute	Rotateq	Vaccine to prevent rotavirus infection	Merck	$45 million (to Paul Royalty Fund)

thinks that the offices are unfairly maligned. "I hear the stories. But they don't hold up under scrutiny," he says.

Certainly TTOs, which are charged with identifying and then exploiting opportunities to commercialize academic inventions, have delivered rich rewards in hundreds of instances. These include bringing several significant antiretrovirals to the clinic to fight HIV/AIDS, and the invention of a way to make the anticancer drug Taxol (paclitaxel) without destroying endangered Pacific yew trees. The particulars of individual royalty agreements between TTOs and companies are confidential, but when TTOs sell off these royalty rights — as they are doing more often with big winners — some mind-boggling numbers are involved (see Table).

In the United States alone, TTOs filed nearly 16,000 new patent applications in 2006, saw their licensees launch 697 products and spun out 553 start-up companies, according to the AUTM. Overall, US technology transfer has been "a big success story", says Mark Rohrbaugh, the director of the NIH Office of Technology Transfer.

Not all academics are dissatisfied. The performance of the TTO at Wake Forest University in Winston-Salem, North Carolina, "has been excellent. I don't think I could have done it without them," says Keith Walter, an ophthalmic surgeon there. Walter's device, Endosaver, which spares fragile tissue during minimally invasive corneal transplantations, is expected to enter clinical trials this summer. It is licensed to Ocular Systems Incorporated, a local company that worked with Walter through numerous iterations of a prototype. Walter notes that the TTO's associate director, Dean Stell, gave him tips he would never have thought of, such as advising him to enter even back-of-the-napkin sketches made during coffee breaks in a log book to protect his intellectual property.

Change of law

The US wave in technology transfer began when the Bayh-Dole Act of 1980 gave universities title to ownership of inventions resulting from research funded by the federal government — title that had formerly belonged to the government. At the time, TTOs in the United States numbered in the single digits. Today, more than 230 universities have them.

The trend was slow to reach Europe. More than half of Switzerland's TTOs were established between 1990 and 2000, for instance. In Italy, more than 40% were established in 2000 and 2001 — just before a change in the law granted title to inventors rather than institutions.

It hasn't always worked. For instance, in Germany, when a law change in 2002 gave universities title to their researchers' inventions, the ministry for education and research funded a TTO for every federal state. But because the initiative was underfunded and regional TTOs are spread too thinly, "I don't know of a single TTO set up from that programme that makes a profit or that even has a therapeutic product visible in the coming three years," says Christian Stein, head of Ascenion, the TTO for most of the life sciences at the Helmholtz and Leibniz Associations, which cover Germany's top bioresearch institutes. By working with the best institutions, and only in the life sciences, Stein's seven-year-old TTO has been able to generate more than €2 million (US$3 million) a year for the last several years in licensing fees and equity sales from exiting spin-offs.

Still, he says: "In terms of professional tech transfer, we are probably at least ten years behind what I see in the United States and quite a few years still behind the United Kingdom."

Some say that things have improved in the United Kingdom, where in the past TTOs have been accused of being inexpert and passive. Nancy Rothwell, vice president of research at the University of Manchester, UK, says that her university's TTO has been helped by a cadre of proactive business-development managers who seek out inventions rather than waiting for inventors to come to them. It has also instituted a policy pledging researchers an unusually high 85% of the income coming back to the university from any discovery that makes money.

Others are lukewarm on the nation's tech-transfer enterprise, which varies hugely between institutions. "Frankly, if there wasn't a need to fill this gap between basic science and product development, we wouldn't need to operate a tech-transfer enterprise," says Ted Bianco, who runs the Wellcome Trust's technology-transfer effort, costing £120 million (US$240 million) in its first year. In groundbreaking efforts such as medical engineering, "we get our inspiration from the United States, seeing how institutions such as Massachusetts General Hospital and Massachusetts Institute of Technology work", he says, citing the US TTOs' more proactive agenda, in which firms are courted for carefully selected inventions and staff are highly qualified with industry experience.

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Even the likes of those institutions, however, fail to impress some commercially-headed entrepreneurs. Chemist Namyong Kim, for example, worked at two Boston-based start-ups before deciding to move to Singapore. He was drawn by the tech-transfer focus of Singapore's A*STAR institutes, which have great connections to companies and investors, and a good supply of grants to assist development. The TTO at A*STAR — called Exploit Technologies — quickly applied for the necessary patents for Kim's miniaturized aqueous bioassay and awarded him US$236,000 to develop a prototype. Kim's two-month-old spin-off, Curiox Biosystems, has already made its first sale of the $13,500 DropArray.

"Everyone in the field knows that these TTOs can be helping or hurting academic researchers," says Kim. "The support here has been quite impressive compared to my experiences in the United States." ■

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