PETER CANNING

Working with the Structural Genomics Consortium, researchers at the University of Oxford, UK, study new and often difficult to target proteins.

TECHNOLOGY TRANSFER

The leap to industry

The science done in university laboratories can change the world, but only when discoveries can be transformed into innovations.

BY JESSICA WAPNER

The process of commercializing the discoveries made in university laboratories has come a long way over the past 30 years or so. "I didn't even know what that meant when I started out," says biomedical engineer David Kaplan at Tufts University in Medford, Massachusetts. Fifteen years and eight companies after his first patent, for a knee ligament made of silk, Kaplan is now well versed in the ways of technology-transfer offices (administrative infrastructure for ushering innovations out of the lab and into private development). The wisdom he has gained boils down to a few simple words: "It's an evolution," he says. And with shifting economic pressures, a drive to accelerate public access to innovations and changes to intellectual property law, technology transfer may be on the cusp of a major evolutionary leap.

Most historians agree that patent legislation originated in the Italian city of Venice in 1474. But for many centuries, universities in Europe and the United States were not involved in bringing new inventions to society. Because many universities were publicly funded, discoveries were published in the scientific literature, but were not patented. Industry and academia operated in vastly different spheres.

Licensing of inventions by academics became more prevalent in the early twentieth century. US chemist Frederick Cottrell received a patent for his device to reduce industrial pollution — an electrostatic precipitator — in 1908. The University of Wisconsin–Madison founded its technology-transfer office in 1925 to disseminate biochemist Harry Steenbock's discovery that irradiating food to increase vitamin D could treat rickets. Steenbock paid his own patent fees of US$300 (equivalent to roughly $4,000 today). When Quaker Oats offered him $1 million for his invention, Steenbock worked with university administrators to create an office that would allow the academic institution to benefit financially. The office licensed Steenbock's technology to Quaker Oats in 1927, leading to the introduction of breakfast cereal fortified with vitamin D. Bodies such as the US National Science Foundation, established in 1950, and the German Research Foundation, founded in 1951, increased government funding for academic research, but legislation allowing the commercialization of discoveries did not keep pace. Discoveries made by scientists through publicly funded research grants became the property of the governments that provided the money.

A few pathways from public invention to private commercialization did exist. The UK established the National Research Development Corporation (NRDC) in 1948 — a government body that led to innovations such as the first hovercraft in the late 1950s. In the United States,

NATURE.COM
To read more about the CRISPR–Cas9 battle, see go.nature.com/96ddzw

private companies could enter into institutional patent agreements with universities, but it was a fraught process, with rules varying among universities and government agencies. By the late 1970s, of the estimated 30,000 patents accrued by the US government through federally funded research, only around 1,200 were licensed and even fewer had made it to market. In Europe, legislation was mostly lacking. Germany's Employees' Inventions Act of 1957 gave more autonomy to academic inventors, but in general there was little interest across Europe in commercializing publicly funded research.

In the United States, the 1980 Bayh–Dole Act catalysed a surge of interest in commercializing academic research. The landmark legislation continues to provide a legal framework for patenting discoveries made using federal grant money. In the United Kingdom, the biggest shift came in 1985, when the government eliminated the monopoly that the British Technology Group, a public body, had on commercializing publicly funded innovations — a move that was followed by an increase in academic entrepreneurship. Several other European countries, including Germany, Denmark and Belgium, also have technology-transfer legislation, but laws governing this practice vary widely. Some are more restrictive on individuals, allowing universities to retain ownership of an invention instead. Others permit inventors to own patents derived from publicly funded research. This variation led the international group the Organisation for Economic Co-operation and Development to consider whether a Bayh–Dole-type policy should be adopted by the organization's member countries.

Since Bayh–Dole was enacted, technology-transfer offices have proliferated at universities in the United States and elsewhere. In 2014, at least 6,300 licences were secured by technology-transfer offices in the United States. Technology transfer has made available discoveries such as cancer drugs, recombinant DNA, imaging diagnostics and nanotechnology — in the United States alone, more than 23,000 patents have been filed by universities.

But technology transfer is facing several challenges. In the United States, which is the largest generator of academic innovations, federal grant budgets have shrunk or at best remained flat since 2003. In the United Kingdom, despite some capital investment, the budget for basic-science research has remained at £4.7 billion (US$6.7 billion) annually for the past 6 years. And how changes to the US patent system will impact commercialization is unknown — the United States has adopted a first-inventor-to-file rather than a first-to-invent structure, initiated by the 2011 Leahy–Smith America Invents Act, bringing it more in line with the rest of the world.

The first-to-invent system awards patents to the individual who first conceived the idea, created a workable prototype and then filed a patent. The first-to-file approach awards the patent to whoever submits the paperwork first, regardless of when the idea was conceived. The change to the US system may reduce interference proceedings — lengthy and costly battles that follow claims to a patent by separate parties, as is currently happening between the Broad Institute of MIT and Harvard and the University of California, Berkeley, over CRISPR–Cas9 gene-editing technology. However, the first-to-file approach could shift the focus away from carefully ensuring that an innovation is workable in favour of racing to file paperwork on an incomplete idea. The change could also favour large companies — with the resources, such as staff and attorneys, to handle large volumes of patents — over smaller companies or independent inventors.

"We're at another inflection point," says John Swartley, executive director of the Penn Center for Innovation (PCI), the technology-transfer office at the University of Pennsylvania in Philadelphia. To face these challenges, technology-transfer offices need to find new ways to work with private companies, scientists and outside investors, while maintaining their own integrity. "We can never forget that we are, at core, an academic institution," says Swartley.

COPING STRATEGIES

One of the most difficult aspects of moving a technology from academic concept to valuable product is crossing the chasm between early innovation and readiness for licensing — a stretch often referred to as the 'valley of death'. "One of the greatest challenges for academic technology transfer is trying to interest either established companies or venture investors in our early-stage discoveries," says Fred Reinhart senior adviser in the technology-transfer office at the University of Massachusetts Amherst.

High-volume crystallization plates used by the Structural Genomics Consortium.

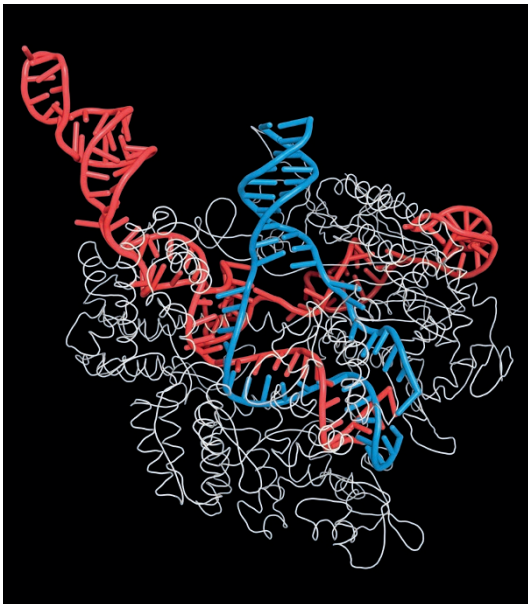
"Almost all of them have gone to later-stage, less risky investments."

That hurdle also exists outside the United States. "There's always been a relative shortage of cash at this early stage," says Steven Schooling, director of engineering and physical sciences at University College of London Business (UCLB), the technology-transfer office at UCL.

Many universities are providing internal funding to bridge the valley of death, along with seed funding for even earlier stages of research when no other grant support exists. At North Carolina State University in Raleigh, the Chancellor's Innovation Fund provides awards of up to $75,000 to researchers whose work has garnered encouraging feedback from an outside company. "It's not huge money," acknowledges Kelly Sexton, director of the office of technology transfer at the university. But the amount is enough to help academics through the proof-of-concept stage. "There's kind of a sweet spot where this can be useful," says Sexton. In January 2016, UCL launched a £50-million UCL Technology Fund, which can be used to support researchers through the proof-of-concept stage. The money is provided by the European Investment Fund (EIF) and technology-commercialization company Imperial Innovations, and will be managed by the venture-capital firm Albion Ventures, which is also a contributor. The aim is to overcome the challenge of attracting and sustaining interest from investors who generally have to wait a long time to see a return. To make the long-term investment more attractive, the fund will pay out an annuity over 15–20 years — an approach that may avoid the drop-off that is frequently seen with the conventional venture-capital model of raising capital in multiple rounds with the hope of reaping benefits from a trade sale or initial public offering. UCLB and Albion decide which researchers receive the funds, but follow strict return-on-investment criteria set by the EIF. "This isn't charity money," says Schooling, "and that means we have to be selective."

Charitable foundations that focus on a single disease are also becoming an increasingly prominent piece of the tech-transfer puzzle — a variety of venture philanthropy (see page S43). The approach has already led to several drug licences. For example, an experimental treatment for multiple myeloma, ricolinostat, was created as a result of research at the Dana-Farber Cancer Institute in Boston, and the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. The investigators formed Acetylon to develop the technology, and the US-based Leukemia and Lymphoma Society contributed $5 million towards the phase I clinical trial. US biotech firm Celgene subsequently invested $100 million in the development of ricolinostat, a payment that included an exclusive option to buy the licence from Acetylon. The drug is now in phase II trials for multiple myeloma. The Leukemia and Lymphoma Society have also partnered with

ELLA HUGHMAN


MOLEKUUL/SPL

Model of the CRISPR–Cas9 gene-editing complex.

Celator Pharmaceuticals in Ewing, New Jersey, to speed up the study of the acute myeloid leukaemia drug CPX-35, including an initial $4.1 million for the phase II study followed by an additional $5 million for the phase III trial.

Some technology-transfer offices are changing their entire approach to working with private companies. At the Penn Centre for Innovation, the focus is shifting towards cultivating a few strong business relationships, rather than cold-calling hundreds of companies for every invention, says Swartley. At some institutions, pharmaceutical companies enter into research agreements with a specific laboratory or investigator, this offers a more collaborative approach to academic research.

The trend towards a more "holistic relationship", as Reinhart puts it, is allowing technology-transfer offices to avoid investing too much time in specific deals. Focusing instead on a long-term relationship between universities and companies enables "a better understanding of mutual needs", says Reinhart. "That's what the smart universities are doing these days." Reinhart cites the Office of Industry Engagement at Georgia Institute of Technology in Atlanta, the Office of Innovation and Industry Engagement at Michigan Technological University, and the Office of Technology Commercialization at Purdue University in West Lafayette, Indiana, as examples of technology-transfer offices moving towards this approach.

Start-up companies launched by principal investigators are becoming increasingly common, particularly when large companies are unwilling to assume the risk, even after the proof-of-concept stage. Building a successful product through a spin-off company can lead to lucrative deals later and allow the original researcher to continue working largely autonomously. In the United States, 818 start-up companies were formed on the basis of academic patents in 2013, a 16% increase from 2012 (L. Pressman *et al. The Economic Contribution of University/Nonprofit Inventions in the United States:1996-2013*; BIO, 2015).

> ***"We can never forget that we are, at core, an academic institution."***

The increase partly stems from universities being seen as sources of innovation and job creation, not merely sheltered places of "learning, teaching, and getting degrees", says Schooling. "We've moved beyond that." According to the US Association of University Technology Managers, 4,000 start-up companies in the United States have formed as a result of university innovations since 1980, and these have led to 3 million jobs. Schooling recalls that in the early 1990s, when he and fellow researchers founded a spin-off for work they had done at Manchester Metropolitan University, UK, his group was viewed as "slightly failed academics". Colleagues questioned their commercial activity. "Nowadays its part of how university academics are assessed," he says.

MORE SERIOUS REPAIR

Although these approaches are changing how technology-transfer offices operate, some researchers see the need for a more severe overhaul. For medical advances in particular, profit-driven privacy and competition spurred by the licensing infrastructure may be obstructing progress. "The current way we're doing drug discovery is too costly, too risky and too slow," says Chas Bountra, a member of the Structural Genomics Consortium (SGC) at the University of Oxford, UK. "The whole process is incredibly inefficient." Companies duplicate efforts and a large proportion of the compounds developed fail to show a benefit in clinical trials. Most troubling of all, he says, is that patients are sometimes treated with experimental medications that would already have been shelved, if data were shared earlier and more openly. "It's a horrendous waste of money, a waste of people's careers, and a waste of patients' willingness to participate in research," says Bountra.

As part of the SGC, Bountra is taking a radically different approach to therapeutic innovation. The consortium receives funding from several pharmaceutical companies, charities and government organizations. The large collection of funders means that resources are pooled and risk is shared, so that no single investor is shouldering the burden of early-stage development. Research is focused solely on novel proteins — often substances that have been deemed impossible to target. The tools developed to generate a potential drug are then made freely available. Data from preclinical studies are published immediately. "We tell the whole world about it," says Bountra.

He is not alone in encouraging the open-innovation approach. The Harvard Stem Cell Institute and the Biodesign programme at Stanford University, California, for example, are also taking steps towards a more open approach. David Brindley, who studies health-care translation at the Centre for the Advancement of Sustainable Medical Innovation (a partnership between Oxford and UCL) contends that the translation of technology from lab to bedside has been slowed by "disincentives for people along the chain to communicate and work together effectively".

Brindley says that changes that better align the interests of academia with industry would help. Tenure applications, for example, could take entrepreneurial activities into consideration. He also advocates altering the conventional financial arrangements that surround university-born innovation. "Academia shouldn't expect industry to pay huge licensing revenue for research they funded in the first place," says Brindley, "and industry needs to be more reasonable in their expectations of research timelines."

Whatever route technology-transfer offices take, the most important need is to stay flexible, particularly in light of the increasing number of gene-based discoveries that raise ethical and proprietary questions that may not have been accounted for when the Bayh-Dole Act was passed. Who owns a gene? Can a gene be owned? The current legal battle over the patent for CRISPR–Cas9 may have a considerable impact on scientific innovation. The gene-editing technique is allowing all manner of genome alterations that could bring huge benefits, such as cures for disease and pest-resistant crops.

Although the financial stakes for the opposing parties are high, the broader relevance of the case may be minimal. Interference proceedings are connected with the first-to-invent patent system, and so when the ruling is made, it may not carry much weight in the first-to-file era. Still, the case could have broader ramifications on university-driven innovation, potentially forcing the creation of new legal frameworks for gene-based discoveries, such as the right to patent these innovations or to specify what can be done with them. Whether the quest to fill personal and university coffers will delay broader distribution of the lifesaving fruits of taxpayer-funded research remains unclear.

The CRISPR–Cas9 controversy stands in stark contrast to the lack of financial incentives favoured by those behind the SGC. As Bountra sees it, that transparency, and the academic freedom that it provides, is paramount to ensure that novel, effective medicines reach people as quickly as possible. "Tomorrow is too late," he says. "They want them today." ■

Jessica Wapner, *a freelance writer in Brooklyn, New York, is the author of* The Philadelphia Chromosome.