This protein belongs to…

The early days of genomics were marked by concerns that wide-ranging gene patents would restrict research and medical discovery. So far, proteomics hasn't toiled under the same cloud. But don't get complacent, warns David Cyranoski.

A simple claim of ownership rarely sparks a wave of widespread panic. But in 1991, the US National Institutes of Health (NIH) managed just that when it claimed intellectual-property rights on some 3,500 genes, based on sequences of tiny fragments of their DNA. The news pushed the NIH researcher who had obtained the sequences, Craig Venter, into the limelight — a position that this pioneer of genomics has delighted in ever since. And it stirred fears around the world that the scientific and medical advances promised by the human genome sequence would be restricted by overarching patent claims.

So in December 2001, when the British biotechnology company Oxford GlycoSciences (OGS) announced that it was trying to patent more than 4,000 proteins linked to disease, you might have expected more howls of outrage. In the event, the news generated barely a ripple of interest — most probably because protein patents have been around for a century or so, without causing anyone a major headache. "We are used to them," says Richard Gold, director of the Centre for Intellectual Property Policy at McGill University in Montreal, Canada. Indeed, patents are generally thought to provide an appropriate financial reward for those who devise useful applications for proteins, while stimulating further research.

But some experts warn that this happy balance might soon be disturbed. Massive projects are promising to solve the structures of thousands of proteins in record time. And recent rulings in US courts, where intellectual-property trends often begin, have set precedents that could make protein patents more obstructive in the proteomic era than they have been in the past. "These trends bode ill for the future of biomedical research," says David Korn, senior vice-president for biomedical and health-sciences research at the Association of American Medical Colleges in Washington DC.

Although they were ultimately denied, the NIH's 1991 gene patents caused alarm because of their huge potential reach. They could have meant that anyone who developed a useful product, such as a drug, by studying a particular gene would have to pay royalties to the researcher who first sequenced a tiny fragment of that gene's DNA. This, many experts argued, would provide a major disincentive to investment in research and development — the exact opposite of what the patent system is supposed to achieve.

Clamp-down on claims

Since then, the US patent office has raised the bar on gene patents. Guidelines issued in December 1999 made the condition of 'utility' a tougher nail to hit. Those hoping to claim a patent on a DNA sequence because it might be useful as a molecular probe or because it can make a protein now have to answer some specific questions. A probe for what, exactly? A protein that does what? "You can't just say you found a gene that might have some value," says Tim Caulfield, an expert in healthcare law at the University of Alberta in Edmonton, Canada.

Decades of experience with patents on proteins have suggested that they don't cast such a long shadow over research and innovation. And so far, at least, the fate of OGS has reinforced the general view that its aggressive patent announcement was nothing to worry about. Less than a year after claiming rights to 4,000 proteins, identified by comparing diseased with healthy tissues, OGS cut one-fifth of its staff. This spring, the cash-strapped company was bought out by Celltech of Slough, west of London. Celltech is retaining OGS's work on cancer, but is trying to sell off the rest of its proteomics operation.

Indeed, protein prospecting has turned out to be a very tough business. Large Scale Biology, based in Vacaville, California, similarly hoped to make a fortune by identifying and patenting a large number of medically important proteins. But it is now concentrating on the narrower goal of producing animal proteins in genetically engineered plants. "When you do the figures, it's just not worth it," says Tom Gallegos, the company's senior director of intellectual property.

It costs a couple of hundred thousand dollars to patent something worldwide. "It's easy to find a lot of proteins and get patents, but with costs like that, you have to be pretty sure that your protein has commercial value," says Yoshiji Fujita, who heads Tokyo Medical University's new Clinical Proteome Center.

Such value isn't easy to come by. Most proteins are initially patented as diagnostic markers to identify patients suffering from a particular disease or from a drug's side effect. "But diagnostic markers often don't even make enough money to pay for the

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Production line: Japan's Genomic Sciences Center in Yokohama aims to churn out the structures of 3,000 proteins over the next few years.

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patent," says Gallegos. "It's a lean market."

The economics change if your protein is a drug target or can itself be used as a drug. The protein erythropoietin, or EPO, for instance, is marketed as a treatment for anaemia and earns billions of dollars a year for Amgen of Thousand Oaks, California, which holds the patent on it. But to figure out whether a protein has therapeutic value generally requires extensive research in the Petri dish and in live animals. "You need hard-working people injecting things into mice," says Gallegos.

ID parade

Massive projects now under way could make identifying therapeutically important proteins much easier. The factory-like approach of Japan's 'Protein 3000' programme and the US Protein Structure Initiative should rapidly determine the structure of thousands of proteins. In theory, this explosion of structural data should help researchers home in on candidates for drug development. In August, the Japanese project, based at the RIKEN Genomic Sciences Center in Yokohama, reported that it had cranked out structures of 613 proteins in its first 18 months.

Structural data alone are not sufficient to claim a patent, however, thanks to an agreement reached in November 2002 by representatives of patent offices from Japan, the European Union and the United States. This has eased fears about overarching protein-patent claims. But projects such as Protein 3000 could still change the intellectual-property landscape. The data from the Japanese programme, for example, will be made available through partnerships to companies in Japan before they are released internationally.

"The fear is that some proteins that have great importance in terms of research on potential therapies will be patented," says Arti Rai, an intellectual-property expert at Duke University in Durham, North Carolina. A company might then attempt to claim ownership of any approach to knocking out the protein, she says.

Some recent court rulings have started to raise concerns that patents on proteins are being interpreted too broadly. In January, Transkaryotic Therapies of Cambridge, Massachusetts, failed to break Amgen's grip on EPO when the US Court of Appeals for the Federal Circuit decided that its rival EPO product infringed Amgen's patents. These patents describe the production of human EPO in hamster ovary cells. Transkaryotic produces a slightly different version of EPO using genetically engineered human cells. So far, the court has broadly supported Amgen's claim that its patent covers any use of mammalian cells for the production of EPO.

Some observers are concerned by this turn of events. "The court is constructing a 'protect R&D investment' strategy without thinking through the implications," says Robert Cook-Deegan, director of the Center for Genome Ethics, Law, and Policy at Duke University. Such precedents could discourage companies from trying to make better versions of protein-based drugs, he says.

For most academics, even broadly interpreted patents have held few fears. US patent law has allowed a 'research exemption' for work with patented tools or materials "solely for amusement or to satisfy idle curiosity, or for strictly philosophical inquiry". Traditionally, this has been interpreted as covering all academic research — a recent survey led by John Walsh at the University of Illinois at Chicago confirmed that researchers at US universities routinely fall back on this exemption without worrying about being charged patent royalties (J. P. Walsh, A. Arora and W. M. Cohen *Science* **299,** 1021; 2003).

Exempt no more

But in the light of a recent ruling from the US Supreme Court, says Cook-Deegan, it is unclear whether this 'gentleman's agreement' can continue. On 27 June, America's highest court ruled on the case of Duke University versus Madey — and according to many intellectual-property experts, the Supreme Court's interpretation of the research exemption means that most academic research would now infringe any relevant patents.

The case relates to a dispute over the use of laser technology developed by John Madey, who worked at Duke until 1998, when he left for the University of Hawaii at Manoa. Madey objected to Duke continuing to use the technology covered by his patents. When Duke cited the research exemption, Madey countered — and the Supreme Court agreed — that the university was using the technology in the business of teaching and getting grants, not to satisfy idle curiosity.

The ruling could have onerous implications for anyone who wants to conduct research on a patented protein — and, indeed, on academic research more generally. "The case says that whether you're at the university or anywhere else, research is not just playing around. Research in and of itself is infringement," says Masashi Miyano, who heads the RIKEN Structural Biophysics Laboratory in Harima, Japan. At the very least, says Cook-Deegan, it may require extensive legal groundwork before researchers are given the green light to work on a patented protein.

The NIH is also worried about the implications of broadly interpreted patents on proteins and other biological molecules. In September, it awarded a $1.2-million grant to Steve Merrill of the National Academy of Sciences in Washington DC for an 18-month study of the issue.

Merrill's team will consider various recommendations to policy-makers, including a stronger research exemption and the encouragement of toned-down licensing agreements that give users the freedom to use patented molecules as they wish. Policies will have to be set soon, Merrill says: "The longer we wait, the more doors will become closed to us." ■

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