

The cell division

Oliver Brüstle fought for more than a decade to pursue and patent human embryonic stem-cell research in Germany. Now his efforts have backfired.

BY ALISON ABBOTT



It was overcast and unseasonably sultry in Luxembourg, home to the European Court of Justice, on the morning of 18 October 2011. But German neuroscientist Oliver Brüstle wasn't sweating when the 13 judges entered the court room in their flowing crimson robes. Not, that is, until they delivered their verdict, which spelt the end of his lengthy fight to defend his patent on human embryonic stem (ES) cells from attack by Greenpeace.

It took barely two minutes for the court's president to summarize aloud the four pages of the judgment. The ruling, which cannot be appealed, upheld Greenpeace's position. It declared that any patent depending even indirectly on human ES-cell lines is outlawed on moral grounds throughout the European Union (EU). Unexpectedly, it added that any research using such cell lines was similarly immoral.

For a few moments Brüstle was so shocked he could barely draw breath. Outside, the clouds burst and rain poured down. "What hurt most personally was the accusation that scientists who work on human ES-cell lines are somehow immoral," says Brüstle, who says he never doubted that he would win the case. "But now I accept it's the end of the road."

That road has been a long and twisted one for Brüstle, one of Europe's leading stem-cell researchers, based at the University of Bonn in Germany. Germany is a scientific powerhouse, but it has always been slow to accept any form of new genetic technology. Long before the patent battle, Brüstle was fighting to pursue research using human ES cells — which can differentiate into many types of mature cell — while the German government vacillated about its legitimacy.

The latest dispute centred on the ethics of patenting discoveries that stem from the use of human embryos. Brüstle argued that patenting was crucial because, without it, industry would not be interested in pursuing what he saw as potentially life-saving therapies. And whereas some people charge that patenting could actually impede research, Brüstle argues that patents held by academics are normally free for other researchers to use. Brüstle admits his battles were lonely, and took their toll on him

and his family, who at one time even found themselves under police protection. Yet he says that he never once considered pulling out. "I just didn't think it right that an environmental organization, rather than a government, should define research agendas," he says.

Brüstle's single-mindedness is not a reflection of an aggressive personality: his aura is calm, not domineering. "I think he's just been driven — rightly — by strong scientific convictions," says stem-cell biologist Elena Cattaneo at the University of Milan, Italy, who has worked with him as part of scientific networks funded by the European Commission. "Oliver has been an important figure in the ethical debate and he deserves a lot of credit," adds Ronald McKay, a stem-cell researcher at the Lieber Institute for Brain Development in Baltimore, Maryland, and a former mentor of Brüstle's.

The reality, however, is that although those convictions have helped to further human ES-cell work in Germany a little, only a handful of research groups have ever tried to work with such cell lines. And Brüstle's patent fight may now have backfired, because the new ruling could hinder researchers working on human ES cells throughout Europe. By declaring such research to be immoral, many fear, the court ruling could prompt funding agencies to stop funding it — and it certainly means that no patent, foreign or home-grown, that involves human ES cells can be defended in Europe. Even Christoph Then, an equally driven one-man crusader against biopatenting who spearheaded Greenpeace's campaign, expressed surprise at the court's wide-reaching condemnation of human ES-cell research. "I don't think anyone has the moral right to patent any sort of life, so this is a happy victory for us," he says. "But our intention was never to stop basic research in the area."

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"It's easy, in hindsight, to question if I was right to take the patent fight so far," Brüstle says now, "and I'm sorry that there has been collateral damage for my colleagues in other countries." But, he adds, he would do exactly the same if he had his time again.



After Oliver Brüstle was granted a patent for his work on human embryonic stem cells, Greenpeace pushed to ‘stop the patenting of life’.

P. LANGROCK/ZENIT/GREENPEACE

“No one could have predicted that what started with a goal to have more liberal rules in Germany would have made Europe ultra-restrictive.”

As a medical student at the University of Ulm in southern Germany, Brüstle fell in love with the brain. He set a career trajectory to become a neurosurgeon, but in the early months of his residency at the University of Erlangen, he felt the irresistible draw of research. “I wanted to do more than just remove brain tumours,” he says. “I wanted to find out how brain disease could be avoided.”

He interrupted his residency in 1993 for a research break in McKay’s lab at the National Institute for Neurological Disorders and Stroke in Bethesda, Maryland. There he studied how human fetal brain cells behaved after they were grafted into the brains of embryonic rats¹. “We joked in the lab that we wanted to see if it would be the American way of adapting to a new environment or the European way of not adapting,” he recalls. The cells adapted.

When, in the mid-1990s, several research groups developed procedures for turning mouse ES cells into heart cells using a cocktail of growth factors, Brüstle adapted the method to generate neural cells². “Suddenly, stem-cell biology was at a point where reconstructive therapy was not just a pipe dream,” he says. Brüstle wanted to be part of the global research effort that would realize it.

Like his stem cells, Brüstle had adapted well to his new home, but he began thinking about returning to Germany to establish an independent scientific career. He was drawn by the newly dynamized research environment, where scientists were being strongly encouraged by universities and the government to think about how their basic research could be commercialized or otherwise put to use for the public good. Patenting in particular was being encouraged. “Newspaper articles had been saying that German scientists were too stupid to patent, unlike American scientists who were helping the US economy — it was a constant lament,” Brüstle recalls.

He returned to Bonn in September 1997, and shortly thereafter submitted his fateful patent on procedures for generating neural

precursors from ES cells to the German Patent Office. It was based on his mouse work, but its claims covered most species, including primates, both non-human and human. He thought that a method to derive endless neural precursors would be bound to prove useful in medicine. “I wasn’t thinking in concrete terms about commercialization,” he says. “I just had an idea that a company might want to license it at some point and that would help translation to the clinic.” The patent was granted in 1999.

The year before, James Thomson, then at the University of Wisconsin–Madison, reported his team’s success in generating the first stem-cell lines from human embryos³. Like many scientists, Brüstle was keen to get hold of the cell lines and translate his animal work to humans. Knowing that Thomson had been swamped with requests for collaboration, he simply booked a flight to Madison. “I told Jamie I would just stay in the hotel until he had time to meet me and talk about research we could do together.” They met, and hatched a plan to work together on ways to generate neural precursor cells from Thomson’s new cell lines.

For Brüstle, this decision also marked the start of his fight for acceptance of human ES-cell work in Germany. He put together a grant application to work on the methods he had devised with Thomson, and in August 2000 submitted it to the DFG, Germany’s main university granting agency. “I had a gut feeling though that its passage may not be smooth,” says Brüstle. “It just wasn’t clear whether the DFG would be allowed to fund such work.” The country’s 1990 Embryo Protection Act forbids research on human embryos but does not refer to research on established ES-cell lines, which didn’t exist when it was written. In 1999, the DFG stated that a ‘societal debate’ was needed on the issue and in the meantime it would fund just adult stem-cell research. Brüstle’s application was a direct challenge to this stance.

Brüstle, who is a practising Catholic, had thought hard about his own moral position. He disagrees with the creation of human embryos specifically for research. But almost all human ES-cell lines have been derived from embryos leftover from fertility treatment that would otherwise

have been destroyed. Brüstle maintains that using them for biomedical research rather than discarding them is the moral imperative.

Ernst-Ludwig Winnacker, a biochemist and then-president of the DFG, decided that Brüstle's application should be peer reviewed. It was highly rated. In May 2001, the DFG opined that human ES-cell research on imported cell lines was legal, morally justified and scientifically necessary. It was ready to fund Brüstle. This was a point of explosion.

Within days the government intervened, asking the DFG to defer giving Brüstle his grant to allow more societal debate. That debate, which grew progressively hotter, took the form of local and national panel discussions, newspaper articles and parliamentary hearings. Some sections of the media, the churches and other groups attacked Brüstle — and, in turn, Brüstle appeared in newspapers and television shows to state his case. His four children had to deal with remarks from schoolmates. "It was a very stressful time," he says.

Elsewhere, other countries were devising their own solutions, amid similarly polarized debates. Some conservative governments, such as Ireland's, tightly restrict human ES-cell research. Bolder ones have been more permissive: in the United Kingdom, for example, the government decided to allow new human ES-cell lines to be derived from spare embryos, and in some cases to allow human embryos to be created for research purposes. In the end, the German government fudged the decision. On 30 January 2002, it passed a law that forbade projects involving newly derived lines but allowed research on cell lines that existed before a specific date. That same year, Brüstle finally got his grant.

MORAL CHALLENGES

The small victory didn't stop the debate. Some groups argued vehemently that the use of any human ES-cell lines was wrong. Brüstle became such a target of vitriol that undercover police officers had to mingle with the audience at his talks.

Given the climate, Brüstle was not particularly surprised when Greenpeace challenged his patent in 2005. The organization invoked the 'ordre public' clause in the EU's Directive on the Legal Protection of Biotechnological Inventions, to which all national patent law must defer. The directive states that inventions whose commercial use could lead to a breach of morality cannot be patented, and uses the commercialization of the human embryo as an example.

A year later, Brüstle arrived at the Federal Patent Court in Munich in an armoured limousine with three police escorts. The judge found in favour of Greenpeace and ordered claims for human ES-cell lines to be removed from his patent. Still, Brüstle was certain that he would be able to overturn the decision on appeal.

What actually ensued, however, was a series of court setbacks and delays. When the Federal Patent Court ruled against Brüstle on appeal, he took the case to the country's Supreme Court. At a hearing in November 2009, the Supreme Court seemed to accept Brüstle's arguments, but, before making its final ruling, decided to refer the case to the European Court of Justice to clarify ambiguous points of patent law regarding the definition and potential commercial use of human embryos and stem cells derived from them. At that stage, even Greenpeace's Christoph Then told the press that he thought his case was lost.

It wasn't. In March 2011, Judge Yves Bot, who was responsible for working the case, delivered his preliminary opinion for the European court. He argued that an invention that had involved destruction of an embryo would be immoral.

Brüstle was still confident that the Grand Chamber, which comprises all 13 judges, would rule the other way. He had read the statements provided by the European Commission and many of the EU member states. None of them — even from the most conservative of countries — asked for patents based on human ES-cell lines to be outlawed.

When the Grand Chamber ruled in October, however, there was no place for more optimism. The judges took the preliminary ruling further,

making it clear that even inventions that indirectly involved destruction of an embryo were immoral and could not be patented. Brüstle walked from the courtroom into a swarm of journalists, and spent the next five hours telling them why he thought the judgment was wrong. "How can a European court rule immoral what national governments have allowed and which national research agencies have funded?" He then drove the two hours home, he says, "too exhausted to feel anything".

Elsewhere, the response to the ruling was muted. German scientific organizations remained silent — although they eventually published a joint statement condemning the judgment on 7 December. "I was quite shocked that no one spoke up after the judgment," says Winnacker, who is now head of the international Human Frontier Science Programme based in Strasbourg, France.

A handful of patent lawyers, companies and scientists in other countries pronounced that patents were not so important anyway and that clarity in the matter has its own advantages. "Industry also wanted clarity, even if that result was tough," says Johan Hyllner, chief executive of Cellartis in Gothenburg, Sweden, which derives cell lines from human ES-cell lines for drug discovery. "Now we know how to proceed and we can always choose to keep trade secrets instead of patenting."

But Brüstle and some other stem-cell scientists and legal experts view those pronouncements as an effort to play down the damage. "Many were afraid that investors or funding agencies would pull out of the area," says stem-cell researcher Christine Mummery at Leiden University Medical Centre in the Netherlands.

Since the ruling, scientists and funding agencies across Europe have been trying to analyse its impact. If academic scientists using human ES cells want to found a biotechnology start-up company, they'll now find it hard, admits Hyllner. "Venture capitalists like to see a strong patent portfolio, and this won't be possible in Europe now." And there are hints that research organizations are getting cold feet about funding the work. On 23 November, the European Parliament's official cross-party working group on bioethics urged zero funding of human ES-cell work in the next multi-billion-euro EU framework research programme, Horizon 2020, on the grounds that the work is now legally challengeable. But a week later, Europe's research commissioner Máire Geoghegan-Quinn said that she wanted to continue funding such research. Scientists expect a fight to ensue.

Through all this, Brüstle says that colleagues using human ES cells have been supportive. No one has publicly expressed regret that Brüstle pushed his case so far.

Brüstle is taking a break from battle, however. Methods for reprogramming adult cells to make stem cells capable of differentiating into many cell types look encouraging, he says, and his own lab now spends 80% of its time in this area. Last month, he published a paper⁴ showing how his team reprogrammed skin cells taken from patients with Machado-Joseph disease into such 'induced pluripotent' stem cells, work that helps explain how the rare disorder attacks neurons. "But we don't yet know if those induced pluripotent cells will work as well — we still need to use human ES cells in research," he says.

On reflection, Brüstle says, the thing he just can't understand is that the tough decision on human ES-cell research and patenting has not been made through reasoned debate by law- and policy-makers, as it has in many other countries. "It's been made instead by a struggle between a single researcher and an environmental organization: was that quite right?" ■ **SEE EDITORIAL P. 291**

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2. Brüstle, O. *et al. Science* **285**, 754–756 (1999).
3. Thomson, J. A. *et al. Science* **282**, 1145–1147 (1998).
4. Koch, P. *et al. Nature* <http://dx.doi.org/10.1038/nature10671> (2011).