

Patents draw new lines in the battle to commercialize stem cells

In September 2008, Japan's patent office issued the first license related to induced pluripotent stem (iPS) cells to Kyoto University's Shinya Yamanaka. Ever since that decision, the stem cell community has waited with bated breath to see how other countries' patent offices would resolve the hundreds of similar applications they've received.

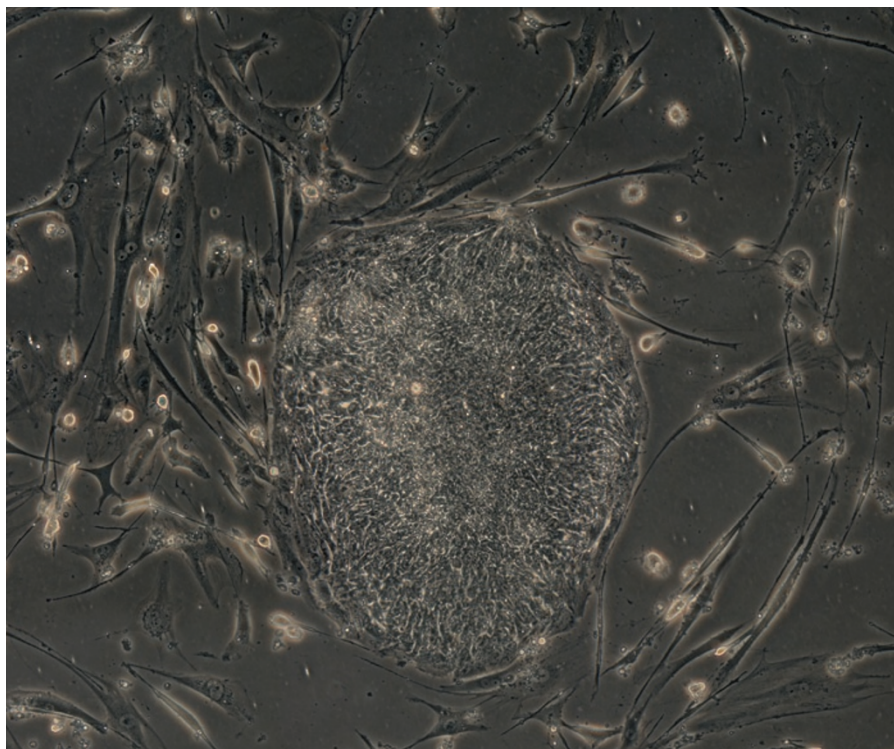
Determining who holds the patent rights to iPS technology is crucial, as these methods are used to coax normal adult cells into becoming tissue-specific cells with therapeutic potential that companies hope to cash in on. Now, the US and UK patent offices have issued their first rulings, and the early decisions indicate that there won't be one dominant patent holder—partly because there is no dominant method used to create the cells.

The US Patent and Trademark Office granted broad-sweeping awards for embryonic stem cells more than a decade ago. But it was only in January that it awarded its first patent for a method of making iPS cells. The patent, which is fairly limited in scope, went to Fate Therapeutics, a San Diego-based company that counts Rudolf Jaenisch of the Whitehead Institute in Cambridge, Massachusetts as one of its scientific founders.

It covers a method invented by Jaenisch and his former postdoc Konrad Hochedlinger, now at the Massachusetts General Hospital in Boston, in 2003 in which researchers can use adult cells that have been genetically engineered to produce a signal when the cells have reverted to an embryonic-like state after other reprogramming genes, small molecules or proteins are added. The method is useful for screening new candidate agents to determine whether they can be used to reprogram adult cells, says Scott Wolchko, Fate's chief financial officer.

But when it comes to creating patient-specific iPS cells, the approach has been supplanted by techniques that do not integrate genes into the cells' genome, says David Resnick, a patent attorney with Nixon Peabody in Boston. As such, the patent is unlikely to affect many other researchers or companies in the field; he says, "in my experience, I don't think anybody is making them this way."

Indeed, the methods used to create iPS cells are rapidly evolving. For example, to create the first reported iPS cells, Yamanaka exposed mouse cells to four genes, those encoding Oct3/4, Klf4, Sox2 and c-Myc (*Cell* **126**, 663–766, 2006). But the UK Intellectual Property Office granted a patent in January for a more basic reprogramming recipe to the



Junyong Yu, University of Wisconsin–Madison

Patently pluripotent: Intellectual property issued for induced stem cells

South San Francisco-based company iPierian for a technique developed by Japanese scientist Kazuhiro Sakurada that uses only the first three of these genes.

"The British patent office clearly showed their opinion and viewpoint based on the facts," says Sakurada, who now heads a lab at Sony Computer Science Laboratories in Tokyo.

Looking ahead

The UK patent "certainly provides a first foot in the door and does presage the fact that we have some important intellectual property that we feel we can prosecute in other jurisdictions," iPierian chief executive John Walker told *Nature Medicine*. "It's a harbinger of things to come [in] the UK, in Europe and in the US."

"This now gives us clarity," adds Ian Wilmot, director of the University of Edinburgh's Centre for Regenerative Medicine who is not affiliated with iPierian. "We now know, in terms of work here in Britain, that there's a company with which we'd have to negotiate" to license iPS-related technology used in experiments.

But the methods to create iPS cells are changing, according to Sheng Ding of the Scripps Research Institute in La Jolla, California, who adds that many researchers now reprogram successfully with even fewer factors. "We are not concerned at all [by this

patent], as we now use even less," says Ding, a scientific founder of Fate and the only researcher to report using a nonviral technique involving this three-factor recipe to coax iPS cells from skin cells (*Cell Stem Cell* **4**, 381–384, 2009).

Ken Taymor, executive director of the Berkeley Center for Law, Business and the Economy in California, contends that neither the US nor the UK patent decisions definitively settle the question of who invented the reprogramming technology first. "Given the frequency with which patents are modified or overturned, I don't think you can look at the mere issuance of a patent as strong evidence that the patent holder versus somebody else who still has a right to challenge the patent is not the true inventor," he says. Yamanaka declined to comment for this story.

Nick Seay, chief technology officer of Madison, Wisconsin-based Cellular Dynamics International, one of Fate and iPierian's main rivals, says the company is not concerned about getting left out of the early intellectual property land grab. "Neither of these patents affects our life, our company or our technology at all," he says. "There are many ways to do iPS...and there will be a lot of patents in this field."

Elie Dolgin, New York