CRISPR patents belong to Broad, says USPTO

The US Patent and Trademark Office (USPTO) announced last month that a set of patents granted to the Broad Institute covering CRISPR editing of eukaryotic genomes does not interfere with patent claims filed by the University of California–Berkeley and the University of Vienna. The win for the Broad and its partners, Harvard University and Massachusetts Institute of Technology (MIT), concludes a year-long battle over the breakthrough technology that has already spawned a host of startup companies seeking to use CRISPR to develop treatments for human and animal health as well as agricultural applications. "Broad has persuaded us that the parties claim patentably distinct subject matter," read the decision of USPTO's Patent Trial and Appeal Board, adding "Broad provided sufficient evidence to show that its claims, which are all limited to CRISPR-Cas9 systems in a eukaryotic environment, are not drawn to the same invention as [University of California's] claims, which are all directed to CRISPR-Cas9 systems not restricted to any environment." In a statement, Berkeley said it respected the board's decision, but maintained that Berkeley biochemist Jennifer Doudna and her collaborator Emmanuel Charpentier, now at Max Planck Institute for Infection Biology in Berlin, were the first to invent the CRISPR system. Doudna said that the ruling would allow USPTO to move forward on her patent application, and that it would "likely" issue the patent, potentially forcing companies eager to use CRISPR to pay licensing fees to both UC and the Broad. "They have a patent on green tennis balls. We [likely] will have a patent on all tennis balls," she said. As *Nature Biotechnology* went to press, Berkeley had not indicated if they would appeal the decision.

> **"Out of those 92% [drugs] that fail, 100% had a lot of really smart people who thought they were going to work. If you were just going to start guessing about drugs you would do a lot of harm, because most of them would do more harm than good."** Robert Califf, outgoing FDA commissioner, criticizes proposals for reducing the agency's powers pointing out that 92% of drugs in clinical testing fail to reach the market because they have unacceptable toxicity, don't work or can't be manufactured safely. (*Forbes*, 23 January 2017)

> **"We know a lot more about how some new code will run, how a new car will corner, how a new recipe will taste, how a new building will look, or how a new movie will do on its first weekend. Those all have their uncertainties, of course… but those uncertainties are tiny compared to the uncertainty of taking a drug into the clinic and giving it to people. I don't think that there's anything else quite like it in the modern industrial world."** Derek Lowe, Vertex Pharmaceuticals' medicinal chemist and blogger, puts drug discovery into perspective. (*In the Pipeline*, 23 January 2017)

drug. That delayed full reimbursement in an already difficult environment.

Berger was still at the helm when negotiations with Takeda began shortly after. "I was open to selling the company if we had the right kind of offer," Berger recalls. Ariad had already sold off future Iclusig royalties to Incline Village, Nevada–based PDL BioPharma in exchange for up to $200 million in cash to help fund brigatinib trials. To ensure the right kind of offer would indeed materialize, Denner appointed a new CEO, Paris Panayiotopoulos, previously president of EMD Serono, who set about polishing up the company in order to maximize its sale price.

Most controversially, Iclusig's price was hiked by 75%, to almost $200,000, during 2016 (*Nat. Biotechnol.* **34**, 1231–1241, 2016), providing a lightning rod for US politicians, including Democratic senator Bernie Sanders, already condemning pharma drug pricing. Berger also criticizes the price rises, calling them "well above" what he would have done. But they did bump up the drug's revenues. A quarter of Ariad's workforce was cut, and European operations were sold to Incyte, along with European Iclusig rights, providing cash to advance the pipeline. Brigatinib was submitted to FDA in June 2016, earlier than anticipated, and received priority review for patients with ALK-positive, Xalkori-resistant non-small cell lung cancer.

The polishing worked. Takeda is paying what may be four (or more) times peak revenues for Iclusig and brigatinib. Iclusig is reduced to a niche product, and brigatinib, still unapproved, is heading for stiff competition, including from Basel, Switzerland–based Novartis' Zykadia (ceritinib) and Roche's Alecensa (alectinib). By any conventional metrics, "all these kinds of transactions appear expensive at first," acknowledges Stelios Papadopoulos, chairman of Biogen, Exelixis and San Diego–based Regulus Therapeutics, and previously an investment banker. When Foster City, California–based Gilead Sciences paid $11 billion for Pharmasset in 2011 (*Nat. Biotechnol.* **30**, 122, 2012), that looked expensive—until the billions started rolling in from hepatitis C drug Sovaldi (sofosbuvir), even if that did contribute to the current volatile pricing climate. Takeda plans to test Iclusig in additional cancer types, and brigatinib, although not first in class, could yet trump its competitors. Preliminary results in a first-line phase 3 trial hints that it may extend progression-free-survival longer than Xalkori. Overall, "it's a great outcome" for Ariad products, people and programs, concludes Berger, who also got rich from the deal.

With drug pricing still facing public and political scrutiny, Ariad may be among the last companies to get away with such blatantly opportunistic price hikes. (Iclusig is now the priciest CML drug in its category.) But its story provides several other lessons for the sector. In clinical development, "there's a real benefit to getting as much data at different doses as possible in your pivotal trial," reflects Berger. Ariad had picked a single dose for Iclusig which, though effective, may have been higher than necessary and contributed to the safety issues in some patients. And those signals don't always show up immediately—perhaps a lesson for regulators on the accelerated approval process. The process is designed to provide early access for patients in need, but withdrawals can cause problems for patients, too. Those that do respond to the drug, many of whom will have no alternative treatment, have to seek special permission to continue to access it (*Oncologist* **20**, 847–848, 2015). Finally, setting up commercial operations is expensive, even for specialist drugs that don't need huge sales forces. Doing so "doesn't make sense for one or two products," says Leerink's Schmidt. Others, like Exelixis, signed up partners to help develop and market their products, hanging on only to US rights to its renal cell carcinoma drug Cabometyx (cabozantinib).

The biotech sector needs grown-up role models, like Biogen, Amgen of Thousand Oaks, California, or Celgene of Summit, New Jersey. Ariad was a fully integrated, global player—but not a sustainably profitable one. It developed products that will continue to make a difference to patients, and its expertise and assets will feed back into the ecosystem. Takeda is unlikely to keep all Ariad's employees. But, especially around the Cambridge, Massachusetts, area where the company was headquartered, "there's an efficient system for recycling talent and resources," notes Papadopoulos. "You cut off the head of one biotech and two will sprout up in its place."

In the case of Actelion, a new biotech sprung up immediately. Cofounder–CEO Jean-Paul Clozel had resisted acquisition for years, including fighting off activist shareholders in 2011, to build a highly profitable, integrated biotech with over half-a-dozen products worth over $2 billion in annual sales. In the end, he made the creation of a new biotech one of the conditions of the deal. Johnson & Johnson gets Actelion's marketed drugs, including its leading pulmonary arterial hypertension franchise, and two late-stage candidates. Actelion II—as yet unnamed—starts out with $1 billion in cash, over a dozen R&D programs and a Swiss listing. "If we're not successful, then I think something must be wrong," Clozel asserted in a January 26 call announcing the deal.

And so the cycle continues.

Melanie Senior *Lyon, France*