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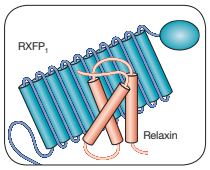
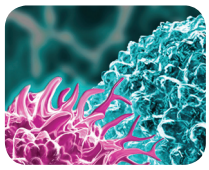


Setback for keenly anticipated heart failure drug Serelaxin p602



Cytokine release syndrome and CAR T-cell therapy p604

Sanofi's dengue vaccine first to complete phase 3 p605

First CRISPR-Cas patent opens race to stake out intellectual property

Start-up firm Editas Medicine has gained the first patent in the burgeoning field of CRISPR-Cas genome editing. In doing so, Editas looks to have stolen a march on its recently founded rival CRISPR Therapeutics. On April 15, the Broad Institute and one of its parent institutions, the Massachusetts Institute of Technology (MIT), both of Cambridge, Massachusetts, were jointly assigned US Patent no. 8697359 ('CRISPR-Cas systems and methods for altering expression of gene products'), arising out of the work of Editas co-founder Feng Zhang, of the Broad Institute. "That issue of a US patent was a big stake in the sand," says Chelsea Loughran, an associate at Wolf, Greenfield & Sacks, a Boston-based intellectual property (IP) law firm. "I think there is a good psychological advantage to getting the first one," agrees her colleague Patricia Granahan, a partner at the firm. In particular, it can help attract funding, Granahan adds.

JESSICA RINALDI/Reuters/Newscom

George Church, who heads a group at Harvard at the forefront of the CRISPR gene editing field and is a co-founder of Boston start-up Editas.

News of the grant did not, however, derail London–based CRISPR Therapeutics' completion of a $25 million Series A round, which it disclosed on April 24 (Basel-based Versant Ventures was the only participant in the deal.) Editas was launched in November 2013 with $43 million in financing from Flagship Ventures, Polaris Partners and Third Rock Ventures, with participation from Partners Innovation Fund. CRISPR Therapeutics and Editas are both tight-lipped about their IP licensing strategies at this point—neither was willing to respond to queries on the issue. As the first movers in a potentially foundational technology for a new wave of molecular medicine applications, each is well positioned to make a substantial impact, but it will take some time before it will be possible to gauge the relative strengths of each company's respective IP claims.

The whole field of genome engineering has been galvanized by the development of an efficient and user-friendly method for introducing targeted deletions in a genome of interest, based on a prokaryotic genetic defense system that relies on clustered, regularly interspaced, short palindromic repeats (CRISPR). These constitute a molecular record, embedded in the host chromosome, of genetic sequences from previously encountered mobile genetic elements, such as viral or plasmid DNA. They form the basis of an RNA-based recognition system that directs DNA nuclease enzymes to cleave matching DNA sequences (*Nature*, **495**, 50–51, 2013).

The co-inventors of the technology, erstwhile collaborators Emmanuelle Charpentier, who holds dual appointments at Hannover Medical School, in Hannover, Germany, and the Helmholtz Centre for Infection Research, in Braunschweig, Germany, and Jennifer Doudna, of the University of California, Berkeley, simplified one such system from *Streptococcus pyogenes* by combining two 'guide' RNAs into a single molecule, which can be programmed to direct nuclease activity to any target site (*Science* **337**, 816–821, 2012). Each is named as co-inventor on a key patent application, which is assigned to the University of California and the University of Vienna, Charpentier's home institution at the time. PCT/US2013/032589 ("Methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription"), which has six named inventors in all, has 155 claims detailing the precise workings of a CRISPR-Cas system for targeted deletion of a DNA sequence or modification of a polypeptide specified by the targeted DNA sequence. As *Nature Biotechnology* went to press, it was still under examination, having been filed on March 15, 2013. The application claims a priority date of May 25, 2012, shortly before an associated paper was accepted for publication, on June 20, 2012, and published, on June 28, 2012 (*Science* **337**, 816–821, 2012).

The two scientists have taken separate routes in seeking to commercialize the technology. Charpentier and Doudna are the scientific founders of CRISPR Therapeutics and Editas, respectively, and each has recruited some big guns to their line-up of co-founders. Nobel laureate and RNA interference pioneer Craig Mello, of the University of Massachusetts Medical School, in Worcester, Massachusetts, is part of the CRISPR Therapeutics team, for example, and George Church, of Harvard Medical School, is included in the Editas line-up.

CRISPR Therapeutics and Editas will, presumably, both have access to the Charpentier-Doudna patent, assuming it is granted, but

Table 1 Selected CRISPR-Cas genome editing patent applications

Publication	Assignees	Title	Filing date	Publication date	Inventors	Priority date
US20100076057A1	Northwestern University (Evanston, Illinois)	Target DNA interference with crRNA	9/23/2009	3/25/2010	Erik J. Sontheimer; Luciano Marraffini	9/23/2008
WO2010075424A2	The Regents of the University of California	Compositions and methods for down-regulating prokaryotic genes	12/22/2012	7/1/2010	Victor Kunin; Susan Yilmaz; Rotem Sorek; Philip Hugenholtz	12/22/2008
WO2013126794A1	Fred Hutchinson Cancer Research Center (Seattle)	Compositions and methods for the treatment of hemoglobinopathies	2/22/2013	8/29/2013	Michael Bender; Mark Groudine; Barry Stoddard; Ryo Takeuchi	2/24/2012
WO2013142578	Vilnius University, Vilnius, Lithuania	RNA-directed DNA cleavage by the Cas9-crRNA complex	3/20/2013	9/26/2013	Virginijus Siksnys; Giedrius Gasiunas; Tautvydas Karvelis; Arvydas Lubys; Lolita Zaliauskiene; Monika Glemzaite; Anja Smith	3/20/2012
WO2013169398	Georgia Tech Research Corporation, Atlanta	Systems and methods for improving nuclease specificity and activity	3/15/2013	1/3/2014	Eli Fine; Thomas Cradick	5/9/2012
WO2013176772 A1	University of Vienna; the Regents of the University of California	Methods and compositions for RNA-directed target DNA modification and for RNA-directed modulation of transcription	3/15/2013	3/6/2014	Emmanuelle Charpentier; Krzysztof Chylinski; Jennifer Doudna; James HD Cate; Martin Jinek; Wendell Lim; Lei Qi	5/25/2012
WO2013181440A1	Baylor College of Medicine (Houston, Texas); University of Washington (Seattle)	Supercoiled minivectors as a tool for DNA repair, alteration and replacement	5/30/2013	12/5/2013	Lynn Zechiedrich; Jonathan Fogg Jr.; Daniel James Catanese; Erol Bakkalbasi; Nancy Maizel; Olivier Humbert	5/30/2012
US20140017214A1	Sangamo Biosciences (Richmond, California)	Methods and compositions for delivery of biologics	7/11/2013	1/16/2014	Gregory Cost	7/11/2012
WO2014011237 A1	Sangamo Biosciences	Methods and compositions for the treatment of lysosomal storage diseases	3/15/2013	1/16/2014	Edward Rebar	7/11/2012
WO2014022702A2	The Regents of the University of California	Methods and compositions for controlling gene expression by RNA processing	8/1/2013	2/6/2014	Jennifer Doudna; Adam Arkin; Lei Qi; Rachel Haurwitz	8/3/2012
WO2014071219A1	Factor Bioscience (Cambridge, Massachusetts)	Methods and products for expressing proteins in cells	11/1/2013	5/8/2014	Matthew Angel; Christopher Rohde	11/1/2012
US8697359B1[a]	The Broad Institute; Massachusetts Institute Of Technology	CRISPR-Cas systems and methods for altering expression of gene products	10/15/2013	4/15/2014	Feng Zhang	12/12/2012
WO2014018423A2	The Broad Institute, MIT	Inducible DNA binding proteins and genome perturbation tools and applications thereof	7/21/2014	1/30/2014	Feng Zhang; Mark Brigham; Le Cong; Silvana Konermann; Neville Espi Sanjhan	7/25/2013

[a]Granted patent. Sources: Cambridge IP Group; Wolf, Greenfield & Sacks (adapted with permission from a table originally published in *Medical Research Law & Policy Report*, 13 MRLR 193 (March 19, 2014) by The Bureau of National Affairs, Inc. (800-372-1033) http://www.bna.com/).

each company's precise IP arrangements are unclear. "What we don't know, of course, is if there is any agreement between the two companies and the two inventors that would give both companies freedom to operate," says Quentin Tannock, chairman of Cambridge IP Group, a Cambridge, UK–based IP consultancy. IP disputes at this stage of the innovation cycle are uncommon, he says. The costs involved and the outstanding commercial and technical risks attached to early-stage technologies are all deterrents to hiring lawyers. The fact that both companies have successfully raised investment suggests IP may not be an issue.

The Broad-MIT patent grant arises out of work led by the Broad Institute's Feng Zhang, another Editas co-founder. He and his co-workers developed two variations of the *S. pyogenes* type II CRISPR-Cas9 system, capable of generating targeted, double-stranded breaks in mouse and human chromosomes, respectively. They codon-optimized for eukaryotic expression the genes encoding the system's key protein components, the *S. pyogenes* RNase III, which in conjunction with trans-acting CRISPR RNA (tracr) is involved in processing pre-CRISPR (cr)RNA to mature crRNA

molecules, and the *S. pyogenes* Cas9 (CRISPR-associated protein 9) DNA nuclease, which cleaves DNA at sites that are complementary to mature crRNA molecules. Zhang's group also attached nuclear localization signals to these constructs, to ensure their compartmentalization in the nucleus (*Science* **339**, 819–823, 2013).

The resulting patent claims a priority date of December 12, 2012, the same date the paper was accepted for publication (it was published online on January 3, 2013). The actual patent application was not filed until October 15, 2013; the entire patent examination process took just six months. "They petitioned for accelerated examination, and they got it," says Loughran. "Why the Berkeley guys didn't take that course I have no idea."

The IP landscape surrounding CRISPR-Cas is, of course, much wider than that part of it controlled by CRISPR Therapeutics and Editas. Granahan and Loughran identified CRISPR-related IP from several sources that could potentially be cited as prior art in future opposition proceedings (*Life Sciences Law & Industry Report* (Bloomberg Bureau of National Affairs, March 2014)). This includes research performed at the Danish food ingredients firm Danisco, which is now part of Wilmington, Delaware–based DuPont; at the University of Georgia; and at Northwestern University in Chicago. Several other research groups and biotech firms have filed patent applications on genome editing tools and applications that come after the Charpentier-Doudna filing although the list is not complete (**Table 1**). "There are probably quite a few patent applications out there that haven't yet entered the public domain," Tannock says.

Despite the excitement surrounding the technology in scientific circles, it hasn't entered the wider public consciousness as yet, although this is likely to change dramatically as the technology matures and ultimately when the first clinical trials begin. Some of the hype surrounding CRISPR has been "really over the top," says Paul Shanks of the Berkeley, California–based Center for Genetics and Society, a not-for-profit group that encourages responsible use of human genetic technologies. "During the embryonic stem cell wars of close to ten years ago now, several people were saying the most likely use [for the technology] was to model diseases in a dish," says Shanks. "That's probably going to be the first use of CRISPR in a way."

Cormac Sheridan *Dublin*

FDA launches two research centers with academia

The US Food and Drug Administration (FDA) in May announced it was establishing two new Centers of Excellence in Regulatory Science and Innovation (CERSIs). One of the centers, which is to focus on improving preclinical safety and efficacy tests as well as clinical trials and evaluations, and on using information sciences to capture diverse data sets, will be set up jointly at the University of California, San Francisco (UCSF) and Stanford University. "The pharmaceutical and biotech industries are facing huge challenges, with the majority of drugs failing in clinical trials because they are not effective," says Kathy Giacomini of the UCSF School of Pharmacy, alluding to the new FDA-sponsored center in California. This partnership aims to develop new computer-based models and methods to predict drug metabolism, toxicity and effectiveness, and help move these technologies out of academia and into practice, Giacomini adds. The second of the new CERSIs, which will be established at Johns Hopkins University in Baltimore, will focus on clinical evaluations, social and behavioral science, and food safety. This brings the number of CERSIs to four, with the two others established in 2011 at the University of Maryland medical campus in Baltimore and at Georgetown University in Washington, DC. "We strongly support regulatory science at FDA and partnerships between government, academia and the private sector to develop new tools and methodologies for evaluating the safety and effectiveness of drugs and biologics," says Cartier Esham, executive vice president, Emerging Companies Section for the Biotechnology Industry Organization (BIO) in Washington, DC.

Jeffrey L Fox

Corrections

The news brief "Microbes unite Novozymes and Monsanto" (**32**, 211, 2014) incorrectly states that BioAg Alliance's work involves microbial enzymes. The alliance will discover, develop and commercialize microbial solutions for agriculture. The error has been corrected in the HTML and PDF versions of the article.

In the news analysis "Master Protocol for squamous cell lung cancer readies for launch" (**32**, 116–118, 2014), Genentech's compound taselisib was incorrectly labeled as pictilisib in Table 1. The error has been corrected in the HTML and PDF versions of the article.

In the news analysis "Engineered tracheas, corneas and arteries enter clinical testing" (**32**, 303–304, 2014), the article incorrectly stated there was one case of rejection in a phase 1 trial of corneal implants, when there were none. There was one case of rejection in the control group that received donor corneas. The error has been corrected in the HTML and PDF versions of the article.