SPOTLIGHT ON CELL BIOLOGY

Edit your future with a career in CRISPR

Some early-career scientists found themselves surfing the wave of CRISPR just as it hit the shore.

By Nic Fleming

SHORTLY AFTER moving to America to start her PhD, Luhan Yang faced a dilemma that will resonate with many scientists. The walls of her lab were adorned with posters on pioneering next-generation sequencing work carried out by colleagues. She could play it safe by following in their footsteps, or risk going into the new field of genome editing.

Yang, who moved from Beijing, China, to begin her research doctorate at Harvard Medical School in Boston, Massachusetts, in 2009, chose the road less travelled. "It would have been easier to get published on next-generation genetic sequencing at that time, but I thought genome editing offered better long-term potential."

The decision paid off. In 2013, Yang was co-first author of a key paper demonstrating that CRISPR-Cas9 can be used to edit the genomes of mammalian cells. Today, as co-founder of the biotech company eGenesis, along with her academic supervisor, George Church, she is playing a leading role in efforts to produce gene-edited pig organs that can safely be transplanted into human patients.

The CRISPR system was discovered, rather than developed. After a bacterium (or archaeon) defeats a hostile virus, a portion of the viral DNA sequence is stored between sections of the microorganism's own DNA called CRISPRs (clustered regularly interspaced short palindromic repeats). When the same virus threatens again, the saved DNA is used as a reference library to make guide RNA, which in turn directs a protein (CRISPR-associated protein; Cas) to snip viral DNA in two.

Due to its ability to identify and target individual strands of DNA, this natural immune defence mechanism has become a powerful, cheap and easy-to-use gene editing tool in the lab.

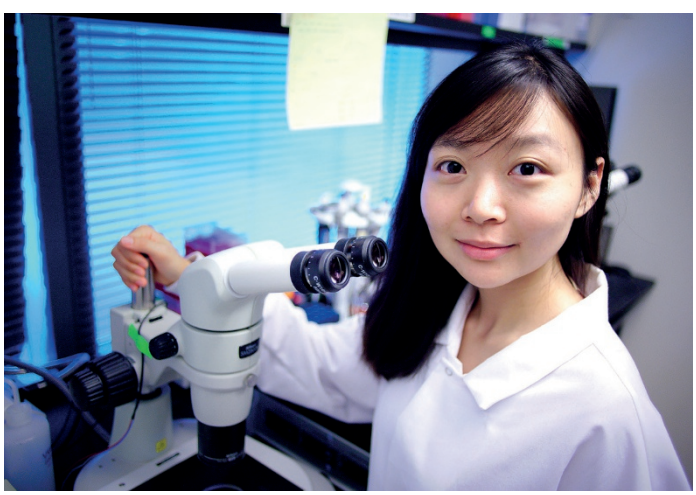
Over the last four years, the technology has been hailed by those in the field as one of the most significant research breakthroughs of the biotech age. "From a technological point of view, it's as big as any advance in the last 50 years," says Jonathan Weissman, a systems biologist at the University of California, San Francisco, who has used CRISPR to develop advanced genome screening techniques.

Outside the lab the technology is still young, but CRISPR-Cas9 and related tools are seen as having huge potential for a long list of applications, including new treatments for a wide range of diseases, editing genes in human embryos, wiping out pathogens and boosting agricultural production.

Structural biologist Martin Jinek was there at the very start of the CRISPR breakthrough. He joined Jennifer Doudna's lab at the University of California, Berkeley (UC Berkeley), as a postdoc in 2007 — the same year the first paper outlining CRISPR's role in the adaptive immune system of bacteria was published. After becoming involved in the lab's intensifying efforts on CRISPR, Jinek was co-first author of a key paper in 2012 that showed Cas9 can be programmed to target specific sequences of DNA using only short strands of RNA. The following year he demonstrated that this technology could be used to edit genes in human cells.

Jinek now runs his own lab investigating the basic molecular mechanisms of CRISPR at the University of Zurich in Switzerland. He warns that scientists will lose out if they don't make time to stay abreast of new developments in their own and related fields. "It's important to keep your eyes open because unexpected developments can come out of nowhere," he says. "It can lead you to great discoveries, and propel your career in unexpected directions."

Back in Boston, Yang believes the rapid emergence of CRISPR-Cas9 and other tools is helping to build bridges between research sectors. "In genomics we have accumulated so much knowledge and so many tools that academia is not the only route for cutting-edge research. It might be possible to have more societal impact by working in industry," she says.



Luhan Yang

LUHAN YANG

Rachel Haurwitz

CAROL QUARTIN

It's a sentiment shared by Rachel Haurwitz, who joined Doudna's lab to work on CRISPR shortly after she started as a graduate at UC Berkeley in 2007. With the technology's commercial potential becoming increasingly obvious, Haurwitz became CEO of Caribou Biosciences, which she launched with Doudna, Jinek and James Berger, then a UC Berkeley professor, in 2011. The company has raised more than $40 million in venture capital and has exclusive licenses to the Doudna lab's intellectual property.

"I loved the basic research I did in the Doudna lab, but it seemed so many steps away from anything that would ever help society," says Haurwitz. In 2014, Caribou launched Intellia Therapeutics, a separate business based in Cambridge, Massachusetts, to develop treatments based on CRISPR, and has formed partnerships with other companies to work on CRISPR applications

MIGUEL RIOPA/AFP/GETTY

in fields including agriculture and industrial biosciences.

Two other CRISPR research pioneers have launched companies to commercialize their discoveries. CRISPR Therapeutics, based in Basel, Switzerland, was founded in 2014 by Emmanuelle Charpentier, now a director at the Max Planck Institute for Infection Biology in Berlin, who carried out early work in the field before collaborating with Doudna. Editas Medicine, also in Cambridge, Massachusetts, was co-founded by Feng Zhang, whose team at the nearby Broad Institute of MIT and Harvard published a key paper in 2013 showing CRISPR-Cas9 could be used to edit mouse and human cells.

And in August 2016, CRISPR Therapeutics joined forces with Bayer to launch Casebia Therapeutics, once again based in Cambridge, to develop new therapies for blood disorders, blindness and congenital heart disease. The outcome of a patent dispute in the US over CRISPR-Cas9 (see **the billion-dollar biotech bust-up**) will have major impacts on all of these companies' prospects.

In the meantime, labs worldwide have been enthusiastically experimenting with the CRISPR system. Data from Addgene — a Cambridge-based non-profit that facilitates the sharing of genetic material for research — gives an idea of the extent of adoption. It has seen demand for genome-editing kits rise from fewer than 400 in 2010 (before the availability of CRISPR-Cas9), to 24,300 in 2015 — of which 95% is for use in CRISPR work.

Joanne Kamens, executive director of Addgene, believes the emergence of genome editing offers important career lessons for scientists. "Having experience of CRISPR on your resume is no longer a big deal because it's so widely used, but those who got in early gained an advantage," says Kamens. "CRISPR offers a reminder to scientists, especially those in training, of the importance of reading the literature, keeping on top of new techniques, and developing technical skills."

Knowledge of more advanced CRISPR applications, though, could still be an asset for a budding molecular biologist. "If researchers have used one of the higher end applications of CRISPR, and are in a position to make a thoughtful and well-designed genome screen and do the follow-up biology, I think that's a terrific position to be in job-wise," says Weissman. "There are a relatively small number of people developing cutting-edge CRISPR technology, and that's certainly a competitive and attractive area."

The experiences of pioneers like Yang, Jinek and Haurwitz certainly offer lessons for scientists thinking about how to shape their careers. However, some of those catapulted into the headlines say that while their hard work has been important, the luck of the draw also played its part.

"We were interested in some pretty fundamental and, frankly, rather esoteric questions about how bacteria and archaea fight off infections, not looking for the next big translational technology," says Haurwitz. "So much of my own personal path was just being in the right place at the right time, paired with colleagues who were willing to trust me with this tremendous opportunity."

Emmanuelle Charpentier and Jennifer Doudna

Having become CEO of a high-profile biotech company at the age of 26, people often ask Haurwitz for advice in how to get into business or engineer their career in another direction. "I typically just stare at them; I have no idea," she admits. "Rather than trying to map things out for the next ten years, people should do what they're passionate about. I think that will take them to more interesting places." ■

CORRECTION

The *Naturejobs* Spotlight on Catalonia (*Nature* **539**, *Naturejobs*; 2016) described Josep Tabernero as the director of the Vall d'Hebron University Hospital. He is, in fact, director of the Vall d'Hebron Institute of Oncology (VHIO) and head of the Medical Oncology Department at the Vall d'Hebron University Hospital. This has been corrected online.

This content was commissioned and edited by the Naturejobs editor

The billion-dollar biotech bust up

Fortunes — and citations in the science history books — will be won and lost when the US Patent and Trademark Office (USPTO) decides who owns the intellectual property of CRISPR-Cas9 as a genome editing tool.

"Everyone is trying to work out how much these applications are going to be worth," Jacob Sherkow, an associate professor at the New York Law School and an ex researcher, told Fortune in January. "Numbers have been bandied about, but we're talking billions."

The dispute dates back to an application in March 2013 to patent CRISPR-Cas9-based genome editing, filed by Jennifer Doudna of the University of California, Berkeley, and colleagues. In 2014 a number of patents were granted for the technique's use in eukaryotes — including humans — to a group led by Feng Zhang of the Broad Institute of MIT and Harvard in Cambridge, Massachusetts.

Following objections from Doudna's team, in January 2016, the USPTO began a review of some of the key patents granted to Zhang. Oral arguments are due to be presented to the court on December 6.

Rachel Haurwitz, CEO of Caribou Biosciences, which she co-founded with Doudna and others, has a lot riding on the outcome. From this experience, Haurwitz recommends that young researchers should learn about intellectual property and how to keep accurate laboratory notebooks. "Those skills are really critical and yet infrequently emphasized in academia," she says.

Sherkow says the dispute is a good reminder to academics that they can still be sued for infringing patents when they are doing basic research.

Perhaps surprisingly, he doesn't think early-stage scientists should be constantly consulting lawyers and thinking about protecting their work. "Do the absolute best collaborative work you possibly can and the fruits of that endeavour will generally come to you," he says.

And if that fails, the law might offer a lucrative alternative. "If you are a research scientist and things are not working out for you, being an intellectual property lawyer with a deep science background is an enormously fun and profitable field," says Sherkow. "No matter what happens with the CRISPR case, the lawyers always win."

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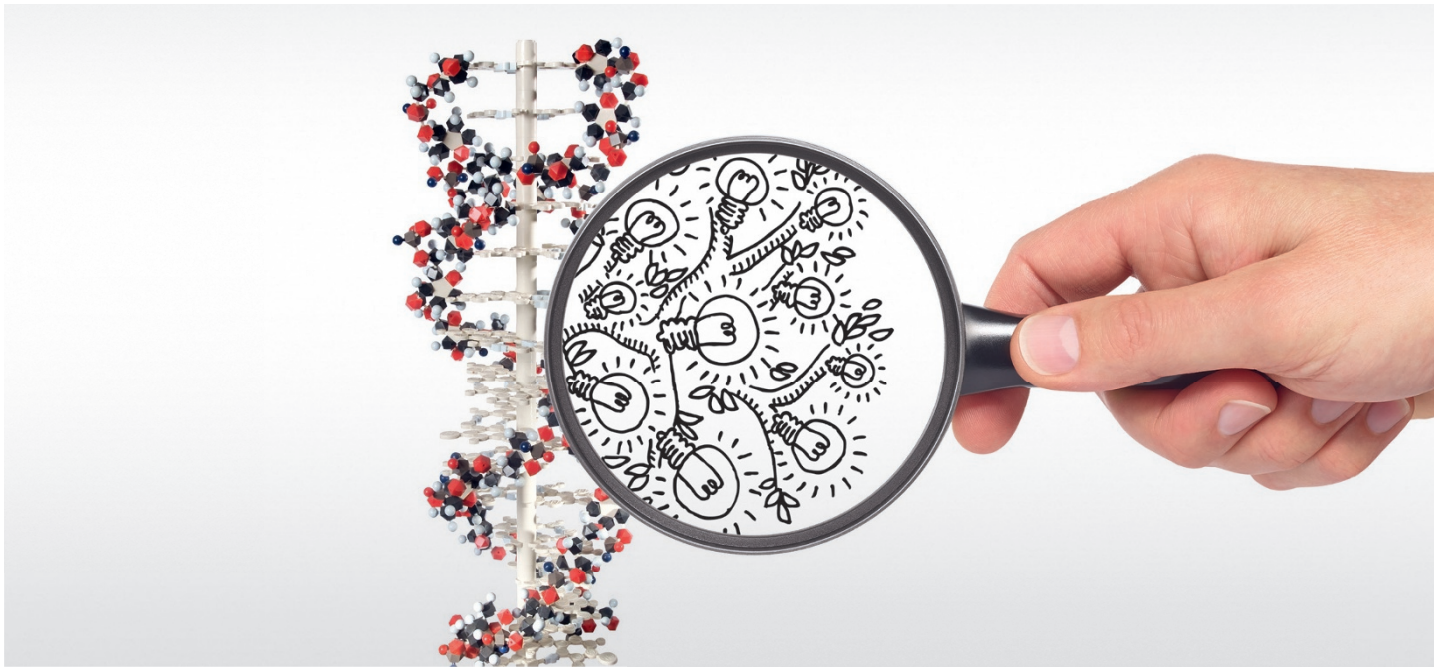

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