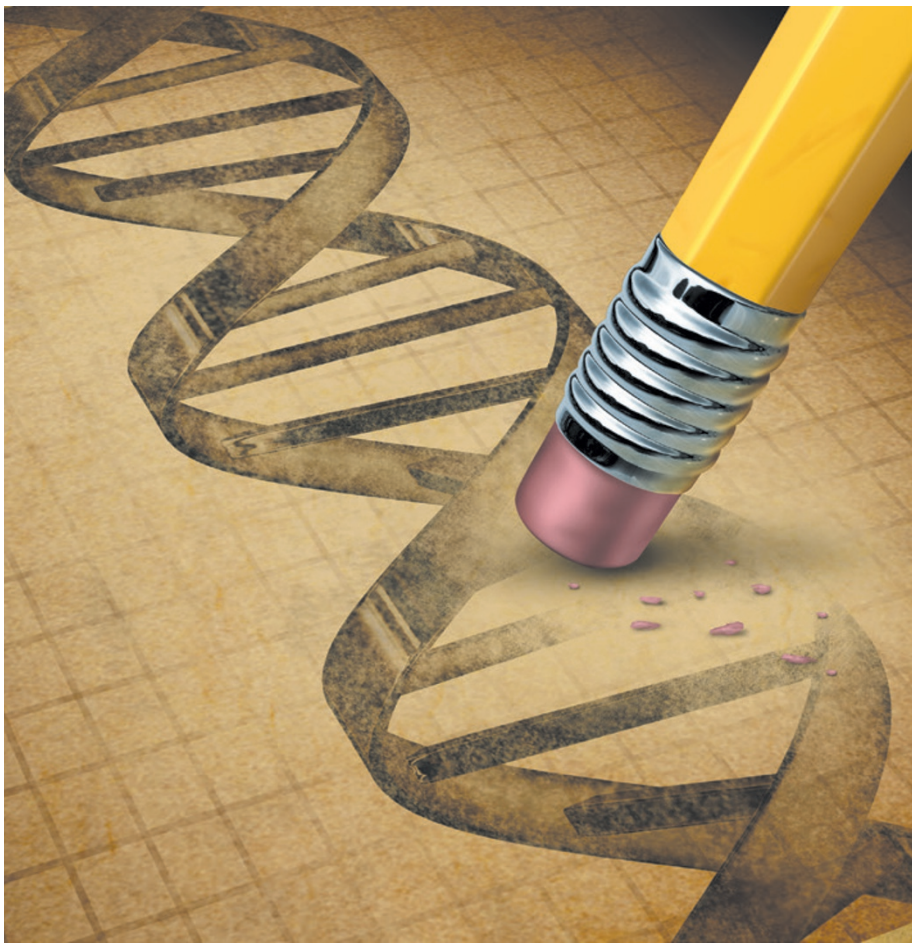

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MOLECULAR BIOLOGY

Genetic touch-ups

Simplified techniques have made the field of gene editing much more accessible to non-specialists.

BY JEFFREY M. PERKEL

Making precision changes in the genetic code of living cells has now become so easy that the power of genome editing can be harnessed by anybody with basic skills in molecular biology (see 'Learning the ropes').

The ease is mainly down to the development of two technologies that can be customized to target specific DNA sites. The technologies — known as transcription activator-like effector nucleases, or TALENs, and clustered regularly interspaced short palindromic repeats (CRISPR–Cas) — are both much simpler to use than earlier techniques and considerably cheaper and easier to make.

This combination means that the field of genome engineering is much more accessible than it was a few years ago, when it required advanced expertise in techniques such as protein engineering, DNA repair and ways to get nucleic acids into cells. The developments have opened up job opportunities along three axes: solving basic biological problems, developing improved technology and finding potential therapies for diseases.

Eric Hendrickson, a biochemist at the University of Minnesota Medical School in Minneapolis, says that the development of CRISPR–Cas was like an "earthquake" in the life sciences. He had spent years trying to perfect a more complex editing system, but migrated most of his work over to the CRISPR–Cas system within a few years of its development. Despite having been in the business for 30–35 years, Hendrickson says that he has never seen anything sweep through science as rapidly as CRISPR–Cas has.

The new ease in editing may be a double-edged sword, however, because what once was a rare skill set has now effectively become commonplace. "For the past decade, if you could go into any job interview and say, 'And by the way, I can do gene targeting,' that was always a big selling point," he says. Today, it holds much less sway.

But it has also boosted the field. Huimin Zhao, a chemical and biomolecular engineer at the University of Illinois at Urbana-Champaign, says that genome engineering is one of the most active subareas of synthetic biology, his research focus.

And Daniel Voytas, a plant researcher and director of the Center for Genome Engineering at the University of Minnesota, says that he screens postdoc applicants not for advanced editing skills but for what might be called genetic green fingers — the ability to genetically modify plant cells and grow them into functional plants.

TECHNICAL JUMP

Some techniques still require advanced expertise. Farjana Fattah, a postdoctoral researcher at the University of Texas Southwestern Medical School in Dallas, says that edits that replace one sequence with another require more technical know-how than those that simply knock out genes, for example.

Fattah developed the ability to make such complicated edits while she was doing her PhD with Hendrickson, and hopes to capitalize on it with a job in biotechnology.

Skills beyond genome editing, such as protein engineering, are also necessary for those interested in designing the next ▶

generation of editing tools. When hiring postdoctoral researchers for such projects, says geneticist George Church of Harvard Medical School in Boston, Massachusetts, he likes to see experience with genome editing or related technology, but it is not crucial. Scientific creativity is, however. "As we're trying to develop transformative, disruptive technologies, maybe there's a slightly higher emphasis on people who think out of the box and are willing to fail quickly and move on," he says.

Those qualities are also in demand at companies that develop commercial editing tools, such as Sigma-Aldrich of St Louis, Missouri. Sigma-Aldrich looks for candidates with skills in bioinformatics, cell culture and genotyping of recombinant cells and animals, says Greg Davis, the company's research and development manager for molecular biotechnology. But experience in using editing systems to make research tools is also a plus, Davis says. "Then you know that they understand the basics of the technology coming in. And they can be ready to implement it immediately or improve on it once they come into the company."

DEVELOPERS

Genome-editing technology is also becoming more popular in the therapeutics sector owing to its potential in reversing genetic disorders and aiding in drug development. AstraZeneca recently started looking for people for postdoctoral positions in precise genome editing in Sweden and the United Kingdom. Mohammad Bohlooly, associate director of research and development, says that the company uses genome-editing technology to create cell and mouse models for identifying and validating potential drug targets, and has ramped up its hiring of both postdoctoral fellows and research scientists.

"Maybe there's a slightly higher emphasis on people who think out of the box."

Sangamo BioSciences in Richmond, California, develops and uses the older zinc-finger protein (ZFP) technology to develop therapeutics. The company has grown from 80 to about 100 employees over the past few years as it moved into clinical trials, says Philip Gregory, chief scientific officer and senior vice-president for research.

The pool includes a large group of people who focus on protein design, Gregory says — a reflection of the fact that ZFPs are harder to work with than TALENs or CRISPRs — but the company is also interested in researchers who understand the processes of DNA repair and gene regulation and can apply those to therapeutics.

Smaller biotech companies are also growing. Editas Medicine of Cambridge, Massachusetts, will be adding a significant number of researchers in the next year or two, says chief operating officer Alexandra Glucksmann.

And CRISPR Therapeutics in Basel, Switzerland, anticipates ramping up its current base of half a dozen staff researchers and off-site consultants to a dozen or so staff researchers by the end of the year, says chief executive, Rodger Novak. It also plans to double that by the end of next year.

It is still too early to say whether genome editing will become a skill that, like PCR, most molecular biologists must learn, or a field of its own. But given the low bar to entry, it is a skill that savvy life scientists should consider learning and applying now, to get a jump on the competition. ■

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EDUCATION

Learning the ropes

The technical bar for genome editing is now relatively low: you need a basic knowledge of molecular biology, some bioinformatics skills and a good understanding of the mechanisms of DNA repair. "Anyone with even master's-level skills in molecular biology can understand the process of making the reagents and could get started on a genome-engineering project," says Daniel Voytas, a plant researcher and director of the Center for Genome Engineering at the University of Minnesota in Minneapolis.

But investment in mastering the process — and identifying problems to apply the techniques to — can yield new skills, potential collaborators and job opportunities. Many resources are now available to help researchers do just that, including web tutorials, short courses and conferences on various aspects of the technologies, particularly the newer ones, known as clustered regularly interspaced short palindromic repeats (CRISPR) and transcription activator-like effector nucleases (TALENs).

For the dedicated learner

Young researchers can establish genome-editing credentials by finding a compelling application in their own work: the tools are affordable and relatively easy to use. "Most labs would be delighted to have their graduate student do a CRISPR experiment as part of their thesis, and that makes them very hireable," says George Church, a geneticist at Harvard Medical School in Boston, Massachusetts. Opportunities for practical experience include:

- Workshop on CRISPR-Cas gene targeting in mice in Bar Harbor, Maine (5–7 November 2014)
  go.nature.com/eeydd6
- RNA Institute symposium on genome editing with CRISPR–Cas in Albany, New York (17–20 March 2015)
  go.nature.com/mzdr5h
- Wellcome Trust course on genetic engineering of mammalian stem cells in Hinxton, UK (16–28 February 2015)
  go.nature.com/ivpi5r

For the do-it-yourselfer

Here are some web-based resources:

- Practical guide to CRISPR
  go.nature.com/xb3zqm
- Webinar on genome editing with CRISPR
  go.nature.com/n7gezu
- Review of CRISPR–Cas systems
  go.nature.com/yve5vr
- CRISPR developments
  go.nature.com/cye5sr
- A video on how to use CRISPR–Cas9
  go.nature.com/9zku7j
- TALEN-based genome editing
  go.nature.com/pwfdcc
- CRISPR-based genome editing
  go.nature.com/vhzlog
- Review of genome editing
  go.nature.com/uulw1z
- Portal for designing CRISPRs
  go.nature.com/myqgyq
- Portal for designing TALENs
  go.nature.com/wxpdmv
- Genome-engineering resources
  go.nature.com/4vmv44

For the networker

Conferences are useful for making contact with academics and industry representatives who are knowledgeable about genome editing. A Federation of American Societies for Experimental Biology meeting in June provided many such opportunities, says biochemist Eric Hendrickson at the University of Minnesota Medical School in Minneapolis. Others include:

- Keystone Symposium on Precision Genome Engineering and Synthetic Biology in Big Sky, Montana (11–16 January 2015)
  go.nature.com/ij5xeh
- Cold Spring Harbor meeting on The CRISPR/CAS Revolution in New York (24–27 September 2015)
  go.nature.com/rbpkeb J.P.