CRISPR genome editing fuels cancer drug discovery

From Our Labs [2]

Author: Eric Bender

Every detail about cancer matters to Rob McDonald. The better his lab knows the molecular underpinnings of the disease, the better the odds of their colleagues discovering new medicines for patients. This explains the Novartis scientist’s excitement about CRISPR-Cas9 genome editing.

“CRISPR is a geneticist’s dream come true,” says McDonald, an expert in target identification for Oncology at the Novartis Institutes for BioMedical Research (NIBR), in Cambridge, Mass. “CRISPR enables us to do experiments that one could only dream of before.”

CRISPR has quickly captivated major scientific journals and the popular press for sparking a revolution in genetic engineering. While the ultimate prize is to eradicate diseases, the technology is already shaping how potential medicines for cancer and other conditions are discovered. NIBR has adopted CRISPR to research potential gene therapies and to identify drug targets.

Novartis researchers in Cambridge and Basel, Switzerland use CRISPR to quickly and precisely investigate thousands of genes related to cancer as potential drug targets. As performed, the effort would have been impossible without the genetic engineering technology. This allows these groups to ask and answer the question, “Is this gene required for the survival of this cancer?”

The technology gives these scientists a tool to home in on specific genes and make precise cuts or patch in new DNA. Compared with an earlier genome editing method called TALEN, the CRISPR system enables researchers to edit genes much more efficiently and 200-times less expensively. TALEN costs about $4,000 per gene and takes months longer to perform than using CRISPR.

“CRISPR is so flexible but also so cheap,” says Yi Yang, a research investigator in NIBR’s Developmental & Molecular Pathways group, whose lab investigates gene editing tools for many diseases.

Additionally, CRISPR offers two huge improvements over RNA interference (RNAi), a gene-silencing method. The first is that CRISPR can achieve complete protein loss as compared to only partial protein reduction via RNAi. The second comes from the improved specificity of CRISPR. While the field is still learning about the drawbacks of CRISPR, RNA interference research has historically been plagued by off-target effects that complicate the interpretation of experiments.
How long before CRISPR impacts cancer treatment? The technology improves the efficiency of cancer drug target selection, aiding decisions on which ones should advance to drug discovery projects, McDonald says.

Seeking answers about the roots of many cancers, scientists have started using CRISPR to study a large collection of cancer cells lines known as the Cancer Cell Line Encyclopedia (CCLE), developed jointly at NIBR and the Broad Institute of MIT and Harvard.

The researchers have also combined CRISPR with other molecular tools to study cancer gene mutations. As described in a March 2015 paper [3] in Cancer Research, Novartis’ Yang and others used CRISPR to attach short protein tags to several genes involved in cancer. The tagged genes create fused proteins that wither quickly unless a shield compound protects them.

Changing the amount of the shield compound mimics how an actual small molecule drug would inhibit the target at different doses—without spending months or years to craft a small-molecule compound targeted to the gene. CRISPR enabled the application of the Degron-KI approach (originally developed by Tom Wandless’s lab at Stanford) to study these genes in a tunable fashion.

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Bill Sellers, Global Head of Oncology at NIBR

It’s CRISPR’s world

CRISPR “is on fire; it’s really taking over cancer biology and many other aspects of biology,” noted Tyler Jacks, Director of MIT’s Koch Institute for Integrative Cancer Research, in a speech [4] at the American Association for Cancer Research annual meeting in April 2015.

Researchers in the Jacks lab, for example, found that CRISPR manipulation let them directly introduce multiple tumor-inducing mutations in normal mice, bypassing the slow and painstaking tasks of genetically engineering mice and then cross-breeding them over generations. Testing hundreds of mutations in mouse models of lung cancer, “in a six-month period we could do things that probably would have taken us four or five years, and I can’t tell you how many dollars, to carry out,” he said.

Of course, as with all genetic tools, “there’s a lot of room for improvement with CRISPR,” Yang notes. Among its drawbacks, CRISPR doesn’t work with all genes and it sometimes attaches to off-target DNA. The Yang lab is among many around the world rapidly developing alternative versions of CRISPR that better address these problems, cleanly activate gene expression or repress them without cutting them, or bring other advantages.

Beyond work in cells and animal models, “the race is on to see who will be first to push CRISPR into clinical applications,” says Yang.

For example, CRISPR could enhance the CAR-T (chimeric antigen receptor T) cell treatments
that have achieved striking early success against certain blood cancers. NIBR’s Immuno-
oncology researchers collaborate with Intellia Therapeutics to study whether CRISPR might
provide better overall control for tweaking CAR-T cells. It also might offer improved ways to
turn off cell activity if patients have an overly strong immune reaction, or to add other
immunotherapy weaponry, he speculates.

“CRISPR is going to revolutionize our understanding of genetic function,” Bill Sellers, Global
Head of Oncology at NIBR, sums up. “And it’s going to massively change how we target
cancer therapeutically.”

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