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Can we edit our genes to fight disease?

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Imagine trying to find and correct a single typo in a novel that's 2.3 million pages long—more than 3,000 times the length of Moby Dick—without computer software. Scientists face an equivalent task when editing the human genome, which contains approximately 3 billion pairs of DNA "letters." An emerging tool called CRISPR makes the job easier. And it's inspiring researchers to pursue new therapeutic programs.

Think of CRISPR as a pair of molecular scissors that's capable of snipping DNA. The tiny shears are combined with an RNA-based targeting molecule that scans the genome for specific sequences and makes a controlled cut at a single site. Novartis recently entered a collaboration with Intellia Therapeutics, a startup biotechnology company, to sharpen this powerful tool for patients.

"We're planning to modify human cells outside the body and then put them back into patients to treat a number of diseases, beginning with certain cancers and hematologic disorders," says Craig Mickanin, who leads a technology-based group at the Novartis Institutes for BioMedical Research (NIBR) within the Developmental & Molecular Pathways department. "We'll be at the forefront of using CRISPR for clinical validation of gene editing."

The team is exploring how CRISPR can enhance a program that Novartis runs in collaboration with the University of Pennsylvania to reengineer T cells and unleash them on cancer in patients. These chimeric antigen receptor (CAR) T cells—ninjas by design—recognize a marker that's unique to the surface of cancer cells and launch an attack.

In early phase clinical trials, the investigational treatment is proving most effective in pediatric patients with acute lymphoblastic leukemia (ALL), generating complete remissions in 36 of 39 children with the relapsed/refractory form of the disease as of late 2014. It's also showing promise in many adults with chronic lymphocytic leukemia (CLL), although the response rate isn't as high. Perhaps the T cells could be modified further to improve efficacy in adults—and to extend the treatment beyond blood cancers to solid tumors.

"There are a number of challenges that we face with the CART program going forward, and we view gene editing as one of the possible solutions," says Phil Gotwals, who leads a CART group at NIBR.

CRISPR also holds potential for the treatment of certain hematological disorders, where defective blood cells can be removed, edited and then returned to patients.

The rise of CRISPR

CRISPR isn't the only gene editing system, but it's the newest and offers several apparent advantages.

Targeting molecular scissors to specific sites in DNA is hard, and each editing system has a different way of doing so. With CRISPR, the targeting is accomplished through an RNA template that matches the DNA to be cut.

"The key advantage of the CRISPR-Cas9 system is that it relies on RNA to recognize specific DNA sequences and direct the cutting machinery," explains Mickanin. "We can quickly and easily design RNA guide

sequences. Then the cutting is done with Cas9, a protein."

Bacteria use a CRISPR-like system to kill invading viruses. In fact, that is where it was discovered. Jennifer Doudna at the University of California, Berkeley was the first to modify the system for use in eukaryotic cells. Labs around the world, including in NIBR, subsequently have used CRISPR-Cas9 to engineer cell lines and animal models. Therapeutic applications are the logical next step.

"The goal is to build and test multiple therapeutic candidates and then rapidly translate our research into potential treatments for patients."

Safety is top of mind for the Novartis/Intellia team members, so the team will start with ex vivo editing outside the body, which allows for more control. After human cells are modified, the researchers can run them through a battery of tests to ensure that they meet stringent requirements before administering them to patients. If all goes well, in vivo editing might be on the horizon.

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List of links present in page

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3. https://prod1.novartis.com/stories/rebuilding-blood