Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/crispr-in-sickle-cell-transforming-care-through-gene-editing/36233/

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CRISPR in Sickle Cell: Transforming Care Through Gene Editing

Announcer:
This is *Project Oncology* on ReachMD. On this episode, we'll hear from Dr. Alexis Leonard, who works in the Department of Hematology at St. Jude's Hospital in Memphis, Tennessee. She'll be discussing using CRISPR to treat sickle cell disease.

Here she is now.

Dr. Leonard:
CRISPR came along in 2012; that was our first reports of using CRISPR technology to create double-stranded breaks in the genome and repair certain genes—for example, the sickle mutation—or create insertions or deletions, more specifically in this case, for increasing fetal hemoglobin in a patient with sickle cell disease. This was discovered by Jennifer Doudna and Emmanuelle Charpentier, for which they received the Nobel Peace Prize. And so, when you see the historical landscape of gene therapy for sickle cell disease, the trials using CRISPR to increase fetal hemoglobin came along about five years after starting the trial using lentiviral gene therapy—so this is around 2018 or so—after we had been able to really use this therapy in preclinical studies and show that it was effective in increasing fetal hemoglobin. And in sickle cell in particular, we know that patients who carry a genetic mutation in their gamma globin genes and have what's known as hereditary persistence of fetal hemoglobin, along with their inherited sickle mutation, in general, those patients do not have disease complications. So it was natural to want to use CRISPR technologies to mimic those patients and genetically modify the cells such that they now make very high levels of fetal hemoglobin, which is the strategy that's employed by Vertex for the exa-cel gene therapy products.

Now, CRISPR, obviously, is new, but it is exceptional at finding exactly where you want to go in the genome. And what we have seen so far in terms of risks—and we certainly have more to learn and to study, but it does appear safe—the concerns that we think about, number one, even though we can use a guide RNA to get the CRISPR to exactly where we want it, there is certainly possibility of off-target effects, so it cuts someplace we don't want it to cut. Cells probably don't like it when there are double-stranded breaks artificially, and they have to repair those, so there are certainly always risks as the cell repairs those double-stranded breaks. And then right now, how we get CRISPR and the machinery that we need into the cells—the hematopoietic stem cells—is fairly toxic to those cells, and so one of the issues we have clinically is that we need to collect a lot of stem cells from patients. And in general, we need to collect more stem cells for patients that are receiving gene therapy using CRISPR than patients who are receiving lentiviral gene therapy. Now, there are still toxicities when you use lentiviral strategies, but the toxicity seems to be higher with the strategies that use CRISPR, and so patients need to collect a lot of cells to account for the losses that occur when we wash and purify and then deliver the CRISPR to ultimately get a product that is sufficient in number back to the patient.

Announcer:
That was Dr. Alexis Leonard talking about using CRISPR to treat sickle cell disease. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!