of isomers with potentially varying efficacy created by other oligonucleotide chemistries. “When you’re looking at the efficiency of exon skipping of a mix of isomers, the readout is an average across isomers,” says Michael Panzara, Wave’s chief medical officer. “Stereochemistry enables us to produce and optimize the isomer we believe performs best.” A phase 1 study of Wave’s exon-51-skipping therapy WVE-210201 (suvodirsen) was recently completed and treatment in an open-label extension study is ongoing.

Down the line, the much-vaunted CRISPR–Cas9 gene-editing technology will most likely step in. CRISPR has already been used with success to skip dystrophin’s exon 23 in the mdx mouse model of DMD, and Eric Olson of University of Texas Southwestern Medical Center, who founded and serves as a chief scientific advisor to Exonics Therapeutics, has also used CRISPR to restore dystrophin expression to 90% of wild type in a mouse model of DMD with a deletion in exon 50, a common mutation in humans.

Much like exon skipping agents, CRISPR corrects how the mutated dystrophin gene is read to produce a shortened but functional protein. Though it cannot fix large deletions in essential parts of the dystrophin gene, particularly the two ends, that still leaves a lot it can do. “In principle, CRISPR can correct up to 80% of DMD mutations,” says Olson. These are essentially the same 80% of DMD mutations that can be targeted with exon skipping. “Patients who can be treated with exon skipping can be treated with CRISPR,” says Olson.

Olson’s group has also restored dystrophin expression in a dog model carrying a mutational ‘hotspot’ in the DMD gene similar to that found in humans. The team used AAV gene to deliver CRISPR gene editing tools, which boosted skeletal muscle dystrophin expression to 3% to 90% of normal depending on the muscle type.

Unlike exon skipping, which requires ongoing treatment, gene editing with CRISPR offers the potential of a one-time fix—although it also comes with the concerns of on-target and off-target

changes. In a mouse study at the Ohio State University Wexner Medical Center, a single intravenous dose of AAV-CRISPR restored dystrophin production and was still present a year later. “This correction is sustained, albeit it at low levels, over an extended period of time and I think that’s really good news,” says Olson, who was not involved in the work.

As the current crop of genetics-based DMD therapies move through clinical development, none of the therapies for DMD in development is positioning themselves as a cure for DMD. All share the more realistic goal of shifting boys and men from a severe DMD phenotype to something resembling the milder Becker muscular dystrophy—a change in clinical picture that would vastly improve patients’ quality of life, and potentially add decades to their life expectancy. □

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Around the world in a month

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