These Drugs Are So Futuristic That Doctors Need New Training

Next-generation treatments on the way for once-incurable diseases can be complicated to test and administer; 'if we can't get it to these patients, the science is lost'

By Amy Dockser Marcus

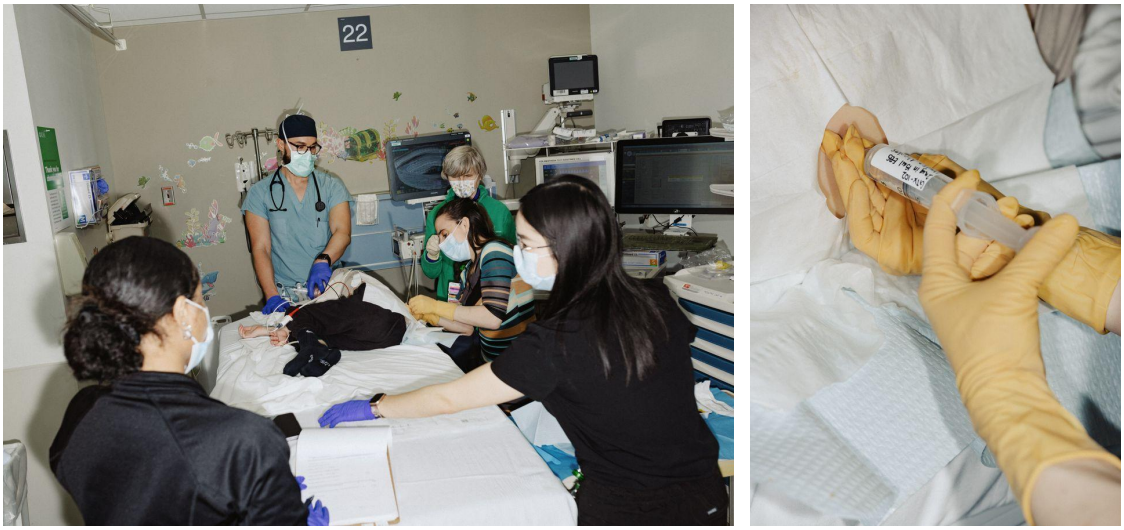
A major obstacle looms for the drugs of the future. Not enough doctors know how to administer them.

For just one rare neurodevelopmental disorder, known as Angelman syndrome, clinical trials are testing four cutting-edge therapies. Twenty more research programs are under way and could yield treatments ready to move into human testing in the next several years, according to Allyson Berent-Weisse, chief scientific officer of the Foundation for Angelman Syndrome Therapeutics, or FAST, and the mother of a child with the disorder.

These promising therapies include antisense oligonucleotides (or ASOs) which affect how proteins inside cells are made; Crispr gene editors that can cut, rewrite, or replace faulty genes; and other novel approaches.

But there's a hitch. Some of these drugs, as well as therapies in development for other conditions, are administered through lumbar punctures, which aren't a routine part of doctors' daily practices. They may involve infusions of a gene packaged inside the shell of a virus, which can lead to potential immune complications and can require close monitoring of patients. Some drugs need to be stored in special conditions, which can take complicated planning and coordination that few doctors have experienced.

"The bottleneck used to be the science and finding drugs," says Dr. Berent-Weisse. "The new bottleneck is having enough people trained to give them."



Dr. Berry-Kravis (in bright green top) trains a doctor to give an ASO to a patient with Angelman syndrome at Rush University Children's Hospital. Right, a closeup on the technique.

That's bringing new efforts to address the problem.

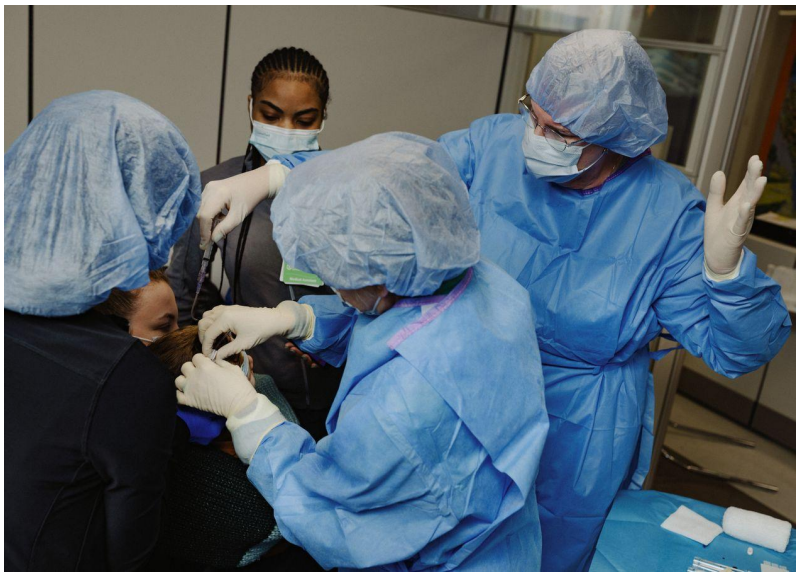
Kite, owned by Gilead Sciences Inc., runs a qualification program that takes around six months for doctors and centers interested in administering the company's CAR T-cell cancer therapy, Yescarta. The therapy, which received Food and Drug Administration approval last year for second-line treatment of adults with a type of lymphoma, involves re-engineering patients' cells and must be stored at minus 150 degrees Celsius (minus 238 degrees Fahrenheit) until it is ready to be used. If the re-engineered cells don't stay frozen during transport and if they aren't thawed in water whose temperature is constantly monitored to remain "not too hot and not too cold"—called the "water bath" method—the therapy can't be infused into the patient, says Deidre Hobbs, vice president of quality at Kite.

"We have groundbreaking science that can change the lives of hematology patients, but if we can't get it to these patients, the science is lost," says Warner Biddle, ad interim head of Kite and global head of commercial.

Spark Therapeutics Inc., a member of the Roche Group and maker of a gene therapy called Luxturna, which the FDA approved in 2017 to treat an inherited retinal disease that can lead to blindness, designated special centers where retinal surgeons receive instruction manuals and hands-on training in how to give the treatment. The surgeons must administer Luxturna through a single injection into the back of each eye, under the retina. "Given the one-time nature of gene therapy, Spark is committed to providing the resources necessary to deliver safe and effective treatment to patients," a company spokesperson said.

FAST, set up in 2008 by parents hoping to hoping to find a cure for Angelman syndrome, which affects children and adults, is providing $5 million to establish a center at Rush University Medical Center in Chicago, Ill., where doctors will receive training on how to run clinical trials and deliver therapies. The disease, caused by the loss of a functioning copy of the gene UBE3A that makes an important protein in the neurons, leaves patients unable to speak and can cause seizures and severe sleep disturbance.

The techniques will apply to other neurodevelopmental disorders, which often use similar treatments. After a year of practice and hands-on experience, the doctors can go back to their own centers and train others, says Alana Newhouse, FAST's president and the mother of a son with Angelman syndrome. Additional money is available for doctors interested in pursuing shorter stints at Rush in order to get practical experience with administering cutting-edge medications, Ms. Newhouse says.



Many doctors recognize that delivering cutting-edge drugs to patients isn't only a science but also an art, says Dr. Berry-Kravis, at right.

The training program will be run by Elizabeth Berry-Kravis, a pediatric neurologist at Rush University who will also serve as the director of the new center, called the Rush Pediatric Neurosciences F.A.S.T Center for Translational Research. Dr. Berry-Kravis is administering novel therapies to patients with neurological disorders including Angelman syndrome, fragile X syndrome, Batten disease, Niemann-Pick disease Type C, and others.

"Doctors are trained to see patients in the clinic. They are not trained in how to open a trial or how to navigate a contract or how to deliver drugs through intrathecal procedures," says Dr. Berry-Kravis. "We will train them. The doctors will get those skills. They will be ready to go out and mimic what we are doing."

Many doctors recognize that delivering cutting-edge drugs to patients isn't only a science but also an art, she says. "There are little techniques involved when giving infusions." When inserting the needle for an infusion into a patient's lower back, direct it toward the brain, for instance. Put patients head-down to let gravity help pull the drug to the brain, she adds, or in some cases use larger volumes in order to push more drug to the brain.

Hospitals often don't have enough space and support staff to rapidly enroll people, or doctors and specialists to administer the drugs, says Dr. Berent-Weisse, who helped devise the idea for a training program based on her own experiences and after speaking with doctors about some of the obstacles they were facing in enrolling patients.

One of the trials already under way at Rush for Angelman syndrome involves GTX-102, an ASO therapy being developed by Ultragenyx Pharmaceutical Inc. Dr. Berent-Weisse is a paid consultant to Ultragenyx.

Emil Kakkis, the CEO of Ultragenyx, says the company has struggled to find enough sites that have doctors and specialists, like pharmacists and anesthesiologists, who know how to open trials and prepare and administer GTX-102. "It is smart to set up training now so there will be a society of doctors in the future who can someday use these drugs," said Dr. Kakkis.

Dr. Berry-Kravis, left, with a patient and mother. Rush University Medical Center hopes later this year to kick off the training program that she will run.

FAST is also considering opening a training center at Yale School of Medicine. As part of that effort, Yale will send someone to take part in the inaugural program at Rush, according to Yong-Hui Jiang, chief of medical genetics and a professor at

Yale School of Medicine. Rush hopes to kick off the training program later this year.

Dr. Jiang, a specialist in the evaluation and treatment of neurodevelopmental disorders such as Angelman syndrome, says many families come to see him for a diagnosis—and ask about potential treatments after they receive it.

In his own lab, Dr. Jiang is working on Crispr gene-editing therapies that he hopes will someday be available for Angelman patients and to treat other rare conditions as well. He and some colleagues founded a company, Couragene, and hope to eventually sponsor a Crispr trial.

Exciting new treatments are ahead, Dr. Jiang tells the families who seek his help. When it comes to delivering them, he acknowledges, “We are all learning together right now.”

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