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Made In China Gene Therapy A Father's Quest To Save Son With UltraRare Condition

A Journey Towards Gene Therapy For Ultra Rare Diseases In China

by Brian Yang

Patient-driven drug development meets the old saying of "where there's a will, there's a way" in China, potentially the world's largest market for rare disease treatments.

When Jian Shu's son Yue first started walking, he noticed that there was something not quite right, as the baby boy seemingly could not keep his body in balance.

Jian took Yue, whose name means happiness in Chinese, to see a doctor, who could not find what was wrong so ordered a gene sequencing test. The result showed that Yue had a type of progressive muscular dystrophy, a rare genetic condition that is usually inherited from a female carrier. But this was puzzling for Jian because when both he and his wife had gene testing they were found not to carry the gene that causes the condition. The reason why their son had dystrophy remained a mystery.

The most common form of muscular dystrophy, Duchenne muscular dystrophy (DMD) affects roughly one in 3,500 newborns, mostly boys. Symptoms start to show from age two and as the condition progresses, most boys have weaker muscular function compared to their peers and by 12 years old they usually lose the ability to walk. Most DMD sufferers die by the age of 20 to 30 due to respiratory function or heart failure.

There was no available treatment for DMD until 2016, when the US FDA approved *Sarepta Therapeutics Inc.*'s Exondys 51 (eteplirsen) for patients with the exon 51 skipping gene mutation. Later, another drug Imflaza (deflazacort), developed by *Marathon Pharmaceuticals LLC* and later acquired by Sarepta Therapeutics Inc., gained approval.

There was still no cure for DMD, but hope started surfacing after several companies began testing experimental gene therapies in humans, notably *Pfizer Inc.* with PF-06939926, Sarepta and rAAVrh74.MHCK7.micro-dystrophin, jointly developed with the Nationwide Children's Hospital, and *Solid Biosciences Inc.*'s SGT-001.

This May, a breakthrough for gene therapy in general came when the US FDA granted the green light to *Novartis AG*' Zolgensma (onasemnogene abeparvovec) for another rare dystrophy, spinal muscular dystrophy. Developed by *AveXis Inc.*, acquired by Novartis last year for $8.7bn, it was the first such treatment approved for a muscular disorder. But is also came with a steep price tag, of $2.1m for the one-time treatment. (Also see "*It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug*" - Scrip, 24 May, 2019.)

Gene Therapy Gains Prominence

Back in China, when Yue's condition progressed, Jian kept looking for answers and eventually learned about a company in Beijing developing vectors used in gene therapies for rare conditions. With a population of 1.3 billion and a large patient pool with rare genetic conditions, it is believed that China will need to develop its own gene therapies, given that such imported products will be simply too costly for what is a largely self-pay market.

This journey will not be easy. Firstly, there needs to be a clear and well-defined regulatory pathway, a necessity for any gene or cell therapy to get approved and launched in any given market. In China, there is currently a confusing "two-track mechanism" for such emerging technologies. This means that both qualified hospitals and biopharma firms can develop therapies, but under two separate regulatory oversight systems. For hospitals, the National Health Commission now oversees all matters governing how such products are developed. The National Medical Products Administration issues rules on how drug companies can develop cell and gene products.

The confusing system has industry regulatory professionals worried that it will lead to lowered quality, redundant costs and wasted investment.

The Beijing vector company, FivePlus Molecular Research Institute, started out as a research service provider and in 2015 re-positioned itself to focus on the development of vectors, which carry and deliver re-engineered genes back into a patient's body. Not long after it started developing an adeno-associated virus (AAV), FivePlus began collaborating with a physician in Wuhan-based Tongji

China's Draft Cell Therapy Guidelines Draws Concern From Industry

By Brian Yang

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New draft guidelines could potentially create

Hospital, a top Class AAA facility in China's central metropolitan area. An eye doctor named Bin Li had specifically asked the company to develop a vector for an experimental study treating patients with Leber's hereditary optic neuropathy.

FivePlus was developing various vectors and AAV had shown superiority due to its safety profile. Physician Li came knocking on the door with the single aim of developing a gene therapy to treat the form of neuropathy, a genetic condition that leads to blindness. After initial trial and error, the study seemed to yield promising results. Between August 2011 and December 2015, a total of nine patients received the treatment at Tongji Hospital, following successful animal experiments. A three-year follow-up of the trial found no serious safety problems and "the results support the use of intravitreal rAAV2-ND4 as an aggressive maneuver in our clinical trial," noted a research paper summarizing the study published in *EBioMedicine in* August 2016. The encouraging results gave FivePlus's founder Xiaoyan Dong confidence to take on the case of Jian's son, who turned out to have a condition so rare that the diagnosis took a toll on the family and the father's quest to find a cure.

parallel clinical pathways for cell and gene therapies in China, and industry executives are worried about different standards for such emerging treatments in a country with the highest number of ongoing cell therapy trials in the world.

Read the full article here

In 2016, gene therapy and its clinical use again entered Chinese researchers' consciousness when the Western China Hospital in Chengdu started the world's first CRISPR gene editing experiment in humans, treating lung cancer patients.

One in 10 Million

When Jian took Yue to visit FivePlus's office in Etown, a suburb of Beijing, his son was finally diagnosed with Emery-Dreifuss muscular dystrophy (EDMD), one of nine forms of muscular dystrophy. The diagnosis came after multiple trips to physicians and rounds of tests. Soon after taking on the case, FivePlus researchers started a primary document review on EDMD and related potential treatment options. In the meantime, the boy's whole gene sequencing results were sent out to other medical specialists in muscular dystrophies both inside and outside China.

China Surprises With First CRISPR Trial Despite Regulatory Lag, Concerns

By Brian Yang

25 Jul 2016

The lack of a comprehensive regulatory pathway has not hindered Chinese researchers from forging ahead with the world's first human clinical study using CRISPR-Cas9 gene editing technology, which will be used to treat advanced lung cancer.

Read the full article here

After further and closer examination, Yue was eventually found specifically to have reducing body myopia (RBM) with FHL1 mutation. If EDMD is a rare muscular dystrophy, RBM is so rare that there are few known cases around the world. After the diagnosis, Jian combed China to find other patients, and so far has found two other families with sufferers. In the US, the total known number of RBM cases is reported to be in the 30s, putting the occurrence rate at roughly one in 10 million.

Help From US Facilities

Due to its ultra-rare nature, RBM has attracted the attention of very few researchers around the world, posing an additional challenge to FivePlus researchers scouting for an animal model. Of two prospects they have found, only one has given them some hope. The Ju Chen Lab at the University of California San Diego (UCSD) was one of the places in the world conducting preclinical research on RBM with the FHL1 mutation. Professor Chen, upon being approached by the FivePlus Beijing team, agreed to provide rats from the lab for FivePlus to conduct the research.

After rounds of email communications and a payment to the school for the animals, a batch of FHL1 gene knockout mice generated in the US laboratory started their journey to China's capital.

Other than the UCSD team, the handful of physicians globally specialized in RMB included Carsten Bonnemann at the Philadelphia Children's Hospital in Pennsylvania, who spends part of his time conducting research at the National Institutes of Health in Bethesda, MD. With slim hopes, Jian decided to seek out Bonnemann's help in diagnosing and treating his son, the determined father undaunted by the huge distance between Hangzhou and Philadelphia.

Working a job at a large national grocery chain in China, Jian had an insurance policy with China Pingan Insurance Co., which luckily covered his trip to seek medical help overseas. After days of back-and-forth arrangements, Jian embarked on the long-sought journey to take Yue to see Bonnemann.

Again, the diagnosis was confirmed. "The mutation that was found is very convincing for this diagnosis and I have no doubt that it's correct," noted the physician. But the diagnosis also came with feelings of hopelessness. "It is very important that the family understand that sadly there currently are no treatments for this disease, in other words, even here at NIH there is no clinical treatment trial for reducing body myopathy," the physician stressed.

But the effective sentence of "no cure, no hope" from one of the most authoritative voices on RMB still did not deter Jian, who by then had signed on FivePlus to test an experimental gene therapy for an ultra-rare condition for which even the world's most prestigious research institute had no treatment options.

Research Setback

Months after the November day when Jian came to FivePlus and signed the research agreement, the batch of RBM rats from UCSD arrived in China in March. After one month of quarantine and rounds of documents, the animals finally arrived at the company's lab.

According to a research paper published by the UCSD team, the rats need to reproduce to ensure sufficient numbers to perform studies, but in China there was nowhere to find suitable mates, so alternatives had to be found. Soon the number of RBM rats expanded to dozens, but strangely they did not develop the condition and die within a certain period as planned. Later research also confirmed the rats failed to develop RBM.

The unexpected results had researchers puzzled, so they started communicating with the UCSD team about the results but no real progress was made. The experimental work thus came to an abrupt halt in June. Seeing no path forward, FivePlus decided to end the project pending a new approach to salvage it. Facing a backlash, the Beijing company reconsidered its decision to tackle some ultra rare conditions, despite the early success with hereditary optic neuropathy.

For Yue's condition, his particular mutation has its challenges. There are distinct splice variants of FHL1, namely FHL1A, FHL1B and FHL1C and the boy's mutation was found to lie in between the variants.

General Challenges

More generally, gene therapy itself remains a complicated process. The eagerness to develop breakthrough technology and to be recognized as a global pioneer among many young Chinese researchers has also caused some concern over the speed and ethical practices involved in gene therapy and editing research in the country.

Last November, Jiankui He from the Shenzhen-based Nanfun Institute of Technology shocked the world with an announcement of the birth of the world's first gene-edited babies. Amid a global outcry over the lack of sufficient ethical clearances and peer reviews, China significantly tightened oversight of gene research studies. (Also see "*China Tightens Clinical Trial Oversight Post Gene-Edited Babies Scandal*" - Pink Sheet, 28 Feb, 2019.)

Gene therapy is not simply a drug product

How One Rogue Scientist Could Sink Global Gene Therapy Progress

By Brian Yang

30 Nov 2018

Amid a global uproar denouncing a Chinese scientist's work to deliver gene-edited twin babies, worries emerge that other valuable future research in the area could be put on hold, effectively crippling industry experts

but is more akin to a surgical process, noted Xiaobing Wu, founder of the FivePlus-associated Ruixi Gene Technology Research Institute. One of Ruixi's early backers included the mother of a young girl with Sanphilippo syndrome, and since then the institute has taken on spinal muscular atrophy and other rare neuromuscular conditions.

and researchers.

Read the full article here

Many uncertainties still surround gene therapy as an emerging treatment modality, and researchers and patients must prepare for these.

Hope Remains For Yue

NIH researcher Bonnemann agreed that for RBM research further studies to gain a better understanding of the disease's mechanism may be the best way forward. "We are currently trying to understand the 'natural history' of the disease and investigate the MRI [magnetic resonance imaging] appearance of the disease, but again, sadly at this time we have no treatment to offer," noted the specialist.

However, Jian is refusing to throw in the towel just yet, and said he was in discussions with other researchers to find a new gene therapy to treat his son's condition. Despite the setbacks, being told there is no cure by a medical expert and facing large out-of-pocket expenses, the father said he had no regrets. His quest to find a cure for his son lives on.