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The **INTRIGUING ORIGINS** Of A Gene Therapy Biopharma

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The first few years of a company's history are usually filled with some unusual — and intriguing — milestones. Voyager Therapeutics is no exception.

Founded in February 2014, the company took the difficult path of pursuing treatments for debilitating diseases such as ALS and Parkinson's. It planned to do so with science rooted in the burgeoning field of gene therapy. Again, not a common or easy choice. But Voyager's science looked so promising early on that Third Rock Ventures, a VC firm focusing on biotech startups, not only invested $45 million to get the company up and running, but even provided an interim CEO in the form of industry heavyweight Mark Levin, cofounder of Third Rock, who had 30+ years of experience launching and building biopharmas.

Intriguing.

It didn't stop there, though. About a year later, another Third Rock executive, Steven Paul, M.D., took over as CEO. Paul brought more than 35 years of neuroscience expertise and an extensive track record in CNS drug discovery and development, specifically as president of Lilly Research Laboratories. On Nov. 11, 2015, Voyager achieved one of those early milestones when it raised $70 million via an IPO.

So, over $115 million raised and two high-profile CEOs from one of the hottest VC firms around, all in less than two years? I was definitely intrigued, so I reached out to Paul to find out more.

THE PROCESS OF FOUNDING VOYAGER THERAPEUTICS

"I think gene therapy's time has come," Paul says matter-of-factly after I ask why he would step away from his advisory role to lead Voyager full time. That prediction about gene therapy, he explains, is based on three years of research by Third Rock during which they spoke with dozens of gene therapy scientific experts. "We're primarily interested in investing in highly innovative companies, and we wanted to explore whether or not gene therapy was the right kind of investment for our firm."

Part of that exploration involved Third Rock holding a minisymposium where they invited a number of the leading experts in AAV (adeno-associated virus) gene therapy. During the meeting, it became clear that developing a company around AAV gene therapy was an intriguing opportunity, and so Third Rock set out to find people who could serve as founders. "We wanted not only gene therapy experts, but also the leading scientific KOLs, and we ended up pulling together a very strong team," he explains. That team consisted of the following four founders:

- **KRYSTOF BANKIEWICZ, M.D., PH.D.** — Kinetics Foundation Chair in Translational Research and Professor in Residence of Neurological Surgery and Neurology, University of California at San Francisco (UCSF)
- **GUANGPING GAO, PH.D.** — Director, University of Massachusetts Medical School (UMMS) Gene Therapy Center & Vector Core; Scientific Director, UMMS-China Program Office; Professor of Molecular Genetics and Microbiology, UMMS
- **MARK KAY, M.D., PH.D.** — Dennis Farrey Family Professor, Head, Division of Human Gene Therapy, Departments of Pediatrics and Genetics, Stanford University School of Medicine
- **PHILLIP ZAMORE, PH.D.** — Howard Hughes Medical Institute Investigator; Gretchen Stone Cook Chair of Biomedical Sciences, Professor of Biochemistry and Molecular Pharmacology, and Chair of the RNA Therapeutics Institute, University of Massachusetts Medical School (UMMS)

According to Paul, the founders made many seminal contributions to Voyager. "They provided expertise on AAV biology, gene-silencing artificial microRNA cassette technology, and many of the viral capsids for delivering genes into the central nervous system." They also helped determine what diseases were ripe for gene therapy. "Krystof Bankiewicz had done some very nice academic studies on Parkinson's disease at UCSF," Paul notes. "We liked the data generated and felt we could optimize, in particular, the delivery and dose of the gene therapy vector Krys [Bankiewicz] was delivering." (Voyager's lead program, VY-AADC for advanced Parkinson's disease, is in a Phase 1B study, and the company anticipates beginning a pivotal Phase 2/3 program and dosing the first patient during the second quarter of 2018.)

After assembling this group, Third Rock spent well over a year determining the elements for what a successful gene therapy company would look like. "In our case, we wanted to engineer these AAV vectors, because we knew the first generation of vectors, while good enough to get Voyager up and running as a company, were probably not going to be the be-all and end-all for delivering genes to the brain and spinal cord," he states. "In fact, we've come up with and in-licensed some extraordinary new AAV capsids that can deliver genes to the brain and spinal cord much more efficiently than the first-generation capsids."

TO INSOURCE OR OUTSOURCE?

One of the next things they had to do was decide how best to manufacture their viral vectors. "Unlike monoclonal antibodies and small molecules, it's not easy to find a CMO that can produce the type of gene therapies being developed at Voyager," says Paul. As a result, in the early days the company was intent on developing its own in-house capabilities to produce and manufacture its AAV vectors, not only for research studies in animals, but in human clinical trials, as well. That decision would change, though, over time. "We decided that owning our own commercial manufacturing facility would not be the most efficient use of capital," Paul explains. Instead, the plan was to own the process and export it to select CMOs, a plan still in use today.

"For us, the CMO selection process began by involving some of our internal technical experts familiar with Voyager's production process platform," Paul relates. "Then we met with multiple CMOs starting to get involved in viral vector manufacturing." Some of those had been in the field of gene therapy, but not many had been involved in AAV. A lot of the AAV work had been done in academic settings, such as Children's Hospital of Philadelphia (CHOP) and Nationwide Children's Hospital in Columbus, OH. "These facilities had very strong AAV gene therapy programs and, as a consequence, had developed their own manufacturing capabilities." Though high quality, Paul believes these centers probably could not get to commercial-grade very easily and might not even want to. "We use a very scalable process that was perfected by one of our founding scientists involving the use of baculovirus Sf-9 insect cells," he states. As such, the company wanted to have close contact with any CMO selected so that internal production team could clearly communicate its process.

Mass Biologics' relative close proximity to Voyager was one of the primary drivers behind it being selected. Good timing also played a role in this decision, as the CMO had recently opened a new manufacturing facility in Fall River, MA. "This afforded us an opportunity to collaboratively build the internal facility with the bioreactors and layout we desired," Paul shares. Since then, Voyager has initiated its first cGMP production campaign for viral vectors for its Parkinson's program. "We have produced a number of GLP lots of this vector at 200-liter scale and are in the midst of developing the GMP vector for the pivotal trials for our Parkinson's study," notes Paul.

MORE INTEREST = MORE OPTIONS FOR GENE THERAPY MANUFACTURING

While Voyager feels good about where it is presently regarding manufacturing, it has been exploring other potential CMOs to work with for its commercial vector program. "We anticipate using the same fundamental process we have developed thus far with Mass Biologics," he says. "But since we first started Voyager, a lot more CMOs have become interested in the field of gene therapy."

However, according to Paul, there is something as or even more important than choosing the right CMO for its future commercial business. "We think what's important is investing in process R&D (i.e., improvements made over time to the Voyager manufacturing process) to make it as efficient and scalable as possible," he says.

"Many processes, whether for insulins, antibodies, or small molecules, need to improve and become more efficient over time, and that's what we're doing right now with our gene therapy manufacturing process." In other words, no matter what CMO Voyager selects for commercial manufacturing, it is incumbent to first have a well-defined and efficient production and manufacturing process and to be able to effectively communicate this process and work closely with a CMO, if it expects a CMO to be able to execute its plans. L

A PRIMER ON GENE THERAPY

We asked Steven Paul, M.D., CEO of Voyager, for a brief overview on gene therapy (for not all of us can claim to be scientists). "Gene therapy is a broad term to describe the delivery of genetic material (i.e., DNA, RNA) to correct the actual genetic mutations or defects that cause a given disease," he begins. "Based on over 25 years of research greatly facilitated by DNA sequencing and the study of genetics, we now know the genetic etiology of a large number of diseases." These diseases are primarily monogenic – disorders caused by a mutation in a single gene – and passed from parents to offspring. In the area of neurological disorders, there's a whole host of diseases where the genes have been identified as well as the exact changes in the base pairs of DNA that cause the genetic mutation. "In many cases we know the exact cellular or biological consequences of these mutations," Paul says. In Parkinson's disease, for example, there is a progressive loss of dopamine neurons in the brain, with early symptoms being shaking, rigidity, slowness of movement, and difficulty with walking.

On the other end of the spectrum there are certain gene mutations that cause a "toxic gain" of function. "Here it's not the loss of the protein causing the disease, but the mutation causes the protein to change or become misfolded, turning it toxic to the cell itself," he clarifies. This is the case in Huntington's disease, as well as in many forms of ALS. "In this type of situation, Voyager is attempting to deliver a vector that silences the gene," Paul notes. This process is known as RNA interference (RNAi). "It's literally a piece of DNA that encodes an antisense RNA molecule, preventing the expression of the messenger RNA for that particular protein and, in essence, knocks that protein down (i.e., silences the gene)," he states. Based on animal models and human genetics, Voyager researchers believe such an approach could markedly reduce progression and, if given early enough, possibly even prevent disease onset.

Paul attributes the current level of excitement surrounding cell and gene therapy as primarily being driven by two factors. "Since the human genome was first sequenced, the field has benefited from new and more powerful DNA sequencing tools that have allowed us to better identify mutations, which has greatly improved our understanding of the genetics of monogenic as well as polygenic diseases," he says. "The other major advancement, in terms of in vivo gene therapy, has been the realization that certain viruses, such as the adeno-associated virus (AAV) capsids, can be engineered to safely deliver genes to a variety of tissues, including the brain and spinal cord as we are pursuing at Voyager."

VOYAGER'S VIRAL VECTOR FOCUS

At Voyager Therapeutics, the focus for deploying its gene therapy technology always has been on CNS diseases affecting the brain and spinal cord – and diseases where there are currently few, if any, treatments. "Take ALS for example," Steven Paul, M.D., CEO of Voyager, states. "Though there is a small molecule drug that extends life by about two months, there is no truly effective treatment that slows down disease progression, and certainly nothing curative." Unfortunately, the same can be said for Huntington's disease, Friedreich's ataxia, Alzheimer's disease, and frontotemporal dementia (FTD), despite researchers possessing a pretty good understanding of the genetic underpinnings of these diseases. "Voyager started focusing on CNS disorders for a number of reasons," Paul explains. "We like the genetics. We understand the targets we're going after, and, in our view, these targets are highly validated." This reduces attrition and increases the probability that these drugs are likely to work when moved into the clinic.

So why are Voyager's AAV vectors different? "When our AAV capsids are injected, they get into the nucleus of the cell where the chromosomes and DNA are located," Paul states. "But AAV vectors don't readily integrate into the DNA of the host cell." This is different from other viruses, such as lentivirus, for example, which, when it gets into the nucleus of the cell, can integrate into the host cell DNA, he explains. "Any time a virus integrates itself into the host genome, there's a risk of causing mutations that can lead to cancer, and this is why lentiviral vectors aren't commonly used much in vivo anymore."

While AAV viral vectors do not readily integrate into the DNA, they do have a disadvantage. When a cell divides into two, the DNA that's in the AAV vector of the parental cell isn't passed on to the daughter cell. As a result, if working in an area where very active cellular proliferation takes place, the effects of the AAV virus will get diluted out over time as new cells won't contain the viral vector that had been delivered. But nerve cells (i.e., neurons) for the most part don't divide, because they are terminally differentiated (i.e., postmitotic). "When Voyager delivers a gene using AAV viral vectors to nerve cells, as in the case of our Parkinson's program, the expression of the gene being delivered is very durable, on the order of many years or perhaps even decades," he attests. "In monkey studies for our Parkinson's program, researchers have delivered a gene that encodes a therapeutic protein allowing for levodopa (L-DOPA), the medicine used to treat Parkinson's patients, to be converted to the neurotransmitter dopamine, which is what is deficient in the brains of these patients." According to Paul, there are many years of monkey data, and over four years of human data, indicating no loss of the delivered gene. Not long ago a research group in Japan reported 15 years' worth of monkey data with no loss of the delivered protein. "This is why we believe our approach has the potential to be a very long-term fix via a one-time treatment," Voyager's CEO affirms.