BIOCENTURY

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Sandrock's new Voyage

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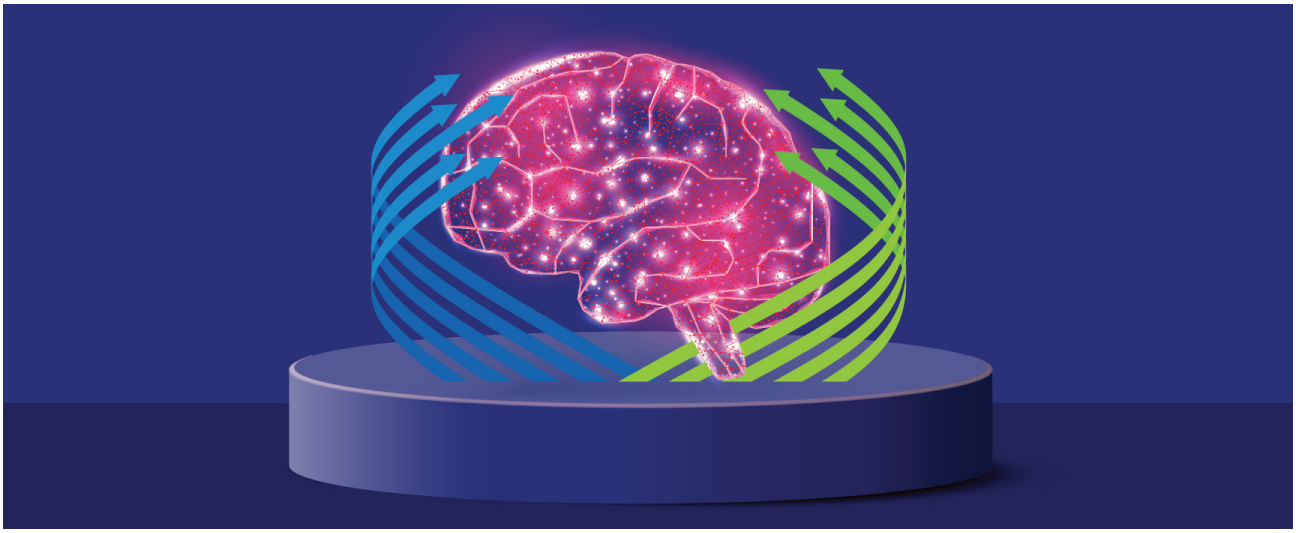


BIOCENTURY & GETTY IMAGES

Al Sandrock may not have completed his neurology-focused mission at Biogen, but he's pushing toward similar goals at the helm of Voyager, with a focus on novel CNS-penetrant gene therapy capsids that he hopes will be the lynchpin for the company's revival.

Two years ago, Voyager Therapeutics Inc. (NASDAQ:VYGR) was in a difficult position. Three partnership deals had imploded, leading to the resignation of the CEO and CMO in May 2021. The refocus on Huntington disease gene therapy VY-HTT01 also failed to pan out, with preclinical toxicity leading to the program's discontinuation.

The company's valuation told the tale. After hitting a near-term peak of $28.38 in July 2019, the stock then fell 90% over the next two-and-a-half years, ending 2021 at $2.86 — all while the broader biotech sector was in the midst of a bull market that saw the SPDR S&P Biotech ETF (XBI) rise 30% over the same period.

Sandrock joined Voyager soon after, initially being appointed to the board in early February 2022 as part of an executive committee before being named CEO in March. Sandrock left Biogen in November 2021 in the wake of the controversial approval and subsequent commercial flop of Alzheimer's therapy Aduhelm aducanumab.

He was joined this month by former Biogen Inc. (NASDAQ:BIIB) colleague George Scangos, who took a board seat at Voyager. Scangos was CEO of Biogen in 2010-17, during which time he narrowed the biotech's focus to neurology.

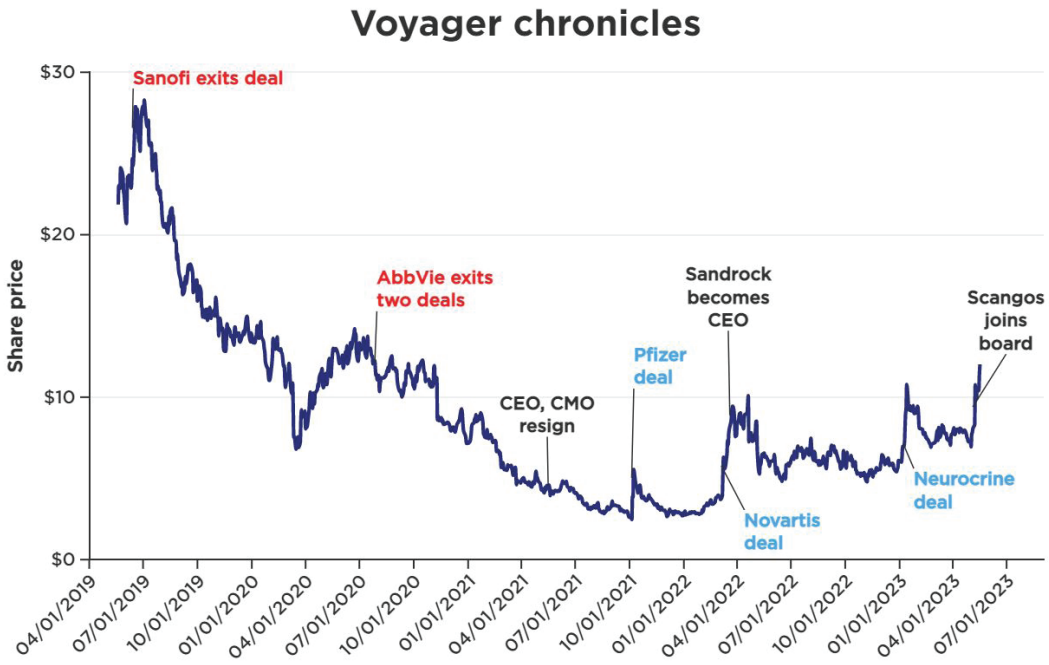
The past year has brought an overhaul of Voyager, from the C-suite to its pipeline and balance sheet. At the core is a focus on the company's TRACER capsid discovery technology, which the biotech believes may overcome many of the challenges that have plagued gene therapies, particularly in neurology.

Tracing out a new pipeline

Voyager is betting that its TRACER-based capsids can solve the long-standing problem of getting gene therapies and other modalities into the brain, by achieving improved tropism for crossing the blood-brain barrier.

"One of the issues has been delivery," Sandrock told BioCentury. "We've been talking about the blood-brain barrier for many decades, and it is still a problem."

Companies have typically taken two different approaches to increasing the CNS penetrance of AAV-based gene therapies:



infusing high doses to ensure some amount of the therapy crosses the blood-brain barrier, or employing some form of direct delivery, which is more invasive.

The serotype AAV9 has often been the vector of choice for gene therapies in neurology because it has the highest tropism for the CNS among the naturally occurring serotypes. Yet all natural AAV vectors still preferentially target the liver, and therefore require large doses that result in a narrow therapeutic window due to hepatotoxicity.

The biggest gene therapy success story, Zolgensma onasemnogene abeparvovec-xioi from Novartis AG (SIX:NOVN; NYSE:NVS), illustrates the challenge. Zolgensma comprises an AAV9 vector that delivers a copy of the SMN1 gene. It was approved in 2019 to treat spinal muscular dystrophy and is administered via intravenous administration.

According to Zolgensma's label, an evaluation of the biodistribution of vector DNA in two patients who died after being treated with the gene therapy showed that the highest levels of vector DNA were found in the liver, with vector DNA detected across many other organ and tissue types, including the spinal cord and brain. Not surprisingly, Zolgensma's label includes a black box warning for serious liver injury and acute liver failure, of which some cases have been fatal. Hepatotoxicity has derailed several gene therapies in recent years.

Direct delivery is also fraught with issues. Sandrock said, "Voyager itself had turned to intraparenchymal delivery, where they were delivering the gene therapy right into the brain. Voyager stopped those programs a couple of years ago because there were some MRI abnormalities."

Direct delivery is an invasive procedure that involves putting catheters into burr holes made in the patient's skull. Introducing vectors directly into the brain has been associated with potentially harmful levels of inflammation, particularly at high vector concentrations.

Sandrock argued that Voyager's TRACER capsids aim to provide the benefits of both approaches.

The platform is based on a library of 100 million engineered capsids with directed mutations or insertions in their surface loops. Screening these capsid variants in non-human primates uncovered a class of capsids that is able to efficiently cross the blood-brain barrier by binding to an undisclosed receptor on the endothelial layer, which Voyager calls receptor X. This binding then leads to the vector crossing the blood-brain barrier via transcytosis.

Receptor X is not transferrin, which is arguably the most widely studied receptor for inducing transcytosis into the brain and the basis of the large molecule transport vehicles of Denali Therapeutics Inc. (NASDAQ:DNLI).

According to CSO Todd Carter, Voyager has preclinical data showing the capsids can also bind to the human ortholog of

receptor X. "That gives us greatly enhanced confidence that we can translate into human beings," he said.

So far, the preclinical data for the CNS-penetrant capsids are promising. Sandrock said they are 1,000-10,000-fold more efficient at crossing the blood-brain barrier than AAV9, and have 5-10-fold decreased delivery to the liver with broad distribution throughout the CNS. "We're obviously looking for that therapeutic window," Carter said. "The more we get to our target tissue and the less we get to off-target tissues, the better. We build that into our capsid profile."

With these capabilities, the TRACER capsids are now at the core of Voyager's internal pipeline. An IND is expected next year for Voyager's SOD1 program, which uses the TRACER capsid to deliver an siRNA to knock down expression of SOD1 in patients with amyotrophic lateral sclerosis.

Sandrock guided development of the now-approved SOD1-targeting antisense therapy Qalsody tofersen when he was at Biogen. The primary benefit of Voyager's approach — encoding an siRNA against the target as a gene therapy — is that the siRNA will be continuously expressed and not require frequent re-dosing, as is the case with Qalsody. It would also be delivered intravenously rather than intrathecally.

The program will serve as an initial test of the company's revamped platform, providing important learnings and, if things go well, possibly bringing additional interest from would-be partners. However, even if it succeeds in the clinic, the product itself may not become a major growth driver for Voyager, as the SOD1 target may only be relevant to the tiny subset of ALS patients who harbor a SOD1 mutation, which Biogen has estimated at about 330 patients in the U.S.

Looking further ahead, Sandrock said future programs will combine the TRACER capsids with promoters that drive expression in specific cell types, giving the company a mechanism for tailoring delivery to the cells of interest in specific disease settings.

"There are diseases that only affect certain cell types. So to be able to target it so specifically, that's one of the promises of gene therapy," Sandrock said.

He also noted that the TRACER platform allows Voyager to develop vectorized versions of many different therapeutic modalities, from mAbs to ASOs or siRNAs, that could benefit from improved CNS exposure.

For example, Voyager has VY-TAU01, an anti-tau mAb in development for Alzheimer's disease that is expected to enter the clinic next year. "Let's say we get proof of concept for the passive antibody that we give IV. We have the option now where we could vectorize it, or we could continue to develop the IV antibody, or we could do both."

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AL SANDROCK, VOYAGER THERAPEUTICS

Voyager already has a vectorized HER2 mAb in preclinical development to treat brain metastases, along with a vectorized anti-tau siRNA for Alzheimer's disease.

BD revival

The preclinical promise of its TRACER capsids has also been key in helping Voyager navigate its way through biotech's bear market over the past two years.

At the end of 3Q21, Voyager had $121.5 million in cash, which provided runway into 2023, based on prior operating expenses. The promise of the TRACER platform led to three deals that substantially extended that runway.

The first was a deal with Pfizer Inc. (NYSE:PFE) in October 2021 for TRACER capsids for neurology and cardiovascular gene therapy candidates that provided $30 million up front and up to $600 million milestones. Then in March 2022, Voyager added $54 million up front in a license option agreement with Novartis for the use of TRACER capsids against three neurology targets. That deal includes up to $1.7 billion in option fees and milestones, plus royalties.

The third deal came in January, when Voyager announced a new collaboration with existing partner Neurocrine Biosciences Inc. (NASDAQ:NBIX), which included worldwide rights for Voyager's preclinical GBA1 program for Parkinson's disease and other GBA1-mediated diseases. That deal brought in $175 million in upfront cash and $39 million in an equity investment, plus up to $1.5 billion in development milestones and $2.7 billion in commercial milestones. Voyager has an option to participate in a 50/50 cost and profit share in the U.S. after Phase I data.

All told, the combined upfront payments plus a few milestone payments pushed Voyager's cash position to $273.3 million at the end of 1Q23, giving the company runway into 2025.

Voyager's acting CBO Allen Nunnally said these types of deals are so attractive because they require almost no additional resources to be allocated. "What's nice is that it is a great form of non-dilutive revenue for us on targets that we wouldn't

otherwise prosecute ourselves because we can't do everything even within neurology," he said. "And we don't have any incremental work when we do those types of transactions. We're just turning the crank on developing great CNS capsids."

He added that Voyager is looking at creative deal structures that could allow start-ups or SMEs to gain access to the TRACER capsids without the high upfront costs, while still providing Voyager with future upside. "We want to find a way to work with those exciting, promising companies," he said.

Sandrock added that while Voyager will "stick to its knitting" in neurology, the TRACER platform has the potential to target virtually any tissue type. Indeed, he said Voyager has prioritized identifying capsids that preferentially target skeletal muscle and the heart.

"There's more than a handful of diseases that affect not just the nervous system, but affect skeletal muscle too, these neuromuscular diseases," he said. "That's the beauty of this TRACER platform. We can look at any organ we want, and we've chosen to focus on the nervous system for now. But we can always expand that."

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