

New Silence ALS Initiative is Giving Hope to Nano-Rare Patients

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Being diagnosed with any illness is unnerving, but imagine you are one of only 30 people in the world to suffer from the illness or at least a particular form of it. Now, imagine that that disease is 100% fatal. That's the reality faced by the Amyotrophic lateral sclerosis (ALS) patients being treated as part of a new initiative between **Columbia University** and non-profit biotech company n-Lorem Foundation.

These diseases – or disease mutations – have been dubbed nano-rare by San Diego-based n-Lorem, whose mission is to find effective treatments for these uniquely afflicted individuals and others like them.

“There are few commercial incentives for pharmaceutical or biotech organizations to pursue the discovery and development of individualized treatments,” n-Lorem Chief Development Officer Sarah Glass, Ph.D. told BioSpace. “The 2021 FDA guidance documents for individualized antisense oligonucleotides have enabled this non-commercial route for n-Lorem’s non-profit model, which is driven entirely by the desire to help patients by embedding the same level of quality that is required for standard commercial drugs.”

In recent years, researchers have come to the consensus that ALS is a heterogeneous disease. This is evidenced by patient subsets that have responded favorably to drugs like Radicava, which was approved in 2017 and BrainStorm Cell Therapeutics’ **NurOwn**, which is still fighting an uphill battle for approval.

Glass said that providing a blanket definition of ALS “almost does [patients] a disservice given the many unique individuals within this patient group. Individuals with ALS that carry a nano-rare mutation are often one of only a few - or perhaps the only one - that are known to have this mutation worldwide.”



Lisa Stockman Mauriello faced a similar situation. Suffering from a particularly lethal A5V mutation within SOD1-ALS, Stockman Mauriello captured the nation’s attention and reinvigorated the ALS community in its fight for expanded access to investigational therapies. Stockman Mauriello was fighting for access to the experimental therapy tofersen, which was being developed by Biogen and Ionis Pharmaceuticals. Tofersen is an antisense oligonucleotide (ASO) that targets a mutation in the superoxide dismutase 1 (SOD1) gene believed to be responsible for the genetic driver in SOD1-ALS, the second most common form of inherited, or familial ALS. This category is rare itself, accounting for just 2% of all ALS cases. Ultimately, tofersen **failed** to achieve its endpoint in Phase III, and although Stockman Mauriello eventually did receive access to the drug, she succumbed to her disease in August 2021. The n-Lorem-Columbia project, *Silence ALS*, is funded by medical nonprofit Target ALS and focuses on developing personalized experimental ASO medicines for nano-rare ALS patients. Currently, eight patients have been accepted into the program. These patients are afflicted with nano-rare mutations in either TDP-43 or CHCHD10.

In the first case, the **TDP-43 protein** is incorrectly ejected from the cell’s nucleus, preventing it from performing essential functions such as ensuring that mRNA is produced correctly, which can produce chaotic effects in affected nerve cells. Mutations in the **CHCHD10 gene** were identified as a genetic cause of ALS in 2014. While the process is not yet well understood, some studies suggest the mutations lead to impaired functioning of mitochondria, the cellular structures that provide the energy necessary for survival. Then, there are separate mutations within both.

“These are genes that are well known in the ALS community. They are very well characterized and have been extensively studied by the research community. Unique mutations may occur in any gene and n-Lorem is learning more and more about the types of mutations and genes that ASOs can target,” Glass said. “The Silence ALS partnership will enable iterative learning to help the broader population over time.”

She explained how ASOs can address these mutations.

“These are short segments of single-stranded genetic material that bind in a sequence-specific manner to RNA to alter the behavior and performance of that target RNA. ASOs can target a specific mutation as well as different variants that uniquely differentiate that patient from others.” Glass added that for some patients, it may be necessary to differentiate the disease-causing allele from the normal allele.

ALS is a progressive, neurodegenerative disease. From the time of diagnosis, a patient can expect to live between 2-5 years. During that time, they will become increasingly paralyzed, losing the ability to walk, talk, eat, swallow and finally, breathe. Glass shared that this is a big part of the reason n-Lorem teamed up with Neil Shneider at Columbia on this initiative.

“The clock is ticking. One of the biggest goals of the partnership is really to introduce efficiencies such as proactive sequencing, acquiring patient cells and other elements that are required to be able to accelerate our ability to develop an individualized therapy,” she said.

One of these efficiencies is ensuring that patients are characterized at an early stage in their disease prognosis. Then, the ultimate end goal would be to “eventually get to the place where we can try to preempt, almost pre-symptomatically be able to develop these ASOs when the natural history of a particular mutation is known.”

Glass shared that there are “thousands and thousands” of nano-rare diseases and patients with nano-rare mutations. Besides ALS, n-Lorem is primarily focused on helping patients with other neurodegenerative diseases as well as those with severe neurodevelopmental, ophthalmologic and kidney diseases. The foundation’s neurological concentration owes to it being where patients are mostly diagnosed from a genetics perspective, she explained.

“Genetic testing and genome sequencing has become much more common in the rare neurological disease space and many neurologists are becoming increasingly aware of the potential of individualized therapies. This is reflected in the fact that many patients for whom n-Lorem is discovering an ASO are affected primarily by neurological manifestations.” Glass said. She clarified that n-Lorem is also already developing ASOs for patients with diseases in other organ systems as well and will continue to expand the breadth of the patients it can help.

It’s been understood for a while now that personalized medicine is the way of the therapeutic future, and initiatives like this one reflect that sentiment.

“As genetic sequencing becomes more common, it has become apparent that more and more pathogenic mutations are nano-rare and will require individualized treatments that are out of scope for commercial organizations,” she said.

Glass suggested that partnering is key to leveraging platform approaches and collective abilities to find commonalities [and therefore therapeutic efficiencies] across some of these nano-rare diseases. “How can we learn and try to think across different genes, different mutations that have a number of similarities and commonalities?” This could ultimately lead to the nano-rare becoming a little less rare.

Glass, who did her Ph.D. in a rare form of cancer, shared that she has always had a passion for genetics and rare diseases. Then in 2020, her own son was diagnosed with a rare disease. Being immersed in drug discovery and development and now having a child with an “N-of-1”

mutation as well, she wondered how one could go about successfully developing a therapy for individual patients.

“At the time, I reached out to Dr. Stan Crooke [founder and CEO of n-Lorem], the pioneer of RNA-targeted drugs,” she said. “I immediately learned a lot and was drawn to the mission. My joining n-Lorem was an organic evolution of my career and represented the true intersection of my personal and professional passions.” Since joining Crooke, Glass has been working feverishly to stand up an infrastructure to enable many more patients to be helped.