NEUROLOGICAL DISEASE UPDATES

NeurologyLive®

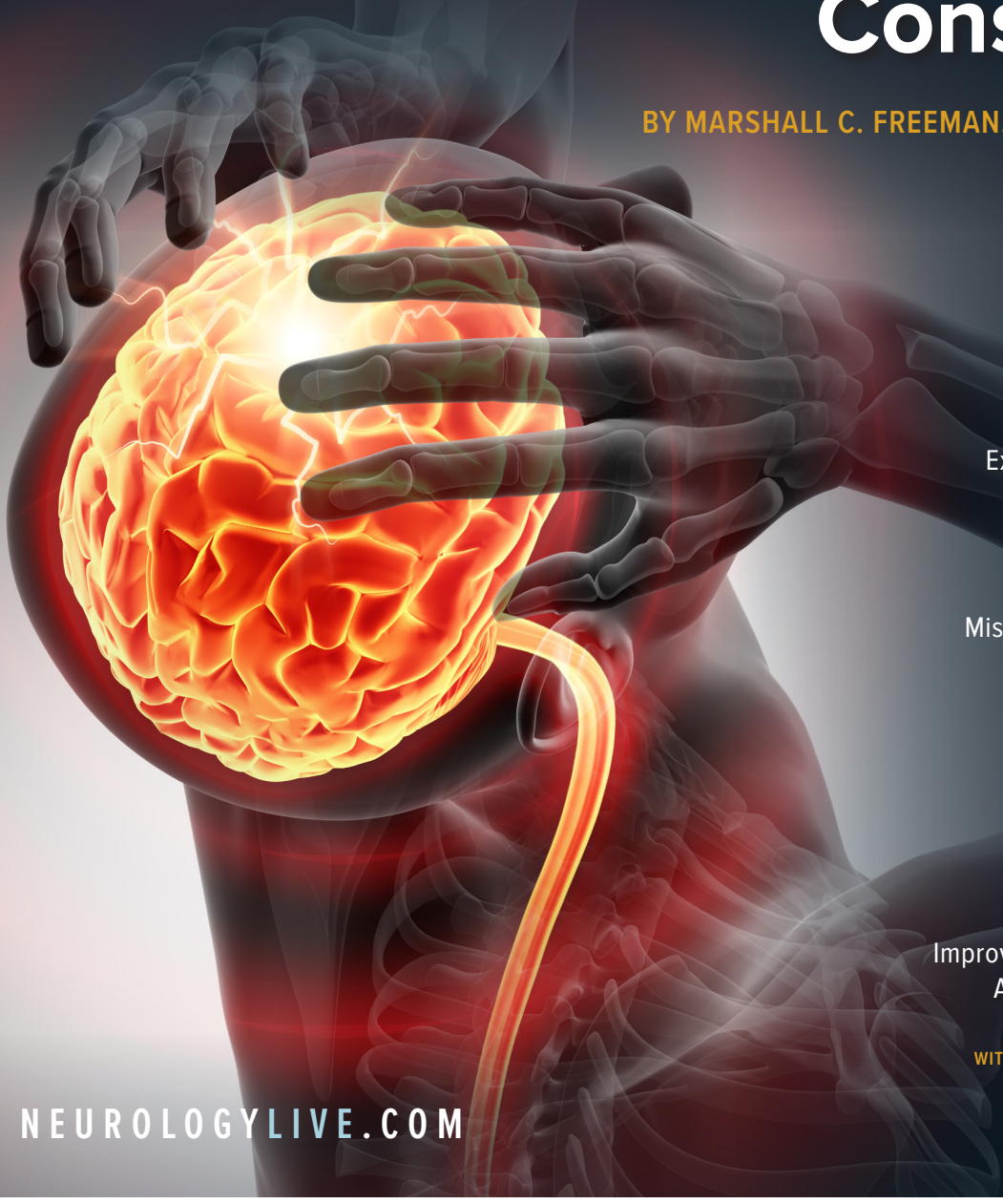
Direct Access To Expert Insight In Neurology

VOL. 4 | NO. 5 | OCTOBER 2021

PER® Physicians' Education Resource, LLC
gotoper.com

Optimizing the Migraine Consultation

BY MARSHALL C. FREEMAN, MD, FAHS, FAAN, FAANEM



+

Accessible Stroke Care for Diverse Populations: The Montefiore Approach

Patient Evaluation for Excessive Daytime Sleepiness
BY LAUREN CHAMBERLAIN, DO; AND ANDREW SPECTOR, MD

A New Approach to Protein Misfolding in Parkinson Disease
BY MANOLO BELLOTTO, PHD

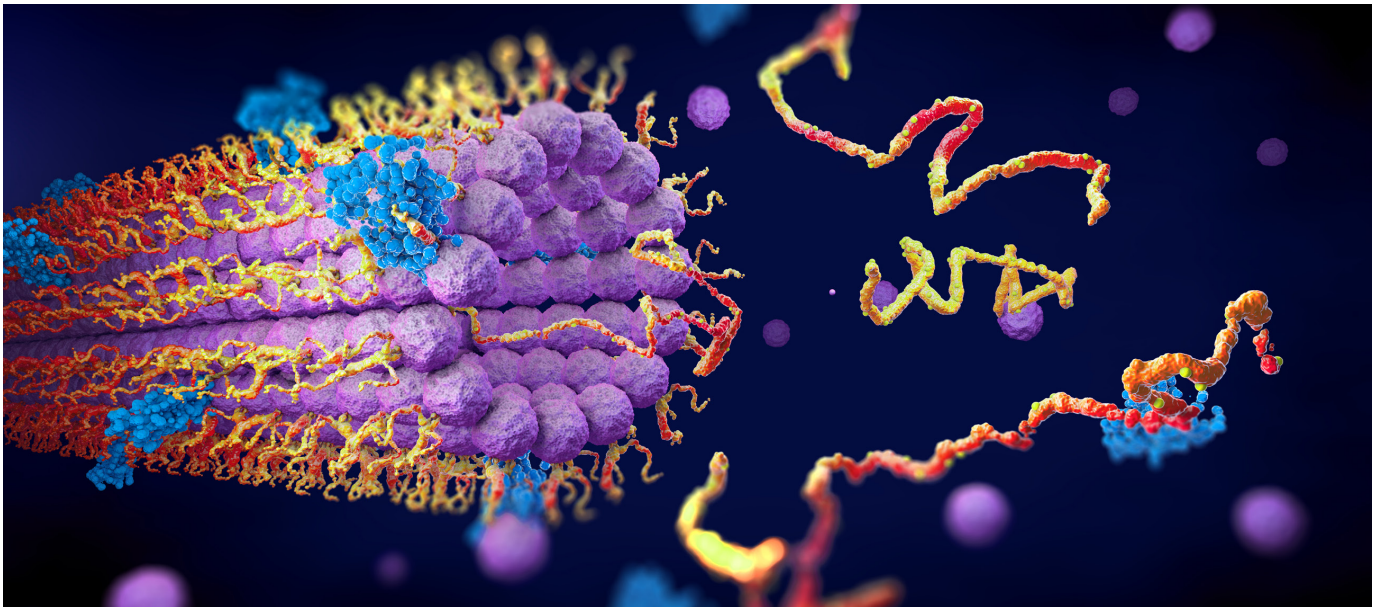
NeuroPathways™

S1P Receptor Modulation in Multiple Sclerosis
BY JENNIFER S. SUN, PHD

CLINICAL VIEWPOINT

Improving Stroke Systems of Care: A Tandem Role for Neurology and Primary Care Physicians
WITH MITCHELL S.V. ELKIND, MD, MS, MPHIL

NEUROLOGYLIVE.COM



A New Approach to Protein Misfolding in Parkinson Disease

By Manolo Bellotto, PhD
President and general manager, Gain Therapeutics

PARKINSON DISEASE (PD) IS A progressive neurodegenerative disorder with an estimated lifetime risk of 3% to 4%. It impacts more than 1 million people in the United States, making it the second largest neurodegenerative disease here after Alzheimer disease.[1] In addition to symptoms such as tremor, bradykinesia, rigidity, and OFF time, patients with PD also suffer from a range of nonmotor indications including psychosis and dementia. PD manifestations have been identified for more than 200 years, yet its mechanisms and pathogenesis have still not yet been fully described. While current therapies provide relief for some symptoms, they do not influence the progression of the disease.

MANOLO BELLOTTO, MD

However, clinical trials investigating potential disease-modifying treatments for PD, focusing on patients with specific gene mutations, are under way. Among the most common risk factors for PD is the presence of mutations in the glucocerebrosidase gene (*GBA1*), which encodes for the lysosomal enzyme beta-glucocerebrosidase (GCase). This risk factor was discovered during a clinical study of patients with Gaucher disease (GD), a rare lysosomal storage disorder. Over time, researchers have acknowledged that mutations in the *GBA1* gene are more prominent than in any other implicated genes within the PD population, including dardarin (leucine-rich repeat kinase 2 [*LRKK2*]), α-synuclein (*SNCA*), and parkin (*PARKIN2*).[2]

Limitations of Current Therapies

Treatments of PD using available drugs have positive symptomatic effects; however, no neuroprotective therapies are available to halt or even slow PD's progression. Treatments include drugs, surgeries, or combinations thereof, and notably, many therapies must be adjusted throughout the course of the disease: Some common ones, including levodopa, lose effectiveness over time and will not have an impact on motor problems caused by, for example, low acetylcholine levels in other pathways.[3] Furthermore, mainstream treatments such as enzyme replacement therapy (ERT) or gene therapy target only a small portion of the patient population, because they are severely limited in their ability to penetrate the blood-brain barrier (BBB).[4] PD treatment usually begins when symptoms start to impair function or result in social embarrassment.

The Intersection of GD, PD, and *GBA1*

A new research area is leveraging disease pathways of GD to find a more effective treatment for PD. As GD research progresses, scientists are discovering stronger links between GD and PD,

© CHRISTOPH BURGSTEDT / ADOBE STOCK

yet much remains to be learned about how and why these 2 diseases are related. Hopefully, important insights into mutual therapeutic options will develop. GD is caused by mutations in the *GBA* gene, which also can lead to reduced levels of GCase activity with the consequent accumulation of a primary substrate, glucosylceramide.[1]

Treatments for GD have been developed that increase visceral GCase levels and decrease lipid storage, although these treatments do not yet address the neurological defects associated with impaired GCase enzyme. Mouse models and induced pluripotent stem cell–derived models have improved our understanding of the GCase function and consequences of its deficiency. These models have been used to test novel therapies, including chaperone proteins (molecular chaperones that assist other proteins to fold properly), histone deacetylase inhibitors, and gene therapy approaches, all of which enhance GCase levels and could prove efficacious in treating PD.[5]

Patients with GD, as well as heterozygous GD carriers, are at increased risk of developing PD and dementia with Lewy bodies. An inverse relationship between GCase and α-synuclein levels has been observed, and even patients with sporadic PD have decreased GCase.[5]

Patients with *GBA1*-associated PD compose about 10% of total PD patient population,6 and while they are indistinguishable from other patients with PD, their disease may progress more rapidly with heightened severity. Research has shown that the onset of motor impairment among *GBA1* mutation carriers who have PD occurs 1.7 to 6.0 years sooner than in those patients with PD who don't have the mutations. Further, about 15% of patients with *GBA1*-associated PD exhibit severe clinical features; the features of the other 85% are usually moderate to severe. Finally, among patients who develop PD when less than 50 years, *GBA1* mutation carriers tend to develop clinical symptoms earlier than those who do not carry the mutation.

GBA1 and Protein Misfolding: An Underlying Biological Issue

Proteins are the primary building block of the human body, and they must maintain their precise 3D structure to ensure normal functionality. The physical process by which a protein chain is translated into its native structure, taking shape from its building blocks, and becomes a biological function as a 3D structure is called protein folding. Protein misfolding is a characteristic of PD and many other neurodegenerative diseases: Misfolded protein aggregation causes toxicities—including endoplasmic reticulum (ER) stress from an accumulation of misfolded proteins within the ER, or cellular toxicity due to an accumulation of the enzyme's substrate within the cells—resulting in cellular death and proteostatic disturbances. In PD, *GBA1* mutations result in the misfolding and subsequent dysfunction of GCase, which leads to the toxic accumulation of synuclein and neuronal cell death. Proteins misfold for many reasons, including genetic mutations and stress-induced molecular changes associated with inflammation or aging.

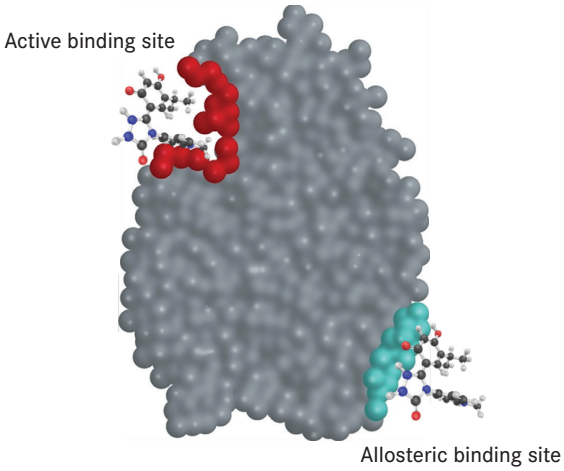
If misfolded proteins can be guided back into their normal structural shape, their function can be restored and catalytic reactions can be reignited. This could also help diminish ER stress by reducing the presence of misfolded proteins in the lumen of ER and eliminating the toxic substrate buildup that causes disease. The current standard of care for diseases characterized by misfolded proteins is to supply new, functional enzymes through ERT or gene therapy. Unfortunately, though, these methods have significant limitations for treating the diseases' neurological symptoms, because replaced enzymes cannot cross the BBB.

Allosteric Binding Sites to Guide Enzymes Back into Their Proper Shape

Binding sites are important locations on enzymes or proteins on which incoming small molecules can attach and create important biochemical reactions. Further, an enzyme can have drugs bind to either its unique active site or nonactive (allosteric) sites. Active sites are generally cavities that exist in the folded state; drugs can be designed to enter them and 'lock things down' in place. The problem for an enzyme like a lysosomal hydrolase is that the active site is where most of the chemical activity happens. Therefore, locking down the structure by binding in the active site might make an enzyme more stable but also may render the site less reactive or productive.

Since most pharmacologic chaperones bind to the active site to stabilize the target enzyme, they must compete with other high concentrations of substrate, generating problems in the potency level achieved. Alternatively, by having a compound bind to an allosteric site, the enzyme's active site remains available to catalyze substrates (**FIGURE 1**).

FIGURE 1. Allosteric and Active Binding Sites.



Allosteric binding sites are away from the active site and employ the idea of locking the protein in the folded state by binding within a cavity that occurs only in the folded state.

Unfortunately, the enzyme's allosteric sites are often unknown, making drug modulatory effects hard to predict. In fact, most

CONTINUED ON PAGE 68 ▶

▶ CONTINUED FROM PAGE 66

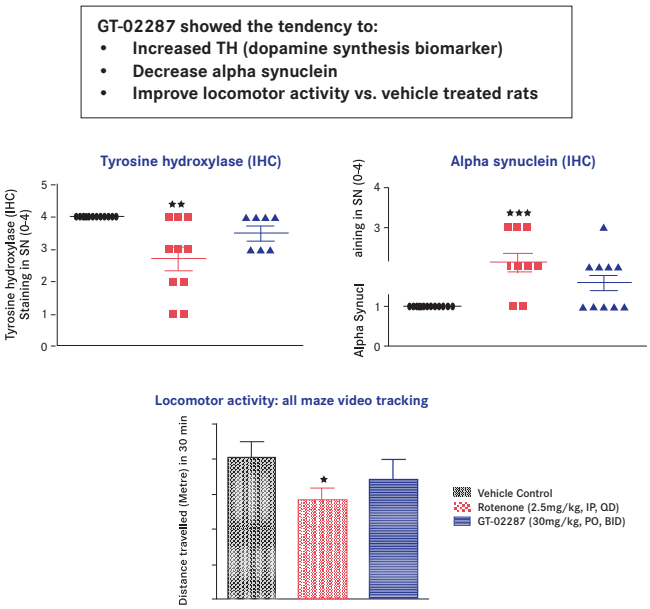
allosteric modulators were discovered serendipitously—for example, through high-throughput screening during lead identification—but the process is still largely inefficient.

In response, Gain Therapeutics, a drug discovery company based in Bethesda, Maryland, has exclusively in-licensed a patented, site-directed enzyme enhancement therapy platform developed by Gain's chief scientific officer, Xavier Barril, PhD, in the Barril Lab at the University of Barcelona. The platform rapidly "finds" previously unidentified allosteric binding sites and can predict such a site's druggability by using libraries that include multimillion compounds; this is in contrast to the current phenotypic cell-based screenings that are intensely laborious. For the first time, these sites can be targeted for therapeutic benefit to correct enzyme misfolding, to restore function, and to eliminate the subsequent toxic substrate buildup that causes disease and malfunction.

Selected compounds called Structurally Targeted Allosteric Regulators (STARs) offer a variety of advantages over traditional therapies; these advantages include streamlined oral dosing, improved delivery to dense tissues such as bone and cartilage, improved delivery across the BBB, and synergy with current gene therapy and ERT approaches.

Allosteric Regulators Open New Treatment Approach for PD

FIGURE 2. In Vivo Rat Model



GT-02287 was administered orally at 30 mg/kg, twice daily, for 7 days. Data is shown as mean (± standard error)(n = 10). Significant difference as compared Rotenone vs. Vehicle control. *P <.05; **P <.01; ***P <.001.

Encouraging results of studies with 2 STAR drug candidates (GT-02287 and GT-02329) were presented at the XXVI World Congress on Parkinson's Disease and Related Disorders in May 2021. These compounds represent a new approach for direct treatment of GBA1-associated PD by guiding misfolded forms of the GCase enzyme to their proper shape and restoring enzymatic activity. In addition, these compounds decrease both phosphorylated and aggregated α-synuclein levels in vitro and in vivo. When delivered orally, GT-02329 successfully penetrated the BBB and enhanced GCase activity and protein levels in the striatum of wild-type mice, while GT-02287 reduced α-synuclein accumulation in both cell culture and rat models of PD. GT-02287 also improved motor activity in rats treated with rotenone, a model of PD that reproduces certain features of the human disease (**FIGURE 2**). Importantly, these compounds reversed the neurodegenerative process observed in a PD in vivo model.[7]

Conclusions

PD treatments to date are limited to managing symptoms; they do not affect patients' inexorable decline. Previously, many promising treatments for PD have ultimately resulted in untenable adverse effects or in failure to cross the BBB. The evolving area of protein folding offers an opportunity to slow or reverse the neurodegenerative process and create improved quality of life for patients. Within the protein folding area, promise is seen with the 2 STAR candidates that could potentially help Parkinson's patients who have *GBA1* gene mutations as well as patients whose GCase protein is misfolded due to inflammation or aging cellular processes. These candidates could enter human clinical studies as soon as 2022, offering some hope for patients who continue to endure these diseases. ■

REFERENCES

1. Toffoli M, Smith L, Schapira AHV. The biochemical basis of interactions between Glucocerebrosidase and alpha-synuclein in GBA1 mutation carriers. *J Neurochem.* 2020;154(1):11-24. doi:10.1111/jnc.14968
2. Skrahina V, Gaber H, Vollstedt EJ, et al. The Rostock International Parkinson's Disease (ROPAD) study: protocol and initial findings. *Mov Disord.* 2021;36(4): 1005-1010. doi:10.1002/mds.28416.
3. Lee TK, Yankee EL. A review on Parkinson's disease treatment. Published online January 25, 2021. *Neuroimmunol Neuroinflammation.* doi:10.20517/2347-8659.2020.58
4. Sands MS. A Hitchhiker's guide to the blood-brain barrier: in trans delivery of a therapeutic enzyme. *Mol Ther.* 2014;22(3):483-484. doi:10.1038/mt.2014.12
5. Do J, McKinney C, Sharma P, Sidransky E. Glucocerebrosidase and its relevance to Parkinson disease. *Mol Neurodegener.* 2019;14(1):36. doi:10.1186/s13024-019-0336-2
6. Riboldi GM, Di Fonzo AB. *GBA,* Gaucher disease, and Parkinson's disease: from genetic to clinic to new therapeutic approaches. *Cells.* 2019;8(4):364. doi:10.3390/cells8040364
7. Maj R. Preclinical development of brain-penetrant structurally targeted allosteric regulators for the treatment of GBA1 Parkinson's Disease and related alpha-synucleopathies. Poster presented at: World Congress on Parkinson's Disease and Related Disorders; May 1-4, 2021; virtual.

FOLLOW US ON TWITTER
@Neurology_Live and stay informed!