Targeting Circuit Abnormalities in Neurodegenerative Disease

Sharan Ram Srinivasan, MD, PhD

1Department of Neurology, University of Michigan, 109 Zina Pitcher Place, Ann Arbor, MI 48109
Running Title: Pharmacological Deep Brain Stimulation for Neurodegeneration

Word count: 3438

Number of text pages: 20

Number of tables: 1

Number of figures: 1

Number of references: 81

Number of words in:

Abstract: 176

Introduction: 306

Discussion: 122

Correspondence to: Sharan R. Srinivasan

109 Zina Pitcher Place

Ann Arbor, MI 48103

Phone: 734-936-9020

Email: sharans@med.umich.edu

List of Abbreviations:

AD, Alzheimer's Disease; CTC, Cerebello-thalamo-cortical; DBS, Deep Brain Stimulation; ECT, Electroconvulsive Therapy; ET, Essential Tremor; GPI, Globus pallidus interna; PD, Parkinson Disease; PET, Positron emission tomography; SCA, Spinocerebellar Ataxia; STN, Subthalamic nucleus; TMS, Transcranial Magnetic Stimulation; VIM, Ventralis intermedius of the thalamus
Abstract

Despite significant improvement in our ability to diagnose both common and rare neurodegenerative diseases and understand their underlying biological mechanisms, there remains a disproportionate lack of effective treatments, reflecting the complexity of these disorders. Successfully advancing novel treatments for neurodegenerative disorders will require reconsideration of traditional approaches, which to date have focused largely on specific disease proteins or cells of origin. In this article, I propose reframing these diseases as conditions of dysfunctional circuitry as a complement to ongoing efforts. Specifically, I review how aberrant spiking is a common downstream mechanism in numerous neurodegenerative diseases, often driven by dysfunction in specific ion channels. Surgical modification of this electrical activity via deep brain stimulation is already an approved modality for many of these disorders. Therefore, restoring proper electrical activity by targeting these channels pharmacologically represents a viable strategy for intervention, not only for symptomatic management but also as a potential disease modifying therapy. Such an approach is likely to be a promising route to treating these devastating disorders, either as monotherapy or in conjunction with current drugs.
Significance Statement

Despite extensive research and improved understanding of the biology driving neurodegenerative disease, there has not been a concomitant increase in approved therapies. Accordingly, it is time to shift our perspective and recognize these diseases as disorders of circuitry in order to yield novel drug targets and new interventions. An approach focused on treating dysfunctional circuitry has the potential to reduce or reverse patient symptoms and potentially modify disease course.
Introduction

An aging population, improved clinical acumen, and ready access to genetic testing has led to a dramatic rise in the diagnosis of both common and rare neurodegenerative diseases (Rocca et al., 2011; Ruano et al., 2014; Savica et al., 2016). Rightfully, the aim of translational scientists has been to intervene early on affected or pre-disposed patients with the hope of preventing neurodegenerative decline. Tremendous efforts have been dedicated towards unveiling the biological underpinnings of neurodegenerative diseases, with a focus on protein aggregation and relevant biochemical pathways in specific cell types (Figure 1A). Thus far, however, directly targeting amyloid-beta, tau, alpha-synuclein, and other major neurodegenerative disease proteins has led to approval of only a single drug, a monoclonal antibody against amyloid-beta for Alzheimer’s Disease (AD) (NCT02484547 and NCT02477800) with minimal clinical benefit. Several other compounds or biologics have advanced to late phase clinical trials, but have failed either due to toxicity, or perhaps even more unsettling, lack of efficacy.

There is thus a glaring need to reconsider our therapeutic strategy in how we approach these diseases and care for those afflicted patients. While targeting protein aggregation or genetic mutations may address a root cause, how these approaches will affect symptomatic patients is unclear and therefore complementary strategies are needed. An examination of downstream mechanisms reveals that dysfunctional electrical signaling is a hallmark in many of these diseases. In this article, I review the evidence for neurodegeneration as a circuit disorder (Figure 1B) and suggest shifting our perspective to this being a druggable target rather than strictly or primarily a manifestation of a cell-based or protein-based disease. In this manner, we can uncover novel therapeutics to complement ongoing efforts against the disease-causing insult. While applicable to many diseases, I will focus the discussion on some of the more common neurodegenerative conditions seen by cognitive and movement disorder neurologists.

Lessons from Our Colleagues

Over decades, collaborative work among neurologists, neurosurgeons, and other specialists has demonstrated that electrical stimulation can have profound short and long-term effects on clinical course. Deep brain stimulation (DBS) is an approved intervention for Parkinson Disease (PD), Dystonia, and
Essential Tremor (ET), and is undergoing evaluation for mood disorders. More recently, non-invasive metrics such as Transcranial Magnetic Stimulation (TMS) have also been used for both movement and mood disorders (Cohen et al., 2022). Even more remotely, electroconvulsive therapy (ECT) has been utilized to great efficacy in psychiatry for decades.

While highly effective, these devices can often be invasive as with DBS, or nonspecific as with TMS and ECT. Emerging work in the DBS field, particularly with closed-loop recording, is providing significant insight into the previously unknown mechanisms and effects of stimulation (Bouthour et al., 2019). However, these instruments lack the true specificity of a targeted pharmacologic agent.

**Disease-based Examples**

Ion channels remain one of the most common drug targets among FDA-approved medications for neurological disorders (Bagal et al., 2013; Kinch, 2015). Until recently, the electrophysiological signature in neurodegenerative diseases remained largely untapped as a drug target despite a clear role in disease pathogenesis. Indeed, aberrant electrical signaling is a hallmark of several disorders and is emerging as a target for intervention (Table 1). Further, as more studies emerge, it is becoming clear that abnormal electrophysiology is not a manifestation of widespread neuronal dysfunction from cellular degeneration but rather is driven by altered activity of specific channels that represent viable targets for intervention. In many cases, the abnormal firing phenotype is seen prior to any cellular loss.

In PD, adverse effects of long-term dopaminergic stimulation (Voon et al., 2009) have led to exploration of downstream pathways for intervention, best exemplified by DBS to the subthalamic nucleus (STN) or globus pallidus interna (GPI) for bradykinesia and rigidity (FDA approved in 2002), along with ventral intermediate nucleus (VIM) for refractory tremor (FDA approved in 1996). Examination of these regions reveals hyperactivity and increased bursting in the STN and GPI (Lobb, 2014), and the STN converts from a tonic firing phase to an abnormal bursting phenotype in PD models (Walters et al., 2007; Tai et al., 2011, 2012). This bursting activity is at least partially driven by T-type calcium channels (TTCCs) and can be rectified with an inhibitor, resulting in improved mobility and reduced dystonia in a 6-hydroxydopamine (6-OHDA) mouse model. Unfortunately, the effects of TTCCs on tremor have been difficult to address due to poor animal models. Notably, compounds targeting L- or P/Q-type calcium
channels did not restore proper electrical activity (Tai et al., 2011), suggesting that these alterations in pathways are specific and not simply a sign of global dysregulation of spiking due to widespread degeneration. Additional studies have shown that glutamate excitotoxicity in PD results from decreased glutamate uptake by glial cells (Iovino et al., 2020), a process that relies on potassium-ATP (K-ATP) channels. Administration of a K-ATP inducer resulted in decreased glutamate and increased dopamine levels in the striatum of a 6-OHDA mouse model of PD (Wang et al., 2005). However, while Kir6.2 K-ATP activation can help with these short-term metabolic demands, it may promote long-term of nigral dopaminergic cells (Liss et al., 2005), offering conflicting evidence on these specific channels as a target in PD. Blockade of small conductance (SK) channels can improve PD symptoms ((Hallworth et al., 2003; Alvarez-Fischer et al., 2013), but SK activation can also attenuate symptoms in cellular and mouse models of PD ((Dolga et al., 2014; Wang et al., 2015). Thus, the specific potassium channel and timing of intervention appears to be crucial for potential intervention in PD.

Dystonia, especially primary, is not classically thought of as a degenerative disease but does offer similar lessons in its response to DBS. Dystonia suffers from a lack of targeted therapies, with care relegated to a trial of muscle relaxants before pursuing botulinum toxin therapy. While the latter therapy is effective, more complex or generalized dystonias can be more difficult to treat by injection, leading to eventual approval of DBS in 2003. Recent genomic studies in primary dystonia patients have revealed several affected pathways, including transcriptional and cell-cycle regulation, interfacing of the nuclear envelope and endoplasmic reticulum, and synaptic function (LeDoux et al., 2013). Despite advancing knowledge of the underlying biochemical pathways, we have not developed novel therapies for dystonia, highlighting the gap between current scientific approach and the efficacy of DBS as a therapeutic intervention. Reconsideration of dystonia as a channelopathy however, does reveal some intriguing targets. Genome-wide association studies in cervical dystonia identified polymorphisms in a sodium leak channel, NALCN, suggestive of dystonia as a channelopathy (Mok et al., 2013). In a healthy mouse model, administration of an L-type calcium channel agonist led to a dystonic phenotype, which was subsequently ameliorated by co-administration of an L-type calcium channel antagonist (Jinnah et al., 2000). Additionally, a splice site mutation in the mouse Scn8a sodium channel gene leads to dystonia (Sprunger et al., 1999). While these early studies demonstrate the ability of ion channel dysfunction to
precipitate dystonia, more work is needed to identify definitive targets tied to the various primary (and secondary) dystonias.

Functional magnetic resonance imaging (fMRI) studies of patients with ET show altered connectivity in the cerebellar-thalamo-cortical (CTC) circuitry in both the resting and active states (Nicoletti et al., 2020; Holtbernd and Shah, 2021). Two of the most common mouse models of ET, the harmaline-induced and Grid2 mutant-based models, demonstrate abnormal neuronal bursting in the inferior olive, ventral intermediate nucleus (VIM), and Purkinje neurons (PCs), which correlates with tremor (Linás and Yarom, 1981; Hua and Lenz, 2005; Brown et al., 2020; Pan et al., 2020). Altering the electrical activity of the VIM via DBS is now an approved therapy for ET, yet the driving channel is not yet clear. At least in CTC circuits, some of this aberrant electrical activity has been attributed to T-type calcium channels, inhibitors of which are already being developed (Handforth et al., 2010; Scott et al., 2022). Genetic analyses of families with ET have also revealed that mutations in the SCN4A gene, which encodes a voltage-gated sodium channel, segregate with the disease (Bergareche et al., 2015; Asif et al., 2021). Records from mutant SCN4A channels show faster activation and inactivation, which likely contributes to oscillation firing. Similarly, mice carrying a mutation in a different sodium channel, SCN8A, can also show a tremor phenotype (Meisler et al., 2001).

Even diverse genetic etiologies with overlapping presentations can share a similar electrophysiological signature, and therefore potentially similar targets. The most common Spinocerebellar Ataxias (SCAs) are autosomal dominantly inherited disorders caused by polyglutamine-coding CAG repeat expansions in different genes. Despite originating from expansions in separate genes, several of these SCAs demonstrate abnormal spiking activity in cerebellar Purkinje cells (PCs) that correlates with motor decline and precedes cellular degeneration (Shakkottai et al., 2011; Dell’Orco et al., 2015, 2017; Chopra et al., 2018; Stoyas et al., 2019). Aberrant PC spiking in SCA mouse models has been shown to derive from decreased activity mainly in calcium-activated potassium channels (Dell’Orco et al., 2015; Chopra et al., 2018), augmentation of which improves motor function and delays cellular atrophy (Chopra et al., 2018; David D Bushart et al., 2021). Interestingly, the predominantly affected potassium channels (KCN3 and KCNA6 vs KCNMA1) do seem to differ in SCA3 vs SCAs 1, 2, and 7, respectively (Shakkottai et al., 2011; Dell’Orco et al., 2015, 2017; Chopra et al., 2018, 2020; Stoyas et al.,
2019; David D. Bushart et al., 2021). Thus, while SCAs do demonstrate electrophysiological dysfunction deriving from a specific channel as in other movement disorders, the exact target may differ based on genetic origin, timing of intervention, and predominant symptoms.

While a full review of dementias is beyond the scope of this article focused on movement disorders, it is worth mentioning that aberrant electrophysiology is also found in AD, the most common neurodegenerative disorder. In pre-syndromic patients identified by CSF biomarkers of AD, fMRI studies have shown evidence of hippocampal hyperactivation and impaired deactivation (Dickerson et al., 2005; Hedden et al., 2009; Quiroz et al., 2010). Further, it appears that soluble amyloid oligomers can induce hippocampal hyperactivity, which can be found even before amyloid plaque formation (Busche et al., 2012). Specifically, Abeta1-42 can increase sustained presynaptic calcium levels via nicotinic acetylcholine receptors (Dougherty et al., 2003), which is thought to contribute to synaptic loss. Restoration of this imbalanced electrical activity can also improve memory deficits and prevent further build-up of amyloid plaques and synaptic loss (Busche et al., 2015; Yuan and Grutzendler, 2016). A recent small Phase 2a Clinical Trial therefore explored the ability of low dose levetiracetam to improve executive function in early AD patients (Vossel et al., 2021). While there was no change on a composite score of executive function, those AD patients with pre-existing epileptiform activity as measured by EEG did demonstrate an improvement in interference naming and spatial navigation. This was a low dose for a short period of time, but it is clear dysfunctional circuitry is likely an early pathogenic contributor to AD and therefore represents an attractive target to minimize disease progression, even as DBS is not yet approved.

The above discussion has largely focused on neuronal dysfunction as the primary drivers of impaired circuitry. However, it is worth noting that neurons exist within a network of astrocytes, oligodendrocytes, and microglia, all of which can regulate circuitry through impacts on metabolism and synaptic connectivity. For example, Kir4.1 contributes to extracellular K+ homeostasis (Djukic et al., 2007; Chever et al., 2010), and loss of function in KCNJ10 can lead to disorders with epilepsy or ataxia (Stockman, 2011). Loss of function mutations in the glutamate transporter SLC1A3 can also lead to episodic ataxia. In microglia, inhibition of the G_i pathway can lead to hyperexcitability and spontaneous seizures in adult mice (Merlini et al., 2021). Thus, while comparatively less studied, these cells also play
critical roles in maintaining functional circuitry and therefore their critical elements represent viable targets as well.

**Pharmacological Deep Brain Stimulation**

Transitioning from cell-of-origin approaches to a circuit-based view of neurodegenerative disease is a daunting proposition. Drugging ion channels is not only complex, but often viewed with trepidation given the potential for numerous adverse effects, including cardiac and epileptiform dysfunction. However, the successes of DBS and even TMS demonstrate the feasibility in engaging electrophysiology and connectivity as a therapeutic strategy. But how are we to mimic device-based stimulation with small molecules? In other words, how are we to achieve "pharmacological DBS"?

As above, the aberrant circuitry seen in clinical disorders does not appear to be a global sequela of neurodegeneration, but rather a focused pathogenic feature deriving from one or a few specific channels. Modern advances in DBS have improved our understanding of the effects of electrical stimulation in key pathological areas. Combined with genomics, transcriptomics, and proteomics, we are now able to identify those channels whose activity we desire to modify. There now remains two major limitations to this approach.

The first is developing an actual pharmacologic compound against said channel. While manual patch-clamp is a high-fidelity and data-intense approach, it is low-throughput and therefore impractical for most drug-discovery purposes. However, fluorescence-based assays (Whiteaker et al., 2001; Beacham et al., 2010), radioisotope flux assays (Terstappen, 1999; Weaver et al., 2004; Liu et al., 2010; Weaver, 2018), and now automated patch clamp platforms (Srinivasan et al., 2022) have emerged as breakthroughs in our ability to screen ion channels. While still early, the development of human-derived stem cell and organoid-based platforms offers a powerful opportunity to evaluate aberrant circuitry and test ion channel modulators in human-based models. The combination of traditional approaches with novel techniques is likely to yield potent and novel therapeutics.

The second major hurdle relates to specificity of the targeted channel. Not only are ion channels widely expressed throughout the nervous system, but they are heavily involved in signaling throughout the body, particularly the cardiac circuitry. While ubiquitous, there are differential expression patterns that
do seem to allow for selective up/downregulation as desired without negatively impacting systemic function. Nevertheless, one suggestion to avoid potential toxicity is to include orthogonal screening against non-neuronal cells, such as cardiac myocytes, to avoid any future concerns. An alternative strategy involves re-engineering small molecules or biologics to adapt to endogenous blood brain barrier (BBB) carrier-mediated transport (Pardridge, 2015), similar to levodopa uptake for treatment of PD (Kageyama et al., 2000). In this scenario, molecules would be screened or modified to increase affinity for BBB transporter as well as desired ion channel target. Such strategies would allow for improved targeting of desired circuitry while minimizing extraneous effects.

**Making it Reality: Next Steps**

Translating circuit-based therapeutics into bedside interventions will also require careful consideration of how we implement these novel drugs and in whom. A key obstacle in drugging aberrant circuitry will be in tracking target engagement. Thus, development of novel compounds must be done with human trials in mind. Converting ion-channel-targeting drugs into positron emission tomography (PET) ligands is an attractive idea, but clinical and statistical significance would rely on larger declines in expression than are typically seen in the diseases discussed in this work. Further, this would indicate a measure of disease progression rather than improved electrical function. As fMRI has been used to demonstrate abnormal connectivity in diseased patients, this technology could be used to examine both static and even dynamic changes as a treatment response. Preliminary studies have been completed in several diseases, including PD (Ji et al., 2018; DiMarzio et al., 2021), ET (Benito-León et al., 2015; Yin et al., 2016), dystonia (Moore et al., 2011; Li et al., 2016), AD (Wang et al., 2006; Agosta et al., 2012), and SCAs 1, 2, 3, 6, and 7 (Jayakumar et al., 2006; Hernandez-Castillo et al., 2014; Cocozza et al., 2015; Falcon et al., 2015; Duarte et al., 2016; Horn et al., 2022). However, more robust patterns, such as comparing rest vs task-based imaging in a **longitudinal manner**, need to be established to allow for determination of target engagement and treatment response. This presents another opportunity to learn from our neurology colleagues in epilepsy, where electrical monitoring via electroencephalography (EEG) is routine and often helpful in tracking treatment efficacy. In PD, EEG has been used to predict cognitive decline (Geraedts et al., 2018), but thus far has not correlated to motor symptoms. Patients with focal
hand dystonia show reduced beta band signal, suggesting impaired connectivity (Jin et al., 2011). Non-linear EEG analysis in a mouse model of SCA3 showed higher alpha and theta energies in disease vs WT mice (Yu et al., 2019), which seemed to correlate with motor dysfunction testing by Morris water maze. However, this study required surgically implanted electrodes and findings were not specific to a single channel. There have been EEG analytes identified that correlate with specific ion channel dysfunction though. For example, T-type calcium channels regulate sigma band power during non-rapid eye movement sleep and therefore this specific EEG change represents a biomarker of target engagement for ET and PD as above (Scott et al., 2022). Similar electrophysiological patterns will need to be established for other specific channels and brain regions, including the cerebellum. However, EEG analysis of subcortical spiking is inherently limited by conventional scalp recording, and so novel techniques may need to be implemented here as well.

Many other diseases beyond those discussed here may be amenable to pharmacological DBS. It behooves us to analyze our current DBS patients to gain insights from extraneous data. What consequences have been noted in inadvertent lead placement? What other neurological symptoms are affected by over-stimulation, beyond the desired change? For example, can we use knowledge of stimulation on dyskinesias in PD to help treat other choreiform disorders? Does over-stimulation of the VIM in ET patients lead to or reduce ataxia? What about lead placement in the posterior fossa, such as the dentate nucleus within the cerebellum? It is also paramount to consider timing of intervention. It is clear that in several disorders, aberrant spiking presents early in disease, but is not always progressive, such as in SCA3 (David D. Bushart et al., 2021; Mayoral-Palarz et al., 2022). Thus, pharmacological DBS may not serve as a panacea, but rather as a targeted intervention for specific indications, best administered in a timely fashion.

Conclusion

The next phase of neurodegenerative therapeutics will require a dramatic shift not only in our disease perspective but a multifaceted approach to drugging these diseases. Given the clinical and pathogenic complexity, it is somewhat unlikely that a single intervention will stop these diseases in their tracks. Combining the efforts of decades of research is more likely to succeed as opposed to searching
for a “silver bullet”. Multidisciplinary therapeutics forums for neurodegenerative disease combining experts from genetics, cell biology, circuitry, and clinical trials would offer critical opportunities for collaboration on successful regimens and must become a mainstay in the scientific community. Implementation of ongoing drug trials with pharmacological DBS is an attractive pathway to success in treating these patients with these devastating diseases.

Acknowledgements
This manuscript was critically reviewed by both Dr. Henry Paulson (University of Michigan) and Dr. Vikram Shakkottai (University of Texas Southwestern), who provided valuable feedback.

Author Contribution:
Wrote or contributed to the writing of the manuscript: The manuscript was drafted and revised by Srinivasan, S.

Conflict of Interest
This author declares no relevant financial conflicts of interest.

Funding
Dr. Srinivasan was funded by the National Institutes of Health [R25NS089450-06].

Figure and Table Legends:

Figure 1. Reframing Neurodegenerative Disorders. (A) Traditional evaluation of neurodegenerative disease has focused on the biochemistry surrounding disease-specific hallmark protein aggregates. These pathways are often explored in specific cell types thought to drive cellular death in focal areas of the brain. (B) A proposal for viewing electrical dysfunction as a shared feature of many, if not most, neurodegenerative disorders. While aberrant disease protein behavior likely contributes to
neurodegeneration, it also may drive aberrant electrical activity, which better correlates with clinical motor symptoms. Ion channel modulation represents an opportunity to restore proper spiking and potentially modify the disease course. KCNMA1, large-conductance potassium channel (BK); TTCCs, T-type calcium channels; SCN4A, voltage-gated sodium channel (Na\textsubscript{v}1.4). Channels shown are representative examples rather than a comprehensive list of targets.
Table 1. Neurodegenerative diseases and potential targets for pharmacological DBS. Summarized here are neurodegenerative disorders for which DBS is already approved, or for which there exists substantial evidence of impaired circuitry. Indicated are relevant targets and known small molecule modulators.

<table>
<thead>
<tr>
<th>Neurodegenerative Disease</th>
<th>Target</th>
<th>Small molecule modulator</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson Disease (PD)</td>
<td>TTCC (blocker)</td>
<td>PRAX-944</td>
<td>Tai et al., 2011; Scott et al., 2022</td>
</tr>
<tr>
<td></td>
<td>K-ATP (inducer)</td>
<td>Iptakalim</td>
<td>Wang et al., 2005</td>
</tr>
<tr>
<td></td>
<td>K-ATP (inducer)</td>
<td>1-methyl-4-phenylpyridinium (MPP+)</td>
<td>Liss et al., 2005</td>
</tr>
<tr>
<td></td>
<td>SK (blockade)</td>
<td>Apamin</td>
<td>Hallworth et al., 2003, Alvarez-Fischer et al., 2013</td>
</tr>
<tr>
<td></td>
<td>SK (activation)</td>
<td>EBIO</td>
<td>Dolga et al., 2014, Wang et al., 2015</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Dihydropyridine</td>
<td>Nifedipine, Nimodipine, Nitrendipine</td>
<td>Jinnah et al., 2000</td>
</tr>
<tr>
<td>Essential Tremor (ET)</td>
<td>TTCC (blocker)</td>
<td>PRAX-944; Zonisamide; NNC-55-0398; Ethesuximide</td>
<td>Scott et al., 2022; Handforth et al., 2010</td>
</tr>
<tr>
<td>Spinocerebellar Ataxia (SCA) types 1, 2, and 7</td>
<td>KCNMA1</td>
<td>4-chloro-N-(5-chloro-2-cyanophenyl)-3-(trifluoromethyl)-benzene-1-sulfonamide</td>
<td>Srinivasan et al., 2022, Bushart et al., 2021</td>
</tr>
<tr>
<td>Alzheimer’s Disease (AD)</td>
<td>Unclear</td>
<td>Levetiracetam</td>
<td>Vossel et al., 2021</td>
</tr>
</tbody>
</table>
REFERENCES


Hallworth NE, Wilson CJ, and Bevan MD (2003) Apamin-sensitive small conductance calcium-activated potassium channels, through their selective coupling to voltage-gated calcium channels, are critical determinants of the


Figure 1.

A. Protein/Cell-of-origin Viewpoint

amyloid beta fibril → Astrocyte → Cortical Neuron → Cortical Atrophy

Tau Tangle

Aggregated alpha-synuclein → Lewy Body → Dopaminergic Neuron → Hippocampal Dysfunction

Polyglutamine Plaque → Purkinje Cell → Substantia Nigra Degeneration

Cerebellar Atrophy

B. Circuit Disorder Viewpoint

Healthy → Mild Clinical Symptoms → Severe Clinical Symptoms

Protein Aggregates

Neurodegeneration

Ion channel Modulators

KCNMA1

SCN4A

TTCCs

Na⁺

Ca²⁺

Progressive Neuronal Dysfunction

Standard of Care