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MEETING NEURODEGENERATIVE DISEASE HEAD-ON WITH EMERGING DRUG DISCOVERY STRATEGIES

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Central nervous system (CNS) diseases represent a significant disease burden and are one of the leading causes of death and disability worldwide.[1] These diseases are diverse and complex, making them difficult to treat and even diagnose.

Chronic neurodegenerative diseases encompass a variety of progressive conditions that affect neurons, including Huntington's disease, Parkinson's

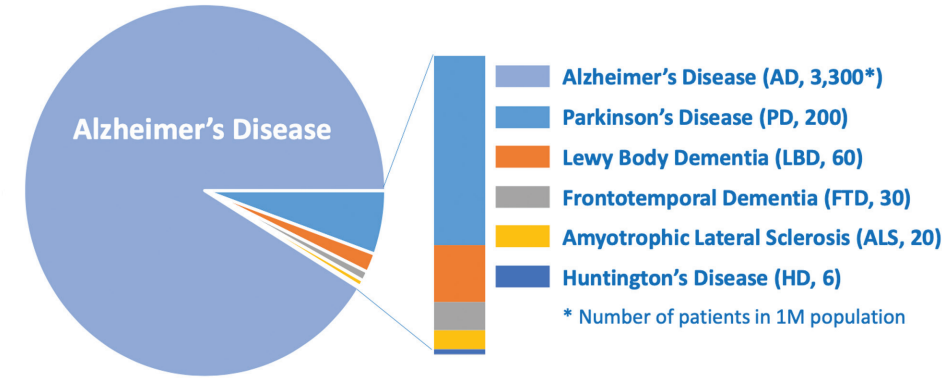

Figure 1. Neurodegenerative disorders and their approximate prevalence.[3]

Source: WuXi AppTec

disease, Alzheimer's disease, and other forms of dementia. They are among the most common (figure 1) and challenging CNS diseases.[2]

"These diseases affect what is special and unique about the human condition," says Hugo Geerts, head of quantitative systems pharmacology neurosciences for the biotechnology company Certara.

Over 50 million people worldwide have some form of dementia. In 2015, the World Health Organization estimated the total global societal cost of such dementia disorders at $818 billion.[4] It also forecast that the global population of people over 60 would more than double by 2050.[4] This demographic change will bring increased illness associated with old age, including dementia and other neurological disorders.

Yet effective treatments for these diseases represent one of the largest unmet medical needs.[1,2] Limited therapeutics are available, and many of those only mitigate symptoms rather than modify or cure the underlying causes. In the US, just under 50 treatments were approved for neurological conditions, excluding psychiatric ones, from 1970 to 2015. Less than half of these target neurodegenerative disorders like Alzheimer's disease and Parkinson's disease.[5]

"With the aging population, the lack of treatments coupled with the cost of care could lead to a complete breakdown of society if no disease-modifying cure is found," Geerts says.

As the global burden of CNS disorders rises, new drug discovery approaches are required to develop effective prevention and treatment.

CHALLENGES TO CNS DRUG DISCOVERY

Despite the prevalence of CNS diseases, development of treatments for them significantly lags that for many non-CNS diseases. In the US, CNS disease–targeting drugs and biologics developed between 2000 and 2017 required an average of 20% more time in clinical development and took 38% longer to receive Food and Drug Administration approval than non-CNS drugs.[6]

"There are a number of different reasons that CNS treatments are so difficult to develop, both during the preclinical and clinical stages," Geerts says.

First, Geerts notes, the disease pathologies themselves are heterogenous and can vary even between individuals with the same diagnosis. Researchers don't fully understand the molecular mechanisms underlying many neurodegenerative diseases, which makes it difficult to identify therapeutic leads, predict treatment efficacy, or establish meaningful readouts related to disease pathology.

"We historically haven't had good biomarkers that reflect on what's happening inside the brain, so it's more difficult to get objective measurements of improvement or functional changes," Geerts says.

The brain is also a difficult organ to reach—the protective blood-brain barrier blocks entry of most molecules. Getting treatments to the intended target requires expertise in synthetic and medicinal chemistry for small-molecule drugs, while larger molecules, such as peptides or antibodies, require assisted transport to cross the barrier.[2]

For monoclonal antibody treatments developed for Alzheimer's disease, less than 1% of the antibody gets into the brain, Geerts says. "This can cause challenges when considering dosing and toxicity."

In addition, Geerts says, preclinical studies are challenging because of the lack of appropriate animal models or the failure of animal models to predict efficacy in humans. Many neurodegenerative diseases have a complex set of causal factors, including environmental and genetic, that can be difficult to fully replicate in the lab.

These challenges can lead to lengthy and complex clinical trials, many of which fail. In the case of Alzheimer's disease, only 0.04% of the 413 Phase 1–3 trials between 2002 and 2012 produced an approved drug.[7] Over the past decade, many pharmaceutical companies have reduced or abandoned research into drug development for neurodegenerative diseases, in part because of the high failure rate in late-stage trials.[8]

PROGRESS IN BIOTECH DRIVES CNS DRUG DISCOVERY

Recent technological advances and renewed investment have spurred a wave of CNS drug discovery, however, and suggest a bright future for it.[3] For example, Verge Genomics recently secured $98 million in new financing for its AI-driven drug discovery platform that includes a large genomic dataset from human brain tissue. Improved disease understanding—thanks partly to breakthrough technologies in genomics, transcriptomics, and proteomics—have enabled scientists to consider new therapeutic approaches.[2]

Better in vitro and in vivo models are also helping improve the translatability of preclinical research. Greater use of human tissue samples and systems to culture

multiple CNS cell types (e.g., neuronal and glial cells) have helped give scientists a better understanding of both the disease mechanism and how treatments work.

The use of neuronal induced pluripotent stem cells (iPSCs) has been a game changer by allowing researchers to more easily study human brain cells and tissue that previously were difficult to access. Patient-derived human iPSCs better recapitulate the specific disease pathology in vitro during preclinical studies.[9] These cells have also been taken beyond traditional 2D systems to develop 3D brain organoids and "brain-on-a-chip" technologies that better mimic the structural and functional aspects of brain tissue.[10]

Technological advancements have also helped researchers get more information from both patient samples and in vitro model systems. Genomic, transcriptomic, and proteomic studies have contributed to a better understanding of the molecular underpinnings of disease and can aid in target identification during drug development. The application of these technologies to preclinical iPSC systems, which offer a virtually unlimited supply of clinically relevant material to study, have opened the field to a breadth of basic science and drug development studies not previously possible.[9] These preclinical systems and technologies can help researchers better predict efficacy and safety, as well as translatability to clinical data.[2,12]

Machine learning combined with large data sets obtained from analysis of genome, proteogenomic, and proteomic preclinical and clinical studies can help jump-start the drug development course by facilitating molecular drug design with specific target protein structures. Notably, machine learning programs can predict protein structures based on sequence and proteome data alone, opening the door for new drug targets and mechanisms.[11]

To study the efficacy of treatments for CNS disease, researchers can use rodent and nonhuman primate models that incorporate genetic changes associated with disease.

Improved understanding of what causes CNS disease is also reflected in improved animal models. Genetic engineering has been applied to develop mouse models of ALS, in which the gene-encoding antioxidant enzyme superoxide dismutase 1 (SOD1) is modified, and Huntington's disease, in which large CAG trinucleotide repeats are expressed.[13,14] Both systems recapitulate aspects of human disease, providing researchers with better preclinical mammalian systems of study.

Experiments can include traditional cognitive studies, such as memory tests, as well as newer strategies for assessing brain function. For example, brain imaging modalities such as electroencephalography (EEG) and functional magnetic resonance imaging can provide more robust and reliable readouts of treatment localization in the brain and its effect on disease progression.[3,15]

New and more reliable biomarkers have also been identified and help improve

clinical trial design. Geerts says these biomarkers, which could be detected in biological fluid samples or in imaging studies, can help improve the design of clinical trials and the process of drug development.

These advances have already had an impact. Gene therapies have been developed to treat Huntington's disease, and in July 2021 the FDA approved Biogen's monoclonal antibody drug aducanumab—the first drug for Alzheimer's disease to be approved in years.[16,17] Focused investments from entities like the Dementia Discovery Fund, established by the venture capital firm SV Health Investors, are also invigorating the field.[18]

In light of the medical need and investment rates, analysts predict that annual revenues in the CNS product market will reach $131 billion by 2025.[19] Careful consideration of development strategies and effective partnerships can help pharmaceutical companies navigate the CNS drug discovery space.

PARTNERSHIPS TO OVERCOME CNS DRUG DISCOVERY CHALLENGES

Because CNS diseases are only going to become more prevalent, developing new treatment approaches is imperative. CNS drug development is challenging, but the technological advances described have made it more achievable. Pharmaceutical companies also have the option to partner with experts to help navigate the drug discovery and development process.

"Many companies had stopped their research programs into neurodegenerative diseases, but now sophisticated technological advances have become more broadly available, including artifical screening of targets, genomics, and proteomics; the use of patient-derived stem cells to build better in vitro models; and better animal study translatability," says Kris Rutten, director at WuXi AppTec, a full-service provider of open-access capabilities and technology in the heath sciences. "All of these tools build confidence when developing a drug candidate and are paving a new way of doing CNS drug development."

New modalities are expanding possible therapeutic avenues, as well. Anti-sense oligonucleotides, siRNA and other RNA therapeutics, monoclonal antibodies, antibody drug conjugates, and gene therapies have arisen as promising treatment regimes in addition to small molecules.[20-22]

Large-molecule drugs like peptides, oligonucleotides, bispecific antibodies, and proteolysis-targeting chimeras are generating a big buzz, Rutten says. WuXi AppTec's integrated platform fully supports these new modalities, he adds, from hit-finding campaigns through lead generation and candidate selection.

CNS drug development requires a particular skill set that spans pharmacological and preclinical investigations and that not every contract research service provider will possess. Those that can offer expertise throughout the discovery and development pipeline can make productive partners to facilitate projects from

early-stage target and lead identification and validation to clinical stage development and manufacturing.

Jamie Bilsland, chief scientific officer at biotech company AstronauTx, says his team was specifically interested in finding a partner with a complete CNS drug discovery and development tool kit to address project needs related to targeting astrocytes in neurodegenerative disorders (figure 2).

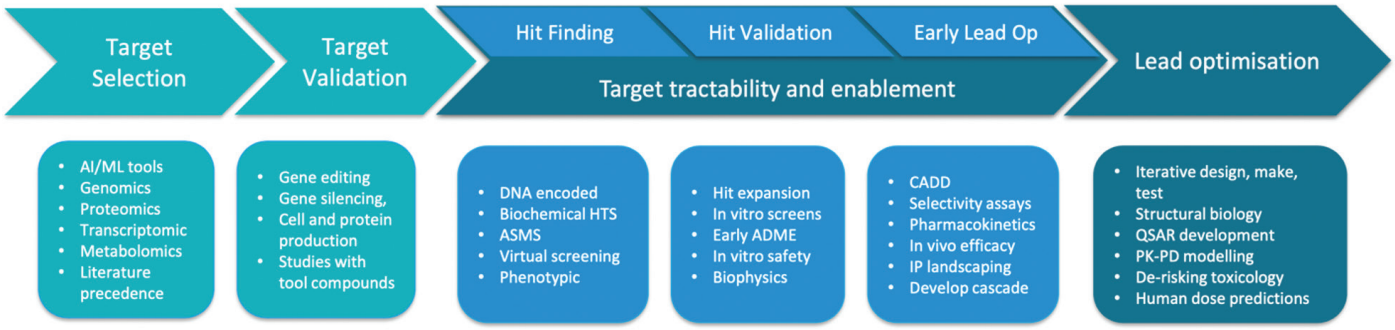

Figure 2: WuXi AppTec's CNS drug development platform encompasses expertise from target selection to lead optimization.[3]

Source WuXi AppTec

CASE STUDY: TARGETING ASTROCYTES IN NEURODEGENERATIVE DISEASE

Astrocytes are a type of nonneuronal cell found in the CNS that are critical for homeostasis and are dysregulated in neurodegeneration. In Alzheimer's disease, for instance, astrocytes appear to be hyperactive, a state that drives neuronal hyperexcitability and contributes to disease progression.

Researchers at AstronauTx have been developing therapeutics for dementia that target astrocytes and restore their homeostatic functions. They have identified a druggable, astrocyte-specific receptor enriched in CNS astrocytes that they call Target 1.

Jamie Bilsland, chief scientific officer at AstronauTx, says the research team partnered with WuXi AppTec to synthesize chemical compounds that block Target 1 and conduct absorption, distribution, metabolism, excretion, and pharmacokinetics studies on these compounds.

The partnership has evolved to include what Bilsland calls a "translational plan" to investigate its therapeutics. The companies will identify clinical biomarkers to understand disease progression and response to treatment, first in plasma and in vitro systems and then in animal models of disease. These data will allow AstronauTx to better understand the drug's pharmacokinetic and pharmacodynamic properties and identify clinical biomarkers for the next stage of development.

These studies involve using EEG to investigate changes in disease progression in a genetic mouse model for Alzheimer's disease. The researchers found that treatment with agents blocking Target 1 caused alterations in the animals' EEGs that suggest their treatment is effective in a preclinical and pathologically relevant setting.

AstronauTx is continuing to investigate Target 1 in transgenic mouse models of Alzheimer's disease in collaboration with WuXi AppTec. The partners plan to start preclinical development in the near future.

"We originally partnered with WuXi AppTec for their synthetic chemistry expertise and to conduct pharmacology screening but have since been working on early-stage development and scale-up of compounds of interest for toxicology studies," Bilsland says. The firm's scale and scope have made it "an ideal partner," he adds.

Specific to CNS drug development, a clear assessment of preclinical models and possible readouts should be a priority. For example, WuXi AppTec has a variety of cellular and animal models for various neurodegenerative diseases and have developed brain-imaging readouts that can track disease progression and treatment effects in living animals.

"We can conduct EEG and electrophysiology readouts in treated animals and use the data plus behavioral studies to understand how treatment is affecting disease progression," says Deming Xu, executive director at WuXi AppTec.[23] Beyond a partner's technical capabilities, Bilsland says, companies should consider the ease of interaction.

"Having the ability to contact someone within our time zone that can speak about our projects and find the best resources available has been valuable," Bilsland says. WuXi AppTec assigns specific project managers to key regions, including China and the US and UK, to work directly with local partners.

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