PharmaVOICE

THERAPEUTIC DIGEST

CENTRAL NERVOUS SYSTEM

EXPLORING THE TRICKY MARKET OF CNS DISORDER THERAPY

IN COLLABORATION WITH thinkgen

NOVEMBER 2020

An Interview With a Medscape Education Data Scientist on the Power of AI in Medical Education

Artificial intelligence (AI) is a rapidly growing field with many applications in the world of medicine, including continuing medical education. Ritu Kumar, Medscape lead data scientist, explains how Medscape Education is harnessing the power of AI.

Explaining AI

"AI is the way in which machines mimic human intelligence. It's a powerful tool with many benefits, including solving problems and creating 'smarter' solutions with algorithms," explains Ritu Kumar. "At Medscape, we use the power of AI to create Precision Education, or education specially designed for and targeted to members who need it most, in the format they prefer. This allows us to go beyond simple segmentation of learners and provide more personalization to our recommended education that matches a member's individual learning journey."

Medscape utilizes the triad of essential elements for AI -- data, tools, and expertise. By leveraging over 25 years of data regarding healthcare professionals' learning preferences, the Medscape machine learning team can build and evolve AI algorithms designed to perform sophisticated predictions and calculations.

Putting AI to Use

"We started by building a hybrid recommendation engine to help us recommend the right education to the right clinicians at the right time during their education journey," says Ms. Kumar. "Using AI tools, we look at the education our clinicians have taken in the past, and compare it to the rest of the education we have available. We are then able to recommend to clinicians that because they found a certain education program useful, other selected programs may also be of interest or relevant to their learning need.

"Our next initiative was focused on natural language processing -- using AI to analyze freeform feedback from members to drive improvements or generate ideas for medical education programs."

Seeing Results

The AI-driven hybrid recommendation engine has yielded great results for Medscape, with increased email conversions and completion of outcomes assessments, both of which show that the right audience is being presented with the right education.

"We are also learning a lot from our members about their preferences, which will allow us to continue to evolve and personalize our education offerings," notes Ms. Kumar.

"We're only just starting to uncover the power of what AI can do. We are always finding innovative approaches to support our members' needs. Our team of machine learning engineers are continuously working to develop new algorithms, and I'm excited about what AI can bring to the future of medical education."

Medscape EDUCATION

Table of Contents

thinkgen Editorial content provided by ThinkGen (www.think-gen.com)
Written by Kristina Erfe Pines

Central Nervous System

Exploring the tricky market of CNS disorder therapy

Central nervous system (CNS) disorders are a group of neurological disorders that affect the structure and/or function of the brain or the spinal column. There are more than 600 diseases of the nervous system. These disorders range from epilepsy, stroke, migraine, Alzheimer's, Parkinson's, dementia, multiple sclerosis, brain injuries, neuro-infections, schizophrenia, psychosis, and other mental disorders. The demand for neurological disease therapies has increased in step with the growing age-related healthcare burden, and so has the potential market size. With the aging of the baby-boomer population, the market for new therapies and cures has grown exponentially. Today's CNS disease market may be on the verge of experiencing the same boom that drove the cancer therapy market.

Innovation is needed in developing more potent drugs and therapies, but due to the complexity of the central nervous system, progress has been an uphill battle for the last decade. This is especially true for neuropsychiatric diseases where targets are poorly defined, difficult to assay, and pose challenges in efficiently validating clinical efficiency of drugs during clinical trials as most diseases progress slowly and develop over the years.

America's biopharmaceutical research companies are developing nearly 450 new medicines to prevent and treat neurological disorders.

Strong opportunities for CNS focused drugs exist. Currently, there is widespread excitement about the advances in CNS research and discovery of novel research in CNS over the past five years. These findings are bringing greater venture capital funding and are resulting in large pharma rebuilding their R&D platforms to address these debilitating diseases that affect so many people in our aging populations. America's biopharmaceutical research companies are developing nearly 450 new medicines to prevent and treat neurological disorders, according to a report by the Pharmaceutical Research and Manufacturers of America (PhRMA)[1].

CNS diseases affect approximately 1 billion people worldwide, according to the World Health Organization (WHO). The global CNS disease market is expected to grow to $128.9 billion by 2025. With innovation and potential to cure neurological diseases at an all-time high, investors and biopharma collaborators are starting to take notice of new gene and cell therapy technologies as viable catalysts for growth.

The Current CNS Disorders Market

For well more than a decade, only a handful of large pharmaceutical companies have kept brain drugs a focus, but that's in stark contrast to 25 years ago, when almost every major developer was pouring money into the category. Sales of Eli Lilly's Prozac enticed rivals to find their own blockbuster antidepressants. Pfizer then brought Zoloft to market, followed by GlaxoSmithKline (GSK) with Paxil. By the early 2000s, a new wave of antipsychotics was helping build multi-billion-dollar neurology businesses for AstraZeneca and Bristol Myers Squibb (BMS).

But AstraZeneca, BMS, GSK, and more recently, Pfizer and Amgen no longer devote significant resources to neuroscience. Others, such as Lilly, Sanofi, and Merck have narrowed their investments and number of drug programs. Often these retreats came after a series of clinical failures that called into question whether money would be better spent elsewhere.

Neuroscience still received healthy levels of early investment, though. It attracted $1.5 billion from venture capitalists in 2018[2], putting it second only to cancer. Their bet may be well placed too, as industry watchers foresee big pharma mounting a return to neuroscience in the next few years, lured by emerging treatments for epilepsy, mood disorders and genetic diseases of the CNS.

Global sales of prescription and over the counter (OTC) CNS disease-related products totaled $86 billion in 2019.

Global sales of prescription and over the counter (OTC) CNS disease-related products totaled $86 billion in 2019. Sales were predicted to grow in 2020, but the field has been one of those hardest hit by the COVID-19 pandemic. The total 2020 forecast fell by $1.4 billion between March and June of 2020, as social distancing and lockdown measures made clinics more difficult to access. But, despite the uncertainties caused by the pandemic, market analysts predict that the CNS product market will expand to $101 billion in 2022 and to $131 billion in 2025[3].

Multiple Sclerosis

Therapies for multiple sclerosis (MS) accounted for seven of the top 15 CNS products and 26% of CNS product sales in 2019 — the highest market share, largely driven by products such as Biogen's Tecfidera (dimethyl fumarate) and Roche's Ocrevus (ocrelizumab). Tecfidera, an oral small-molecule drug, was the best-selling CNS product in 2019, with sales of $4.4 billion[4]. But Roche's injectable monoclonal antibody (mAB) Ocrevus, the product in the current top 15 that has the largest forecasted growth in sales up to 2025 — $3.9 billion — could steal Tecfidera's crown as early as 2022[5]. How soon this could happen could depend, in part, on a patent battle between Biogen and Mylan, which could see Tecfidera's patent life cut short from 2028 to 2021[6]. The loss of patent protection for Novartis' oral small-molecule drug Gilenya (fingolimod) is also expected to lead to a large drop of sales of $2.6 billion by 2025.

Antipsychotics

Antipsychotic products were third in the CNS market ranking of 2019. They are predicted to retain this position in 2022 and 2025, with Johnson & Johnson's intravenous schizophrenia drug Invega Sustenna (paliperidone palmitate) a long-standing sales driver in this field, having been approved back in 2009[7]. Among the emerging products in this area, Acadia Pharmaceuticals' Parkinson's disease antipsychotics Nuplazid (pimavanserin) has the greatest forecasted growth in sales: $2.5 billion[8].

Anti-Epileptics

Anti-epileptics account for 12% of the market. Antidepressants and psychostimulants each took 6% of CNS market share, but the two markets are forecasted to trend in the opposite direction in the next few years. Antidepressant product sales such as Rexulti (brexpiprazole). Sales of psychostimulants, in contrast, are set to fall from $5.2 billion to $3.2 billion over the same period, owing to a decline in sales of Takeda's Vyvanse (lisdexamfetamine dimesylate), which is used to treat attention-deficit hyperactivity disorder and is anticipated to lose patent protection in 2023[9].

Recent Deals

Recent deals in the CNS area highlight growing interest in gene therapy approaches, encouraged by the U.S. Food and Drug Administration (FDA) approval of Zolgensma for SMA in 2019[10]. In February 2020, for example, Biogen announced a $2.72 billion licensing deal with Sangamo Therapeutics to develop and commercialize gene regulation therapies based on Sangamo's zinc finger platform to treat Alzheimer's disease, Parkinson's disease, and other neurological diseases[11]. In January 2019, Neurocrine Biosciences signed a similar deal with Voyager Therapeutics to

develop and commercialize a series of gene therapy programs for neurodegenerative diseases, including VY-AADC for Parkinson's disease[12]. Neurocrine agreed to provide funding for ongoing development of each program.

Biogen also signed a deal agreeing to pay Pfizer $75 million upfront and up to $635 million in milestones for PF-05251749, a drug candidate intended to improve behavioral and neurological symptoms in disorders by modulating circadian rhythms[13]. This adds diversity to Biogen's investments in the failure-stricken area of Alzheimer's disease, where its amyloid-targeted mAb aducanumab is now being considered for approval by the FDA. The agency's decision, expected by early next year, could have big implications not just for Biogen but for the CNS field overall[14].

Recent Exits

Recent exits, however, could hint that neuroscience isn't yet seen as a near-term opportunity. Amgen terminated drug programs in schizophrenia and Alzheimer's disease before leaving neuroscience almost entirely in late 2019[15]. Pfizer's story is similar. It had drugs fail in Alzheimer's and Huntington's disease in the years leading up to 2018, when the company decided to take a handful of compounds and create a CNS-focused spin-out with Bain Capital[16]. Pfizer said the move allowed it to redirect money to areas of greater expertise. Across neuroscience, clinical failures have stacked up because drug makers didn't know enough about how to make diseases work. These failures then made further investments a riskier proposition for big pharma. At the same time, researchers were developing impressive new drugs in different diseases, most notably cancer, which spurred large companies to reprioritize. Since most didn't have an extensive list of promising brain drugs, neuroscience research proved easier to discontinue.

A consequence of reprioritization, however, is a relative lack of big pharma resources invested in developing new, effective therapies for some of the world's most common illnesses. While "me-too" cancer drugs proliferate, there are few, if any, novel treatments for diseases like Alzheimer's, Parkinson's, and depression, each of which affect millions of patients.

Experts believe that just a few positive studies may be all it takes to bring big pharma back in. That's been true with gene therapy as well as with immune-oncology, which produced some of the world's best-selling drugs, including Merck's Keytruda and BMS' Opdivo.

That pressure may explain why many big pharma companies continue to study Alzheimer's drugs even if they're not deeply involved in neuroscience. Analysts expect the first Alzheimer's treatment on the market that shows an effect on the disease, rather than just its symptoms, would become an

instant blockbuster. Yet, neurodegenerative disorders such as Alzheimer's and Parkinson's have proven exceptionally challenging, due in part to their tangled biological roots.

AstraZeneca, Lilly, Merck, Novartis, Pfizer, and Roche each saw experimental Alzheimer's treatments fail in late-stage testing. Biogen, a top player in neuroscience, plans on asking regulators to greenlight[17] a drug that works in a similar way to its peers' failed attempts, but controversial clinical data make its efficacy the subject of intense debate[18] .

Gene Therapy

Genetic research and subsequent gene therapies could revolutionize the treatment for diseases afflicting the brain. Advances such as genetic sequencing and new DNA editing technologies are giving scientists extensively more information on brain behaviors and feedback.

For example, gene therapy and advanced technologies have emerging opportunities to provide treatment for Parkinson's disease (PD), according to review findings published in Polish Journal of Neurology and Neurosurgery[19]. Currently, vector-based intracerebral gene therapies are being used to treat specific neurodegenerative conditions. While these therapies have been included in clinical trials for PD and other similar conditions, there has yet to be a breakthrough treatment. However, researchers note that new molecular agents, device innovations, and improved neurosurgical techniques have unlocked the potential of therapies delivered directly via infusion into the CNS.

Current research has the potential to increase the quality of life and delay cognitive decline for patients diagnosed with neurological disorders. For example, scientists are beginning to understand more about the genes that affect the development of Alzheimer's disease. Such discoveries could lead to new research pathways to help find ways to slow, delay, or reverse the effects of the disease. According to an Alzheimer's Association 2015 report,[20] a treatment that delays the onset of Alzheimer's by five years could reduce the cost of care for the disease by $367 billion a year in 2050[21].

Though an Alzheimer's solution looks far off, drug makers have notched victories in other neurological diseases like spinal muscular atrophy (SMA), in which a genetic defect causes patients' muscles to waste away. Effective therapies from Biogen and Novartis have come to market since the end of 2016, and a third from Roche was approved April 2020.

Drug makers now have better tools to manipulate and correct genes than in the 1990s and early 2000s. As a result, diseases tied to single genetic defects, such as SMA, seem easier to target and

less risky — attributes that would appeal to pharmaceutical companies looking for an entry point back into neuroscience. There are already a couple of examples of this, with Pfizer getting into Duchenne muscular dystrophy through its acquisition of Bamboo Therapeutics and Roche showing interest in a Huntington's program developed by Ionis Pharmaceuticals. That's not to say these illnesses are easily treatable. The newfound excitement around Huntington's, for example, belies the fact that no drug has yet been proven to change the course of the disease.

Regenxbio

It was Regenxbio's NAV Technology Platform that Avexis licensed to develop Zolgensma, the first cure for spinal muscular atrophy (SMA) and a monumental triumph of modern medicine[22]. SMA is a fatal childhood neuromuscular disease caused by a mutation in a single gene. The $2.1 million FDA-approved therapy is the result of a collaboration of Novartis, Avexis, and Regenxbio, and is also only one of two gene therapies with neurological indications worldwide. Zolgensma's success is the de facto blueprint for biotechnology companies with their sights set on treating neurological diseases[23].

Beyond Zolgensma, Regenxbio has 16 other licensed product candidates for CNS indications that are moving through clinical trials, including one in Phase III and six in Phase I/II.

Regenxbio entered into licensing agreements with Lysogene and Sarepta Therapeutics to develop, LYS-SAF302, the only Mucopolysaccharidosis Type IIIA (MPS IIIA) treatment currently in a Phase III trial[24]. MPS IIIA, also known as Sanfilippo syndrome, is a group of rare genetic lysosomal storage diseases with no approved treatments. MPS III is characterized by aggressive behavior, seizures, loss of speech or vision, an inability to sleep, and premature death. An estimated 70% of children with MPS III do not reach age 18.

The six Phase I/II trials include various licensing agreements for the potential treatment of SMA Type II and III, a type of Parkinson's disease, two other potential treatments for MPS IIIA, one for MPS IIIB, and another infantile disease known as ceroid lipofuscinosis neuronal 1 (CLN1).

Neuronascent

Neuronascent of Clarksville, Md., announced the FDA clearance of its investigational new drug (IND) application for its oral glia-to-neuron conversion drug, NNI-362, in May 2019 and began placebo-controlled Phase IA trials in August 2019[25]. The company, founded by CEO Judith Kelleher-Andersson, Ph.D., received $2.5 million the fall of 2018 from the National Institute of Aging (NIA) and is expected to report primary outcomes in April 2020.

Recently, a preclinical study demonstrated that embryonic cells can restore cognitive function and reduce seizures following traumatic brain injury (TBI). These promising results indicate that cellular replacement may be possibly in the nervous system despite its intrinsic complexity.

Innovators at the forefront of biotechnology may be set to develop and test therapies that replenish lost brain cells, but only time will tell if programming and/or re-growing a patient's lost cells can safely and effectively cure neurological diseases.

AgeneBio

AgeneBio's late-stage clinical pipeline consists of novel drugs being tested for their ability to restore brain function in patients living with neurodegenerative diseases. AGB101, the company's lead drug, is a candidate therapy for mild cognitive impairment (MCI) caused by Alzheimer's disease and is currently in a Phase III pivotal trial that is being funded by Alzheimer's Drug Discovery Foundation and the NIA[26]. AGB101 is an FDA-approved anticonvulsant drug, levetiracetam, in a proprietary extended-release formulation that targets hyperactivity specifically in the hippocampus.

Neuraly

Neuraly, a biopharmaceutical company spun out of Johns Hopkins University, was acquired by the global biotech company D&D Pharmatech in 2019. The novel compounds in Neuraly's discovery and early clinical pipelines target pathways involved in neurodegenerative disorders.

Since no currently available drugs cure degenerative brain diseases, symptom reduction or delay in disease progression are desired outcomes for drug makers. Nerauly's lead compound, NLY01, aims to slow disease progression by inhibiting a negative form of glial cell activation that produces neurotoxicity in the brain[27]. NLY01 is being tested for indications in Parkinson's disease and Alzheimer's disease in separate Phase I trials.

NeuroDiagnostics

As with Zolgensma, early diagnosis and treatment may increase the therapeutic potential of drugs targeting the nervous system. Therefore, companies targeting neurodegenerative diseases and patients suffering from them stand to win when safe and effective early diagnostic technologies are commercialized.

NeuroDiagnostics created Discern, a test that they claim reduces the time to diagnosis and provides highly accurate results when diagnosing Alzheimer's disease. A major challenge of diagnosis has

previously been the difficulty of distinguishing Alzheimer's disease from other illnesses as the therapeutic window narrows[28].

The Discern test uses a small skin sample to biopsy fibroblasts, which are connective tissue cells that affected in some inherited forms of neurodegenerative diseases. These cells are examined off-site for the presence of Alzheimer's disease hallmarks like diminished capacity to activate checkpoint proteins. Successful early detection via potential diagnostics could have a significant impact on the R&D costs and efficacy of CNS treatments.

Companies aiming to diagnose neurological diseases from peripheral blood, skin, or other minimally invasive tissues can expect an overall lower cost burden on the path to commercialization. Since diagnostic tests like these do not typically require clinical trials to enter the market, they represent accessible products to create, license, and commercialize that leverage the collective knowledge of biomarker biology to serve the growing need for early detection technologies that are accurate, painless, inexpensive, and straightforward.

Experimental Autoimmune Encephalomyelitis (EAE)

Recent research is integrating novel technologies and enabling a more defined understanding of disease mechanisms in autoimmune diseases of the CNS. Animal models EAE enable the study of "aspects" of human diseases; However, these models are poorly suited for drug testing or assessing disease etiology[29,30]. Moreover, one of the major challenges in the field constitutes achieving integration of human data obtained using diverse methodologies and from different tissues.

Clinical Trial Management

The foundation of therapeutic advances in CNS lies in novel drug discovery methods.

The foundation of therapeutic advances in CNS lies in novel drug discovery methods. But what about when the molecules reach clinical trials? So much investment and time goes into getting the CNS indicated therapeutics into studies in man, it would be terrible if clinical sites dropped the ball on simple things like managing the temperature-controlled drugs on-site.

According to the Good Distribution Practices (GDP) requirements, if stability data of a product in development requires certain temperature handling, the clinical site must have documented proof those investigational CNS medicines have been kept within defined

temperatures in storage and during transport to worldwide clinical sites. If they don't, clinical sites and their sponsors face serious consequences from regulatory authorities and ethics committee violations that could impact trial timelines and delay the novel therapeutics entry in market.

Unlike earlier life cycle challenges, maintaining drug stability during clinical trials is very manageable with robust technology that is readily available. As the CNS investigational medicines are distributed to clinical trial sites, temperature monitoring plays an important role in maintaining product stability.

For stability and temperature management on-site, while the CNS investigational medicines are in storage in refrigerators or freezers, there is new technology in the field of digital data loggers, called independent monitoring. These are stand-alone, self-powered systems — virtually "hands-free" base and sensor systems. They allow clinical staff to spend more time with patients, instead of manually recording temperatures. Reports are generated simply by connecting the base to a computer using a USB connection.

Conclusion

Neurological disorders significantly outnumber diseases in other therapeutic areas, inflict higher treatment and loss of productivity costs than cancer, cardiovascular disease, and diabetes put together and are growing in incidence faster than any other disease class in the EU and the United States. More than 600 known neurological disorders now top the leading disease list in the developed world. In Europe, 38% of the population is said to be affected by brain disorders[31], whose burden in 2010 was estimated to be €798 billion, or $944 billion. Over the coming years, the European Brain Council has forecasted a further 20% increase in neurologic illness in the EU[32].

To exacerbate the problem, ageing populations have never before borne so much impact on the global total. As cardiovascular, infectious, and oncology treatments ameliorated, higher survivability meant that the incidence of diseases of "old age," such as dementia and AD, strokes, Parkinson's, and progressive hearing loss, increased. AD and stroke have been identified as the fastest-growing threats to US health, ahead of autoimmune disorders and diabetes[33].

Despite the high risks, the rewards of developing the next AD medication appear to be much higher. Indeed, even a relatively mediocre Alzheimer's treatment approved by the FDA could break a new blockbuster sales record. And this is why, despite varying strategies, Big pharma is re-emerging and toeing neuro-pharmaceutical development.

NOTES:

[1] "Nearly 450 Medicines for Neurological Disorders." Pharmaceutical Research and Manufacturers of America (PhRMA), Washington DC, July 2013.

[2] "A view into the central nervous system disorders market." Nature. September 2020.

[3] "A view into the central nervous system disorders market." Nature. September 2020.

[4] Sagonowsky E. "Biogen top 20 pharma companies by 2019." Fierce Pharma. April 2020.

[5] "Dominant Ocrevus predicted to hit $6.8 billion in sales by 2025." Pharma Letter. April 2019.

[6] "Dominant Ocrevus predicted to hit $6.8 billion in sales by 2025." Pharma Letter. April 2019.

[7] "Schizophrenia drugs market 2020 overview trend and forecast to 2024." MarketWatch. April 2020.

[8] "Schizophrenia drugs market 2020 overview trend and forecast to 2024." MarketWatch. April 2020.

[9] "ADHD drugs do not improve cognition in healthy college students." ScienceDaily. July 2018.

[10] Weintraub A. "Novartis cites 'transformative' data on Zolgensma as it rolls out SMA gene therapy in Europe." Fierce Pharma. October 2020.

[11] Jensen K. "Sangamo, Novartis team up to develop genetic medicines for autism, other brain disorders." BioPharmaDrive. July 2020.

[12] Keown A "Neurocrine and Voyager team up on huge deal for gene therapy in Parkinson's." BioSpace. January 29, 2019.

[13] Gardner J. "Biogen finds $75M home for Pfizer Alzheimer's drug." BioPharmaDrive. January 2020.

[14] Gardner J. "Biogen finds $75M home for Pfizer Alzheimer's drug." BioPharmaDrive. January 2020.

[15] Dunn A. "Amgen exits neuroscience R&D as pharma pulls back from field." BioPharmaDrive. October 2019.

[16] Dunn A. "Pfizer, Bain Capital launch neuroscience company backed with $350M." BioPharmaDrive. October 2018.

[17] Bell J. "In major surprise, Biogen will ask FDA to approve Alzheimer's drug aducanumab." BioPharmaDrive. October 2019.

[18] Bell J. "The clearest picture of Biogen's Alzheimer's drug is still fuzzy." BioPharmaDrive. December 2019.

[19] Fiandaca MS, et al. "Advancing gene therapies, methods, and technologies for Parkinson disease and other neurological disorders." Polish Journal of Neurology and Neurosurgery. June 18, 2020.

[20] "Changing trajectory of Alzheimer's disease: how treatment by 2025 saves lives and dollars." Alzheimer's Association. 2015.

[21] "Changing trajectory of Alzheimer's disease: how treatment by 2025 saves lives and dollars." Alzheimer's Association. 2015.

[22] "REGENXBIO announces first FDA approval of gene therapy based on its proprietary NAV technology platform." PR Newswire. May 2019.

[23] "REGENXBIO announces first FDA approval of gene therapy based on its proprietary NAV technology platform." PR Newswire. May 2019.

[24] "Sarepta and Lysogene announce exclusive license agreement for LYS-SAF302, a late stage gene therapy for the treatment of MPS IIIA and grant of option rights to an additional CNS gene therapy candidate." Global Newswire. October 2018.

[25] Neuronascent announces FDA clearance of IND application for NNI-362 an aging therapy to treat Alzheimer's disease." Global Newswire. May 2019.

[26] "AgeneBio announces first patient enrollment in the phase 3 clinical trial to evaluate AGB101 to treat amnestic mild cognitive impairment due to Alzheimer's disease." PR Newswire. January 2019.

[27] Pena A. "First patient dosed in Neuraly's NLY01 trial testing safety, efficacy." Parkinson's News Today. March 2020.

[28] McCarty M. "Breakthrough status granted to AD test by Neurodiagnostics." BioWorld. October 2018.

[29] Korn T, Kallies A. "T cell responses in the central nervous system." Nature Reviews Immunology. 2017.

[30] Becher B, et al. "Cytokine networks in neuroinflammation." Nature Reviews Immunology. 2017.

[31] "Growing brain disorders lead to call for more research." British Neuroscience Association. January 2013.

[32] "Growing brain disorders lead to call for more research." British Neuroscience Association. January 2013.

[33] "Neurological diseases on the rise." European-Hospital. May 2013.

RESOURCES:

"ADHD drugs do not improve cognition in healthy college students." ScienceDaily. July 2018.

"AgeneBio announces first patient enrollment in the phase 3 clinical trial to evaluate AGB101 to treat amnestic mild cognitive impairment due to Alzheimer's disease." PR Newswire. January 2019.

"A view into the central nervous system disorders market." Nature. September 2020.

"Changing trajectory of Alzheimer's disease: how treatment by 2025 saves lives and dollars." Alzheimer's Association. 2015.

"Dominant Ocrevus predicted to hit $6.8 billion in sales by 2025." Pharma Letter. April 2019.

"Growing brain disorders lead to call for more research." British Neuroscience Association. January 2013.

"Nearly 450 Medicines for Neurological Disorders." Pharmaceutical Research and Manufacturers of America (PhRMA), Washington DC, July 2013.

"Neurological diseases on the rise." European-Hospital. May 2013.

"Neuronascent announces FDA clearance of IND application for NNI-362 an aging therapy to treat Alzheimer's disease." Global Newswire. May 2019.

"Novel Drug Approvals for 2020. FDA. Opened November 3, 2020 https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020

"REGENXBIO announces first FDA approval of gene therapy based on its proprietary NAV technology platform." PR Newswire. May 2019.

"Schizophrenia drugs market 2020 overview trend and forecast to 2024." MarketWatch. April 2020.

"Therapeutic advances in CNS." Elpro. April 2018

"Therapeutic development in the absence of predictive animal models of nervous system disorders: proceedings of a workshop." National Academies of Sciences. March 2017.

Becher B, et al. "Cytokine networks in neuroinflammation." Nature Reviews Immunology. 2017.

Bell J. "Big pharma backed away from brain drugs. Is a return in sight?" BioPharmaDrive. January 2020.

Bell J. "In major surprise, Biogen will ask FDA to approve Alzheimer's drug aducanumab." BioPharmaDrive. October 2019.

Bell J. "The clearest picture of Biogen's Alzheimer's drug is still fuzzy." BioPharmaDrive. December 2019.

Brown S. " Why the next biotech boom could be sparked by therapies for neurological disorders." BioBuzz. 2019.

Dunn A. "Amgen exits neuroscience R&D as pharma pulls back from field." BioPharmaDrive. October 2019.

Dunn A. "Pfizer, Bain Capital launch neuroscience company backed with $350M." BioPharmaDrive. October 2018.

Fiandaca MS, et al. "Advancing gene therapies, methods, and technologies for Parkinson disease and other neurological

disorders." Polish Journal of Neurology and Neurosurgery. June 18, 2020.

Gardner J. "Biogen finds $75M home for Pfizer Alzheimer's drug." BioPharmaDrive. January 2020.

Gavidia, M. "What innovations, technologies are emerging in the pipeline of Parkinson disease treatment." AJMC. June 2020.

Grikoff V, Kaczmarek L. "The need for new approaches in CNS drug discovery: why drugs have failed, and what can be done to improve outcomes." Neuropharmacology. February 2018.

Jensen K. "Sangamo, Novartis team up to develop genetic medicines for autism, other brain disorders." BioPharmaDrive. July 2020.

Keown A "Neurocrine and Voyager team up on huge deal for gene therapy in Parkinson's." BioSpace. January 29, 2019.

Korn T, Kallies A. "T cell responses in the central nervous system." Nature Reviews Immunology. 2017.

Kumar A, et al. "Therapeutic advances for Huntington's disease." Brain Sciences. 2020.

McCarty M. "Breakthrough status granted to AD test by Neurodiagnostics." BioWorld. October 2018.

Meyer zu Horste G, et al. "Next generation neuroimmunology: new technologies to understand central nervous system autoimmunity." Trends in Immunology. March 2020.

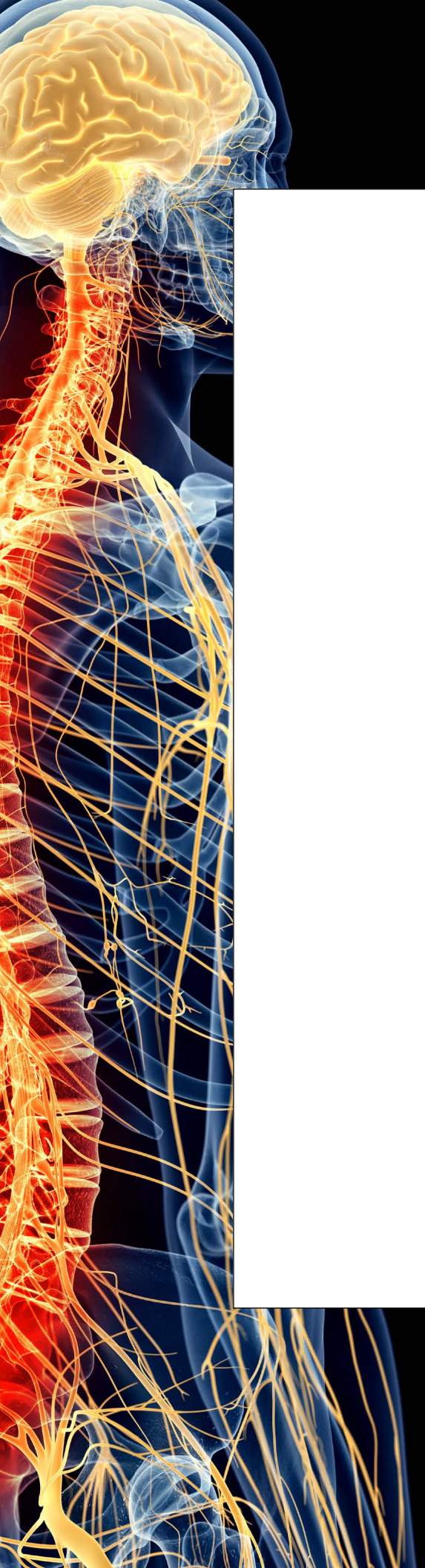
Pena A. "First patient dosed in Neuraly's NLY01 trial testing safety, efficacy." Parkinson's News Today. March 2020.

Sagonowsky E. "Biogen top 20 pharma companies by 2019." Fierce Pharma. April 2020.

"Sarepta and Lysogene announce exclusive license agreement for LYS-SAF302, a late stage gene therapy for the treatment of MPS IIIA and grant of option rights to an additional CNS gene therapy candidate." Global Newswire. October 2018.

Shannon K. "Recent advances in the treatment of Huntington's disease: targeting DNA and RNA." CNS Drugs. January 2020.

Weintraub A. "Novartis cites 'transformative' data on Zolgensma as it rolls out SMA gene therapy in Europe." Fierce Pharma. October 2020.



PharmaVOICE THERAPEUTIC DIGESTS

2020 THERAPEUTIC TOPICS:

Gene Therapy

Mental Health

Alzheimer's Disease

Medical Cannabis

Diabetes

Infectious Diseases

Oncology

Cardiology

Digital Therapeutics

Women's Health

Central Nervous System

Rare Disease

www.pharmavoice.com