Next-Generation Medicines for Neurological and Neurodegenerative Disorders: From Discovery to Commercialization

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Abstract

This book delves deeply into the discovery, preclinical and clinical development, and commercialization of next-generation medicines designed to treat neurological and neurodegenerative disorders. The book also covers pharmacologic targeting of the gut-brain axis in neurological and neurodegenerative disorders, the associated obstacles, challenges, and technologies involved, and the role of nanomedicines in addressing some of those challenges. The editors invited leading scientists and researchers with established credentials in CNS drug development and related technologies to contribute to the writing of the chapters. As a consequence, the editor and the readers are presented with a unique perspective of a selection of novel ideas, technologies, and medicines that have the potential to transform the current therapeutic landscape. The book is aimed primarily toward those in the pharmaceutical industry and academia who are involved in the development of drugs for treating CNS disorders. It will also serve as a valuable resource for technology transfer organizations and venture capital firms for selecting and investing in therapeutic ideas for treating CNS disorders. When we think of neurological and neurodegenerative disorders, we typically think of old age-related diseases such as Alzheimer's or Parkinson's disorders. While it is true that these diseases are responsible for the bulk of the societal and economic cost of CNS disorders, it is also true that CNS disorders are typically difficult to treat as a collective group because they have many general challenges in drug development in common, regardless of patient population or phase of life.

Keywords: Neurological and Neurodegenerative Disorders, Preclinical and Clinical Development of Next-Generation Medicines, Gut-Brain Axis Pharmacologic Targeting, Obstacles in CNS Drug Development, Nanomedicines in Neurodegenerative Disorders, CNS Drug Development Technologies, Challenges in CNS Drug Development, Innovative CNS Therapeutic Ideas, Transforming the Therapeutic Landscape, Pharmaceutical Industry, and Academia in CNS Development, Technology Transfer in CNS Therapies, Venture Capital and CNS Drug Investment, Alzheimer's Disease and Parkinson's Disease, Societal and Economic Costs of CNS Disorders, Drug Development Challenges Across CNS Disorders, Aging-Related Neurodegenerative Disorders, CNS Drug Development for Diverse Patient Populations.

1. Introduction

Neurological disorders impose a considerable burden on patients and society due to their high prevalence and severe disability. Such disorders can be classified into two main categories: neurological disorders associated with the alteration of normal brain function, such as epilepsy, headache, and sleep disorders; and neurological disorders related to brain tissue damage at the macroscopic and microscopic levels, such as brain injury, stroke, and neurodegenerative diseases. The former group is accounted for by their high prevalence in the general population and the latter group by their major contribution to disability-adjusted life years lost. Among neurological disorders, Alzheimer's disease and Parkinson's disease are the most prevalent age-related neurodegenerative diseases, which have been proposed to be the focus of the so-called "pandemic of dementia" due to the increased life expectancy and thus increased number of aging populations.

Compared to the number of novel therapies for the treatment of other systemic diseases, the supply of advanced treatment options for neurological disorders remains limited. More specifically, there is no disease-modifying therapy for neurodegenerative diseases at all, and the most available treatments have only symptomatic effects. Although the lack of druggable biological targets has traditionally been attributed to the limited progress of drug supply for neurological disorders, this belief is being challenged by recently proposed methods, including minimally invasive biomarker measurements, improved opportunities for human genomics investigations, and innovative study designs utilizing big clinical and biomedical data. Indeed, several next-generation therapeutic modalities, including novel vaccines and passive immunotherapies, have shown substantial efficacy in Alzheimer's disease, and numerous novel disease-modifying therapies for neurodegenerative diseases are currently in development. However, there are still various challenges to consider when translating next-generation therapeutics from discovery to commercialization.

1.1. Significance of Neurological Disorders in Modern Medicine

In modern medicine, an increasing number of therapeutic options are available to treat prevalent and impactful health issues, such as cardiovascular disease, diabetes and obesity, developmental disorders, immunological deficiencies and diseases, infectious diseases, musculoskeletal dysfunction, neoplasia, respiratory problems, trauma, and tissue injuries. There are limitations in treatments for neurological disorders and neurodegenerative diseases. Specifically, there are limited proactive and efficacious treatments to ameliorate or skip the deterioration phase of these disorders. Examples of

such diseases include Alzheimer's and Huntington's diseases, amyotrophic lateral sclerosis, schizophrenia, myasthenia gravis, multiple sclerosis, neurological pain resulting from injuries and infections, epilepsy, and autism. Neurological disorders make up 4 of the top 10 causes of disability-adjusted life years in the world.

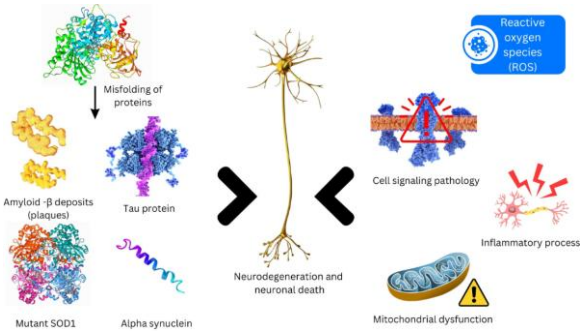

Fig 1 : Therapeutic Innovations in Neurodegenerative Disorders

In this natural history of these disorders, intervention before, during, or soon after the degeneration may prevent, minimize, or ameliorate its consequences. To progress towards this reality, we will need to come up with state-of-the-art nucleic acid-based and small molecule-based therapies that target upstream, innovative therapeutic strategies to enhance cellular health and cellular repair in the nervous system, translation of research concepts to clinical proof of concept studies and, finally, regulatory submission and approval. Developmental therapeutics are not possible without research and concept studies in model systems. Experimental approach development, exploration, and data generation, detrimental cause exploration, and compound discovery are essential components of potential future therapies from discovery to commercialization. As such, we describe here state-of-the-art technologies that have achievable feasibility for the generation of next-generation neurological and neurodegenerative disorder pharmaceuticals to alleviate patient burden worldwide.

2. Overview of Neurological and Neurodegenerative Disorders

The brain and spinal cord are central to the central nervous system (CNS). Motor, sensory, and cognitive functions are performed by neurons in the CNS. The CNS's functioning is influenced by astrocytes, oligodendrocytes, ependymal cells, and microglia. Damage to the CNS can result in neurological disorders, which are conditions that affect nerve function. Brain activity affects bodily sensations, and damage to the CNS can lead to temporary or permanent loss of these functions. Neurological disorders have an impact on all ages and ethnicities and challenge people physically and emotionally. Examples of neurological disorders include peripheral neuropathy, epilepsy, Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis, and cerebral strokes. Epidemiological studies indicate that the burden of neurological disorders is large and growing, and neurological disorders will be the leading cause of disability worldwide. Neurodegenerative disorders are diseases that cause the progressive degeneration of specific neural systems. These disorders impact the quality of life of many older persons worldwide and are associated with significant medical, social, and economic burdens. Neurodegeneration is a hallmark of several diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, and is characterized by the selective loss of specific neurons in the CNS, with evidence of gliosis and the accumulation of protein aggregates, some of which are associated with neuroinflammation. The causes and mechanisms of neurodegeneration are poorly understood but are rooted in defects in cellular homeostatic mechanisms, oxidative stress, mitochondrial dysfunction, synaptic dysfunction, and protein metabolism. While the concept of "neurodegeneration" is highly recognized and widely accepted, a major complicating factor regarding its use is that, inherently, it implies that neurodegeneration is a process that involves the setting in motion of one or more aberrant cellular pathways. Indeed, "neurodegenerative disorders" encompass a range of CNS disorders, which differ in their timing of onset, clinical presentations, prognosis, and pathologic features.

Equation 1 : Therapeutic Discovery Efficiency:

$$E_d = \frac{C_n \times T_v}{R_t}$$

where:

- E_d = Discovery efficiency score
- C_n = Number of candidate novel compounds
- T_v = Target validation strength
- R_t = Research timeline duration

2.1. Understanding the Spectrum of Neurological and Neurodegenerative Disorders

Neurological and neurodegenerative disorders present a significant challenge for society and healthcare systems globally. These disorders are characterized by the progressive degeneration of nerve cells, leading to cognitive, sensory, motor, and behavioral deficits, among other diseases, resulting in high morbidity and mortality rates. Neurological disorders affect

approximately 1 in 6 people, while neurodegenerative diseases affect approximately 1 in 20 people over 65 years of age, and 1 in 105 people over 85 years. The global population is rapidly aging, which is predicted to see a significant increase in neurodegenerative disease cases by 2050, with enormous implications for future resource allocation. Neurological and neurodegenerative diseases place an economic burden upon society, with collective global costs of care exceeding $900 billion per year and increasing. With few proposed treatments available, and even fewer capable of addressing the underlying causes of these diseases, funding for research and development is, and has been, crucial.

The term "neurological disorder" encompasses over six hundred conditions that are classified around the dysfunction of the central and peripheral nervous system. These disorders primarily cause alterations to the neurological system and can result in impaired mobility, speech or communication, sensory disruption, facial paralysis, memory loss, cognitive deficits, debilitating seizures, and debilitating psychological status, among other conditions. Due to the vast complexity of the neurological system and the interconnectivity of multiple body systems, the underlying causes of these disorders can vary between genetic predisposition and environmental triggers. Furthermore, no shame or stigma is associated with neurological disease and, while research focusing on animal models of single genes has been beneficial in enhancing our understanding of these conditions, the genetic etiology, epidemiology, pathology, and treatment of the majority of these disorders remains largely unconsolidated and underfunded. These disorders include relatively known conditions, such as epilepsy, migraines, and traumatic brain injury, to rarer ones, such as intra-operative awareness, Devic's disease, nervous colic, bovine spastic paralysis, hyponatremic seizures, brain aneurysms, and neurocomplications.

3. Current Treatment Landscape

Across the world, neurological and neurodegenerative disorders significantly impact the aging population. Moreover, due to the cancer being largely successful, it is expected the incidence will further grow and create a healthcare burden. Specific diseases, such as Alzheimer's disease, frontotemporal dementia, or amyotrophic lateral sclerosis, and others, like pain or drug abuse-induced organic cerebral disorders, disrupt the balance of neurotransmitters and other signalers in various parts of the nervous system, lead to altered neuronal function, nerve cell injury and/or cell death in different areas of the central nervous system, resulting in loss of sensory or motor functions, behavioral changes, and death. Nevertheless, there are common characteristics among the diseases, which often coincide, indicating that there might be cross-talk between neighboring cell systems that could be targeted to tackle the illness. Available common therapeutic options are limited and can only alleviate or modify the symptoms to some extent, therefore alternative therapeutic approaches are necessary as the underlying pathological mechanisms are usually not well understood and targeting one single pathway, such as proinflammation, oxidative stress, or calcium overload, is not sufficient for an effective treatment.

Currently, two major therapeutic approaches are available to mitigate the disorder-causing symptoms – pharmacological treatments, which are mainly symptomatic, and non-pharmacological treatments, which give a holistic view and aim at improved quality of life. Pharmacological therapies can boost deficits or dysfunctional neurotransmission or reduce toxic substances, such as deposits formed by misfolded proteins, but the side effects could result in poor compliance. Non-pharmacological therapies contain cognitive behavioral or supportive psychotherapy, art and music therapy, dance therapy, and neuropsychological rehabilitation. Moreover, nutritional therapy focuses on improved nutrition to reduce risk factors for concomitant diseases, such as obesity, diabetes, hypertension, heart disease, and stroke.

3.1. Pharmacological Approaches

As of 2023, there remain no disease-modifying drugs targeting factors in the actual pathogenesis of AD with no clear association with any of the pathways affected by the pharmacological approaches addressed in this section. Nevertheless, across current medical guidelines, the following are recommended for management of cognitive and/or functional symptoms of AD: (i) cholinergic therapies, including acetylcholinesterase inhibitors; (ii) memantine, a non-competitive NMDA receptor antagonist; and (iii) symptomatic treatments, including atypical antipsychotics, SSRIs, trazodone; and more recently registered, in Europe, and being evaluated in USA, NDAs. In this section, cholinergic therapies and symptomatic treatments are addressed.

Based on the observations of lowered levels of cerebrospinal fluid acetylcholine esterase activity in AD and the effects of cholinergic augmentation, more than a century ago, the first cholinesterase inhibitor available was physostigmine, from the Calabar bean. Although at that time, the effect was only on cognition, the feeding behavior of a patient with symptoms ameliorated after the oral administration. Unfortunately, physostigmine is short-lasting, with an associated high incidence of side effects. Following its failure as a serious therapeutic for the dementias, and few additional added, reversible acetylcholine esterase inhibitors with a very short-half-life, the majority of studies trying to ameliorate symptoms of AD were focused on increasing the levels of cholinergic release by drug delivery modulation strategies.

3.2. Non-Pharmacological Therapies

Studies show that non-pharmacological therapies may be effective against some diseases. Stimulation of neural circuits by light, electrical, or magnetic activity can modulate the functional architecture of neural circuits preventing atrophies and cognitive decline. Deep brain stimulation has been applied to movement disorders, for instance, pain, depression, alcoholism, and Tourette syndrome. Clinical evidence has shown that repetitive transcranial magnetic stimulation is effective against cognitive and functional impairment in Alzheimer's patients, by enhancing neural activity through stimulation of the left dorso-lateral prefrontal cortex and suppressing activity on the right using neuronavigated

stimulation. This can also increase the production of neurotrophic factors which are critical for neurogenesis, and facilitate cognitive functions, for instance, memory and attention.

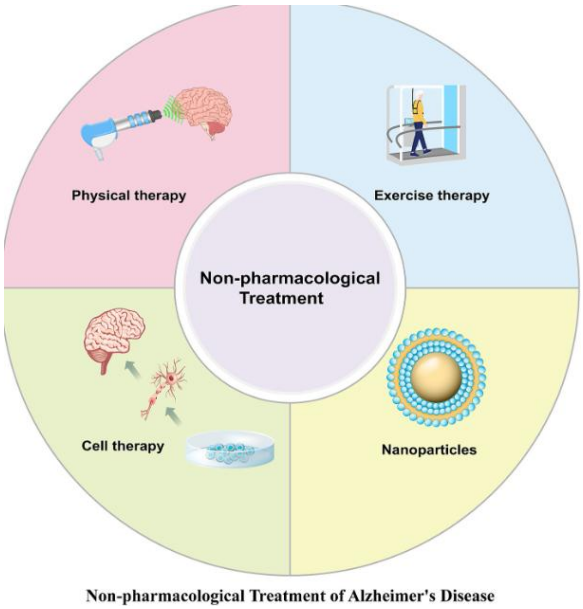

Fig 2 : Non-pharmacological treatment of Alzheimer's disease

In addition to that, neurofeedback combined with visual and/or auditory jambs is also associated with increased heart rate variability and improvement of the autonomic functions involved in cognitive impairment. Transcranial direct current stimulation can modulate cortical excitability, facilitating learning and memory processes, while anodal stimulation boosts excitability, cathodal can have the opposite effects. This can also improve language in patients with aphasia and enhance muscle motor learning in post-stroke patients. Optogenetic stimulation has the highest target specificity and spatial-temporal precision of all stimulation approaches. It has been widely applied in animal models. It is also possible to apply synchronized stimulation of multiple circuits, enabling a concerted scotopic and photopic drive and a more life-like reconstruction of optic projections. Mechanisms along their application to neural circuits relevant for psychiatric disorders.

4. Emerging Therapies and Technologies

Next-generation medicines have the potential to offer new and revolutionary therapeutic options for previously inaccessible diseases. They can be applied at the deep entry points of diseases and play an important role in a customized medicine toolbox. These medicines include gene therapy, stem cell therapy, biologics, and nanomedicine. Each area will be reviewed in this chapter and promise important new options for next-generation medicines.

1. Gene Therapy

Factor IX is associated with defective blood coagulation and with the clinical symptoms of hemophilia B, or Christmas disease. Viral gene therapy is now underway in phase 1—3 clinical evaluations and seems to be effective in replenishing factor IX levels in patients with this disease by venturing beyond use in rare monogenic disorders. This study is a vector-based clinical trial that is one of the largest of its kind with clinical noncompressed data that addresses the most relevant issues related to liver-restricted production of factor IX. This is true both for technical issues, such as maximally achieved factor IX levels or time taken to reach these levels, but also for clinical endpoints, such as thromboembolic events and long-term production of factor IX on the order of years rather than months and assessed via the unit of measure of IU/ml/hr. Gene therapy remains a major trend in the treatment of human diseases and is one of the hallmarks of the oncology field.

2. Stem Cell Therapy

Stem cell therapy is another attractive and next-generation medicine. Stem cells have the potential and malleability to develop into a wide variety of specialized cell types, making them a promising source of cells to treat numerous diseases. Induced pluripotent stem (iPS) cells derived from a patient's somatic cells offer the potential to reconstruct nervous tissue by transplanting patient-specific neurons. Transplantation of iPS-derived neurons could represent a promising therapeutic strategy to promote functional recovery and repair spinal cord injury (SCI). This method may be attractive and able to promote tissue repair and regeneration in SCI patients in the future. Recent research indicated that using biomaterials might be effective for controlling host–graft interactions when integrating iPS-derived progenitors into host tissues in SCI. However, fundamental issues need to be addressed, including the risk of teratoma formation from contaminations of pluripotent stem cells, as well as ethical problems that may be associated with such therapies.

4.1. Gene Therapy

Gene therapy has in recent times transited from the laboratory to the clinical product stage, with several marketed products now in use in patients. Following a slow start, further critical developments include the advent of viral vectors with substantially improved safety–efficacy profiles, the remarkable reduction in the cost of synthesis of plasmids for adeno-

associated virus assembly enabling large-scale viral vector production, and the increasing human experience with the use of directed, reliable gene-editing technologies. There are now several hundred other gene therapy products in development targeting several indications including monogenic and polygenic disorders and several cancers. Yet more are being planned to treat diseases of interest including vascular and connective tissue diseases, and neurodegenerative disorders.
Although its potential was first demonstrated by several studies with the use of several gene delivery vectors, the first demonstrations of gene therapy in neurological applications arose from human expiratory risks of gene therapy applied to inborn errors of metabolism, particularly myeloid and hepatic diseases accompanied by excessive gene expression. The strategy involved AAV-mediated gene therapy placing a gene under the control of a liver-specific promoter, injected into a cranial vein, and effects seen highlighting the potential of liver and peripheral organ gene delivery for other metabolic conditions. Over the past 25 years, large-scale experimental studies have confirmed the principle of AAV-mediated gene therapy and the identified laboratory advances have facilitated similar studies in humans. Initial work principally focused on AAV-mediated hepatic gene therapy. After these lab and clinical studies to express and secrete functional therapeutic proteins in humans, AAVs were engineered to deliver a stable genetic payload, particularly for extrahepatic tissue and organ diseases, additional neurological conditions linked to both monogenic disease and polygenic disease mechanisms.

4.2. Stem Cell Therapy

An entirely novel approach to treat neurological disorders originally took root with the concept of cell replacement therapy, first considered for Parkinson's disease. The idea that dopaminergic neurons could be transplanted into the striatum - the nigrostriatal target area - received considerable experimental backing from studies showing that fetal-origin dopaminergic neuron transplants could ameliorate Parkinsonian motor symptoms in treated monkeys, as well as in patients with Parkinson's disease. This stimulated interest in the development of surgical procedures to transplant embryonic dopaminergic neurons, but the severe shortage of transplantable tissue soon raised the question of whether it would be possible to generate unlimited dopaminergic neurons from stem cells, either derived from embryonic neural tissue, or other tissues with the ability for totipotency.
Substantial advances in this direction have been made since, both in embryonic and pluripotent stem cell biology, with the realization that small molecules can be used to facilitate the conversion of pluripotent stem cells into definitive-lineage progenitors that can then be transplanted into the nigrostriatal territory. These technological advances spurred interest even by large pharmaceutical companies, with researchers and clinicians realizing that pluripotent stem cell-based regenerative medicine for Parkinson's disease seems to be coming through, even if this has been severely delayed. Other biotechnology companies currently have ATMPs for neurodegenerative disorders in clinical trials, as they also move ahead with the development of novel and promising gene therapies for spinal muscular atrophy and Huntington's disease.

4.3. Biologics and Biopharmaceuticals

Biologics represent a diverse category of medical products produced through biological processes. These include traditionally defined biologicals such as vaccines, blood derivatives, and gene-modifying biologics, and are commonly classified according to the specific technological platform used to produce them, such as gene therapy, antisense, small RNA, monoclonal antibodies, or fusion proteins targeting a disease-modifying process. The term biopharmaceuticals is often used synonymously with biologics but better describes a subset endemic to the pharmaceutical industry: large, stable proteins developed primarily for treatment purposes such as antibodies, enzymes, hormones, immune modulators, coagulation factors, or cytokines. Since their introduction, biologics have made important contributions to improving the treatment of cancer, hemophilia, Crohn's disease, Huntington's disease, Alzheimer's disease, and other major public health concerns related to neurological disorders. Progress has also been made in the development of cell therapies for preclinical muscular and Huntington's disease. Neurological disorders are frequently associated with disturbances in biological signaling cascades, arising either systemically or locally in the central nervous system. Disruption or alteration of such signaling can be targeted using antisense deoxyribonucleic acid or small interfering ribonucleic acid. By restoring pathologically altered signaling pathways to homeostasis, genetically encoded CNS-guided signaling quieting therapies may bring about broad improvements in the symptomology of a wide variety of neurologic and neurodegenerative diseases. Recent proof of concept studies have demonstrated not only the feasibility but also the utility of this approach. Importantly, CNS-delivered RNA therapeutics have the advantage over other biopharmaceuticals in that they are much smaller, able to diffuse rapidly and to larger volumes of the target diseased tissue within the CNS, and present a limited and well-defined off-target dose, which is less than or equal to the fully characterized dose for FDA-approved RNA therapeutics for non-CNS indications. More importantly, FDA-approved RNA therapeutics for peripheral use can be safely administered repeatedly at CNS doses 100 times higher owing to a large safety margin from abundant, accessible peripheral tissues.

4.4. Nanomedicine

Nanotechnology is an area of research and technology development that focuses on building things, usually physical objects, on the scale of molecules and molecular structures. Nanotechnology has been termed a “Key Enabling Technology” (KET) because it can accelerate innovation across a broad range of sectors, including health. With increased breakthroughs in nanotechnology, nanomedicine has gained in recent years increased importance as it can improve the efficacy of molecules and targets of interest, but also improve the delivery and transport of molecules within the body and across complex biological barriers like the blood-brain barrier. Nanomedicine can be defined as the application of

nanotechnology in medicine. In recent years, we have witnessed a multidisciplinary research effort among many high-technology areas that provide the ground for the development of advanced new therapies and diagnostics in healthcare, termed next-generation medicines.

As a new therapeutic agent, nanocarriers can improve the pharmacokinetic parameters of loaded drugs by modulating drug distribution, allowing for controlled release of drugs at the site of action, and increasing the stability of drugs against enzymatic degradation. The approved liposome-based products for treating cancer have set an example for drug encapsulation in nanocarriers mostly for anticancer care. However, among the nanocarrier design, lipid-based drug delivery systems have received increasing interest both as drug transporters due to their well-established biocompatibility and bioavailability and as therapeutic agents themselves. Although the first-generation lipid-based drug carriers have been abandoned because of their problems related to the difficulty of large-scale production, instability, and high production cost, the incorporation of new materials and techniques for the design and preparation of novel lipid-based drug carriers or carrier formulations with improved performance and reduced side effects is required and can boost the successful application of lipid carriers shortly.

5. Drug Discovery and Development Process

The drug discovery pathway requires immense collaboration and resources. Despite technical and scientific advancements, discovering and developing a drug with commercial success is extremely difficult and cumbersome. The burgeoning technological achievements in medicinal chemistry, genomics, structural biology, proteomics, and new platforms in pharmaceutical genomics and research have provided exciting opportunities for drug discovery and development. Albeit costly, this work has immense potential and can avail a plethora of new drug candidates to fill the vast gap of needs in the clinic and beyond. The drug discovery and development process from target identification to market application for neurological disorders has relevance for many medicines to be introduced in the market.

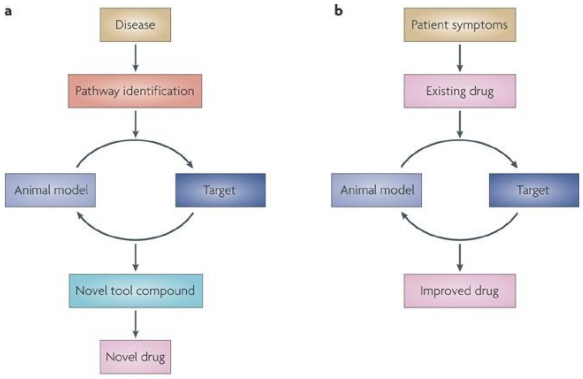

Fig 3 : Drug development for CNS disorders

The major steps in the drug discovery and development process are shown in the flowchart. The first step involves target identification and validation using target identification methodologies. Target validation ensures that a drug acting on the identified target would have effects, for example, biomarkers overexpression in the patient population, effects of a genetic knockout mouse/human model, effects using inhibitors, etc. The second step involves high-throughput screening of chemical and genomic/bioinformatic small molecule libraries against the target to obtain lead candidates, then medicinal chemistry to design, optimize, and validate more potent drug candidates through structure-activity relationship studies leading to candidate selection. The third step involves preclinical studies to ascertain lead optimization and finally progressing to investigate the chemical formulation in basic animal model studies before undergoing different phases of clinical trials and application for regulatory approval.

5.1. Target Identification

The preclinical drug discovery and development process, with a focus on new chemical entities (NCEs), typically starts with target identification and validation, followed by lead optimization and preclinical testing before human clinical trials. The full process can take 15 years or more and become increasingly expensive and risky with each iteration of this process. Target selection is often done based on an understanding of the genetic underpinning of the disorder(s). For instance, researchers have focused on specific targets for various disorders, while other genes are emerging targets for different pathologies. The processes of tumorigenesis might suggest a dual neuroinflammatory microglial activation approach. Multiple pathways have been proposed for the rare forms of certain diseases.

Neurotransmitter and neuromodulator receptors or transporters, as well as ion channels and cellular transporters, have historically targeted neurodegenerative disorders for repurposing and neuroinflammatory agents. In contrast, the development of NCEs has involved agents targeting glia, supporting cells, neurogenesis, and a dynamic compartmentalized function of cells other than neurons involved in the disease process. Researchers have realized that it is necessary to pursue both pathways, which is one of the many benefits of considering drug repurposing alongside NCE development. Researchers have also come to appreciate that the drug development pathway for repurposing is different

from that for NCEs, in that target validation for repurposing is much less involved, although target validation and target relationship issues already usually exist.

5.2. Lead Optimization

Lead optimization is critical in the drug discovery process as it moves the lead compound closer to its final, active form. Compounds need to have favorable pharmacokinetics and pharmacodynamics to register good efficacy in clinical trials. However, many lead compounds exhibit either poor solubility, stability, permeability, or metabolic stability, which needs to be addressed. Several techniques have become widespread in lead optimization. One technology involves changing the linker and hydrophobic groups, which have to be optimized to obtain soluble compounds, hence lowering toxicity and improving bioavailability. Another tool referred to as isosteres makes use of chemical structures that have similar physical properties to other molecular features in a drug molecule. It is used if certain agonists or antagonists need to show a decreased activity due to bone-methyl ether oxidation during the drug action. The replacement of lead functional groups with suitable isosteric groups leads to increased metabolic stability and a raised duration of action.

In silico drug design tools are increasingly used by pharmaceutical companies to virtual screen libraries of compounds against a target. These tools are not used in isolation but as part of an integrated process that should take into consideration algorithms perturbing ligand flexibility and protein flexibility to simulate proper binding poses and free energy for binding. Such algorithms are widely used for optimizing ligand binding using various calculations and maps. In addition, some programs, integrated with automated ligand binding site search programs, accept ligand and protein flexibility and sample conformations to screen a good number of diverse compounds in active site pockets. Lead optimization is regarded as the most disappointing and hard part of the drug design process for specialists in both academia and industries. Each step of this process could take several months and can be expensive, with many studies on different compounds, but the number of available treatments for neurological and neurodegenerative disorders is wide and work has been developed over the years to overcome the bottleneck of this critical process from lead compounds to lead drugs.

5.3. Preclinical Studies

Preclinical studies consist of pharmacokinetics, pharmacodynamics, and toxicity studies. In these studies, animal models that undergo the most similar pathological process to humans are selected and then need to evaluate the effect of drugs on disease improvement, concurrent sample collection, pathological mechanism study, etc. In absorption and distribution, firstly the drugs can be administrated through parenteral and orthogonal to compare the effect of different administration systems. The distribution of the drugs can be analyzed using tissues or the microdialysis method, as the concentrations in CSF and the brain are most significant.

The metabolism of drugs is critical for determining how effective and safe the drug is. For metabolism sample collection, drug concentrations in urine and feces can be detected. Meanwhile, in vivo, imaging identification methods, such as LC-MS, radioisotope, and metabolite identification methods can also be used. In toxicity analysis, the demand on the two species which includes one non-rodent, and a drug concentrated on the main target organs needs to be determined. Researchers mainly used clinical toxicity index including specific organ function indicators, non-specific index, and histopathological to increase the effectiveness of the studies. With the further development of drugs for the elderly, children, and pregnant women, toxicokinetics needs to be determined and the comfort of children and elderly people should be considered. As for pregnant and lactating women, organ specimens of aborted fetuses can be determined.

If the required toxicity has been determined and in turn to pass the committee review, the whole study would be performed and combined samples which can write a study report for drug application review. Ultimately, the efficiency in the whole segment will affect the timetable and success ratio of drug development, including a selection of proper clinical species and the use of experimental technology.

Equation 2 : Clinical Progression Probability:

$$P_c = \sigma(\lambda_1 B_m + \lambda_2 S_r + \lambda_3 E_o)$$

where:

- P_c = Probability of advancing through clinical trials
- σ = Sigmoid activation function
- B_m = Biomarker reliability
- S_r = Safety profile robustness
- E_o = Early outcome success rate
- $\lambda_1, \lambda_2, \lambda_3$ = Feature weights

5.4. Clinical Trials Phases

Clinical trials are typically divided into four phases and vary concerning trial size as well as patient population. Phase I trials generally enroll a small number of healthy volunteers and are designed to measure safety, drug metabolism, and pharmacokinetics. Approximately 70% of all drugs that enter clinical development fail and a large proportion of early failures are attributable to safety concerns. Phase II trials involve hundreds of patients and are generally designed to

evaluate clinical efficacy and identify the most effective doses and schedules for treatment. In Phase III trials several hundred to several thousand patients are randomized to the experimental or control arm in a double-blinded fashion to confirm efficacy, verify the safety profile, and evaluate the product's benefit-risk relationship. Phase III trials follow strict regulatory guidelines; any substantial changes require approval from the regulatory agency. Phase IV trials are conducted after a product is approved and on the market. They are also known as post-marketing surveillance studies and aim to monitor the drug's effect on the general population as well as its long-term effectiveness and impact on the patient's quality of life. These trials may also study the potential therapeutic effects of the product in different patient populations as well as new indications not previously tested before the product's approval.

6. Regulatory Considerations

The discovery of small molecules and complex biologics can lead to next-generation medicines for neurological and neurodegenerative disorders. However, there are significant hurdles or limitations to overcome before implementation in the clinical setting. In this chapter, we address various regulatory considerations for next-generation medicines. Initiating clinical studies to translate modalities from bench to bedside often requires years of research and hundreds of millions of dollars for new chemical entities. There are also tedious and expensive processes to develop combination chemotherapies or investigate new uses and dosing for old drugs. Regulatory authorities have issued guidelines on how to conduct the actual clinical trials and how to report the different steps including the description of interim analysis and what happens if a safety concern arises. These documents summarize existing knowledge, expert advice, and policy preferences of the different institutes and provide an essential basis to discuss on which grounds assumptions for the approval of investigational new drugs and marketing authorization applications are made to encourage drug development.

Currently, the systems used by the different authorities to evaluate investigational new drugs and marketing authorization applications do not provide specifically structured data sets that come together in an automated grading algorithm but are rather human-based processes that vary strongly with the different institutes and experienced reviewers. In this chapter, we present a collection of recently published regulatory documents for experimental drugs to provide a stimulating overview of the various developments for next-generation medicines. The special focus lies on trials that explore the therapeutic range of new chemical entities and experimental drugs for licensed indications.

6.1. FDA Guidelines

The FDA is responsible for evaluating the preclinical and clinical data submitted by a sponsor for a specific indication and then determining whether the information is sufficient to support the intended use or if there are any additional concerns. The FDA has developed regulations and policies that guide sponsors on the information needed to support a request for approval of a new drug. For the development of new drugs, including new indications for approved drugs, sponsors submit to the FDA an investigational new drug application before initiation of testing in human subjects. For studies involving the nervous system, the FDA has produced specific guidance documents that include establishing safety and efficacy for drugs intended to treat neurological disorders, questions and answers on the IND regulations, pharmacology studies to support biologics for neurological and psychiatric indications, and guidance on the content of investigational new drug applications for products intended to treat multiple sclerosis.

The Federal Food, Drug, and Cosmetic Act and the Public Health Service Act require proof of safety and efficacy before a product can be marketed. Most INDs submitted to the FDA for neurological indications are for drugs intending to relieve symptoms. Therefore, sponsors often use surrogate endpoints for efficacy, efficacy in a specific population, as well as confirmatory studies. Modifications to the usual requirements for submitting additional IND-enabling studies in the request for expedited development; the release of draft and final guidance documents on evaluating the effectiveness of products to treat, prevent, or diagnose neurological disorders, including amyotrophic lateral sclerosis, Duchenne muscular dystrophy, Huntington's disease, multiple sclerosis, and Parkinson's disease; support the emergence of the development for neuromodulators and neuroprotectants.

6.2. EMA Regulations

Regulatory approval is key in ensuring a product's safety and effectiveness. For novel scientific approaches, such as next-generation therapies for CNS disorders, timely feedback from regulators is essential to progress with streamlined drug development. Formal advice from the CAT is available at 2 different stages of development: Type A advice at the preclinical or exploratory development stage and Type B advice once the medicinal product is being manufactured according to GMP but before starting clinical studies. Type A advice aims to discuss the suitability of preclinical and clinical development, including CMC development. These CAT meetings are highly recommended for ATMPs that use novel delivery routes or do not require a specific clinical indication. Type B CAT meetings may also be requested to ensure that the development meets the specific needs in terms of the quality and preclinical testing of the product in a timely and effective manner. In these procedures, the EMA CAT co-chairs screen the requests and select the most important questions to be answered, consulting experts where appropriate.

6.3. Global Regulatory Landscape

Regulatory frameworks for investigational medical products vary from country to country and thus may require different clinical trial activities for a multinational clinical trial. In addition, a key consideration is when obtaining an investigational product from the manufacturer in one country and delivering it to another country, both pair 1 and pair 2 regulations must

be adhered to. Moreover, global sponsors must also consider the implications for worldwide clinical trial activities of the different regulatory requirements and timeframes to obtain an IND and an IMPD depending on the region.
The regulations are similar to those outlined for the US but include additional clauses. Investigational products shipped into Australia must be accompanied by an import permit. Biological products manufactured outside Australia require the establishment of a Biologics License Application. Canada requires the development of a Canadian Clinical Trial Application to undergo clinical trial activities within Canada. Moreover, approval for CMC information is also required in addition to the Canadian CTA. Like Canada, Germany also requires a Drugs Regulatory Authority Application for Therapy. Japan, China, Hong Kong, Taiwan, Singapore, and India all also have country-specific INDs. South Africa requires investigational products to be registered under the Medicines Control Council Act.

7. Commercialization Strategies

Considerations for the strategy to achieve patient access and commercialization of a next-generation medicine typically require starting early in the development plan. In particular, the unmet need and potential impact on disease progression and patient quality of life in the target population must be defined early. Economic value must be demonstrated to access and incentivize local pricing and reimbursement decisions and commercial strategies must align with localized health systems and reimbursers' needs and goals. The overall approach must align with the company's strategy and what local markets prioritize for access to the next-generation medicine. Some commonly discussed components of a commercialization strategy include market analysis, pricing and reimbursement, and marketing and distribution.

Market Analysis

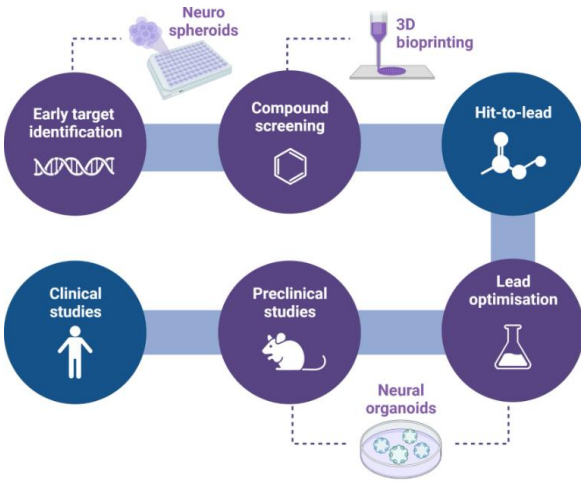

Fig 4 : 3D models of neurodegeneration

Market research explores the addressable patient population, identifies which patient characteristics matter most, and understands how to reach those patients most effectively. Engaging with stakeholders early in the clinical development process will inform the path to optimizing available data and broaden its applicability to commercialization discussions. It will also be important in establishing healthcare professional relationships that can support ongoing data generation needs and advocate for patient access. Feedback during study design, especially in critical success factors or endpoints, will help de-risk the development plan and optimize the evidence package. Designing and executing studies that offer new tools or data to help payers determine value is needed in an increasingly cost-conscious market for next-generation medicines.

7.1. Market Analysis

Market analysis is a vital part of a commercialization strategy, providing insight into the external factors that could affect business operations. The market analysis includes an overview of the neurology market including demographics and unique challenges, unmet medical needs, market segmentation, market drivers, market forecasts, barriers to entry, competitive landscape, and regulatory requirements. Each crucial element will be discussed below.
Neurology and neurodegenerative disorder conditions including Alzheimer's disease, Parkinson's disease, epilepsy, psychiatric illnesses, sleep disorder, and multiple sclerosis are becoming a rising public health concern due to the increase in the aging population, changing lifestyle, and workplace pressure. For instance, approximately 5.5 million Americans are living with AD, and by 2060, this number could rise to 14 million. Since the need is pressing, also the potential of next-generation drug products to satisfy current market needs is especially large. These products can overcome current limitations and challenges from existing drugs. For example, the number of AD patients is projected to exceed 14 million by 2050. Still, no drug in the market can stop or reverse the disease. Hence, next-generation medications designed to modify the disease course are urgently required. Any successful next-generation compound can generate multi-billion market revenues, considering the number of living AD patients, and large treatment costs.

While the market potential of next-generation products is very large, commercialization of next-generation products is burdened with challenges. One major challenge is the overly high burden of proof to enter the market. The stringent regulatory framework on novel compounds would ask for a higher burden of evidence from the companies before clinical trials. The other to mention would be increasing technical challenges during the development. With rapidly advancing technology, shortcomings from early-stage hypotheses may propel a challenge for confirmation during further stage translation. As a result, many next-generation products may fail even in early development stages, and higher capital investment would be needed to bring a single product to market.

7.2. Pricing and Reimbursement

Introduction In developing next-generation medicines for the treatment of neurological and neurodegenerative disorders, it is critical to develop strategies for pricing and reimbursement early in the commercialization process. Because these medicines are for diseases affecting significant portions of the population often for long periods, they will cost considerable amounts for both government health budgets and insurers reimbursing most of these costs, or for out-of-pocket payments for people and families who are uninsured or underinsured. Theory suggests that prices and reimbursement levels will be based on the difference between the new medicine's incremental benefits and its incremental costs. Because the new medicines will likely reduce healthcare spending as a result of improved outcomes in treated patients, including improvements in disease-modifying and health-related function, reductions of long-term care costs, lost productivity costs, and out-of-pocket spending, the willingness-to-pay estimates used for pricing and reimbursement will likely be very high. Evidence of incremental health improvements versus alternatives, plus the demonstration and documentation of the reduction in affected patients' disability and loss of independent functioning, sharing the burden of performance of daily activities, and enhancing productivity must be the focus of economic analyses. Because the foundational hypothesis underlying demonstrated neurobiology and new clinical trial designs is that these new approaches will afford significant improvements in disability and loss of independent functioning over longer durations than the previous generation treatments, the results of cost-effectiveness analyses, regardless of the methodology employed, and likely social willingness-to-pay benchmarks, should bolster payer interest in and willingness to reimburse and support the price of these new therapies.

7.3. Marketing and Distribution

Marketing and distribution of pharmaceutical products are two different activities performed by different departments or divisions of a full-service pharmaceutical company. Pharmaceutical marketing is a suite of activities that various departments or divisions of a pharmaceutical company use to push medication through the distribution chain to patients and ensure patient adherence. Marketing performed by or on behalf of the pharmaceutical manufacturer includes but is not limited to, advertising through multiple channels, public relations, sales promotion, personal selling, direct marketing, and distribution. These activities take place in both the consumer and professional markets. Marketing directed at consumers is called consumer or direct-to-consumer advertising. Advertising medication directly to patients is allowed in only two countries in the world. Marketing directed at physicians is called professional or, in the older literature, physician marketing. Professional marketing is much more extensive than consumer marketing. It is responsible for the vast majority of advertising expenditures made by pharmaceutical companies. Distribution is an uninterrupted supply chain of independent companies and individuals who help transport the product from the manufacturer to the patient.

Distribution strategy determines how the drug is delivered from the manufacturer to the pharmacy or physician's office. The simplest distribution strategy utilizes a single manufacturer/wholesaler/retailer channel to move the manufacturer's product from the manufacturer directly to the pharmacy or physician's office. Most specialty drugs are delivered exclusively through specialty pharmacy distributors. Schedule II narcotic products are restricted to an exclusive channel through distributor wholesalers, pharmacies, and hospitals. In the United States, medicines may be distributed through both wholesale and retail channels. Products that do not require a prescription are sold through a variety of retail outlets, including supermarkets and convenience stores. Retail pharmacies and drugstores sell both prescription and non-prescription drugs.

8. Challenges in Development and Commercialization

From discovery to commercialization, the path of drug development is one fraught with myriad challenges. The pharmaceutical industry has amassed vast experience in clearing these hurdles for the design of efficacious therapies for a variety of somatic diseases. The development of novel therapeutics for afflictions of the nervous system can prove even more burdensome and hazardous: neurologic and neurodegenerative disorders are not congruent with the development of drugs for pain relief or addressing somatic diseases affecting other organ systems. Goals must achieve efficacy, in large longitudinal Phase III trials, at addressing the slow course of the disease, the requirement that drugs safely induce sustained modification or a change in the natural history of illness, and the collection of an extensive database demonstrating that long-term use of therapeutic agents will have no associated toxicity. Further, drugs to address a variety of neurological and neurodegenerative disorders also have to be marketed and made available at affordable prices in the face of limited financial resources dedicated to addressing these diseases. For all of these reasons, novel drug development for addressing neurologic and neurodegenerative disorders remains little incentivized and presents its unique challenges across the rubric of scientific exploration, technical achievement, financial cost, and patenting and commercialization.

The scientific and technical challenges plaguing drug discovery, in general, are heightened for the development of therapeutics dedicated to the treatment of neurologic and neurodegenerative disorders. The blood-brain barrier, the

effective separation of the central nervous system from the systemic circulation, protects the development of the brain but also greatly complicates and often limits access to the brain by molecules meant to rescue and restore the function and viability of its inhabitants, neurons. Most drugs currently in use are huge, hydrophilic molecules or proteins that penetrate the blood-brain barrier inefficiently, if at all. They also face the fraught endeavor of having tiny therapeutic windows for their safe use or that engage numerous pathways, many still being researched, and not just one but a variety of neural circuits. Finances needed to engage in processes of monetary costs while developing efficacious drugs for utilization in the frail elder population are considerable.

8.1. Scientific and Technical Challenges

Developing a product has costs, risks, and hurdles intrinsic to that development, as well as commercial and financial aspects. The product must be discovered, developed, characterized, and validated in vitro, in vivo, in preclinical models, and as safe and efficacious in humans. For neurodegenerative disorders, whether rare, sporadic, or common, the financial costs are very high, while the clinical pathways are challenging. There is increasing awareness that these difficulties are even higher for neurological diseases that have extra layers of risk and involve therapeutic avenues that are not restricted to pharmacological interventions at various developmental phases, extending to surgical and bioengineered modalities. Research and development must deliver brain-penetrating, therapeutic, commercially viable compounds that focus on the resolution of a core or initiating the pathological process and modify the natural history of the disorder. In classical small-molecule and macromolecular companies, this is the core of the discovery and development process. While strides in identifying risk factors or pathways towards gene therapy have been made for rare and neurological diseases, these are not yet accelerated by funding at the level that large agencies demand investing in potential gene modulators. Given that the disruptive pathways for inflammatory dementia and aged-related tau modification have not been endorsed, there is, therefore, more research needed in penetrating compounds associated with the resolution or even arrest of the tau and glial or macrophage axis. There are several other targets involved in this disease niche that show promise, be it used in pairs or on their own.

8.2. Financial and Economic Barriers

Prefilled syringes, genetically modified organisms, pen injectors, delivery devices, and monoclonal antibodies are examples of cutting-edge and well-known pharmaceutical and biopharmaceutical products. Each of these product categories must be expounded upon in terms of their features, timeframes, estimated costs, and current industry practice to develop financial models that allow us to assess properly the available financing instruments and also the options and exit strategies of the invested capital. However, these financial models are non-existent for the simple reason that no industry group has developed them.

The lack of financial models impairs the ability of private or public organizations – overall, not-for-profit organizations – to use their resources optimally. The fact that they have little experience in drug commercial development and manufacture generally means they cannot afford to lose money. As a consequence, they must likely set their employees' salaries above the existing market wages, use some services without considering the price tag, and/or invest excessively to make up for their inexperience. Hence, before providing funds, a not-for-profit organization should request the company to prepare a financial model. Provided that the not-for-profit organization has experience in drug development and the scientific and technical capabilities to perform a critical review. If the model is reliable and industry-accepted, the not-for-profit organization could invest using the business metrics that ascribe a probability of success to such ventures.

8.3. Ethical Considerations

Collectively, the above challenges and potential barriers to hybrid therapies also represent ethical considerations relevant to their adoption and acceptance. Professional organizations representing the interests of biomedical researchers have publicly called for the development of guidelines for the use of biological materials derived from human subjects or embryos. The rationale for this guidance is based on the historical ethical concerns regarding the potential commercial exploitation of patients and the possibility of inadvertently causing overall more harm than good even if a given study is successful. Hybrids such as CT-004, which have been used safely in patients for 10 years, would seem to require only minimal comment since they have already demonstrated a reasonable safety and tolerability profile. Yet the ethical concerns previously articulated by various organizations are magnified with the development of more advanced and less well-studied combinations of cell and gene therapies. In particular, patients suffering from rare neurological diseases may be exposed to hybrid therapies where neither component is efficacious, or the hybrid itself has not been clinically studied before, creating a situation more reflective of clinical research than clinical practice.

The design and regulation of clinical studies to investigate the potential use of CTs, GTs, and hybrids in human subjects with neurological or neurodegenerative disorders also raise important ethical issues. With the advent of advancements in biotechnology, it is easy to imagine a time when these ethical spaces might not exist — hybrids are commercially available, and the onus is on the provider to ensure that their use is safe and appropriate for a given patient. However, at present, we do not yet live in this world. No hybrid or combination therapy has been approved.

9. Case Studies of Successful Next-Generation Medicines

Next-generation medicines are innovative therapeutic technologies, such as genetic therapies, cell therapies, and novel protein technologies that alter the current paradigm of treatment and have demonstrated efficacy in the nervous system, paving the way for their application in other neurological diseases.

1. Case Study 1: Gene Therapy for ALS

Amyotrophic lateral sclerosis (ALS) is a severe neuromuscular disease resulting from degeneration of upper and lower motor neurons. ALS is genetically heterogeneous; mutations in superoxide dismutase 1 and the gene for repeat expansion in intron 1 of the C9ORF72 gene have been implicated in the largest familial forms of ALS. Inhibition of mutated SOD1 and C9ORF72 repeat-associated non-AUG translation products by gene therapy traveling through the bloodstream and systemic distribution is an attractive approach to treat SOD1- and C9ORF72-related ALS. Local intrathecal administration will probably be required in larger patients and will result in asymmetric distribution and lower efficacy in treating familial ALS compared to PAMs. However, the possible toxicity risk of larger doses and their use in healthy subjects must be better evaluated before being applied clinically.

2. Case Study 2: Stem Cells in Parkinson's Disease

Parkinson's disease is a common neurodegenerative disease that involves the degeneration of dopaminergic neurons in the substantia nigra. A cell therapy approach for PD is based on the transplantation of dopaminergic neurons derived from human pluripotent stem cells, which may support the symmetry of grafted cells and sequent motor improvement. This encourages not only functional recovery in patients but also their quality of life. In this context, the establishment of a well-defined, standardized protocol that allows the generation of high-quality cells for implantation into patients with PD is critical.

3. Case Study 3: Novel Antibody Treatments

Monoclonal antibodies against amyloid accumulation have been approved for dementia due to Alzheimer's disease. However, no monoclonal antibodies to treat neurological diseases have been approved for use outside the nervous system. More generally, the situation of protein therapeutics applied to diseases associated with the nervous system is somewhat more encouraging than with small drugs applied to the central nervous system, given that normal proteins and antibodies are originally large compared to small molecules.

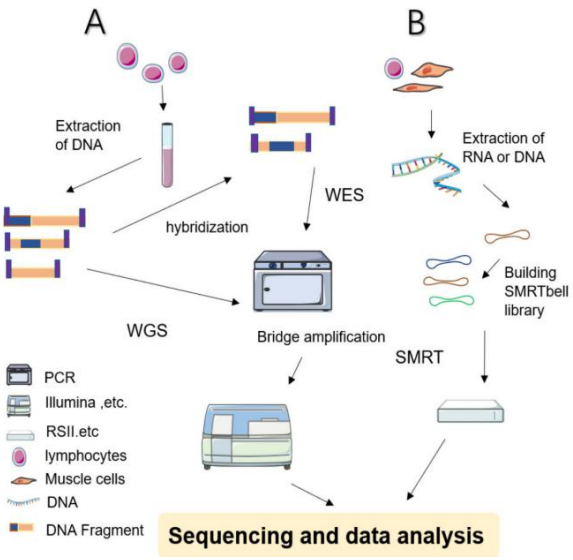

Fig 5 : Next-Generation Sequencing Technologies and Neurogenetic Diseases

9.1. Case Study 1: Gene Therapy for ALS

Abstract: In recent years, there have been considerable advances in the biotechnology industry devoted to the development of next-generation medicines for neurological and neurodegenerative disorders. In this chapter, we explore case studies of three of these next-generation medicines that have entered or are on the verge of entering the clinic for these diseases: gene therapy for spinal cord motor neuron degeneration due to mutations in amyotrophic lateral sclerosis, stem cell that secretes dopamine for the treatment of Parkinson's disease, and next-generation bispecific antibodies blocking both amyloid-beta and tau aggregation in Alzheimer's disease. We also discuss the lessons learned from these case studies that may be helpful in the development of further next-generation medicines in this field. These medicines are the first wave of many next-generation medicines about to emerge over the next decade, taking advantage of the many new technologies developed in the past few years. The development of next-generation medicines is urgently needed as the course of neurological and neurodegenerative disorders remains unaddressed by conventional small-molecule and antibody treatments.

1. Case Study 1: Gene Therapy for ALS

Gene therapy aims to exploit the ability of nucleic acids to produce therapeutic proteins intended to treat disease-associated protein imbalances. Transduction of antisense oligodeoxynucleotides, aptameric nucleic acid constructs, or plasmids encoding small interfering RNA into cells can lead to sequence-specific inhibition of gene expression. The dystrophin

gene, which is excessively large because of its coding for a large protein, has been envisioned to be treated by gene therapy during the past 2 decades. Development of this ancestral approach to treatment is currently being led by DMDs. More recently, in ALS, clearly urgent needs, and types of diseases that may be easily treated, led to a wave of phase 1 and phase 2 clinical trials on familial ALS patients. The results published are mostly positive and strongly encouraging for further testing. These trials are also the first instances of gene therapy applied to the nervous system in humans.
Gene therapy for the entire ALS caused by gene mutation has been driven to the clinic by the very severe, fast course of the disease. Development of this type of treatment has indicated and demonstrated that ALS is an accessible target. Because of the extremely low number of patients who experience such mutations, a collaboration between the representatives of ALS patient organizations, biotech and pharmaceutical companies, and regulatory authorities has led to rapid and specific treatment and bypasses the various steps that are usually required during the testing of medication.

Equation 3 : Commercialization Potential Index:

$$C_p = \delta(M_d \times T_a \times R_s)$$

where:

- C_p = Commercialization potential score
- δ = Normalization factor
- M_d = Market demand factor
- T_a = Therapeutic area competitiveness
- R_s = Regulatory success likelihood

9.2. Case Study 2: Stem Cells in Parkinson's Disease

In recent years, stem cell technology has generated considerable excitement and the potential to deliver next-generation medicines for many neurodegenerative diseases including Parkinson's Disease. Cell replacement therapy for Parkinson's Disease is based on the premise that humans are capable of producing new neurons capable of releasing dopamine in the striatum that support behavioral function. This wave of enthusiasm for stem cells is not surprising; preclinical rodent studies have reported successful recovery of spontaneous motor function and improvements in striatal potentiation in rodents receiving embryonic dopamine neuron transplants that partially reversed depletions induced by a neurotoxin.
However, early clinical transplant studies using fetal-derived midbrain dopamine neurons in Parkinson's Disease patients reported variable and often disappointing outcomes. Moreover, teratoma formation was documented in some transplant patients. Subsequently, the hypodopaminergic Parkinson's Disease state was established to actively inhibit successful dopaminergic functional plasticity following embryonic cell transplant into aged Parkinson's Disease animals, which may also have underlined the patient variability observed in clinical studies. Over the past 15 years, the development of safer induced pluripotent stem cells that can be differentiated into dopaminergic neurons has offered but not yet delivered a cure for Parkinson's Disease. Three critical factors served to delay autologous induced-pluripotent stem cell application until now; the need to develop safe, efficient, and low-cost induced-pluripotent stem cell differentiation protocols using defined media and growth factors; the lengthy cost and time associated with patient-specific autologous induced-pluripotent stem cell application in the clinic; and the need for extensive preclinical validation and optimization before moving into the clinic. Notably, banks of preclinical allogeneic, human embryonic stem cells have been developed around the world. The International Society for Stem Cell Research Guidelines recommend stringent powerful justification for innovation in early-phase human clinical trials using novel induced pluripotent stem cell-based technologies.

9.3. Case Study 3: Novel Antibody Treatments

Monoclonal antibodies are a medicine category that has become very successful in various diseases, especially oncology and immunology. Their application in the treatment of Alzheimer’s disease is now on the way to follow suit. After decades of inconclusive clinical trial results, a new wave of antibodies, notably targeting the amyloid-beta peptide and tau protein, are finally showing success. Physicians are now able to offer patients with early-stage AD treatment options to delay disease progression. Whether these antibody treatments can alter the natural history of the disease remains to be seen in ongoing long-term studies, and whether treatment of patients at later disease stages can also be beneficial in terms of long-term outcomes is another important area of intermittent research. While related antibody therapies against tau appear to be next-generation medicines in AD, an increasing list also includes prevention and treatment of tauopathies such as progressive supranuclear palsy frontotemporal dementia, and parkinsonism linked to chromosome 17.
Earlier this year, cases of amyloid-related imaging abnormalities, a side effect from AD monoclonal antibodies targeting amyloid-beta, were reported in individuals with the rare hereditary Alzheimer's phenotype influenced by the PSEN1 mutation who took a monoclonal antibody targeting tau. This led to a temporary suspension of clinical research on that specific monoclonal antibody until the patient's symptoms, including confusion and headache, improved. While these observations underscore the importance of continuously monitoring individuals engaged in ongoing clinical research, understanding ARIA effects could help researchers develop a better response plan in future cases.

10. Future Directions in Neurological Medicine

The next generation of medicine for neurological disorders must be innovative as well as directed. Current experimental and clinical research in the neurological field suffers from a lack of specificity, targeting, and genetic factors that normally drive better mechanistic understanding of other disease vectors. Important advances have been made - including more targeted delivery systems, clarified polygenetic effects on disease, improved biomarker identification, and using cutting-edge AI and machine learning to develop models. Nevertheless, a next-generation approach is needed to take this field to the next stage.

In this review, we focus on three particular domains that are underrepresented in discussions about the future directions of neurological medicine. Personalized medicine approaches must be used in the clinical setting to drive the selection of patient populations for new and emerging therapeutic modalities. The integration of cutting-edge AI and machine learning tools could bring both improved experimental designs as well as novel biomarker and early effect identification strategies. Finally, more inclusive clinical research efforts regarding global health disparities in neurological disorders and associated outcomes would diversify the research pool and lead to better therapies that could be deployed across different populations.

10.1. Personalized Medicine Approaches

In recent years, there has been a push toward designing specific or multiplexed medicines against a personalized signature of a person's disease. In neurological and neurodegenerative disorders, this concept is being rapidly integrated into the development of diagnostic tools to enable early-stage identification of affected individuals before irreversible damage occurs, as well as to define compartment- versus system-specific signatures of dysregulation pathways and biomarkers for responsive and resistant therapeutic targets. Neurological and neurodegenerative disorders are rather unique in their markedly heterogeneous, acute, episodic, or progressive clinical manifestations, and well-defined behavioral, cognitive, mood, motor, neuroanatomical, and neurofunctional signatures. Personalized medicine efforts focused on understanding the underlying causes of CNS diseases are yielding an unprecedented number of potential strategies for designing and developing medications for CNS disorders. Given the diverse causes of CNS diseases, initial optimum personalized design is ideally matched with companion diagnostics to identify specific pathological signaling cascades or biophysical/biochemical alterations present in a particular individual or group of individuals suffering from a specific CNS disorder at any given time. Validation of strategies to individually and/or collectively ameliorate or reverse some aspect of disease pathology from basic experimental and preclinical models of disease is essential to successfully creating a clinically safe and effective medicine ready for the regulatory approval process and introduction into the pharmaceutical marketplace.

10.2. Integration of AI and Machine Learning

While the human mind created sophisticated rules and mathematics to solve problems and create solutions, no artificial intelligence or machine learning system created by humans has progressed to a point of true general intelligence. AI and ML products created by humans are not to be mistaken for general intelligence. They represent a powerful set of standardized tools that, like other tools, can and should be integrated into a well-planned, thoughtful set of approaches, informed by domain knowledge, creativity, insight, experience, and human vision at both the institutional and corporate levels as well as real-world decision-making and execution by experts in domain knowledge, creativity, insight, experience, and human vision. However, through collaborative partnerships, discovery and development approaches in the future will harness the power of harmonizing the tools of AI and ML with humans working with creativity, insight, experience, ‘looks good – looks bad’, etc. Cutting-edge AI/ML will catalyze connections and integrate known/unknown pieces of the puzzle to help solve highly complex problems in front of discovery and development scientists such as defining which of the thousands of potential indications for a particular molecule are worth pursuing and which patients to enroll in a clinical trial. AI/ML can help along each stage in translation, from connecting which experimental preclinical setting model/molecule/test parameter in what stage with which clinical test outcomes for different disease indications to improve predictive value.

10.3. Global Health Perspectives

The discovery and development of next-generation medicinal products offer great promise for the prevention and/or cure for many diseases, as vested by the previously embellished successes of the pharmaceutical sector. However, these apparent successes mask several systemic flaws regarding the costs and time delays associated with the delivery of new products. Similar to other acute and chronic health conditions prevalent within the global footprint, neurological and neurodegenerative diseases have achieved increasing dominance within the global burden of disease.

The waves of demographic aging internationally, along with increased rates of trauma due to conflict or natural disaster, and epicenters of already weighted non-communicable diseases (NCDs), including neurological and neurodegenerative diseases, present a demanding need for investment in R&D that is structural and localizable. Deep and relevant strategies of philanthropic initiatives include regional health consensus that defines the burden of disease relevant to that region, explores the pathways of potential prevention or intervention, becomes engaged in collaborative and synergistic translational, interdisciplinary, intersectional teams that have an impact on relevant NCD pathways that are responsive to innovation and develop an academic-industrial program of investment by that region. Finally, a strong emphasis must be placed on policy recommendations that ensure equitable access to affordable interventions, and sustainable recapitalization of healthcare that allows access at all socio-economic levels within global regions. An underlying ethos

of Global Health Equity must drive the curricular and structural capacities within the field of Neurological Drug Discovery and Development.

11. Conclusion

1. Summary and Implications for the Future of Neurological Care

This book provides a comprehensive overview of next-generation medicines for neurological and neurodegenerative disorders, with contributions from world-leading experts across a range of disciplines who provide perspectives on therapies across the product spectrum from preclinical and clinical development through to regulation and commercialization. Within these pages are details of the latest advances in our understanding of nervous system physiology, pathology, and the technology platforms harnessed to create innovative new medicines to treat CNS diseases, as well as their potential to radically change the clinical, economic, and societal paradigms surrounding neurological care over the coming years. Neurological and neurodegenerative diseases are increasing worldwide, driven by aging and other changing demographics. Current treatments are often frustratingly inadequate, with limitations on patient selection and treatment efficacy. This globally important area of research is now being driven by the investment of considerable time and resources, alongside the emergence of transformative technologies for drug discovery, development, and delivery, with relentless efforts to translate advances in our understanding of disease processes in individuals into novel next-generation medicines. These assets range from treatments that aim to modify disease pathophysiology by targeting underlying biological processes, rather than symptoms, to enabling therapies that deliver next-generation gene and cell-based medicines to their proper targets in the CNS.

These discoveries bring considerable promise and hope to patients with CNS diseases and their families. However, with promise comes immense challenges. These include the inherent complexity of the problems we are working to address, the often-tightening financing milieu for drug development, and the difficulty in delivering innovative products for diseases whose unmet needs have remained neglected for so long. Collaborative integrated efforts by industry, academic, and regulatory partners will be critical to robustly shape and effectively deliver sensible solutions to accelerate the development of the next-generation medicines against CNS diseases and maximize the chances of success.

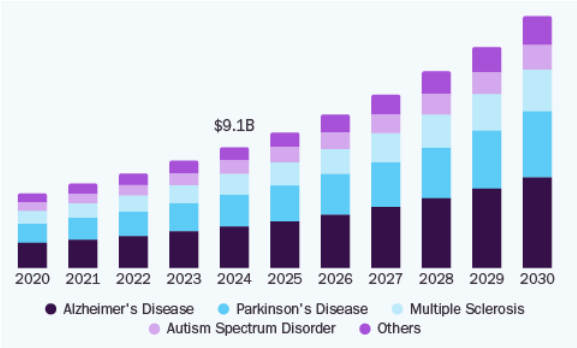

Fig 6 : Neurological Biomarkers Market Size

11.1. Summary and Implications for the Future of Neurological Care

A large global burden is created by neurological and neurodegenerative diseases, including the costs related to lost productivity, caregiving, and healthcare itself, with Alzheimer's disease and other dementias such as Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, and a host of rare childhood-onset and adult-onset neurodegenerative diseases being particularly affected. There is a need for better pathways for the discovery, development, and commercialization of next-generation medicines targeting prevention, disease modification, and treatment. The chapters contained in this book are written by leaders and representatives from different aspects of the broad ecosystem that impacts medicine development in this field and discuss innovative approaches to stem the tide of ineffective current treatment approaches and develop overlooked next-generation approaches to target disease mechanisms and progression. Collectively, this volume serves to review knowledge and data regarding innovative approaches to disease modification and prevention, along with an overview of the need for broader disease mechanism considerations beyond the traditional disease of interest, whether that be Alzheimer's disease, transit amplification network disorders like Huntington's disease, or the many other protein folding, protein aggregation, clearance, engagement, and proteostasis disorders, along with the role that drugs with similar mechanisms targeting additional or network associated disorders can play. Multiple approaches such as developing therapies that have the potential to be used earlier in the time course of a disease, such as for prevention, need to be explored. The relative lack of progress against neurological diseases in recent decades, despite the potentially substantial medical need and business opportunity, points to a need for additional platforms for serendipitous discovery as well as a different and renewed commitment to collaborative science.

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