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Chapter 7: Emerging therapies for neurological and neurodegenerative diseases: From lab to life

7.1. Introduction to Neurological Disorders

Neurologic disorders, which include neurological troubles and mental diseases, represent a major burden on public health, costing economies billions of dollars every year. The clinical expression of neurologic diseases is very heterogeneous and the underlying causes are also very diverse, including head and spinal malformations, infection, vascular or traumatic damage, metabolic alterations, and neurodegeneration. While some neurologic conditions are congenital, the majority of them occur later in life. Neurologic illnesses affect people from all age ranges, from infants with congenital disorders to adults with stroke or tumors, and patients with neurocriptopathies such as Alzheimer's disease, Parkinson's disease, and prion disease (Chang et al., 2023; El-Amin et al., 2023; Morrison et al., 2024).

Sadly, many neurological disorders remain incurable and, when available, therapeutic options usually provide only limited symptomatic relief. The landscape of new and innovative therapeutic options for patients with neurological problems is scarce and it is also complicated because of the large number of neurological disorders and underlying causes that patients can have. Outside of the general classification based on etiology described above, neurological diseases are currently classified based on their clinical manifestation pattern. Thus, for example, some disorders share symptoms and mechanisms and could benefit from a similar therapeutic approach. These include "neurodegenerative" diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, or neuroinflammatory diseases such as multiple sclerosis. Other examples are psychiatric conditions including mood or anxiety disorders, schizophrenia, and autism spectrum such as Tourette syndrome or obsessive-compulsive

disorder, which have recently been associated with genetic dysregulation in the balance between inhibition and excitation of neurons (Sullivan et al., 2024; Nguyen et al., 2025).

7.1.1. Understanding the Landscape of Neurological Disorders

Neurological disorders are a fascinating and important area of medicine and have only recently received the recognition and importance they deserve due to the prevalence and healthcare costs associated with these diseases. These diseases are often poorly treated and are associated with the greatest degree of disability of medical illnesses, underscoring the need for more drug discovery efforts towards these diseases. The public and patient advocacy efforts, combined with the progress being made in our understanding of disease biology coupled with innovative therapeutic modalities, have accelerated interest in drug discovery for these diseases. There are over 600 diseases classified as neurological disorders. Neurological diseases affect approximately 1 in 6 of the total population and account for about 6 million deaths each year, in addition to the estimated 1 billion people currently living with a neurological disorder. Neurological disorders are the leading cause of disability worldwide and come at a large economic cost as current estimates place the cost of neurological disorders at over 400 billion dollars.

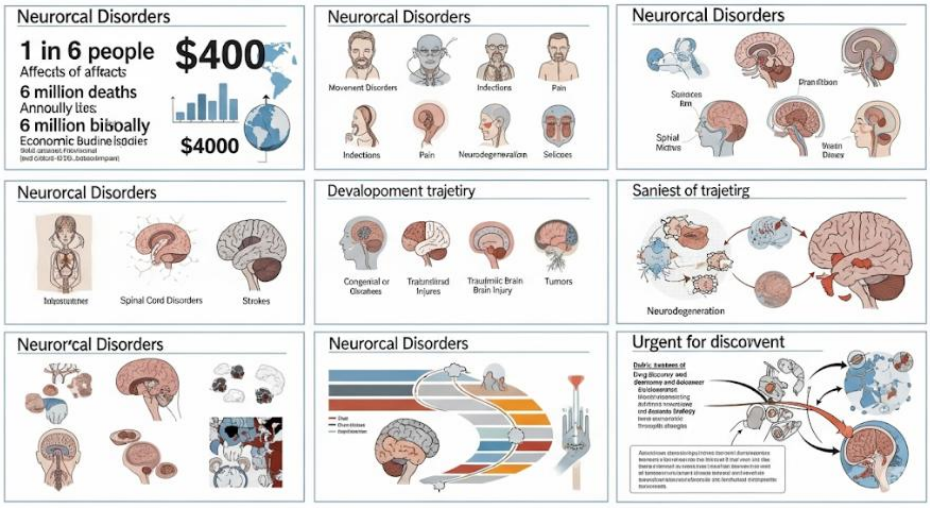

Fig 7 . 1 : A Global Crisis: Neurological Diseases in Focus

Neurological disorders can occur throughout the entire life span. These disorders can arise following congenital/early childhood injury, develop during adolescence, and manifest throughout a patient's adult life, or by neurodegeneration/disease in later life. Neurological disorders are classified into various subtypes including movement disorders, neurodegenerative disorders, infections, pain, peripheral nerve disorders,

seizure disorders, spinal cord disorders, stroke, traumatic brain injury, and tumors. The neurological disorders most commonly associated with disability are dementias, including Alzheimer's disease, cerebrovascular accidents including strokes, and migraine disorders.

7.2. Overview of Neurodegenerative Diseases

Neurodegenerative diseases (NDs) are a group of progressive disorders characterized by degeneration and loss of structure and function of the neuronal or glial cells in the central and peripheral nervous systems. NDs are grouped according to specific symptoms that appear over time. These include difficulties with movement, mental function, vision, memory, and abnormal eye movements due to toxic protein accumulation, proteostasis dysfunction, cellular stress and exhaustion, mitochondrial dysfunction, microglia dysfunction, neuroinflammation, and oxidative stress. These disorders can be sporadic or hereditary, and their underlying causes are often unknown. Genetic or familial forms are conferred by penetrant mutations in specific genes and often have an earlier presentation and more aggressive course. However, the vast majority of cases are sporadic forms, whose etiology is more complex and likely involves a combination of genetic and other risk factors, such as environmental toxins, metals, and infectious agents.

NDs can be classified according to their first affected neuronal population and primary clinical deficits. For example, diseases of the motor system include motor neuron disorders, such as amyotrophic lateral sclerosis, and movement disorders such as synucleinopathies and tauopathies. These disorders involve the degeneration of movements and other functions that are pathologically linked, such as strength, motor control, attention and memory control, social and behavioral dysfunction, and expression and production of sensory disarticulation and speech and language.

7.2.1. Classification and Types of Neurodegenerative Diseases

Neurodegenerative disorders (NDDs) have many underlying factors, including genetic mutations, environmental toxins, protein misfolding, and aggregation. NDDs are common in human society due to an increased life expectancy. These disorders result in deficits in cognitive functions and movement control, and further result in burdens to affected patients' families and society. Neurological diseases can be classified with regard to clinical symptoms, pathogenesis, or the structures and systems associated with the pathologies. Neurodegenerative diseases can also be classified about the structure of the nervous system: peripheral nervous system disorders, such as amyotrophic lateral sclerosis, spinal muscular atrophy, or peripheral sensory neuropathy; disorders with

myelin sheath pathologies, such as multiple sclerosis, Charcot-Marie Tooth syndrome, or hereditary spastic paraplegia; or diseases with neuronal infiltration, such as Alzheimer's disease, or prion diseases.

Neurodegenerative disorders are traditionally classified according to the affected neuronal subtypes, and clinical symptoms. Neurodegenerative movement disorders include the genetic forms of Parkinson's disease, such as Parkin- or PINK1-related Parkinson's disease, and some rare neurodegenerative diseases that cause Parkinsonism, including multiple system atrophy, progressive supranuclear palsy, or Huntington's disease. Cognitive disorders include Alzheimer's disease, frontotemporal dementia, and other dementias associated with tauopathies, such as dementia pugilistica. Notably, there are shared features and overlapping syndrome among these disorders. Although clinical guidelines exist, the diagnostic criteria for each disease have not been strictly enforced.

7.3. Current Treatment Paradigms

Understanding the role of neurological disorders in brain dynamics, which basically explores its ability to register and integrate outside information, creates the ground to explore the best treatment to restore or modulate those alterations. The general idea is to re-establish an adequate interaction with the outside environment. Therefore, the current treatment strategies try to fill in the lack of stimulation, reflect the increasing evidence of neuroplasticity, and stimulate the brain in a more specific manner. Having in mind the proven protection of physical exercise, the general idea is to maintain some level of stimulation, even if achieved by modulating some disordered circuitries. In this view, sensors that transfer the motor execution signals to actuators able to modulate the brain dynamics alongside physical rehabilitation therapy could be designed. These ideas are strictly related to our ability to understand brain network dynamics employing Brain-Computer Interfaces and are pushed forward by the neuro-protheses technology.

Motor disorders are classically treated with drugs acting on neurotransmitter systems such as dopaminergic and glutamatergic, or with invasive surgery to either restore normal functions or, more recently, to improve the motor function while coupling it with rehabilitation. Additionally, we are witnessing a new era of neuromodulatory therapy using focused ultrasound technology. In addition, on the non-invasive side, transcranial magnetic stimulation and transcranial electrical stimulation have been used as modulatory therapy by targeting specific dysfunctional brain areas. For all the above-mentioned treatments, the results are strongly dependent upon the patient's characteristics and the disorder.

7.3.1. Advancements in Therapeutic Strategies

Customized therapy for patients with neurological disorders is currently an unattainable goal, and the therapeutic arsenal employed for their treatment is often a suboptimal one. There is great diversity in the etiology and development of these diseases, and particular moto phenotypes are given conceptual designations, such as major depression, dystonia, oral tremor, noradrenergic dysautonomia, social awareness, rage impact, faced blindness, etc. These conceptions dictate monoaminergic pharmacoresistances that are the concrete marks of these clinical photos. Disease outcome lies in a delicate, but evident balance between neuroplasticity and cellular resilience. Currently, available therapies are far from being ideally pleiotropic to avoid permissible adverse effects. Biogenic amines undergo a logical dissolution during disease-related neuroplasticity as a legitimate pathophysiological outcome. Contemporary drug treatments are often limited to only three biogenic amines, i.e., dopamine, serotonin, and norepinephrine, and specifics of the target illness dictate what monoamine is substituted using trial-and-error tests. Moreover, when putative ethnicity-driven genome polymorphisms are taken into consideration, the clinical shaping of abnormal mood states, mood-coupled psychoses, and psychoneuromodulation becomes blurred.

Highly effective treatments are targeted at manifold drug actions, i.e., are multi-targeted in their action mode; as an illustration, such drugs concurrently hit different targets, such as muscarinic M1, dopamine D1 and D2, norepinephrine α1 and β1, serotonin 5-HT1A, 5-HT2, 5-HT6, GABA-A, adrenergic β1, glycine, nitric oxide, vanilloid TRPV1, SREBP-1, corticotropin-releasing factor-1, and neurotrophins. Moreover, therapies devoid of the problem of specificity and which modify cellular resilience are less than favorable as well. Experimental infections or alterations in homeostasis affecting the immune system have been proven to skew the development of brain disorders. Various cerebrospinal virulent or vaccine model infections have been used to investigate the immune system and disease modulation. No doubt biogenically sequenced vaccines/users of adjuvants/probiotics affecting the gut-microbiota-brain axis can be enriching strategies against brain disease development.

7.4. Innovative Research Approaches

Since the discovery of stem cells and their unique tissue-repairing activities in the 1990s, there has been a flurry of interest in using stem cells as a source of transplantation therapy for neurological and neurodegenerative diseases. Many fundamental biological questions have resulted from such interest; for example, what are the origins of the neural stem/progenitor cells present in the developing and adult nervous systems? Do these stem cells continue to provide repair activity during injury? What are the signals that govern stem/progenitor cell regeneration in the pathological state? A simultaneous focus

on basic and translational investigations is critical to facilitate the bench-to-bedside journey of these therapies and their eventual successful introduction into the clinic and to expand the exciting promise of stem cell therapies for peripheral and central neurotrauma, multiple sclerosis, and neurodegenerative diseases such as spinal muscular atrophy, Alzheimer's disease, and Parkinson's disease. In this chapter, we will discuss how stem cells are currently being used in laboratories and clinics and summarize cutting-edge strategies for their use, including enhanced engraftment, reprogramming of local progenitor cells, cell homing, improved cellular bioengineering, and novel delivery methods. Innovative stem cell strategies may potentially provide benefits for a wide range of neurological and neurodegenerative diseases. Although some of these strategies are currently being explored, many of these ideas may provide early promises for the future clinical use of stem cell strategies. Discussions of stem cell biology, some translational studies, and the challenges that lie ahead will be provided in context. Understanding how cells function and interact in vivo will influence future improvements in both transplant- and regenerative cell-derived therapies for neurological and neurodegenerative diseases.

7.4.1. Cutting-Edge Strategies in Neurological Research

Customarily, the study of neural function has been greatly restricted by technical limitations in examining human neuroscience. Human CNSs are both highly inaccessible and highly complicated structures. Yet, this significant limitation has begun to lessen during the past two decades because of rapid advances in technology. Newer technologies have both alleviated the technical restrictions characteristic of earlier eras and bolstered our knowledge of active circuits and cellular processes. Even with current technologies, however, the study of human CNS function is limited in many ways and poses some difficult challenges that will be addressed throughout this chapter. We also provide examples of some promising current and future studies of human CNS function and discuss their likely contributions to our understanding of neurological functions and disorders, as well as possible therapeutic applications.

Ongoing efforts to improve modern neuroscience technology are likely to achieve even greater breakthroughs in the future that may greatly aid in understanding individual differences in the neurobiology of different neurological disorders affecting localized brain regions, neural circuits, neuromodulators, or combinations thereof. Clinical therapies may also see additional breakthroughs because of improved technology. Meanwhile, better technology will facilitate studies of the neurobiological basis of disorders found in special populations, such as children or aging, and other ingrained individual differences, including those related to sex, intelligence, cultural background, and underlying genetic influences. The work stemming from these foreseeable

developments calls for innovative and interdisciplinary approaches employing advances in molecular and cellular biology, neuroimaging, neuromodulation, neural interfacing, neuroendocrinology, and genetics. These approaches and others promise to support better ways to help patients suffering from CNS disorders regain their quality of life in ways heretofore unimaginable.

7.5. Stem Cell Therapy

Introduction Stem cells have the unique potential to self-renew and differentiate into multiple cell types. These properties make these cells attractive candidates for regenerative medicine, including brain repair. Several neurological diseases afflict the nervous system by directly affecting neuronal populations, leading to cell death and behavioral deficits. In these cases – or in neurodegenerative diseases, in which aging and a gradual process of neurodegeneration create a toxic environment for neurons and where survival of afferent neurons is compromised – stem cell therapy can function by replacing or stimulating endogenous neurogenesis of lost neuronal populations. Mechanisms of Action Regenerative therapies rely on several mechanisms of action. The first mechanism could be the generation of the right cell type; however, in many neurological diseases, the affected neuronal population cannot be easily generated. Instead, regenerative therapies can function by providing trophic support to help repair damaged neuronal populations. As stem cells can migrate to the damaged area or zone of injury and release several growth factors, cytokines, and neurotrophic and immunomodulatory factors, promoting a microenvironment conducive to nerve repair, stem cell therapy has gained acceptance in preclinical and clinical studies of many neurological diseases. A second mechanism is the prevention of a toxic environment in which neuronal cell death occurs, reducing glial activation and promoting glial scar resolution. Other proposed mechanisms include endothelial cells and blood vessel repair; the creation of an extracellular matrix to protect injured areas; the pruning of distortional connections; and forming “just-in-time” protection through paracrine effects, in which stem cells produce high levels of molecules to promote recovery. The outcome of these multiple mechanisms of action implies that the secretome rather than the stem cells themselves are responsible for the regenerative effects.

7.5.1. Mechanisms of Action

Stem cells are cells that can self-renew and differentiate into numerous specialized cell types, including neuronal and glial cells. The ability of stem cells to renew themselves and to generate other cell types is what makes them unique. Adult stem cells, or somatic stem cells, are undifferentiated cells found throughout the body. In certain tissues, such

as the brain, the spinal cord, and the retina, these stem cells are capable of dividing and generating immature precursor cells. To ameliorate damage, recovery, and complication from an insult, these immature precursor cells can migrate to injured areas and further differentiate into neurons and glia, routing themselves and sending out processes to reconnect with other neurons. Thus, the neurogenic potential, endogenous neurogenesis, and capacity of somatic stem cells and their precursors to generate neurons and glia and to migrate into injured areas of the brain, spinal cord, and retina make them viable targets for regenerative medicine in the treatment of NCDs.

Oxidative stress, chronic inflammation, and metabolic dysfunction are the initial primary mechanisms of both TBI and neurodegenerative diseases. A more sustained primary pathology involving metabolic abnormalities in neurotransmitters and neuroglial cell function ensues over time, resulting in neuronal cell loss with subsequent neurological deficits as seen in various TBI. The dual etiology of these events, both acute and chronic, is common to both disease mechanisms and makes stem cell and stem cell-derived immature neural precursor cell-based therapy a more attractive option for both injury types of early response and later-stage regenerative therapeutic targets. These stem cells and stem cell-derived immature neural precursor cells exert neuroprotection by promoting the repair of the damaged areas, balancing the aberrant functions of astrocytes and microglia, and decreasing oxidative stress and chronic inflammation.

7.5.2. Clinical Trials and Outcomes

One of the major contributions of stem cell therapy may be in its neuroprotective effects, such as reducing inflammation, the release of neurotrophic factors, delaying or preventing cells from dying, and remyelination of axons by oligodendrocytes. In a study in aged mice, the intrathecal injection of mesenchymal stem cells at the peak of injury associated with the purging of damaged oligodendrocyte progenitors improved locomoting in experimental autoimmune encephalomyelitis-induced neurogenic claudication, with a clear reduction of spinal damage, inflammatory mediators, and increased levels of cytokines associated with MSC engraftment. The stimulating effect of delirium on recovery through the recruitment or increased activity of MSCs has been tested in EAE.

MSCs rapidly recognize damaged areas of CNS, increasing their ability and essentially, the increased number of recruited cells may have a determining factor in the obtention of a therapeutic effect. Moreover, their effect in the reduction of immunological dysregulation has been pointed out as one of the strongest mechanisms of action in the promotion of recovery and delay of disability in EAE treatment. For example, in studies of EAE induced by peptide 1-87, MSCs were shown to migrate toward the affected area in a time-dependent manner, with the relative number of cells peaking at D7. These

observations were confirmed by the increased capacity of MSCs to migrate on a model of beta1-and beta2-integrin-blockade EAE. Furthermore, the combined action of the integrity of the blood-brain barrier and the presence of proinflammatory cytokines in peripheral blood have been proposed as triggers of MSC mobilization. These cellular responses involve the expression of key transcription factors associated with neurogenesis processes which is the basis of mobilization and subsequent MSC activity in MS.

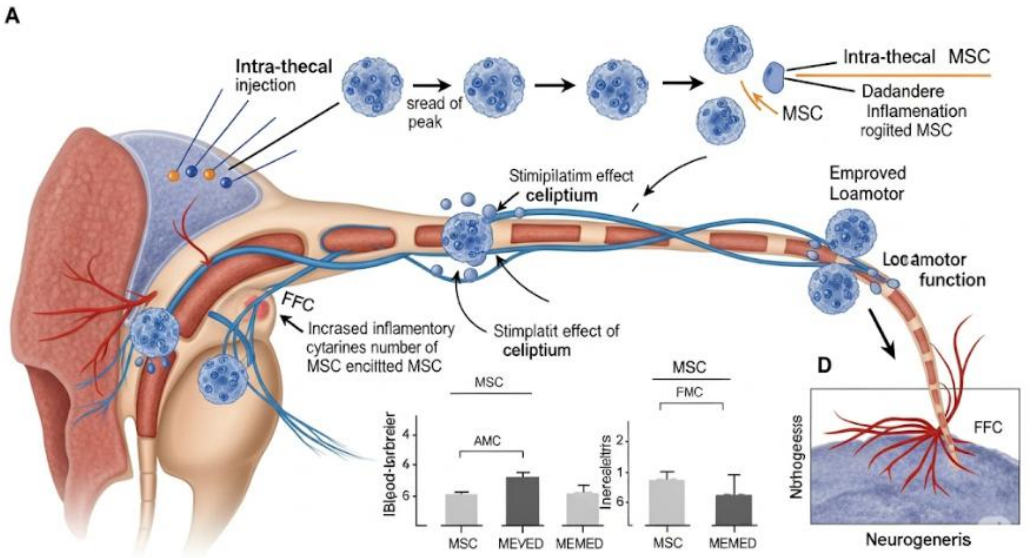

Fig 7 . 2 : Neuroprotection Through Stem Cell Therapy

7.6. Gene Therapy

Neurodegenerative disorders exhibit various molecular and cellular conditions which have made therapies extremely difficult to develop. In recent decades, the advent of gene therapy has revealed a new light in both basic and translational research. Treating diseases at their roots by correcting the molecular deficit has opened many possibilities for curing not only rare genetic disorders but also common complex diseases. Although gene therapy is still facing clinical challenges such as delivery to the target tissue, immunogenicity, and persistence of the delivered gene, many progressions have been obtained in translational research, leading clinical trials in neurodegenerative diseases. One of the most promising techniques involves vectors, and efforts are being made to reach specific delivery, vectors with no or low immunogenicity in order to achieve long-term expression, and the method of delivery itself.

Preclinical and clinical trial results have triggered initiatives to perform innovative cerebral gene therapy protocols and develop cutting-edge devices to achieve improved

safety and potential restorative efficacy. On the other hand, cellular-based gene therapy also represents an interesting alternative approach to correct missing proteins or convey gene products in the local environment, leading to a composite effect. Intra-ventricular and intra-nasal routes have unveiled the effective distribution of vectors and the potential restoration of pathways. In this perspective, we will focus on the methods of delivery, techniques, strategies, and challenges of cellular gene therapy employed in neurological disorders. We will present additional alternative routes, innovative devices, and strategies to target both CNS and systemic routes, opening new avenues to fight against both rare and frequent diseases. We will give more emphasis to both cellular and gene therapy approaches being developed against major rare childhood lysosomal disorders with a unifying view.

7.6.1. Techniques and Technologies

Gene therapy in general refers to replacing, enhancing, or repairing dysregulated or misexpressed genes to limit disease phenotype, either through direct delivery of genetic material or through modulation of endogenous genes. The genetic material used as therapeutic approaches could be either nucleic acids or genetic modifying elements for gene editing. These therapeutic genetic materials are being delivered into cells, tissues, or organs through either in-vivo delivery or ex-vivo delivery: a living organism is directly being transmitted, or one type collected from a living organism is being modified separately and re-introduced into the host respectively. The typical nucleic acid intended to be used as a therapeutic approach could either be DNA or RNA.

Gene therapy has rapidly developed over nearly 4 decades and recently began to be utilized for the treatment of patients. Notably, the initial approval of gene therapy clinical trials was highly promising, including for severe disorders such as Leber Congenital Amaurosis, Severe Combined Immunodeficiency Disease, and X-linked SCID deferred T cell development. The recent revelation of innovative technologies has increased the safety, specificity, potency, and efficiency of genetic modification markedly. These exciting technologies will create even more opportunities for neurological and neurodegenerative disease gene therapy discovery and development.

7.6.2. Case Studies

In order to complete and further explore some aspects covered in section 5.3, we would like to exemplify how gene therapy is tested preclinically and even clinically for neurological diseases and what type of therapeutic effects it is able to deliver. This will however only be a few examples since the number of academic laboratories, companies, and universities delivering preclinical or clinical gene therapies is steadily growing.

Starting with what is possibly the most advanced gene therapy for serious neurological disorders, we would like to move on to discuss novel gene therapies for biogenic amine transporter disorders, genetic epilepsy, and frontotemporal dementia.

If given early enough, gene therapy can cure unsuspected infants suffering from Spinal Muscular Atrophy Type 1 (SMA). The gene therapy uses a vector to deliver the human SMN1 cDNA into motor neuron nuclei, allowing for the translation of the SMN protein. Considering the most recent long-term follow-up data, both gene therapy and early initiation of treatment with an inhibitor of SMN2 alternative splicing have shown remarkable effects in terms of survival, motor development and function, and reduction of therapy burden in symptomatic infants with SMA Type 1. Such data set the stage for a possible combination of these novel treatments in SMA Type 1. It remains to be tested whether this combined treatment is also beneficial in pre-symptomatic newborns.

The development of new vectors and delivery modes also provides the potential to bring gene therapy for both common and rare CNS disorders closer to the clinics. To reduce and even reverse motor and cognitive impairment in Angelman syndrome, in addition to offering ideas to treat other genetic disorders of CNS, have used non-invasive ultrasound-guided delivery of a vector into the CNS of an angiogenetic and propulsive model. Moreover, an innovative lipid nanoparticle delivery system mimicking biological nanovesicles would allow 100% gene editing efficiency in all brain cells. Other lipid nanoparticles would enable successive targeting not only of specific cell types in the CNS and peripheral blood vessels or throughout the body.

7.7. Monoclonal Antibodies

Monoclonal antibodies (mAbs) are the result of pioneering work with the development of hybridoma technology that makes it possible to generate a stable source of highly specific antibodies. Their high specificity provided the ability to use these engineered tools for the detection and isolation of virtually any antigen of interest and in the subsequent use of mAbs as clinical therapy, not without important technical advances that allow their use as therapeutics. mAbs have several advantages over alternative small-molecule inhibitors, including their high affinity and specificity, capacity for humanization, modular design, capacity for large-scale production, and well-defined pharmacokinetics. mAbs are used in clinical practice primarily as immunotherapy agents in hematological oncology, solid tumors, and most recently in infectious diseases with the advent of COVID-19.

mAbs function principally by perturbing the immune system or cells in various ways, for example, by activating a component of the immune system, blocking a ligand or receptor function, delivering a cytotoxic payload, or even as pharmacokinetic enhancers

of endogenous proteins. The therapeutic use of mAbs is well-established in hematological oncology and more recently in solid tumors and autoimmune diseases. There is also a recently very active section of mAbs to be used therapeutically in the context of Alzheimer's disease, both for therapeutic but also increasingly for preventive purposes in the presymptomatic phase. In addition, there is a large number of antibodies under development for other neurodegenerative diseases, including mAbs that target amyloid in the context of α-synuclein inclusion diseases, tau-targeting mAbs, but also neuroinflammation-targeting antibodies. This chapter aims to provide an overview of the clinical results with mAbs already widely used in patients with neurological diseases, for which we want to focus on the use of passive immune therapy in Alzheimer's disease, but also other potential targets, such as tau, α-synuclein, neuroinflammation, prions, and B-cell depleting mAbs therapy.

7.7.1. Development and Applications

Monoclonal antibodies (mAb) are antibodies that are derived from a single clone of B cells. The promise of being able to generate any antibody of choice for therapeutic use was seen as the 'magic bullet' concept more than 100 years ago. Hybridoma technology, developed in 1975, made the magic of the past a reality. The first mAb, muromonab-CD3, was approved for transplantation rejection. The last decades have seen an avalanche of mAbs developed for multiple diseases including malignancy, autoimmune diseases, and infectious diseases. By now, over 100 mAb therapeutics are licensed in different parts of the world.

Starting in the 1990s, monoclonal antibodies have also become available for use in the treatment of diseases of the nervous system. The majority are used in the treatment of neurological cancer; several mAb has been approved for use in glioma and lymphoma. Other mAb is widely used against autoimmune neurological diseases including multiple sclerosis, myasthenia gravis, and neuromyelitis optica. Recently, mAb has been used for the treatment of headaches and Alzheimer's disease. Furthermore, due to their target specificity and large surface area, mAb are the carriers of choice for delivering drugs or imaging agents to diseased cells, and innovative target-specific antibody-drug- or -imaging-agent conjugates are currently under active investigation. With the experience gained over the last decades and the knowledge about the requirements mAbs should meet to be effective and safe, the use of mAb in the different fields of Neurology is expected to further increase shortly.

7.7.2. Efficacy in Clinical Settings

Antibody therapy is presently the focus of almost unparalleled investigation and investment in the biomedical research community. Validation of the utility of protein and antibody therapeutics has driven the exploration of many mechanisms in multiple conditions, and many candidates have sufficient pre-clinical promise, to justify rapid translation into human subjects to address unmet clinical needs. Antibody therapies for neurological disease have been pursued in models of autoimmune demyelination, associated positivity, blood-brain barrier cytokine-mediated leakage, amyloid-mediated neuroinflammation, idiopathic or immune-associated neurodegeneration, encephalitis, autoantibody-induced neurodegeneration, paraneoplastic-neurodegeneration, and autoantibody-mediated neurologic injury models of traumatic brain injury and multiple concussions. More broadly, studies implicating antibody-mediated effects on neuro-inflammation, microglia, apoptosis, synaptic plasticity, oligodendrocytes, and glial dynamics in scarring, are paving the way for clinical studies of multiple neurologic conditions.

Currently, several mechanistic modalities are in-stage human clinical exploration, including neuroinflammation; neurodegeneration and aging; synaptic plasticity; and repair and regeneration. Novel antibodies targeting specific pathogens, complement, immune-mediated excitotoxicity, or injury-induced adaptive autoimmunity, hold promise for underlying microbiome-driven disease modification and protection of circuits. These novel considerations are critical for the success of neuroprotective therapeutic trials, as they integrate with the therapeutic mission of enhancing endogenous defenses against established neuroinflammatory activation, restoration of intraneuronal transport dynamics, and stimulation of aberrant immune primed CNS repair. Further development of small molecule approaches to modulate these innate defenses against neurodegeneration are revealed by clinical studies on small molecules to inhibit the facilitation of nuclear activity, to advance currently underutilized pleiotropic properties, of pathogen, immune, and repair-modulating antibody-based therapies.

7.8. Neuroprotective Agents

Neuroprotective agents are a group of drugs which promote cell survival in adverse conditions. Neuroprotection is not a very specific term: it is related to the prevention of neuronal death by drugs acting in different cellular and molecular processes. Neurodegenerative processes are characterized by deregulation of a multitude of pathways, including neurotrophic factor signaling, proteostasis, autophagic/lysosomal degradation, mitochondrial function, synaptic homeostasis, inflammation, and oxidative stress, among others. Therefore, many of the neurotransmission-related drugs used in

clinical practice, such as antidepressants, antipsychotics, and antiepileptics, have been proposed as neuroprotective agents and some of them have shown some convincing preclinical and clinical efficacy in certain conditions, such as Parkinson's disease. However, the survival of a cell in pathological/physiological conditions is profoundly influenced by the surrounding environmental conditions. Therefore, drugs acting in modifying imbalanced neuroinflammatory or oxidative stress responses have been proposed in the last few years.

A multitude of innovative drug candidates with potential neuroprotective properties are being developed, including glial modulators, sensors of reactive species, autophagy modulators, and senolytic agents, among others. Repositioning already marketed drugs with certain neuroprotective properties is also a viable and attractive strategy. Developing new compounds based on herbal extracts which have been traditionally used in indigenous medical systems is an attractive area in drug development and some of these plant-derived candidates have also been used to relieve neurological and psychiatric symptoms. Non-pharmacological therapies showing some potential for neuroprotection include ketogenic diets, transcranial magnetic stimulation, deep brain stimulation, and exercise. With the potential of precision medicine, biomarker-driven clinical trials personalized and designed on putative-specific targets are expected. Better stratification of patients in clinical trials using particular biomarkers may help to enhance the outcomes of these trials and the identification of conditions and specific patients who are responsive to these new therapies.

7.8.1. Mechanisms of Neuroprotection

Neuroprotective therapy refers to diverse approaches that mitigate the detrimental effects of neurodegeneration by targeting the mechanisms of neuronal cell death. Since cell death is the common final pathway in a considerable number of neurological diseases, the search for specific neuroprotective agents has become a frequent area of interest. Cell death and neurodegeneration are induced by alterations in several intracellular pathways that, in the case of neurodegenerative diseases, are chronically activated. Degenerative processes are promoted by several injuries that can be intrinsic and extrinsic to the cell. The ability of a compound to interfere with one or more of these common issues may be a key factor in the effectiveness of the proposed neuroprotection. Neuroprotective mechanisms are usually defined by the nature of the injuries that they can correct, thereby restoring the normal homeostatic state of the neuron. Restoration of the physiological level of neurotrophins, including neurotrophins in cell culture, or the modulation of neurotrophin expression in vivo, constitute mechanisms of neuroprotection that have been used to define pharmacological compounds. Restoration of mitochondrial functions can define neuroprotection. ATP depletion, accumulation of

metabolic by-products, lowered pH, excessive production, or mitochondrial depolarization are biochemical hallmarks of mitochondrial malfunctioning, which trigger cell death via necrosis or apoptosis. Brain insults may cause an elevation of intracellular calcium and depletion of calcium stores in the rough endoplasmic reticulum, which may also be associated with the elevation of cytosolic activity. Microglia, upon activation, migrate towards sites of compromised neuronal survival where they have deleterious effects by inducing neuronal cell death through the release of pro-inflammatory molecules, which can trigger apoptotic and necrotic cell death.

7.8.2. Recent Advances

The investigation of the neuroprotective ability of traditional medicines against neurodegenerative diseases has increased in recent years. These neuroprotective substances from nature may target genes and proteins to express a protective role for neurons when under insult from intrinsic and extrinsic stimuli. Here we have summarized the recent information on the mechanisms of neuroprotection of curcumin, ginsenosides, fisetin, ginger, and other electrophilic compounds against Alzheimer's disease. Its neuroprotective actions are mediated via modulation of phosphorylation of tau and APP secretion cleaved via activation and inhibition of related kinases and phosphatases.

Curcumin, the orange pigment located in the roots of the turmeric plant, protects neurons by enhancing the function of the ubiquitin-proteasome system to degrade misfolded and aggregation-prone proteins, i.e. tau hyperphosphorylated at threonine 181 and additional serine residues, and mutated α-synuclein and huntingtin. Disturbance of the ubiquitin-proteasome pathway is inadequately understood in the pathophysiology of neurodegenerative diseases, but modulation of tau phosphorylation via ubiquitin-proteasome system by curcumin and its analogs represents a potential new direction in tau research. Moreover, the pigment might have protective effects on other protein misfolding diseases, such as Parkinson's and Huntington's diseases. Here we review current knowledge on the effects of herbal-derived neuroprotective agents on tau versus APP underlining the putative signaling networks involved. The beneficial effects include reducing the levels of tau or β-amyloid, the cleaving product of APP, promoting the production of neuroprotective APPα, and restoring tau and APP ratios. Piceatannol from the white seeds of edible plant delay reduces acetylated tau, while d-chiro-inositol helps ameliorate the increased ratio of tau/APP in aged rats with the disease.

7.9. Conclusion

Neurological and neurodegenerative diseases are a growing global concern due to the increasing incidences of related disorders. Emerging therapies may offer great impact and change the disease outcome. Here we summarize the recently developed therapy strategies, with a focus on our product, the rAAV Two-hybrid gene delivery system, with no disease-modifying treatment in clinical use yet. The advent of new technologies has increased our understanding of how to develop and implement candidate therapies. Gene therapy has evolved from the replacement of missing or reduced gene products to addressing the up- and downregulation of specific genes or gene products involved in pathogenic pathways. Innovative strategies are in continuous development to better target gene delivery, especially RNA therapies. Oligonucleotides, small interfering RNA, and antisense oligonucleotides have been shown in preclinical models to ameliorate muscular, neuronal, and ocular disorders. RNA errors can be addressed by using the RNA repair toolbox or searching for open reading frames. Antitranscriptional strategies diminish “toxic” mRNA, while gene knockdown also reduces deleterious transcribed products. CRISPR genome editing technologies have progressed from initial research to 1st in human studies, showing both safety and efficacy.

The advent of monoclonal antibodies opened up the therapeutic area far beyond cancer and inflammatory diseases. Several amyloid-targeting monoclonal antibodies are in late-stage trials, with changes in amyloid burden but no major amelioration of symptoms yet. Passive vaccination based on monoclonal antibodies and tau-targeted monoclonal antibodies are in development and testing. Small molecule therapies have achieved an enhanced variety, addressing the gut-brain axis or modulating the scaffolding function of amyloid for tau-related processes. The tools and pathways developed in preclinical models are available for clinical testing, which will enhance possible success in the future.

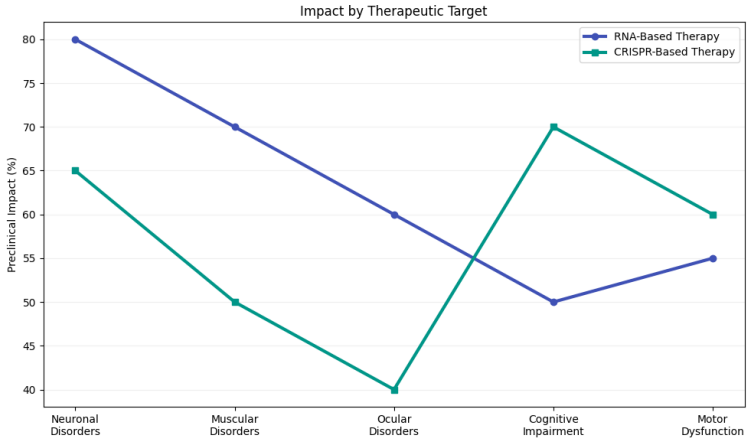

Fig 7 . 3 : Impact by Therapeutic Target

7.9.1. Summary and Future Directions

Through the investigation of novel scientific discoveries, neurological and neurodegenerative conditions that chronically debilitate the activities of daily living seem to have possible therapeutical strategies that have or are about to leave the lab. Curative therapies that clinically inverse the effects responsible for these chronic illnesses in human patients are still scarce. In this chapter, we explored both established and emerging therapies for the treatment of well-known and discussed neural diseases, such as Alzheimer's Disease and Parkinson's Disease, and neurological conditions for which little therapeutic intervention exists, such as Tinnitus and Amyotrophic Lateral Sclerosis. We also discussed various therapies in both the preclinical and clinical testing phases.

It is possible to note that although neuromodulatory, glycemic, and other therapies are not specific niched solutions to the discussed ailments, they have a beneficial effect on a wide array of conditions. Nevertheless, it is noticeable that little effort has been made to translate these therapeutic strategies into the health industry and use them widely for the amelioration of chronic neurological symptoms. It is also observable that although animal models are being used efficiently for the preclinical investigation of several therapies, it is common to have only a select number of experimental animals to be used within each preclinical trial. This might influence the statistical validity of achieving reliable positive outcomes from these investigations and also hamper more robust translational efforts to bring effective results to patients. Solutions should be made in order to increase the consistency, reliability, and statistical robustness of molecular, behavioral, and clinical outcomes favoring the use of therapeutic candidates in clinical settings. Particularly, the protocol for listening blades or tinnitus pitch gap test should be ameliorated so that preclinical volunteers and patients might be able to report their improving scores more clearly.

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