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Engineering Experimental Models for Neurodegenerative Diseases

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ABSTRACT

Neurodegenerative diseases (NDs), including Alzheimer's, Parkinson's, Huntington's, and ALS, present significant challenges due to their complex pathophysiology and increasing prevalence. Effective experimental models are essential for understanding disease mechanisms and developing treatments. This paper examines various engineering-driven approaches to ND modeling, including genetic, cellular, and organ-on-a-chip technologies. Integrating bioengineering techniques, such as biomaterials, biosensors, and microfluidics, enhances the physiological relevance of in vitro and in vivo models. Despite advances, limitations persist in replicating disease heterogeneity and progression. Continued interdisciplinary collaboration is crucial for refining experimental models and accelerating therapeutic breakthroughs.

Keywords: Neurodegenerative diseases, experimental models, bioengineering, induced pluripotent stem cells (iPSCs), organ-on-a-chip, genetic models, biomaterials.

INTRODUCTION

There is an ever-growing need for the development of informed and cross-disciplined approaches toward the understanding, prevention, and management of the most complex conditions in neuroscience, such as neurodegenerative disorders. In the context of scientifically and economically challenging times for neuroscience, there is a rapidly expanding demand for novel and cheap in vitro preparations, capable of bridging the gap between the abstractions of low-cost experimental modelling and the sufficient biological validity to be still informative for biology. In this frame, in the recent years recognizing the need for effective multidisciplinary approaches, capable of playing out the common interests of traditional experimental biologists and their engineering colleagues as well as for the effective literacy and open-enough attitude of both investigators, novel experimental systems designed, developed, and experimented with by the interplay between Engineers and Biologists with relevant experience and expertise in Biomolecular Engineering, Molecular Medicine, and Molecular and Cell Biology are analyzed. A glossary, including definitions of all the relevant acronyms and disciplines, can be found at the end of this paper. The principal results presented and discussed are the following: the definition of dedicated neurodegeneration/excitotoxicity-based experimental protocols, that are developed and applied to different tissue-engineered CNS in vitro models and addressed to specifically assess new strategies of brain neuronal damage as occurring in several neurodegeneration-based and neuroinflammation-related diseases; the experimental implementation and testing of a relevant number of chosen engineering innovative solutions, namely ad-hoc designed microfabricated biosensors and custom preparation of certain biodegradable scaffolds, able to provide a significant technological support to the biological experimental set-ups to develop and run the above-proposed protocols; a deep biological study, including both morphological and electrophysiological analyses, that also ensures and enlightens experimental results [1, 2].

Overview Of Neurodegenerative Diseases

Neurodegenerative diseases (ND) are characterized by the progressive degeneration and death of nerve cells, leading to diverse motor, cognitive, and homeostatic dysfunctions. Symptoms usually start with movement and mental function difficulties that worsen over time. There is significant overlap in the molecular processes of various neurodegenerative disorders, complicating diagnosis, which typically relies

on specific symptoms of neuronal degeneration. Major ND disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. A key feature is the misfolding of proteins, causing insoluble aggregates that exacerbate neurodegeneration. Initial symptoms can manifest as seizures or movement issues, followed by cognitive disruptions. The variability of symptoms and progression among patients complicates treatment. The incidence of ND is rising in Western countries due to aging populations, leading to substantial societal costs. Efforts to study the molecular mechanisms behind neurodegeneration are increasing in response to these trends [3, 4].

Importance of Experimental Models

Experimental models have been instrumental in understanding the mechanisms of neurodegeneration at molecular, cellular, and systems levels, often revealing critical insights that have stimulated further work. This helps elucidate these diseases in vitro, in vivo, in silico, and ex vivo. The models are useful for testing a hypothesis in a controlled environment that mimics a defined disease condition, for example, protein aggregates, and abnormal proteins between cells or spreading protein pathology. The observation that a model resembles a histopathological and clinical phenotype in humans has also triggered efforts to manipulate the risk factors to mitigate, slow down, or stop the pathological disease process. In this sense, it is essential to take experimental findings as an opportunity rather than a prescription for therapeutic intervention. Although it has created a certain enthusiasm that a moderate-to-robust effect in model systems may directly convey the strongest support for the exploitation of the discovered target for therapeutics in the clinic. At the same time, the results have cast a critical eye on the relevance of current model systems and the 'reproducibility' of drug effects across different models, both of which bespeak a general need for deepening the understanding of preclinical model systems. There are important reasons to sustain and further enhance investment in the development of innovative and refined experimental models. First, validation and innovation of experimental models is a progressive and collaborative endeavour that typically requires close interactions among expert researchers in different disciplines, including molecular and cellular biology, genetics, biochemistry, histology, neuropathology, electrophysiology, and imaging. Studies that have led to the detailed characterisation of early disease phenotypes in response to distinct initiating insults in different model systems and have been instrumental for patient stratification have succeeded based on interdisciplinary approaches. Second, the pace and extent of methodological advances and resulting disease knowledge are such that refinement and development of model systems must necessarily be pursued continuously. Moreover, the translation of gained insights into novel or improved experimental models is likely to further catalyse the search for druggable targets adapted to the defined model disease scenario [5, 6].

Types of Neurodegenerative Diseases

Neurodegenerative diseases (NDs) are a large, cumulative group of disorders characterized by a complex process in which neurons present in unique regions of the nervous system progressively degenerate and die. Despite there being a considerable number of NDs, they all have in common the loss of neurons that lead to a gradient decline in the quality of life of the affected individual. Symptoms of NDs are heterogeneous. They can be motor, as in Parkinson's and amyotrophic lateral sclerosis (ALS), or cognitive, as in Alzheimer's disease and frontotemporal dementia (FTD). The heterogeneity of NDs presents a challenge to find a common path in which disease can be originated, with all the current evidence suggesting that it arises from a combination of genetic susceptibility and environmental exposure. Many NDs share a range of similar pathophysiological processes, representing the existence of shared phenotypic and molecular alterations involved in the early stages of the disease. On the other hand, it is the unique complex interaction between the shared early processes and the specific insults present in each disease that lead to the final fatal neurodegeneration underpinning the symptoms of the disease. The progressive nature of neurodegeneration spreads the initial insult to diverse components of the neurons and also to different anatomical areas for different NDs. Each neurodegenerative process is accompanied by the formation of toxic species that seem to spread the pathology to nearby regions. This has led to the formulation of the prion-like hypothesis of neurodegeneration. Overlapping and unique pathological features of both generic apoptosis and specific processes underlying each disorder are necessary to have a complete insight into ND pathogenesis. Post-mortem tissue from human sufferers remains the gold standard for the definitive diagnosis of NDs. Commonly, neuropathological analysis of the brains is used to identify the presence of aggregated protein deposits, together with the observation of cell loss and the presence of gliosis in specific brain areas in which it is known to occur in the illness under investigation [7, 8].

Genetic Models

In studying neurodegenerative diseases, genetic models are crucial for understanding genetic contributions, disease mechanisms, and susceptibility genes. Various methods exist for creating these models, including isolating disease-related genes and generating knockout models or introducing mutations via transgenic techniques. Gene targeting can produce a range of genetic alterations like point mutations and deletions. Many neurodegenerative diseases are associated with specific gene mutations, allowing for the investigation of molecular mechanisms and identification of new therapeutic targets. For instance, familial Alzheimer's disease involves missense mutations, and transgenic mice replicating these mutations exhibit amyloid plaques and progressive memory loss with age. Mouse models with specific gene mutations closely mimic human diseases, making it easier to differentiate the impact of gene mutations from aging. Reproducing disease-specific traits in genetically modified animals aids further analysis, including characterizing brain regions affected in humans and testing drug treatments within the context of disease progression. However, studying the pathogenic mechanisms in genetically modified animals remains challenging, as these models don't fully replicate the complex human disease phenotypes and numerous pathogenic pathways. Nonetheless, successful genetically based models have advanced research in neurodegenerative diseases, enabling simpler application of new genetic insights in future model development. Future studies should focus on creating complex models with multiple genetic and environmental factors to enhance understanding [9, 10].

Transgenic Mouse Models

In 1981, the first transgenic mice were generated through the introduction of extra-chromosomal DNA in the mouse genome. This technique has been a cornerstone in the study of several human diseases, including those related to the nervous system. It consists in the introduction of at least one copy of a gene (most frequently associated with a human disease) into the mouse genome through the use of microinjection. The availability of transgenic models from the early stage of the investigation of the disease of interest can immediately provide unique insights into the disease progression and pathology. Nevertheless, this is a double-edged sword as transgenic AD mouse models have been studied for more than 15 years, and there are only marginal advances in the understanding and the treatment of the human disease 11. Mice overexpressing mutant forms of either APP, of the presenilins, or other proteins contain characteristic hallmarks of AD. Besides the creation of transgenic models, induced models are also available and advantageous for the study of Parkinson's disease (PD). Since the early 90s, the involvement of α-synuclein in the etiopathology of PD has prompted the development of several transgenic mouse models overexpressing either wild-type or mutant forms of the protein. As in the case of AD mouse models, these mice display typical deposits of α-synuclein in the neurons. However, like for AD, there are still several open questions regarding the formation of the protein aggregates and to their role in the pathophysiology of the disease. Transgenic PD animal models have provided unique information and a few good examples of correlation between protein aggregates and neurodegeneration. The evident advantage of using these models is the possibility of studying the effect of a gene during the entire life span of the animal. As a result, it has been possible to investigate in a detailed manner the short and long-term consequences of prolonged expression of a gene thought to be the cause of a particular disease. However, perhaps because of the number of transgenic models and the plethora of results, the interpretation of these data should be taken with caution. Indeed, there are many controversial results among different transgenic lines, and not all of the data published could be replicated in different laboratories [12, 13].

Knockout and Knock-In Models

To investigate genetic contributions to neurodegenerative diseases (NDs) is essential, as they are genetic diseases influenced by complex interactions among genetic, epigenetic, molecular, and environmental factors. Recent advances in genome sequencing have identified numerous genes associated with various NDs, facilitating the creation of genetically engineered mouse models to explore pathogenic mechanisms. Knockout mice are created to inactivate a gene by replacing part of it with a selection marker, preventing the production of subsequent transcript and protein. In contrast, knock-in mice have transgenic cDNA or modified gene sequences inserted into their genome under the control of an endogenous promoter, allowing expression with key regulatory features of the host gene. NDs present a major public health challenge, particularly in an aging population, but pathological mechanisms remain unclear. There is currently no cure for most neurodegenerative diseases (NDD), which account for 1% of all dementias. They are debilitating conditions characterized by brain tissue abnormalities and cell death, leading to cognitive, motor, and emotional symptoms. NDs like Alzheimer's (AD) and Huntington's (HD) diseases

affect specific neuronal populations and exhibit distinct symptoms. HD is dominantly inherited, typically appearing in midlife, and causes extensive neuronal loss in the striatum and cortex, while AD is age-dependent and mainly sporadic, leading to synaptic dysfunction and memory loss. As the disease progresses, cognitive decline mirrors many age-dependent changes seen in HD. Understanding the biology underlying NDD initiation and progression is critical for elucidating disease pathogenesis and identifying molecular targets for early diagnostic tools and effective treatments. Accelerating the preclinical screening of new drug candidates and gene therapies requires robust animal model systems in specialized research facilities. Additionally, comprehending how gene alterations lead to illness can clarify which cellular and molecular targets need repair. The functional replacement of disrupted genes and the effects of disease-causing mutations remain largely unresolved questions. Nevertheless, genetically engineered animal models have provided valuable insights into the etiology of genetic diseases [14, 15].

Cellular Models

The study of neurological disorders has long been hampered by the complex and poorly understood nature of the human brain, mainly due to the lack of suitable experimental models. Cellular models, comprising a wide range of systems from primary neurons to immortalized cell lines, have been developed to understand the cellular mechanisms underlying neurodegenerative diseases. Such models are advantageous as they can be easily manipulated and maintained in a lab setting while also carrying lower ethical concerns compared to animal models. It also can be adopted to assess various experimental methodologies, including drug screening, gene editing, investigative cellular pathogenesis, or a phase of cellular proteins. However, the challenge of translating findings from laboratory cellular models to broad-spectrum organisms has led to a variety of experimental models, each offering a unique view of disease pathology and ideally addressing distinct research questions. In addition to more traditional model systems, significant innovations in cellular technology provide novel and exciting possibilities to accelerate the study of disease mechanisms and the discovery of therapeutic compounds. The many breakthroughs advanced through cellular models have underscored the vital role they envision in the understanding and treatment of diseases. For example, neurogenin-2, a transcription factor involved in neuronal differentiation, reprogrammed mouse and human fibroblast cells into striatal GABAergic medium spiny neurons, which could promote axonogenesis when cocultured with striatal cell lines. A separate study employed patient-specific induced pluripotent stem cell-derived forebrain medium spiny neurons to reveal a critical developmental window before neuronal commitment that was disrupted in patients with Huntington's disease. Other experiments leveraged the transcriptional consequences of glutamine repeat expansion in endogenous ataxin-7 to reveal gene-specific expression profiles in SCA7-patient-derived induced neurons, thereby identifying potential therapeutic targets [16, 17].

Induced Pluripotent Stem Cells (IPSCS)

Neurodegenerative diseases are characterized by increased organismal age and gradual central nervous system dysfunction affecting life quality and significantly shortening life span both in humans and animals. However, how these processes occur and how to prevent and cure these diseases are still unclear, and there is no perfect whole repair method. The models in vitro have not been able to faithfully simulate the entire development and progression of such diseases and thus cannot carry out large-scale mechanism research and drug screening. Theoretically, the disease status of a person's body originates from the cells of the body, and DNA and genes may have a more direct and substantial impact on disease status. The advent of induced pluripotent stem cells (iPS cells, iPSCs) may provide revolutionary tools for research of the pathogenesis of diseases and the development of new drugs. iPS cells are pluripotent stem cells that are generated from somatic cells, such as human fibroblasts. The iPS cells can differentiate into various somatic cells. Thus, with iPS cells, biomedical researchers can establish patient-specific cellular model systems. So, much work has been done or will be done with this innovative tool to pave the way to establish its potential value for research and the medical field. Differentiation of human embryonic stem cells, as well as iPS cells, has demonstrated the potential to generate cell lineage-specific cell types suitable for the study of various human diseases. As most human neurodegenerative diseases are largely undetermined for their etiology or origin of neural cell types and occur in a complicated living organism, it is very difficult or even impossible to directly perform loss-of-function or gain-in-function experiments with patient cells of original disease states. Hence, a major advantage of modeling diseases with iPS cells is the capability to circumvent the above dilemma. Many attempts have been completed to use iPS cell-based models to mimic diseases, such as Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD), which shed light on the study of the pathophysiological features of these diseases. Moreover, these cellular models serve as a platform for high-throughput drug screens. Early studies, for example, by the

integration of cell lines or primary cells from affected individuals, and later, thanks to iPS cells, such tools have allowed better the understanding of diseases, and capacity to identify points of intervention for therapy [18, 19].

Organ-on-A-Chip Technology

Engineering experimental models to study and characterize molecular disease-initiating mechanisms and differentiate them from the progression of chronic neurodegenerative pathology has been pursued across various research fields. Significant advancements are expected from organ-on-a-chip technologies, which model human physiology in vitro and are relevant to neurodegenerative diseases. An organ-on-a-chip combines living human cells and tissue characteristics in a controlled microfluidic environment on a miniature scale. The complexity of human organs, each with diverse cells and functions, highlights the challenges in creating physiologically relevant in vitro models. Tissue engineering advancements promise improved fabrication and design to develop platforms that combine different organ models or entire body-on-a-chip to better predict drug effects or disease modeling. The blood-brain barrier, crucial in neuron interactions and brain homeostasis, has been modeled in several organ-on-a-chip systems, enhancing understanding of its role in neurodegenerative disease onset and progression. Findings suggest damage to this barrier precedes the accumulation of amyloid-beta and cell death, with dysfunction exacerbating these effects. This emerging research field provides novel insights for disease models relevant to the human body and explores new therapeutic targets, particularly concerning the vascular system. Innovative models integrating neurons with "microglia-on-a-chip" further investigate neuroinflammation and its interaction with the vasculature, presenting challenges in miniaturization and scaling. Additional topics include developing bio-integrable materials to maintain cell function and addressing challenges in connecting different organ models while preserving accurate physiological conditions. A promising frontier exists in using patient-derived cells for modeling human physiology, paving the way for personalized medicine, and fostering collaborative efforts among neuroscientists, bioengineers, and pharmacologists for optimizing these new research tools and disease models [20, 21].

In Vitro Models

It is widely accepted that control over and detailed understanding of the recreation of an environment is necessary to observe and understand underlying phenomena. The study of computational models has allowed this level of control and insight in a variety of disciplines over the past century. Machine learning models, for instance, are based on this very concept. They can shed light on highly complex and non-linear systems and are applied in biology to model neurodegenerative disease, migration of neural crest cells, and so on. The pathways are known to underlie the evolution of Alzheimer's disease, and usually a description in the form of a set of ordinary differential equations is used. With this model tool, the temporal behaviour of the system can be monitored in silico in the presence of realistic perturbations. Below are outlined some of the in vitro models that are widespread in the field of neurodegeneration. They have enlightened the progression of disease understanding and the testing of potential therapeutics. They span simple cell cultures to models containing a higher degree of complexity, such as organotypic slices. Advantages aside, avoid unethical procedures. Most importantly, in vitro models allow hypothesis testing as they offer the opportunity to manipulate cellular pathways genetically or through drug treatment and to ascertain their effect on disease phenotypes. By using these models, several toxic cellular processes that underlie the pathobiology of neurodegenerative phenotypes have been uncovered. Nevertheless, the shortcomings of these models are widely known; they do not consider complex tissue interactions and hence cannot give a tissue-level perspective. However, for their high level of experimental control, they can provide a detailed cellular and molecular explanation of any occurring neurodegenerative phenotype. Noteworthy, for the perspective of tissue-level modelling, they can be advantageously associated with other experimental approaches, including post-mortem data analysis or MRI. This encourages the use of in vitro models as a key starting point for any new computational platform. In this regard, it is worth mentioning key discoveries using in vitro approaches in the field of neurodegeneration [22, 23].

Primary Neuronal Cultures

Immortalized cell lines have been a popular tool for cellular neurobiologists and neuronal disease researchers for studying neurodegenerative processes for over 20 years. However, despite their advantages of immortalization, these cell lines often fail to emulate the characteristics of their in vivo counterparts. Immortalized cell lines have been shown to lose their specific properties (i.e., electrophysiological activities, neuromodulation properties), and they do not faithfully replicate the in vivo responses of neurons to a variety of physiological and pathological stimuli. This issue becomes

particularly important due to the increasing evidence that in neurodegenerative diseases, protective or degenerative effects are specific for particular types of brain cells. Therefore, physiologically relevant experiments in a system that emulates neuronal cells most realistically seem to be imminent. A popular alternative to immortalized cell lines is primary neuronal cultures. For the past years, dissociation methods have been established that allow prolonged maintenance of these cultures and that, when combined with other methods, allow answering relevant biology of neurons questions. Indeed, substantial progress has been made in establishing secondary or even (self-)perpetuating lines of primary neurons. Given its prospected further expansion, it seems reasonable to delineate or understand these cultures and the methodologies that are currently available. This issue is particularly important for the neuroscience field due to its fundamental character for understanding the mechanisms of neuronal function in both the physiological and pathological states. These cultures can be treated differently and expanded with other methods to answer biologically relevant questions. The increased versatility and capabilities of adult neuronal cultures will be particularly helpful to further understand the unraveling role of the timing of neurodegenerative processes in aging and disease [24, 25].

Challenges in Modeling Neurodegenerative Diseases

It is expected that ongoing funding by institutional supporters will enhance informatics initiatives and shape future directions. With significant changes from past discipline-specific research support, an analysis of these opportunities and potential challenges is crucial to inform funding decisions and guide future strategies. Recommendations for improving institutional and funder practices include focused investments in data-centric researcher support and evidence-based evaluations of proposed initiatives. The challenge of modeling human neurodegenerative diseases (ND) is significant in neuroscience and clinical research. ND, such as major depressive disorders (MDD), are complex and irreversible, influenced by genetic, physiological, neural, and environmental factors linked to age. Researching the development and progression of NDD in human brains faces scientific and ethical barriers. Current mammalian models show anatomical and functional discrepancies for studying MDD, requiring careful selection. Additionally, MDD presents variability in neural degeneration's rate and order. The complexity of Alzheimer's disease (AD) and the sporadic nature of Parkinson's disease (PD) highlight difficulties in balancing model relevance with interpretability. Existing techniques may overlook applicable disease biomarkers, and actual markers of AD, PD, and other mood disorders might be unidentified. Environmental risk factors' timing, grading, and type are also crucial in NDD progression, while manipulating neurotoxic agents or genetics does not yield specific early-stage models. It is vital to acknowledge that not all ND models fit every research question. [26, 27].

Limitations of Current Models

There is an undisputed need to improve our experimental models to better recapitulate the complexity of human neurodegenerative diseases. While a "larger bag of toys" is desirable to more exactly mirror patient-to-patient variability of genetic defects and environmental factors, two limitations stand out in current models failing in drug discovery, - already well appreciated for cancer research (toxicity/predictability issues). First, none of the extant experimental models – ranging from cultured human patient-derived cells via different animal species to patients themselves – reflect focalization/staging effects in proteinopathies or synucleinopathies, i.e., different, complexially orchestrated pathological proteins spreading over different CNS nuclei and regions in clearly defined time frames. Instead, they focus on initial steps (synthesis or misfolding, in some rare cases, guide by genetic mutations). There is no translational continuity between the narrow-minded, artificially reduced cognitive constructs of these experimental models and the full-blown pattern of the corresponding human diseases (differences in NPC, cell types affected, prevalent cellular protein defects). Secondly, studies on various animal models have constantly reproduced the same phenomena, even using analyses in different laboratories, with different patients/samples and substantially diverse experimental conditions. In contrast, the results of more complex and costly experiments, including clinical trials on hundreds of human patients, have often been misleading, with findings not replicating/matching the previous results in only rare cases. In light of these unsatisfactory facts, new models have been developed, more closely mimicking the initial clinical stages and biochemistry of the patient's brain, recapitulating cortical-to-striatal pathology through intracortical fibrillar α-synuclein injections. The widespread use of more reliable experimental designs, comprehensive analysis strategies, and meta-analytical approaches has the potential to provide pieces of evidence that will be robustly verified across different models, laboratories, platforms, biobanks, or patients.

Ethical Considerations

Growing attention is being devoted to the study of neurodegenerative diseases, a collective term for conditions that are characterised by slow and irreversible degeneration of the central and peripheral nervous systems. Part of this attention has focussed on the modelling of these diseases in experimental models to better analyse the pathological mechanisms of the disease or to test therapeutic strategies. Nonetheless, the ethical implications of such models are so far limited, and the discussion is still mostly focussed on the ethical aspects related to the studies in human subjects. However, there is a broad spectrum of ethical considerations that have not yet been properly addressed. In this review, the complexity of considerations related to the use of experimental models, especially in the context of neurodegenerative diseases, is analysed. Ethical considerations have moral implications on research, such as the use of animal models, for example. For research on animal models, these implications refer to all matters covered by animal ethics, such as the 3Rs principle, but in neurodegeneration-related studies of animals, particular attention must be paid to reduce as much as possible the suffering and to ensure the welfare of the experimental animals. Experimental models are also used for research exploiting human-derived materials. The most common example in this regard is the production of neural cells from stem cells and the analyses of how they differ from healthy ones. In this case, the main ethical concern is to ensure that the donor is aware of the potential uses of the cells derived from their donation and to guarantee respect for the rights of the donor. However, the ethical considerations of research on experimental models go well beyond compliance with legal regulations and ethical guidelines, and the scientific community must be aware of the broader spectrum of ethical concerns. Still, the need to strike a balance between the thirst for knowledge at all costs and the ethical responsibility of scientists to society and individuals remains unchanged. If the public expects scientists to also consider non-scientific issues when addressing delicate topics, research that could be interpreted as risky or ethically sensitive will receive public scrutiny and possibly increase the likelihood of discontinuation. Collaboration between scientists, ethicists, and regulatory bodies will be crucial for navigating this complexity, also because simple and uniform guidelines do not exist for all issues. Similarly to other aspects of research, funding availability will also play a significant role which of the many ideas proposed will be feasible, although in this case, regulatory requirements will probably be the main determinants. Ethical concerns will continue to revolve around the progress of knowledge, on which the scientific community is called to play an attentive role and not to limit the spectrum of its considerations to established laws and guidelines [16, 28].

CONCLUSION

Advancing neurodegenerative disease research requires the continuous refinement of experimental models through interdisciplinary collaboration between engineers, biologists, and clinicians. While current models provide valuable insights into disease mechanisms, they remain limited in capturing patient-specific variability and disease progression. Innovations in bioengineering, including iPSC-derived neural models and organ-on-a-chip systems, offer promising solutions for improving model accuracy and translational potential. Ethical considerations must also be addressed to balance scientific progress with responsible research practices. By integrating advanced technologies with biological research, the field can move closer to developing effective treatments and ultimately finding cures for these devastating diseases.

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