VIEWPOINTS

Basic Science in Movement Disorders: Fueling the Engine of Translation into Clinical Practice

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ABSTRACT: Basic Science is crucial for the advancement of clinical care for Movement Disorders. Here, we provide brief updates on how basic science is important for understanding disease mechanisms, disease prevention, disease diagnosis, development of novel therapies and to establish the basis for personalized medicine. We conclude the viewpoint by a call to action to further improve interactions between clinician and basic scientists. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: basic science; Parkinson's disease; movement disorders; translational research

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Since the founding of movement disorders as a neurology subspecialty, basic science research has been instrumental for understanding pathophysiology and for advancing the technologies available to diagnose and treat these neurological diseases. In this way, the work of basic scientists in the laboratory has fueled the engine that drives clinical developments and can be viewed as complementary to the efforts of neurologists in the clinic to improve the daily life of those affected by movement disorders.

Striking examples of how synergies between basic science and clinical research have transformed everyday practice in a movement disorders clinic include the development of levodopa for treatment of Parkinson's disease (PD),[1] including Nobel Prize-winning work,[2] and the use of deep brain stimulation (DBS) for treatment of multiple movement disorders, based on research awarded the Lasker Prize.[3] The discoveries that led to both clinical mainstays required a back-and-forth between the bench and the bedside; for example, the clinical discovery of MPTP-induced parkinsonism[4] led to the development of animal models[5] that enabled physiologists to test working hypotheses related to DBS.[6] Additional examples of commonplace clinical activities that required basic science for their discovery and development include the use of recombinant botulinum toxin as a therapy[7] and the application of molecular biology-based techniques for the diagnoses of a wide range of genetic movement disorders.

With science and technology advancing at an accelerated pace, continued groundbreaking discoveries in basic science research are expected to enhance patient care for individuals affected by movement disorders in the coming years. In this context, a breadth of initiatives are needed to facilitate and bolster the connections between basic and clinical specialists. As an example of such initiatives, the International Parkinson and Movement Disorder Society (MDS) Basic Science Special Interest Group was established to contribute to the training and updating of clinical neurologists and neuroscientists on the forefront of research related to genetics, imaging, biomarkers, preclinical models, and pathophysiological mechanisms of movement disorders and their therapies.[8] In this Viewpoint, we discuss how basic science plays an instrumental role in contributing to our understanding of disease mechanisms, preventive strategies, diagnoses, therapy development, and personalized medicine of movement disorders now and in the future.

Basic Science for Understanding Disease Mechanisms

Understanding the underlying mechanisms of movement disorders through basic research helps unravel the complex interplay between genetic, environmental, and lifestyle factors that contribute to their development. This knowledge enables the identification of potential risk factors, illuminating our understanding of disease progression, and provides insights into novel therapeutic targets. For instance, genetic discoveries have been instrumental for our understanding of genes and pathways implicated in movement disorders. This has enabled basic researchers to test hypotheses using a variety of disease models, ranging from simple cell models to more complex animal models.[9] Further, genetic discoveries have been leveraged by both academic and industry researchers for therapeutic development.

Advances in molecular biology technologies will continue to allow for more of the genome to be explored in a larger number of individuals, including those that have been underrepresented in the study of movement disorders.[10] Likewise, such advances will enable us to further interrogate the contribution of epigenetics and epitranscriptomics to the modulation of gene expression at the single-cell level.[11] Moreover, studies in human induced pluripotent stem cells (iPSC) and in organoids will also provide pathophysiological insights into distinct movement disorders.[12]

Advances in artificial intelligence (AI) and in machine learning algorithms for studying 'big data', including various 'omics' (eg, genomics, epigenomics, transcriptomics, proteomics, lipidomics, metabolomics) and imaging data, will continue to facilitate breakthroughs in several areas. An example at the molecular level is the ability to predict protein structure using approaches such as AlphaFold2, which represents a leap forward in our ability to develop drugs to specifically target proteins involved in pathogenic pathways.[13] With AI-guided gene editing,[14] the discovery of small molecules[15] or targeted protein degradation technologies[16] is evolving at an incredibly rapid pace. This will expedite new discoveries of disease mechanisms and the development of novel treatment strategies.

Basic Science and Disease Prevention

Basic science research is instrumental in identifying potential risk factors and understanding the early stages of movement disorders. By elucidating the molecular, cellular, and physiological changes that occur prior to the onset of the typical disease features, researchers can explore strategies for early detection and interventions to delay or prevent the disease altogether. This knowledge can inform public health policies, lifestyle recommendations, and targeted interventions to reduce the overall burden of movement disorders. For example, exercise and nutrition are emerging as important lifestyle factors that can influence the progression of PD.[17]

The groundbreaking discoveries in the 1990s that first implicated α-synuclein (αSyn) in PD[18,19] opened a whole field of research that is still bearing fruit. For example, tools developed from basic science discoveries – such as αSyn seed amplification assays (αSyn-SAA),[20] which evolved from our understanding of the process of αSyn aggregation kinetics in vitro – are allowing for the identification of earlier stages of PD when these interventions and others could potentially prevent or delay the onset of PD.[21,22] In the same way, the combination of epidemiological and basic science data has recently shed light on the possible role of pesticide exposure in increasing the susceptibility for developing PD,[23] and provided the evidence needed to advocate for changes in governmental policies. Back translating clinical findings into laboratory models will, in turn, enable scientists to decipher the molecular mechanisms underlying the effects observed.

Basic Science and Disease Diagnosis

Basic science research has helped tremendously in developing diagnostic tools and criteria for movement disorders. For instance, by studying the underlying molecular mechanisms and early signs and symptoms, researchers have been able to advance biomarkers associated with PD that promise to differentiate PD from other similar conditions, thereby improving diagnostic accuracy. αSyn-SAA have been developed based on the early discovery made by basic scientists that recombinant αSyn forms fibrils in vitro, as mentioned above,[24] together with basic science research in the prion field that identified seeding properties of aggregation-prone proteins.[25,26] Through several iterations, αSyn-SAA capable of identifying seed-competent αSyn in cerebrospinal fluid, skin, or blood[27] of individuals with a synucleinopathy are being established and making their path towards clinical practice.[20] This recent progress illustrates how current efforts to implement biological markers can impact improved disease classification and staging systems of PD.[21,22,28]

On a separate front, efforts by physicists have resulted in the development of magnetic resonance imaging sequences that can detect neuromelanin-like signals[29] and of magnetic resonance spectroscopy to detect glucose and neurotransmitter metabolism alterations,[30] providing additional disease-specific information that could help in stratifying study populations and providing clinical endpoints for judging the effects of new therapies. Excitingly, chemists have recently identified first-generation αSyn positron emission tomography tracers that promise to revolutionize the way we study and diagnose synucleinopathies.[31,32] Thus, there is great hope that these imaging approaches will, hopefully, complement the currently used dopamine imaging in the clinical setting in the near future. Further, clinical neurophysiological studies using both invasive (eg, DBS) and non-invasive brain stimulation techniques could aid in refining the diagnosis, localization, and patient-specific targets with symptom-specific stimulation parameters and facilitate the development of novel therapies in movement disorders.[33]

Basic Science and the Development of Novel Therapies

Understanding movement disorders' basic mechanisms is the only road for rationalizing targeted therapeutics. In this context, basic research helps identify specific molecular pathways, neurotransmitter systems, brain circuitries, and genetic factors involved in disease. This combined knowledge forms the basis for developing novel drugs, gene and cell replacement therapies, and other interventions aimed at modifying disease progression, alleviating symptoms, and improving patients' quality of life. Neurodegenerative diseases such as Huntington's disease (HD) tend now to be considered as neurodevelopmental disorders, eventually provoking neurodegeneration.[34] Multiple strategies have recently been applied to the development of targeted therapy for HD, including antisense oligonucleotides which would not be possible without the basic science understanding of RNA silencing.[35] For PD, the first large clinical trials targeting αSyn[36,37] with many expected over the upcoming years, are all based on more than 25 years of basic science research focused on the role of αSyn in PD.

Importantly, the design of clinical trials is increasingly guided by our understanding of the underlying pathobiology of disease. While there have been numerous successes for symptomatic therapies in movement disorders, there have been few thus far for disease-modifying therapies. Regardless, negative clinical trials are valuable in our understanding of the basic mechanisms of disease and, in this context, the back-and-forth between the bench and the beside should continue as a major goal in the field. Advances in clinical design are anticipated to accelerate the translation from innovative basic science discoveries to the actual clinical testing.

Basic Science as the Basis for Personalized Medicine

Movement disorders, such as PD, are heterogeneous disorders likely with different biological subtypes. Therefore, it is important to define the biological basis of each movement disorder,[38] as it is highly plausible that patients may respond differently to different treatments. Basic science efforts should enable the identification of biomarkers and

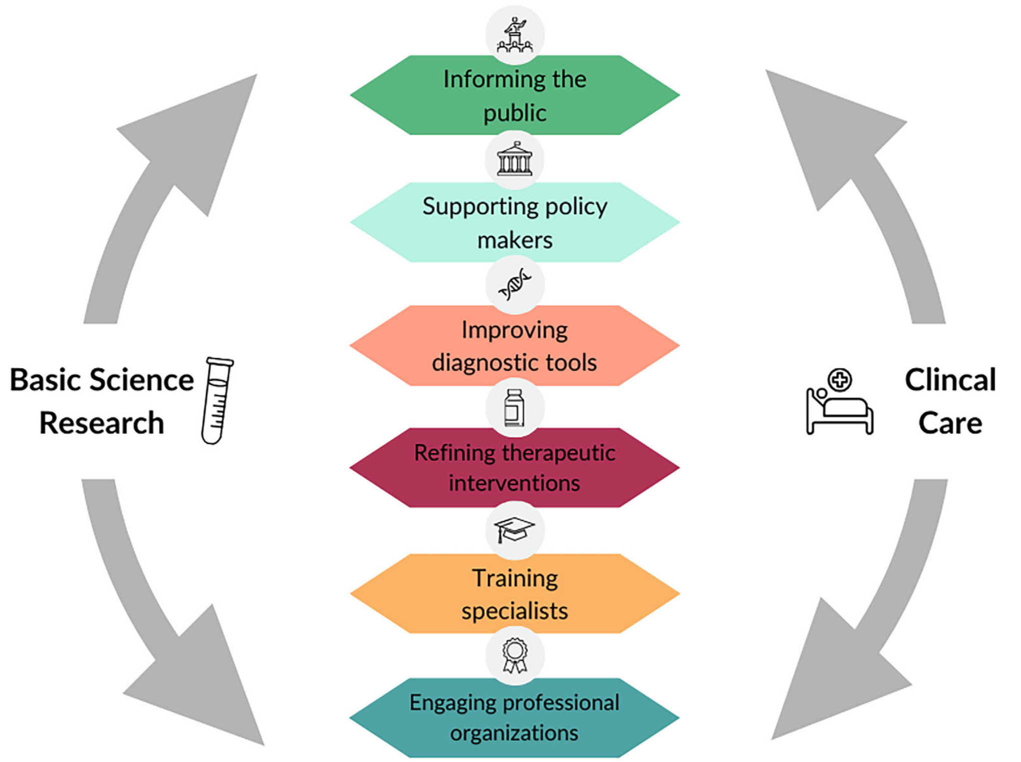

FIG. 1. The relationship between basic science research and clinical care for movement disorders. [Color figure can be viewed at wileyonlinelibrary.com]

genetic factors that can help distinguish different types of movement disorders and predict individual responses to specific therapies. This knowledge has the potential to guide clinicians in tailoring treatment plans to each patient's unique characteristics, leading to more personalized and effective care.

Call to Action

In summary, basic science is essential to clinical practice in general, and many examples in movement disorders are true demonstrations of the indissociable relationship between the two for improving healthcare. Basic science informs diagnosis, treatment development, personalized medicine, understanding disease mechanisms, disease progression, and the development of preventive strategies. While basic science still does not answer all open questions in the field of movement disorders, it is undeniable that by bridging the gap between laboratory findings and clinical applications, basic science research enhances patient care and improves outcomes for individuals affected by movement disorders.

Despite the clear contributions of basic science to clinical practice, communication between researchers in both fields has happened mainly via scientific publications. Basic science aspects are increasing in complexity, and it is not always feasible for those in the clinic to remain in step with the rapid advances being made in the laboratory. Thus, we argue that additional collaborative efforts must be pursued to take full advantage of the potential impact of an even closer interaction (Fig. 1). Optimized communication – for example, through combined scientific meetings where both sides explain their fields and plan joint implementation, through joint translational training programs of professionals (such as MD/PhD training) that can then easily bridge between the two fields, and through fostering exchange programs for clinicians to work in a basic science laboratory and for basic scientists to participate in the clinic – are all measures that need to be considered. Engaging the next generation of researchers is crucial as this will foster the incorporation of fresh perspectives from both young clinicians and basic scientists, stimulating groundbreaking ideas, particularly with their adaptability and eagerness to learn. These are not always easy to implement, as clinicians tend to be overstretched in their clinical duties, and basic scientists are tied to tight schedules to complete their experiments and training programs, but finding ways to bolster the interactions between the two domains worldwide will be ever more important for advancing translational research, promoting further understanding of disease mechanisms, and more successful applications in clinical practice.

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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