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Movement Disorders in 2012:

Advancing research toward novel therapeutic approaches

Nikolaus R. McFarland and

Center for Movement Disorders & Neurorestoration, Department of Neurology, University of Florida, College of Medicine, Gainesville, FL 32610, USA

Michael S. Okun

Center for Movement Disorders & Neurorestoration, Department of Neurology, University of Florida, College of Medicine, Gainesville, FL 32610, USA

Abstract

Standfirst—Research in movement disorders in 2012 had led to advances in understanding the pathogenic mechanisms of disease and to development of potential novel therapeutic approaches. Key advances include elucidating mechanisms of spreading neurodegenerative pathology, immunotherapy, stem cells, genetics and deep brain stimulation in Parkinsonisms and related disorders.

Despite recent advances in our understanding of the pathogenesis and treatment of movement disorders, such as Parkinson disease (PD), many of these syndromes remain challenging to both diagnose and treat. Additionally, disease-modifying therapies remain elusive. Basic advances in the understanding of the pathophysiology of these disorders and their translation from the bench to the bedside will result in better diagnostics and the development of novel therapeutics. Research in 2012 has moved the field closer to these goals, and there has been important progress in multiple areas including basic and clinical work in Parkinsonism(s), dystonia, Huntington disease, essential tremor, and tic disorders. We highlight some of the recent and key advances in each area that are collectively leading to a better understanding of basic pathophysiology and novel approaches to therapy.

A major pathological hallmark of PD and related disorders is the presence of Lewy body pathology as well as the concomitant neurodegeneration associated with the abnormal accumulation and deposition of α -synuclein. Increasing evidence exist to support the hypothesis of prion-like spread of pathology via cell to cell transmission of pathological forms of proteins such as α -synuclein.¹ However, unanswered questions remain about the mode of transmission of pathological α -synuclein species and their role in disease pathogenesis. Building upon previous work demonstrating precipitation of Lewy body-like pathology and neurodegeneration with preformed α -synuclein fibrils, Luk and colleagues recently showed that intracerebral injections of exogenous preformed fibrils or brain homogenates taken from old, symptomatic A53T transgenic mice (which express A53T human α -synuclein) into younger, asymptomatic mice could accelerate Lewy pathology.² In the inoculated animals, widespread synuclein pathology, including the presence of misfolded and hyperphosphorylated α -synuclein and intracellular Lewy-like inclusions, was observed, with resultant decrease in survival. The findings provide further evidence for prion-like spread and propagation of synucleinopathy and cell-cell transmission of

Correspondence: M. S. Okun, okun@neurology.ufl.edu.

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pathological proteins. Furthermore, exogenous preformed α -synuclein fibrils are sufficient to produce this cascade of events and accelerate the disease phenotype *in vivo*. On the basis of these findings, targeting cell-to-cell transmission to block the spread of synucleinopathy is a promising approach for therapeutic development in synucleinopathies such PD.

Increasing evidence points to the release of extracellular α -synuclein from neurons as playing an important role in the transmission of pathology. Approaches such as passive and active immunization to target α -synuclein have shown promise in synucleinopathy models, reducing α -synuclein accumulation and associated neurodegeneration.^{3, 4} The exact mechanism of action, however, remains unclear. Bae *et al.*, in a study published in the *Journal of Neuroscience*, hypothesized that antibodies against α -synuclein target extracellular α -synuclein and aid microglia in the clearance of pathological protein species, thus prevent cell-to-cell propagation of pathology.⁵ They showed that α -synuclein antibodies complexed with extracellular aggregates are taken up by microglia through surface Fc receptors. When inside the microglia these immune complexes were delivered to lysosomes for degradation. Intracerebral injection of α -synuclein antibody in a transgenic mouse model also resulted in α -synuclein clearance, and specifically reduced neuron to astroglia transmission of the protein, promoting microglial uptake and removal of extracellular α -synuclein. These studies help to further elucidate not only the mechanism of cell-to-cell transmission of α -synuclein, but also that of potential immunotherapy for PD and related disorders.

Advances in other synucleinopathies such multiple system atrophy (MSA)—a disorder in which standard Parkinson therapies often fail—have also occurred. Following an initial open-label trial of autologous mesenchymal stem cells (MSCs) in MSA that resulted in criticism from researchers in the field but also hope for a novel therapy, Lee *et al.* reported in *Annals of Neurology* the results of a 1-year randomized clinical trial of MSCs in MSA.⁶ The therapeutic mechanism of MSCs in neurodegenerative disease is debated but they are capable of differentiating into various cell types under specific conditions and also of secreting potentially neuroprotective trophic factors. In this study, vehicle or MSCs were administered to patients intra-arterially followed by thrice-monthly intravenous infusions. Notably, 27 of 33 enrolled subjects completed the study and all demonstrated delayed progression in the Unified MSA Rating Scale. However, no difference was observed in the UMSARS daily living scores between the two groups, indicating that the treatment predominantly affected motor deficits. Secondary outcomes, including functional (FDG-PET) and structural brain imaging (MRI), also indicated beneficial effects of MSC therapy. Although encouraging, this study had several limitations. It was performed in a single centre and included only patients with cerebellar-predominant MSA, which prevents extrapolation to Parkinsonism-predominant MSA—a form of MSA that is more frequently encountered by physicians in North America and Europe. Importantly, a third of patients who received either vehicle or MSCs had ischemic lesions on MRI, raising interventional risk issues. The effects were also transient indicating the need for repeated therapy. Although these major concerns will need to be resolved for future application, this study clearly highlights a potential novel therapeutic approach to MSA, and possibly to other neurodegenerative disorders.

Induced pluripotent stem cells (iPSCs) have potential of becoming a powerful therapy to treat neurodegenerative diseases. Patient-derived iPSCs provide a source of stem cells for autologous transplantation and avoid the risk of rejection associated with allogenic transplants. The main drawback of this therapy is that patient-derived iPSCs harbor the disease-causing mutation. An and colleagues performed a proof-of-concept experiment in which the Huntington disease (HD) repeat expansion was corrected in patient-derived iPSCs.⁷ Fibroblasts isolated from patients with HD were reprogrammed into iPSCs, and the

HD repeat was corrected by providing a normal copy of the Huntingtin gene and stimulating homologous recombination. Genome-corrected iPSCs demonstrated reversal of molecular phenotypes—including defects in apoptosis, BDNF levels, signaling and bioenergetics—that were evident in the non-corrected HD iPSCs. Importantly, the genome-corrected iPSCs retained pluripotency, differentiating not only into neural stem cells (NSCs) but also striatal neurons *in vitro* and *in vivo*. Strikingly, when transplanted into the striatum of the R6/2 mouse model of HD, NSCs derived from the genome-corrected iPSCs populated the striatum and differentiated into GABA-aminobutyric acid-releasing medium spiny neurons and astrocytes. However, whether the iPSCs could reverse the behavioural deficits and early lethality seen in the R6/2 mouse was not reported. This study highlights the utility and feasibility of patient-derived iPSCs as a future therapeutic option and has far-reaching implications not only for HD but also for all neurodegenerative disorders that are underpinned by a known gene mutation.

Deep brain stimulation (DBS) has revolutionized therapy for Parkinson disease and dystonia, but increasingly is also being considered for use in other conditions such as Tourette syndrome. In a recent study, highly medically resistant Tourette syndrome patients were implanted with centromedian thalamic DBS. The authors show in a series of studies that scheduled rather than chronic stimulation may suppress tics.⁸ More importantly, however, was the observation of a clinical correlation between the presence of gamma band activity and decreased tic severity. There was a temporal correlation between the power of gamma band activity and tic suppression. In Parkinson's disease, the beta band has emerged as an important physiological marker.⁹ In Tourette syndrome, modulation of gamma band may be a critical element to the success of any new therapeutic.^{9,10}

Together the advances highlighted here demonstrate continued progress in understanding the pathological mechanisms of movement disorders and the critical nature of these findings in developing novel therapeutics. Translating these basic findings into new approaches to target these diseases will be essential to advance future therapies.

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Key advances

- Innoculation of brain with pathological α -synuclein results in rapidly progressive accumulation, seeding of endogenous α -synuclein and neurodegenerative pathology²
- Administration of α -synuclein antibodies prevents neuronal transmission and promotes microglial uptake and degradation of α -synuclein, supporting extracellular synuclein as a potential therapeutic target in PD⁵
- Mesenchymal stem cell therapy in multiple system atrophy may represent an exciting potential novel therapeutic advance but requires further study⁶
- The genetic defect in HD, an expanded CAG repeat, can be corrected in pluripotent stem cells derived from HD patients and reverses associated disease pathology in neural stem cells⁷
- Scheduled rather than chronic deep brain stimulation may suppress tics and correlates with gamma band activity⁸