Journal of Parkinson's Disease 7 (2017) S1–S2
DOI 10.3233/JPD-179008
IOS Press

Introduction

Milestones in 200 Years of Parkinson's Disease Research

Brundin Patrik*
Van Andel Research Institute, Center for Neurodegenerative Science, Grand Rapids, MI, USA

This year is the 200th anniversary of the first published description by James Parkinson of the disease that would come to bear his name. To mark this occasion this special issue of *Journal of Parkinson's Disease* features invited commentaries by those responsible for some of the greatest advances in understanding and treating the disease since it was first characterized, describing how these advances came about and their lasting impact, with the advantage of hindsight. We are indeed fortunate to have contributions from many of those who played key roles in reaching these milestones in Parkinson's disease research.

In a wonderful piece of storytelling, Oleh Hornykiewicz recounts the remarkable mixture of science, intrigue and politics behind his work in the 1950's and early 1960's that triggered the modern era of Parkinson's disease research: the discovery of the dopamine deficit in the brain of patients with Parkinsons'. My Co-Editor-in-Chief Bill Langston relates the fascinating string of events in the 1980's that led him to discover the toxic effects of MPTP on nigral dopamine neurons. This led to the development of several important animal models for the disease and provided early insight into the possibility that mitochondrial dysfunction and oxidative stress could be important players in disease pathogenesis.

In the 1990's the pace of important discoveries increased dramatically. In terms of treatment, two advances stand out. Anders Björklund and Olle Lindvall recount their pioneering cell transplantation studies aimed at replacing dopaminergic neurons in Parkinson's patients. This research area has gone through many interesting phases of development and remains very active today with plans for several clinical trials using pluripotent stem cells as starting material. Marwan Hariz's scholarly and lively account chronicles the birth of deep brain stimulation (DBS) targeting the subthalamic nucleus for treatment of symptoms of Parkinson's disease, described by David Marsden the most important discovery since levodopa and its evolution up to the present day.

That decade also witnessed the beginnings of a much better understanding of the molecular underpinnings of Parkinson's disease. Robert Nussbaum relates the exciting story of identifying the first mutations in the alpha-synuclein gene that cause rare forms of hereditary Parkinson's disease. Michel Goedert, Ross Jakes and Maria Grazia Spillantini, tell how this finding almost immediately was shown to have enormous implications when they demonstrated that the Lewy bodies from patients with the more common sporadic form of the disease are largely made up of aggregated alpha-synuclein. The realisation that aggregated alpha-synuclein is at the core of Parkinson's disease pathology completely transformed the research. The focus shifted to why proteins misfold and why cells fail to clear the aggregates. Alpha-synuclein has also emerged as one of the most exciting therapeutic targets. In their article, Heiko Braak and Kelly Del Tredici compellingly recount the controversy that surrounded the development of the landmark six-stage model for brain Lewy body pathology related to sporadic Parkinson's

*Correspondence to: Brundin Patrik, Van Andel Research Institute, Center for Neurodegenerative Science, Grand Rapids, MI, USA; E-mail: Patrik.Brundin@vai.org.

ISSN 1877-7171/17/$35.00

disease. This observation led to ideas that the disease might be triggered in enteric nervous system and olfactory bulb, and it spawned the hypothesis of a prion-like role for misfolded alpha-synuclein – a vibrant area of current research.

John Hardy, Thomas Gasser and Andrew Singleton describe how the list of mutations associated with Parkinson's disease was then impressively extended this century. Each mutation has given exciting ideas about molecular mechanisms that contribute to the disease pathogenesis, and this groundbreaking observations might eventually lead to new therapies that interfere with the disease process.

In compiling this special issue, we discussed the fact that there have also been major recent advances in understanding better how the disease impacts the patients' lives and how life-style factors play a role in improving quality of life. For example, a greater appreciation of the non-motor symptoms of Parkinson's disease and a growing realisation that physical exercise might be of benefit. While these are tremendous advances, we view them more as important research trends and it was difficult to pin-point individual discoveries that played defining roles. Hopefully, these areas can be highlighted when we revisit the major advances in 10 years from now. One might also foresee that 10 years from now we will be able describe research on how to accurately predict who will develop Parkinson's disease, and that it will be possible to use precision medicine to define distinct subtypes of the disease. Furthermore, given the pace of recent discoveries, we hope that the 210th year commemorative issue will describe treatments that slow Parkinson's disease progression, which are glaringly absent from the first 200 years of Parkinson's research. What is certain, is that the milestones described in this issue form the foundations upon which such a treatment will be built.