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## Smart biomarkers and innovative disease-modifying therapies for Parkinson's disease



Roche Neuroscience is developing medicines for a range of serious neurological diseases, including multiple sclerosis, Alzheimer's disease, autism, schizophrenia, spinal muscular atrophy and Parkinson's disease (PD).

Our commitment to PD began more than four decades ago with the development of symptomatic treatments for motor deficits. Notwithstanding these and other achievements in the field, PD remains an area of high unmet medical need: current therapies improve some of the symptoms, but do not affect the underlying disease processes and therefore eventually become ineffective and can lead to debilitating side effects (levodopa induced dyskinesia, for example). PD is a slowly progressive neurodegenerative disorder that affects both the central and the peripheral nervous system, resulting in a wide spectrum of worsening motor (tremor, rigidity, bradykinesia, falls and dysphagia) and non-motor symptoms (constipation, urinary symptoms, hypotension, REM sleep behaviour disorder, hyposmia, fatigue, pain, depression, psychosis and dementia). Indeed, recent discoveries in genetics, disease biology and early clinical manifestations paint a clearer, but more complex picture of PD. A disease modifying therapy that targets the underlying pathophysiology could slow the progression of, and delay or even prevent the emergence of many of these clinical manifestations.

Roche Neuroscience focuses on early intervention and personalized treatment for serious neurological disorders, and has adopted a mechanism-based drug-discovery strategy. For PD, α-synuclein (α-syn) is a rational target, having a central role in disease pathogenesis. It has multiple functions in the body and is best described as a regulator of vesicular transport and neurotransmitter release in the synaptic terminals of neurons. In the disease state, it may acquire a conformation with neurotoxic properties, which can propagate from neuron to neuron.

There is a strong link between α-syn genetics and PD[1]. Multiplications and certain point mutations in *SNCA*, the gene encoding α-syn, lead to familial PD, and genome-wide association studies place *SNCA* as the top genetic risk factor for those who develop the sporadic form of the disease. Moreover, the disease is pathologically defined by the presence of intraneuronal accumulation of abnormal α-syn, known as Lewy bodies or Lewy neurites. Also, levels of certain forms of α-syn seem to change in the cerebrospinal fluid (CSF) of patients with PD[2]. Intriguingly, abnormal accumulation of α-syn also occurs

*Parkinson's disease — it could be you and me.* *The typical image of someone with PD is that of an older person with tremor, slow movements, shuffling gait and a hunched posture. The truth is, PD can affect people at any stage of their lives, interfering with their ability to live an independent and fulfilling life and causing additional financial, physical and psychological strain for their families and carers, as well as society. The photographer Anders M. Leines aims to change the image of PD with portraits of patients with early-onset PD. To learn more, visit* **www.facebook.com/thisisparkinsons**

in the peripheral nervous system, possibly starting a decade or more before clinical diagnosis of PD, which relies mostly on motor symptoms[3].

In 2013, Roche entered a worldwide collaboration with Prothena to co-develop and co-promote antibodies for the treatment of PD and related synucleinopathies. The lead candidate is a monoclonal antibody that targets α-syn. It is in early clinical development to test the hypothesis that binding extracellular α-syn will prevent neuron-to-neuron propagation and further aggregation of α-syn, thereby mitigating neurodegeneration and slowing clinical progression.

## Current clinical development activities are complemented by several lines of research
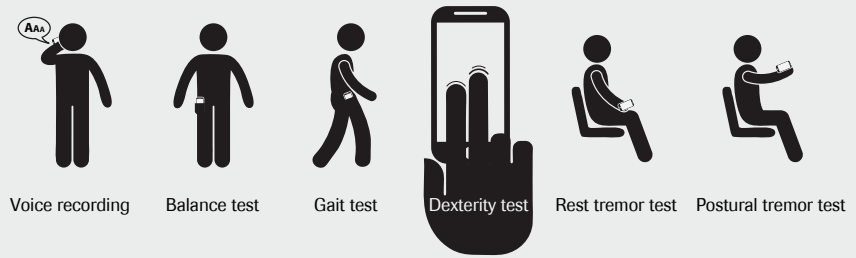
*a) In-house drug-discovery activities and academic research collaborations.* This is a wide-ranging programme, including the generation and characterization of human α-syn transgenic mice[4,5] (which have been made widely available to the scientific community), exploration of new *in vivo* models of α-syn pathology propagation[6] and investigation of immune mechanisms in neuron-to-neuron propagation of α-syn from the peripheral to the central nervous system[7]. In addition, neurons derived from inducible pluripotent stem cells of sporadic and familial forms of PD are being studied, and high-resolution electron microscopy, immunofluorescence and mass spectrometry analysis are being used to study Lewy pathology in post-mortem PD brain specimens.

*b) Identification and development of novel PD biomarkers that are related to the disease mechanism and may improve early diagnosis.* This includes sponsorship of the Parkinson's Progression Markers Initiative (PPMI, www.ppmi-info.org) and active research collaboration in the α-syn PET Tracer Consortium, both spearheaded by the Michael J. Fox Foundation (MJFF, www.michaeljfox.org). Within the scope of PPMI, a collaboration is ongoing with Roche Diagnostics. This is based on their immunoassay expertise in the development of testing solutions for Alzheimer's disease, and is an effort intended for biomarker research, but not for diagnostic or therapeutic purposes. Such public–private partnerships are indispensable for advancing the understanding of diseases and enabling better clinical studies. Roche and Prothena are also exploring the generation of high-sensitivity immunoassays for the detection of rare pathological forms of α-syn in CSF.

*c) Smartphone-based monitoring of patients during clinical trials.* Roche is pioneering a smartphone-based monitoring system for patients with PD. This will complement the conventional physician-led assessments, which are limited by availability of expert centres, are resource intensive and represent only a snapshot in time. By contrast, app-based tests continuously measure the patient's symptoms and thus thoroughly capture day-to-day fluctuations. A first in-house-developed app is being tested in our α-syn immunotherapy clinical programme, with patients following a daily routine with the app for the duration of the trial. The early data collected so far



**ACTIVE TESTS**
Patients are asked to complete six tests on the App at the same time each day, ideally in the morning.

Voice recording  Balance test  Gait test  Dexterity test  Rest tremor test  Postural tremor test

**DATA UPLOAD** Captured data is automatically uploaded via WIFI to a secure server.

**PASSIVE MONITORING** Patients then carry their smartphone around as they go about their daily activities.

*Roche smartphone app for monitoring patients with Parkinson's disease during clinical trials. Every day, data from six active tests and passive monitoring of daily routines are collected from subjects in the trial. The data are uploaded on an ongoing basis, enabling continuous adherence monitoring and analysis of the data. To learn more, visit* **www.roche.com** *and search for 'smartphone'.*

provide information on patients' symptom fluctuations, disease progression and impact on daily living. We envision using the app in clinical development to enable more objective, continuous measures of response to treatment to complement conventional assessment methods.

Roche Neuroscience is committed to developing novel and urgently needed disease-modifying therapies for people with PD. As we reach a turning point in our understanding of the biology of PD, we can expand our ability to translate science into new medicines. Success requires that we foster key collaborations and partnerships, and combine internal research and development efforts with our biomarker expertise. 'Smart' biomarkers will be crucial for identifying and monitoring patients who need early intervention with personalized treatments. With our passion and commitment to defeat this disease, we hope to improve the lives of people with PD, their families and carers.

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