“Parkinson’s disease: new insights in pathophysiology and treatment”
GENERAL INFORMATION

VENUE
The Symposium will take place at the:
International Congress Centrum (ICC) Berlin
Room B
Neue Kantstraße / Ecke Messedamm
Berlin, Germany
www.icc-berlin.com

LANGUAGE
The official language of the Symposium will be English.

TRAVEL INFORMATION
Berlin is the capital of the Federal Republic of Germany. Berlin is a center of culture, politics, media, science and serves as a continental hub for air and rail transport. Its economy is primarily based on the service sector, encompassing a diverse range of industries, media corporations, congress and convention venues. The metropolis is home to world-renowned universities, research institutes and museums and is one of the most visited tourist destinations in Europe. Sites of interest include the Brandenburg Gate, an iconic landmark of Berlin and Germany, the Berliner Dom, the Reichstag building, traditional seat of the German Parliament and the Konzerthaus (Concert Hall). Around one third of the city’s territory is composed of forests, parks, gardens, rivers and lakes.
Serono Symposia International Foundation

A SATELLITE SYMPOSIUM HELD DURING THE 20TH ENS (EUROPEAN NEUROLOGICAL SOCIETY) MEETING

“Parkinson’s disease: new insights in pathophysiology and treatment”

Berlin, Germany - June 22, 2010

AIM OF THE SYMPOSIUM

Parkinson’s Disease with its complexity in etiology, clinical manifestations and therapeutic approaches is very challenging for neurologists and for all health care professionals to deal with. Each achievement in the understanding of pathophysiological mechanisms often stimulates new lines of research. The aim of this Symposium is to give an overview of the most recent advances in pathogenetic mechanisms definition and stem cell therapy, and of future trends in research.

LEARNING OBJECTIVES

At the end of this Symposium participants will have:
• Updates on some of the most relevant pathogenetic mechanisms of Parkinson’s Disease
• A review of stem cells treatment in Parkinson’s disease
• An overview of future trends in research and clinical approaches to Parkinson’s Disease

TARGET AUDIENCE

Scientists, clinicians, biologists, working in the field of neurology, will benefit from this Symposium.

ACCREDITATION

Serono Symposia International Foundation (www.seronomousposia.org) has submitted this program “Parkinson’s disease: new insights in pathophysiology and treatment” (June 22, 2010 - Berlin, Germany) for accreditation by the Royal College of Physicians, London, UK.
CHAIRMAN

Giancarlo Comi
Department of Neurology
University Vita-Salute
IRCCS San Raffaele
Milan, Italy

LIST OF SPEAKERS

Roger Alistair Barker
Department of Clinical Neuroscience
Cambridge Centre for Brain Repair
University of Cambridge
Cambridge, UK

Thomas Gasser
Department of Neurodegenerative Diseases
Hertie-Institute for Clinical Brain Research
University of Tübingen
Tübingen, Germany

Heinz Reichmann
Department of Neurology
University of Technology Dresden
Dresden, Germany

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Serono Symposia International Foundation
is a Swiss Foundation with headquarters in
14, rue du Rhône, 1204 Genève, Switzerland
TUESDAY - JUNE 22, 2010

Chairman: Giancarlo Comi, Italy

12.15  Serono Symposia International Foundation (SSIF) Opening
       SSIF Scientific Committee President Giancarlo Comi, Italy

12.20  L1:  Mitochondrial dysfunction in Parkinson’s Disease
       Heinz Reichmann, Germany

12.45  L2:  Stem cell therapies in Parkinson’s Disease
       Roger Alistair Barker, UK

13.10  L3:  The future of Parkinson’s Disease
       Thomas Gasser, Germany

13.35  Concluding remarks
       Giancarlo Comi, Italy

13.45  End of the Symposium
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The following faculty members have provided information regarding significant commercial relationships and/or discussions of investigational or non-European Medicines Agency (EMEA)/ Food and Drug Administration (FDA) approved (off-label) uses of drugs:

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<tr>
<th>Name</th>
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<tr>
<td>Roger Alistair Barker</td>
<td>Declared receipt of grants support from the PDS UK; EU through an FP7 grant and MRC and receipt of honoraria or consultation fees from Teva Lundbeck.</td>
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<tr>
<td>Giancarlo Comi</td>
<td>Declared receipt of honoraria or consultation fees from Serono Symposia International Foundation, Bayer Schering, Merck Serono International, Sanofi-Aventis, Biogen-Dompé, Teva Pharmaceutical Industries Ltd, Novartis.</td>
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<tr>
<td>Thomas Gasser</td>
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<td>Heinz Reichmann</td>
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ABSTRACTS
(L1 – L3)
MITOCHONDRIAL DYSFUNCTION IN PARKINSON’S DISEASE

Heinz Reichmann
Department of Neurology, University of Technology Dresden, Dresden, Germany

Parkinson’s disease (PD) is the most frequent movement disorder due to a progressive loss of dopaminergic neurons. Most cases (80-90%) occur sporadically with unknown cause, but there are meanwhile several monogenetic forms of PD. These gene defects offer a new option to study etiopathogenesis and malfunction in PD. It is remarkable that in both instances, sporadic and familial, mitochondrial dysfunction is an early event. Mitochondrial energy metabolism is of high importance for cell survival. The intramitochondrially located respiratory chain represents the final common pathway for oxidative metabolism and is composed of over 70 different polypeptide subunits that form 5 enzyme complexes situated in the inner mitochondrial membrane. These complexes are unique in that they are formed by the complementation of two separate genomes: the nuclear and mitochondrial (mt) genome. Human complex I consists of more than 40 subunits, 7 of which are encoded by the mtDNA. In addition, one subunit of complex III, three subunits of complex IV and two subunits of complex V are encoded by the mt DNA. Defects of the respiratory chain would be expected to have severe consequences for the metabolic homeostasis of the cell (increased radical formation, decreased energy production). Accumulating evidence shows that complex I deficiency plays an important role in the etiopathogenesis of PD. Decreased complex I activity has been described in the substantia nigra pars compacta, platelets, leucocytes and skeletal muscle from PD patients. It was obvious to check for a defect in the mt genome as a cause of this enzyme defect. Initial results with normal Southern blot technique showed no deletions, while the more sensitive PCR method indicated the occurrence of deletions. There is speculation on the possibility that a combination of otherwise harmless base changes in the mt DNA might be responsible for the reduced complex I activity in PD, rather than an individual mutation. In the meantime, we have created fibroblast cell cultures from 8 PD patients with abnormal respiratory chain (complex I defect in four patients, complex I defect associated with complex IV defect in two patients and an isolated complex IV defect in two patients). To find out whether these defects reside in the nuclear or mt genome we have prepared cytoplasmic hybrids. We could show that the molecular defect must reside in the mt DNA in some patients and in others there is indication for a nuclear defect. Besides mutations of the mt DNA it is well known that PD patients have an increase in 8-OH-deoxyguanosine due to the increase in free radicals. This may also impair mitochondrial function. Finally, mitochondrial dysfunction (fusion, migration) is important for neurotransmission, synaptic maintenance and neuronal survival. At least two genetically caused familial PD forms (PINK1 and Parkin) are partly due to such deficiencies in mitochondrial dynamics. It is also interesting that the new pathological hallmark of PD, α-synuclein, is transported into the mitochondria and accumulates there, thus impairing mitochondrial function. Thus, there is good evidence that mitochondrial impairment causes, not only energy crisis and apoptosis, but also results in an increase in oxidative stress and malfunction of mitochondrial dynamics. It is a new interesting option to speculate whether treatment of this malfunction may improve the condition of PD patients.
STEM CELL THERAPIES IN PARKINSON’S DISEASE

Roger Alistair Barker
Department of Clinical Neuroscience, Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK

Parkinson’s disease (PD) is a chronic neurodegenerative condition of the brain that presents with a range of abnormalities including a combination of a movement disorder with cognitive deficits. The aetiology of PD is unknown in the vast majority of cases, but the pathology targets the nigrostriatal dopaminergic neurons with the formation of alpha synuclein positive Lewy bodies. As such the disease offers an attractive target for cell based therapies, with the primary aim (in most cases) being to replace these lost cells through the implantation of exogenously derived dopaminergic neurons.

This was originally undertaken in the 1980s using allografted cells derived from the developing midbrain and the open label clinical studies that evolved out of this work in the 1990s demonstrated that this approach could produce striking long term clinical benefits in some individuals. This clinical improvement correlated with evidence of dopaminergic cell survival using functional imaging with PET as well as in some post-mortem studies. However over the last ten years, two NIH supported double blind placebo controlled trials have failed to replicate these benefits and also reported significant side-effects- most notably the development of dyskinesias relating to the grafts.

Whilst the basis for these dyskinesias has been debated, as has the failure of these studies to show benefits, the growth of stem cell sources for brain repair has evolved and with this an expectation that they will translate into treating patients with PD.

In this talk I will re-examine the reasons as to why the clinical trials using fetal dopaminergic cells have failed to produce consistent robust benefits and what this will mean for the translation of stem cell based therapies to the clinic for PD.
THE FUTURE OF PARKINSON’S DISEASE

Thomas Gasser
Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

Over the last few years, genetic studies provided unforeseen insight into the molecular pathogenesis of Parkinson’s disease (PD). Several genes for rare monogenic forms of the disorder have been identified. Point mutations as well as duplications and triplications have been identified in the gene for α-synuclein (SNCA) in a few families, but mutations in the gene for LRRK2 have been found to be a much more common cause of autosomal-dominant PD. Mutations in several genes are linked to recessive early-onset variants of PD: parkin, DJ-1, PINK1. The molecular pathways identified through these genes seem to converge in a few crucial cellular processes: protein aggregation, integrity of the cytoskeleton, mitochondrial integrity and oxidative stress.

Evidence is emerging from genome-wide association studies (GWAS) that low penetrance variants in some (or maybe even most) of these genes may also play a role in the etiology of the common sporadic form of PD. In addition, rare variants in some other genes, such as the Gaucher’s disease associated glucocerebrosidase A (GBA) may also significantly influence the disease risk. The contribution of these rare genetic variants to a common disease like PD is still poorly understood, but it will most certainly be unraveled by systematic whole exome sequencing, which will be the next technological breakthrough.

Thus, an increasingly complex network of genetic variants of different effect strengths and frequency, all contributing to disease risk and progression, is emerging. These findings provide the “genetic entry points” to identify molecular targets and readouts necessary to design rational disease-modifying treatments.

Eventually, we will see PD as a syndrome of complex genetic etiology, and we will treat the disease, preferably in the pre-symptomatic phase, using a personalized approach taking into account an individual profile of risk variants.