MeFoPa Mendelian forms of Parkinson's disease

Newsletter, No.2, Nov.2011

Summary of MEFOPA

Mendelian forms of Parkinson's Disease (PD) are a group of rare diseases which recapitulate many of the clinical, pathological and biochemical features of the common sporadic form of the disorder, and are therefore seen as model diseases which allow to study the underlying pathogenic molecular mechanisms and pathways. It is the understanding of PD pathways that is the prerequisite for the development of novel disease modifying and neuroprotective treatments. It is likely that those treatments will benefit all PD patients, as it becomes increasingly clear that the gene products and their interaction partners identified in rare Mendelian variants also play a crucial role in the sporadic disease.

Mendelian forms of PD can be divided into two groups: autosomal-dominant forms caused by mutations in the genes for a-synuclein (SNCA) and for leucine rich repeat kinase 2 (LRRK2), and autosomal-recessive forms caused by mutations in the genes for parkin (PRKN), Pten-induced kinase-1 (PINK-1), and the oncogene DJ1.

The mutations in the dominant genes are thought to cause PD by a gain-of-function mechanism. SNCA- as well as most cases of LRRK2-related PD are pathologically characterized by aggregates of a-synuclein ("Lewy-pathology"). It is therefore appropriate to assume that the pathogenic mechanisms of SNCA- and LRRK2-related PD interconnect. Research on the pathogenesis of those forms of Mendelian PD is coordinated in subproject 1.

Autosomal-recessive mutations in the genes for parkin, PINK-1 and DJ1 are believed to exert their pathogenic effect due to loss of some essential protective function. There is converging evidence suggesting that dysfunction of all recessive PD genes contribute to a state of increased cellular stress due to mitochondrial dysfunction and increased burden of radical oxygen species (ROS) and that at least two of the recessive PD genes, parkin and PINK1, operate within one single pathway. The molecular underpinnings of recessive forms of Mendelian PD will therefore also be investigated together, in subproject 2.

The findings in the basic science work-packages of the first two subprojects will directly feed into subproject 3, where a European registry and biobank for patients with rare Mendelian forms of PD will be established in order to advance investigations of biomarkers.

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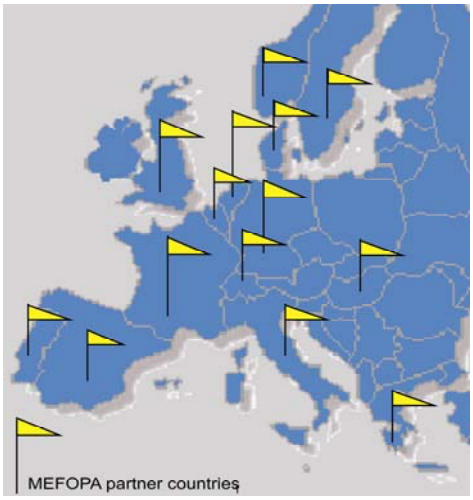
MEFOPA partners



- University of Tuebingen, Germany: Thomas Gasser, Olaf Riess, Saskia Biskup, Philipp Kahle, Peter Bauer, Michael Bonin, Holm Graessner
- Biomedical Research Foundation of the Acadamy of Athens, Greece: Leonidas Stefanis
- Lund University, Sweden: Deniz Kirik, Christer Nilsson
- University of Aarhus, Denmark: Poul-Henning Jensen
- Instituto de Medicina Molecular Lisbon, Portugal: Tiago Outeiro
- The Chancellor, Masters and Scholars of the University of Cambridge, UK: David Rubinsztein
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- Institut National de la Sante et de la Recherche Medicale (INSERM), France: Alexis Brice, Olga Corti
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- Fundación Ilundain, San Sebastián, Spain: JFM Masso
- Semmelweis University Budapest, Hungary: Benjamin Bereznai
- Vrije Universiteit: Vereniging voor christelijk hoger onderwijs, wetenschappelijk onderzoek en patientenzorg, Netherlands: Guus Smit
- University Hospital Oslo, Norway: Mathias Toft
- University College London, UK: Nicholas Wood
- United Arab Emirates University, Faculty of Medicine and Health Science: Omar El Agnaf

Meetings

1) Preparatory meeting, Frankfurt, 05. October 2009

2) Kick-off meeting, Paris, 18.Mai 2010

3) Board meetings, (i) Tübingen, 19. November 2010, (ii) Amsterdam, 9. April 2011, Web conference, 18. November 2011.

4) Annual meeting and board meeting, Amsterdam, 8./9. April 2011

Results

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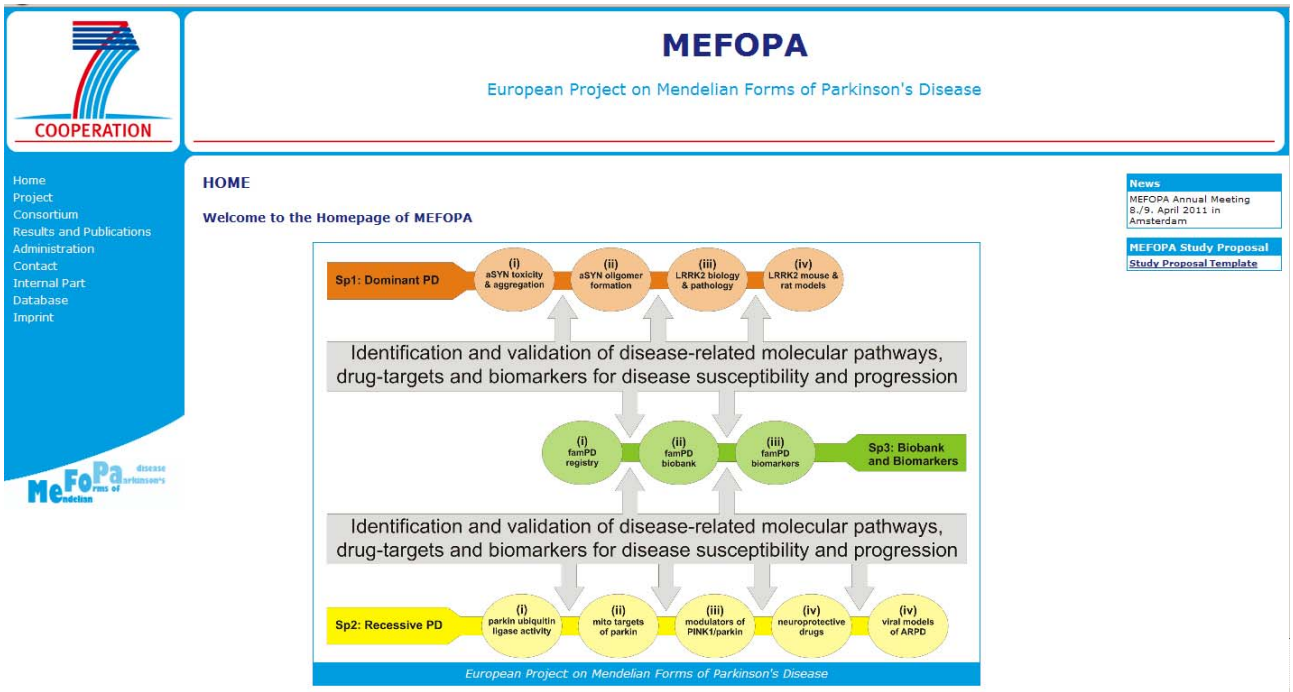

Publications out already:

- Winslow AR, Chen CW, Corrochano S, Acevedo-Arozena A, Gordon DE, Peden AA, Lichtenberg M, Menzies FM, Ravikumar B, Imarisio S, Brown S, O'Kane CJ, Rubinsztein DC. (2010) α-Synuclein impairs macroautophagy: implications for Parkinson's disease. **Journal of Cell Biology**. 190(6):1023-37. 20/09/2010
- Ashley R Winslow and David C Rubinsztein.(2011) The Parkinson disease protein α-synuclein inhibits autophagy. **Autophagy** 7(4): 429–431.
- Lichtenberg M, Mansilla A, Zecchini VR, Fleming A, Rubinsztein DC. (2011) The Parkinson's disease protein LRRK2 impairs proteasome substrate clearance without affecting proteasome catalytic activity. **Cell Death and Disease**. Aug 25;2:e196. doi: 10.1038/cddis.2011.81.

- Katerina Vamvaca et al. (2011) N-terminal deletion does not affect alpha-synuclein membrane binding, self-association and toxicity in human neuroblastoma cells, unlike yeast. **Journal of Neurochemistry**. 10.1111/j.1471-4159.2011.07431.
- Evangelia Emmanouilidou et al. (2011) Assessment of α-synuclein secretion in mouse and human brain parenchyma. **PLoS ONE** 6(7):e22225.
- Marina Moraitou et al. (2011) β-Glucocerebrosidase gene mutations in two cohorts of Greek patients with sporadic Parkinson's disease. **Molecular Genetics and Metabolism** 2011 Sep-Oct;104(1-2):149-52.
- Kathrin Brockmann et al. (2011) GBA-associated PD presents with nonmotor characteristics. **Neurology** 77(3):276-801.
- Van der Perren A., Toelen J., Coun F., Van den Haute C., Heeman B., Carlon M., Reumers V., Vandenberghe L.H., Wilson J.M., Debyser Z. and Baekelandt V. (2011) Efficient transduction of dopaminergic neurons in rat substantia nigra by different adeno-associated viral vector serotypes. **Gene Therapy** 18(5):517-27.
- Heeman B., Van den Haute C., Aelvoet S.-A., Valsecchi F., Rodenburg R., Reumers V., Debyser Z., Callewaert G., Koopman W.J.H., Willems P.H.G.M. and Baekelandt V. (2011) Depletion of PINK1 affects mitochondrial metabolism, calcium homeostasis and energy maintenance. **J of Cell Science** 124 (7):1115-25.
- Deleersnijder A., Desender L., Munck S., Pottel H., Buée L., Debyser Z., Baekelandt V. and Gerard M. (2011) Comparative analysis of different peptidyl-prolylisomerases reveals FK506-binding protein 12 as the most potent enhancer of α-synuclein aggregation. **J. Biol. Chem** 286:26687-26701.
- Claudia Schulte et al. (2011) Genetic basis of Parkinson´s disease: inheritance, penetrance, and expression. **The Application of Clinical Genetics** 2011:4; 67-80
- Thomas Gasser et al. (2011) Milestones in PD Genetics. **Movement Disorders** 6 26(6):1042-1048.
- Sorin Breit et al. (2010) Effective long-term subthalamic stimulatin in PARK8 positive Parkinson´s disease. **Journal of Neurology** 7: 1205-7.
- Thomas Gasser et al. (2010) Identifying PD-causing genes and genetic susceptibility factors: current approaches and future prospects. **Progress in brain research** 2010;183:3-20.
- Susanne Gräber et al. (2011) Self estimated quality of life in monogenetic Parkinson´s disease. Movement Disorders 1: 182-190.
- Imam SZ et al. (2011) Novel regulation of parkin function through c-Abl-mediated tyrosine phosphorylation: implications for Parkinson's disease. **J Neurosci**. 31(1): 157-163.
- Springer W et al. (2011) Regulation of PINK1-Parkin-mediated mitophagy. A**utophagy** 7(3): 266 – 278.
- Geisler S et al. (2011) The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. **Autophagy** 6(7): 871 – 878.
- Kieper N et al. (2010) Modulation of mitochondrial function and morphology by interaction of Omi/HtrA2 with the mitochondrial fusion factor OPA1. **Experimental Cell Research** 316(7): 1213

Recruitment of patients after half of the project (18 months):

Entity	Number
All	**268** (319)
SNCA symptomatic asymptomatic	**29** **24** **5**
LRRK2 symptomatic asymptomatic	**128** **87** **41**
Parkin homozygous heterozygous	**63** **37** **26**
PINK1 homozygous heterozygous	**48** **16** **32**
Other mutations and controls	51