Comprehensive assessment of endophenotypes in neurodegenerative diseases – translating impaired molecular signalling pathways into novel therapeutic strategies for Parkinson’s disease – PEARL

https://neurodegenerationresearch.eu/survey/comprehensive-assessment-of-endophenotypes-in-neurodegenerative-diseases-translating-impaired-molecular-signalling-pathways-into-novel-therapeutic-strategies-for-parkinsons-disease-pearl/

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Luxembourg

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Comprehensive assessment of endophenotypes in neurodegenerative diseases - translating impaired molecular signalling pathways into novel therapeutic strategies for Parkinson's disease - PEARL

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FNR

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Emerging concepts of the genetic architecture of complex neurological diseases, i.e. Parkinson's disease (PD), indicate an underlying heterogeneity and underscore the imperative for personalized therapeutic strategies according to different pathophysiological subtypes of these common diseases. Genetic and functional studies point to a distinct number of molecular pathways that are likely to be involved in the causation of the neurodegenerative process with monogenic forms of PD representing 'prototypes' or extremes of these pathways. For instance, mutations in genes responsible for early onset PD cause impaired mitochondrial function and dynamics. Indeed for a substantial subgroup of sporadic PD patients an underlying mitochondrial pathology has been suggested based on reduced complex I activity in appr. 30% of the patients. This was considered as a first hint towards a mitochondrial endophenotype, where neurodegeneration is related to impaired mitochondrial function. Increasing knowledge on genetic causes of PD and subsequent studies of cellular phenotypes indicate a larger spectrum of cell-type-specific dysfunctions, that besides impaired mitochondrial homeostasis may involve additional phenotypes related to protein misfolding, neuroinflammation, synaptic dysfunction or impaired lysosomal degradation in neurodegeneration in PD. Previous clinical trials on neuroprotective compounds did not consider the presence of potential subtypes of PD and therefore may have failed due to the heterogeneity of patients with different underlying pathologies. In order to comprehensively address the major research imperatives for translational neuroscience in neurodegeneration, the present proposal integrates a clinical and basic research programme for the identification and modulation of relevant molecular signaling pathways in the pathogenesis of PD: Aim 1: Implementation of a clinically well-characterized PD patient cohort including acquisition of clinical data and effective banking of diverse biospecimens Aim 2: Integration of state-of-the-art patient-based cellular models into a systematic research program to define relevant disease-associated phenotypes Aim 3: Dissection of the molecular signalling network of neurodegeneration leading to the identification of differentially regulated genes, proteins or metabolites as potential biomarkers of disease Aim 4: Implementation of cutting-edge induced pluripotent stem cell-(iPSC)-derived cellular models to define robust cellular phenotypes in vitro Aim 5: Integration of disease-associated cellular readouts in iPSC-derived neurons into automated HTS/HCS technology for pharmacological modulation Aim 6: Confirmation of hit compounds in different iPSC-derived cellular models of the disease ex vivo Aim 7: Validation of hit compounds in different animal models of PD Therefore the present Research Programme will provide insight into complex disease mechanisms by applying state-of-the-art 'Omics'-technologies to neurons derived from iPSC of well-characterized monogenic PD patients that carry mutations in genes related to relevant cellular phenotypes, e.g. DJ-1 and Parkin for mitochondrial dysfunction. The integration of these large amounts of data in close collaboration with the Luxembourg Centre for Systems Biomedicine (LCSB), that provides unique expertise in the area of systems biology and disease-modeling, will identify novel biomarkers and therapeutic targets. The development of functional readouts in patient-based cellular models (iPSC) then allows for comprehensive high troughput screening approaches in combination with high content cellular readouts to identify novel disease modifying compounds for PD. This comprehensive approach allows for the successful translation of preclinical discoveries back to the clinic including advanced diagnostics and treatments for PD.

Lay Summary
Further information available at:

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Investments > €500k

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