PUBLISHABLE FINAL ACTIVITY REPORT

Title: INNOVATIVE DIAGNOSTIC APPROACHES FOR BIOMARKERS IN PARKINSON DISEASE

Acronym: INDABIP
Project number: LSH-037050
EC contribution: 1.600.000 €
Duration: 36 months
Starting date: 01/12/2006
Instrument:STREP

Key issues

Summary
The INDABIP project aims to identify biomarkers for the early diagnostics of Parkinson disease. Biomarkers are any type of biological molecules that are present in people suffering a specific disease, even when the symptoms are mild, but that are not present in people free from the disease or suffering from other diseases. The identification of the early indications of the development of a neurodegenerative disease is the basis for preventive treatment strategies, which aim to control of the disease at early stages rather than when irreparable neurological damage has been caused.

Problem
Parkinson disease (PD), a specific type of a group of neurodegenerative disorders called synucleinopathies, is the second most common neurodegenerative disorder worldwide. Many neurodegenerative disorders are preceded by a pre-symptomatic phase, probably lasting years, during which degeneration and death of neurons occurs before any clinical symptoms appear. One major challenge of clinical research is to improve early detection of these diseases by developing tools to move diagnosis backward in the neurodegeneration temporal course. Thus, the central objective of this INDABIP proposal is the identification of molecular markers that hallmark the onset of a cellular dysfunction in the brain areas involved in PD, that enable to identify at-risk groups both for disease onset and progression during the pre-clinical period.

Aim:
While biomarkers can take many forms; the INDABIP project aimed to identify relevant proteins, mRNA, and differentially matured RNAs, whose analysis can be transformed in diagnostic tests. The brain damage in Parkinson Disease and other neurodegenerative diseases is progressive, and the early detection of biomarkers may help to identify individuals that have started to develop the disease by opening a window for therapeutic treatment and prevention.
While most biomarkers are mere reporters of the disease state, others may actually be key factors in the processes that lead to the onset and development of the disease. The second aim of the INDABIP project is therefore to identify these key factors and to evaluate their potential as a drug targets.
To study the development and evaluate potential targets and therapies for Parkinson Disease, biological models are needed, in which the events that occur in the patient are mimetized. A target is any molecular entity (transcript, protein,…) that can be interfered with to interrupt the chain of events leading to the onset or development of the disease. We will develop novel *in vitro* models for Parkinson Disease based on cell cultures for the

development of a high throughput screening Platform, and use these for *in vitro* target validation experiments.
Finally, we will initiate a screen for potential drugs interacting with selected molecular targets.

Results:

The Partners of the INDABIP project have identified potential diagnostic markers that are currently being evaluated for their potential to be translated to peripheric detection in serum samples.

The results of the INDABIP project will be presented at xxx , where we will interact with Parkinson Disease Patients Organization to discuss and promote the possible future implantation of diagnostic assays based on the biomarkers identified in the National Health Systems.

Potential applications:

Early diagnostics becomes really helpful when appropriate treatments become available that can prevent the further development of the incipient disease. Within the INDABIP project, tools have been developed to screen for drugs that can prevent the further development of Parkinson disease and initiate the process of drug development,

INDABIP Participants

Private companies:
Oryzon genomics S.A. (Spain);
Genfit S.A. (France)

Academic partners:
Prof. Isidro Ferrer (Fundació Privada Institut d'Investigació Biomèdica de Bellvitge, Spain)
Prof. Hans Kretschmar (Ludwig-Maximilians Institute- University of Munich Zentrum für Neuropathologie und Prionforschung, Germany)
Prof. Irina Alafuzoff (Kuopio University, Department of neurology and neuroscience, Finland)
Prof. Regis Bordet (Department of Pharmacology, Faculty of Medicine, UL2le University Hospital, France)

Results

Our **major achievements** are

- the genome wide analysis of gene expression for the different regions of the brains from patients affected by Parkinson disease, and the validation of selected markers.
- the generation and analysis of genome wide analysis of differential splice forms generated in patients affected by Parkinson disease. Differential splicing allows for the formation of different transcripts and protein isoforms from the same gene. While the human genome contains about 22000 genes, the number of

different RNA messengers and proteins generated from these genes is estimated to be much higher. Some of these variants are specifically associated with human diseases, and using our genome wide splice analysis platform, we have found differentially splice genes in Parkinson disease.

- the generation of detailed expression data of over 20 proteins in PD vs normal brains.
- the identification of biomarkers that can be evaluated for their potential as targets to modify the course of the development of the disease, and the detailed characterization of the inhibition.
- the generation of compounds that inhibit the function of a target selected in the course of the project and that is able to cross the blood brain barrier .

Scientific and societal impact

In 1990 started a project that was going to change our perception of science: The Human Genome Project (HGP). After more than 13 years, the cooperative international effort of many countries and institutions lead to determine the complete sequence of the 3 billion DNA bases in the human genome and to the discovery of all the estimated 20,000-25,000 human genes and make them accessible for further biological study. This impressive fulcrum that represents the knowledge of human genome and the genomes from many other species hallmarks the beginning of a new era in biology. The massive amount of data generated by genome projects worldwide and its consolidation through newly designed databases opens new venues for understanding how gene networks control complex biological processes through a labyrinth of pathways, networks, chemistry, and mechanics.

This new understanding the operation, function, and coordination of genome information will open a new way to investigate how diseases appear and develop. In the case of neurological diseases the -omic investigation in the different areas of the brain is providing new lights to be combined with cell biology, imaging, anatomy and physiology derived from patterning, specification and circuit formation of the different neuron subpopulations

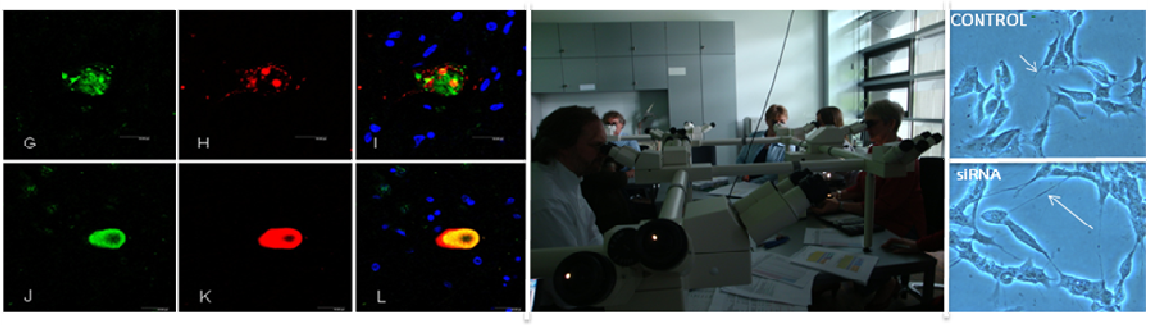
Thus, the understanding of basic developmental mechanisms can shed new light in neurodegenerative disorders as Alzheimer and Parkinson diseases. In that sense, there is increasing evidence suggesting that research on the genetic mechanism underlying the fundamental dysfunctions from dopaminergic neurons and other target neuronal populations is crucial for understanding the etiology of Parkinson disease, and can be relevant for other related disorders as Incidental Lewy body disease, and Diffuse Lewy Body disease and Dementia with Lewy bodies. Additionally, our research program goes one step further in trying to exploit the full potential of genome information to underpin applications to human health in terms of discover and validate early diagnostic molecular tools and to identify new pharmacological targets from which to try new therapies more successful than the existing ones.

SME involvement

INDABIP is a SME driven and SME coordinated project.

Oryzon genomics is a Barcelona based biotech company which contributes to the Project with experience in DNA chip technologies and bioinformatics applied to the discovery of biomarkers in neurodegenerative and oncological diseases. The Company will perform analysis of gene expression, splicing and methylation analysis in the Project.

Genfit is a biopharmaceutical company based in Lille (France) with solid knowledge in the field of gene regulation. The Company has gained a solid experience in the analysis of the family of transcription factors known as 'nuclear receptors' and has developed innovative strategies to screen for drug candidates that target and modulate these receptors. Genfit will also bring its experience in animal models to the project. Both companies believe in the power of the symbiosis between academic and SME partners



and are determined to add a long term product-oriented vision to the project.

INDABIP contact details

Project coordinator

Tamara Maes, Ph.D. Oryzon genomics S.A., Carrer Baldiri i Reixac 15-21, Barcelona, Spain.
Email: tmaes@oryzon.com Phone: (+34) 934037196. Fax: (+34) 934034792.
Lab web page: www.oryzon.com

Project assistant

Minerva Elias, Oryzon genomics S:A, Carrer Baldiri i Reixac 15-21, Barcelona, Spain.
Email: melias@oryzon.com Phone: (+34) 934037196. Fax: (+34) 934034792.
Lab web page: www.oryzon.com

Indabip web page

http://www.indabip.eu