ERA-Net Neuron

NEWSLETTER 9

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Intermediate Symposium of the First Transnational Call of ERA Net NEURON on "Neurodegenerativediseases of the central nervous system", in Rome, Italy

NEWS FROM ERA NET NEURON

The new topic for the 4th NEURON joint call for proposals will be: "European Research Projects on Cerebrovascular Diseases". The call will be launched in early 2011.

The review process of the 3rd joint call for proposals "European Research Projects on Mental Disorders" is finalized. Eleven proposals were selected for funding with a total budget of 9.8 m €. Detailed information on the funded projects will be published soon.

The winner of the 2nd "ERA-Net NEURON Young scientists paper award" is Jens Schwamborn for his work with the Austrian Academy of Sciences. He will be awarded 5000 € and will be invited to a major neuroscience meeting of his choice.

Foreword

Marlies Dorlöchter, ERA-Net NEURON coordinator

Neurodegenerative diseases are a growing burden to industrialized countries. With increasing life expectancies in modern societies, prevalences of neurodegenerative disorders are rising dramatically. Support of research into this field is of the utmost urgency for funding organizations. Effective interventions for neurodegenerative disorders need to be uncovered in the near future to avoid staggering financial, societal and emotional costs of such aging-related brain disorders. For this reason, in 2008, ERA-Net NEURON launched its first joint call for proposals on "Neurodegenerative diseases of the central nervous system". Twelve projects comprising 45 subprojects from ten countries were funded for three years with a total funding volume of about ten million euros. By now, projects are half-way through their runtime: Time for an interim evaluation! Project leaders presented their first results at the ERA-Net NEURON intermediate symposium in Rome. Collaborations proved to be buzzing, first exciting results were reported and even publications in top-class journals such as "Science" and "Nature" could be listed.

We can say as early as today that research supported by ERA-Net NEURON will be contributing substantially to a better understanding of neurodegenerative diseases. We are very much looking forward to the next 1.5 years.

Funded by the European Commission

More information can be found in our web page
http://www.neuron-eranet.eu/index.php

IPSOALS: MODELING SPORADIC ALS IN MOTOR NEURONS BY GENETIC REPROGRAMMING OF PATIENT SKIN FIBROBLASTS

"Given the very good progress of this project and the highly ambitious questions asked, we will certainly willing to collaborate after the end of the funding period"

Main achievements of the consortium

Amyotrophic lateral sclerosis (ALS) represents a neurodegenerative disease with considerable clinical, genetic and pathological heterogeneity. Stem cell biology holds enormous potential for modelling ALS disease mechanisms and to unravel commonalities and differences between different forms of ALS.The ERANET iPSoALS consortium has successfully established techniques for the generation of disease-relevant iPS and ESC clones, their differentiation into neurons, motor neurons and motor neuron subtypes and the analysis of organelle dysfunction with sophisticated imaging tools. In particular, the consortium succeeded to derive motor neurons from human embryonic stem cell lines (hESCs) engineered to express specific familial ALS-linked gene SOD1 mutations. In addition, neurons and motor neurons were obtained by genetic reprogramming of fibroblasts via induced pluripotent stem cells (iPS).

The advantages of the transnational collaboration to each one of the partners

Each team succeeded to set up specific materials and tools which to be shared with the partners:The Paris team (JM Heard/D Bohl) succeeded to reprogram human skin fibroblasts from normal volunteers into iPS clones and demonstrated full pluripotency and normal karyotype of the latter. The Jerusalem team (B Reubinoff) engineered hESCs to express the familial ALS-linked superoxide 1 mutant G93A or its wildtype counterpart. The Marseille team (G Haase) established FACS (fluorescent-activated cell sorting) as a routine method to isolate ALS-relevant motor neurons from mice. The Munich team (T Misgeld) studied mitochondrial pathology and axonal transport in several lines of mutant SOD1 mice by in vivo optical imaging of single organelles. Strong axes of collaboration have been established between the teams, mainly (1) between Paris and Marseille, in order to differentiate and isolate patient-derived human motor neurons, (2) between Marseille and Munich, to establish mitochondria imaging in cultured mouse motor neurons, and (3) between Jerusalem and Munich, to plan mitochondrial imaging experiments in human ES cell-derived motor neurons.

Project Partners:

Dr. Georg Haase
(Project Coordinator)
INSERM
Marseille, France

Prof. Dr. Benjamin Reubinoff
Hadassah Hebrew University
Medical Center
Jerusalem, Israel

Prof. Dr. Peter Andersen
Umea University
Umeå, Sweden

Dr. Jean Michel Heard
Institut Pasteur
Paris, France

Dr. Thomas Misgeld
Technische Universität
München
München, Germany

ERMCC-NDEG: THE ACTIVITY-DRIVEN ER-MITOCHONDRIA CALCIUM CYCLE (ERMCC) AND PROTEIN MISFOLDING IN NEURODEGENERATIVE DISEASES: FINDING TARGETS FOR THERAPY

"One third into the project preliminary results open new avenues for the collaborators to plan follow up projects which will extent and further develop the current concept of ERMCC deregulation in neurodegenerative diseases"

Main achievements of the consortium

The ERMCC-NDEG consortium aims to identify molecular determinants which control the activity of an ER mitochondria calcium cycle (ERMCC) in neurons. Our working hypothesis is based on previous works by Berridge & Berridge, and postulates that this ERMCC connects synaptic signalling, energy metabolism and structural metabolism of neurons, and fundamentally regulates neuronal survival. Defects in this cycle will lead to neurodegeneration, and by identifying molecular regulators one may be able to develop ERMCC stabilizing drugs for neuroprotection in diseases like Alzheimer's or Parkinson's disease or amyotrophic lateral sclerosis (ALS). Molecules acting on ERMCC targets will then be tested in follow up projects in disease models and patients. Eventually, one may be able to reduce the personal and societal impact of some of the most terrible and expensive to treat and care for diseases known to man which are on the rise in an ageing population.

The advantages of the transnational collaboration to each one of the partners

The participating partners from Spain, Italy and Germany combine basic physiology, neurobiology, neurochemistry and neuroimaging approaches to characterize molecular events regulating the ERMCC. The combined methodologies allow in depth analyses of molecular processes in mitochondrial and endoplasmic reticulum function, dynamic morphology, impact on intracellular signalling, cell survival, and interaction on neurons with glial neighbourhood in single cell preparations, neuron-like and neuronal cultures, and brain slice preparations. Thus the collaboration bridges between methodologies which are otherwise hard if not impossible to combine in a single laboratory. Staff exchange and regular meetings promote interactive development of ideas and new experiments to achieve the collaborations goals.

Project Partners:

PD Dr. Julian Grosskreutz
(Project Coordinator)
Friedrich-Schiller-University Jena
Jena, Germany

Dr. Bernhard Keller
University of Göttingen
Göttingen, Germany

Prof. Dr. Javier Garcia-Sancho
University of Valladolid
Valladolid, Spain

Dr. Maria Teresa Carri
Fondazione S. Luca IRCCS
Rome, Italy

Publications:

* ***BMC Neuroscience 22 June 2009***
* ***Cell Calcium 47 (2010)***
* ***Mol Pharmacol 75:478–489, 2009***

EPITHERAPY: AN EPIGENETIC APPROACH TOWARDS THE RECOVERY OF NEURONAL NETWORK PLASTICITY AND COGNITIVE FUNCTION IN NEURODEGENE RATIVE DISEASE

"Our collaboration has been extremely fruitful so far, and we will continue to collaborate beyond the funding period".

Main achievements of the consortium

Epigenetic mechanisms such as histone-modification are key-regulators of gene-environment interactions. Importantly, such epigenetic mechanisms have recently been implicated with the pathogenesis of neurodegenerative diseases. The EPITHERAPY consortium has now made important progress towards a better understanding of how epigenetic processes contribute to disease progression and how this knowledge can be translated into diagnosis and therapeutic approaches. For example we found an epigenetic signature of the aging brain that may be used as an early biomarker for AD pathogenesis. Moreover, we now have a better understanding about potential epigenetic drug targets. To this end we used genetic models to elucidate which epigenetic modulators could serve as drug targets. On the other hand we also gained important insight, which epigenetic modulator are not good drug targets, or may have even detrimental function. Based on this knowledge we are now testing/aiming to develop, in collaboration, selective compounds that specifically affect the identified epigenetic drug targets.

The advantages of the transnational collaboration to each one of the partners

Because neurodegenerative pathologies involve multiple sources of changes in the biological functioning of the brain, the fact that our consortium resembles a unique combination of expertise is of utmost importance. For example, members of this consortium have a long-standing interesting in AD or HD pathogenesis. Along with the fact that both diseases involve epigenetic deregulation this allows for important novel insights. Since one memberof the consortium is an expert neuronal network plasticity using innovative in vivo recording technology we are able to investigate the biological correlates of neurodegeneration and memory impairment at all levels, from the plasticity of the transcription machinery to behaviour. This does not only allow each member to gain a deeper understanding with respect to its own expertise but allows us to understand pathogenic processes on the systems level

Project Partners

Dr. Andre Fischer
(Project Coordinator)
Georg-August Universität Göttingen
Göttingen, Germany

Dr. Angel Barco
Consejo Superior de Investigaciones Científicas
Spain

Dr. Xavier Leinekuge
Centre National de la Recherche Scientifique
Talence, France

Publications:

* ***Bio Chem (2009)***
* ***Science (2010)***

nEUROsyn: MOLECULAR MECHANISMS UNDERLYING SYNAPTIC DYSFUNCTION IN PROTOTYPIC NEURODEGENERATIVE DISEASES RELATED TO PROTEIN MISFOLDING

"Particularly satisfying were the interactions and synergies between the groups and we foresee a continuation of the collaboration after the end of funding".

Main achievements of the consortium

This project is a transnational and interdisciplinary study of the mechanisms leading to impaired synaptic and neuronal loss in two neurodegenerative conditions that may be considered the prototype of neurodegeneration, namely Alzheimer's disease and Huntington's disease. Understanding the molecular mechanisms underlying this process could lead to the identification of new therapeutic targets for interventional strategies in the early stages of disease.In the first year, the scientific activities of the project followed the forecasts set out in the original program.

The advantages of the transnational collaboration to each one of the partners

The aim of the present proposal is to integrate the specific technological and conceptual knowledge, and research tools available in a group of Laboratories, from Italy, Spain and Sweden in a single network. The current research aims and methodological competences of the participating partners are sufficiently closely related for there to be worthwhile and productive interactions, and still sufficiently different to stimulate novel, strong and creative synergies. The project is designed to explore synaptic neuronal disturbances in a series of integrated approaches that exploited the spectrum of expertises of the research Units. The study involves the generation and use of transgenic mice, the subcellular imaging of synaptic components, the transcriptional regulation of components that control Ca2+ spatially and temporally. Thus, the work foreseen has used first rate expertise in the generation and use of cellular (unit 1, 1A, 1B,) and animal models of diseases (Unit 1 and 2 and 4), in imaging technology (Unit 3), in the cellular and subcellular biochemistry of signaling functions (unit 1,1A,1B2,3 4), and in the area of mitochondrial bioenergetics (unit 1A, 1B, 2 and 3).

Project Partners:

Dr. Fabrizio Tagliavini
(Project Coordinator)
Fondazione IRCCS - Istituto Neurologico Carlo Besta
Milano, Italy

Dr. Josè Ramon Naranjo
Consejo Superior de Investigaciones Cientificas
Cantoblanco Madrid, Spain

Dr. Giuliano Binetti
IRCCS Centro San Giovanni di Dio-Fatebenefratelli
Brescia, Italy

Dr. Jia-Yi Li
Lund University
Lund, Sweden

Publications:

* ***Journal of Alzheimer's Disease (2010)***
* ***Science (2009)***
* ***Journal of Alzheimer's disease (2009)***
* ***Neurobiology of Aging (2009)***
* ***Acta Neuropathol (2010)***
* ***Neurobiol Aging (2010)***
* ***Proteomics (2010)***

ADTest: ROLE OF PROTEASES AND THEIR INHIBITORS IN PATHOPHYSIOLOGY AND DIAGNOSIS OF ALZHEIMER DISEASE

"Since three of the four partners have been involved in common projects before this programme began, it is obvious that collaboration will extend over the end of the funding period".

Main achievements of the consortium

Our approach is to bring together people from different fields of dementia research (clinical work, translational science, basic science, structural biology) to accelerate the interval from he discovery of a potential biomarker or a biomarker profile to elucidating the biological significance in the pathophysiology of dementia. In order to define an appropriate set of fluids and brain samples for the validation of novel biomarkers we have begun an collaboration with a group in Columbia and have characterized a large cohort of familial AD patients clinically, morphologically and biochemically.

The advantages of the transnational collaboration to each one of the partners

Since we are joining partner with unique clinical and or scientific abilities and direct links to industry we believe that as a consortium we can work (i) faster, (ii) more target oriented, (iii) more creative than as individual research groups.

Project Partners:

Prof. Dr. Markus Glatzel
(Project Coordinator)
Uniwversity Medical Center
Hamburg-Eppendorf
Hamburg, Germany

Dr. Holger Jahn University
Medical Center Hamburg-
Eppendorf Hamburg, Germany

Dr. Tim Clausen
Institute of Molecular Pathology
Vienna, Austria

Prof. Dr. Isidro Ferrer
Hospital Universitario de Bellvitge
Hospitalet de LLobregat, Spain

Publications:

* ***AD Test Annual scientific progress report 2009***

ProGene: PROTECTING AGAINST NEURODEGENERATION BY SOMATIC GENE THERAPY

"The collaboration will be continued in any case".

Main achievements of the consortium

Molecules, to be transduced by somatic gene therapy to prevent neurodegenerative cells death, i.e. inhibitors of CDK4 and CDK6 have been cloned into viral vectors and functionally been tested both under in vitro and iv vivo conditions. The approach for cell-specific gene transfer has further been extended to non-viral vectors using polyethylenimines, complexed to antibodies or rvg-peptide, recognising specifically cell surface molecules. Lentivirus vector systems which allow a regulable expression of the transgene of interest were successfully developed and tested. Experiments have been conducted in animal models of neurodegnerative disorders using both viral and non-viral vectors, validating functionally efficient properties of vectors for gene transfer to the CNS. Biodistribution of vectors will further be optimized and validated tools for CNS-gene transfer will subsequently be translated into clinical application. Our main scientific achievements so far: to have established non-intergating viral vectors that effectively transduce neurons

The advantages of the transnational collaboration to each one of the partners

and as thus, can be used as vectors for somatic gene therapy of CNS disorders.
The main collaboration was built between a group in the UK which provides technical knowhow on the vectors, and the German group which follows a more translation approach to use this technical tool in animal models of CNS disorders.

Project Partners:

Prof. Dr. Thomas Arendt
(Project Coordinator)
University of Leipzig
Leipzig, Germany

Prof. Dr. James Uney
University of Bristol
Bristol, United Kingdom

Prof. Dr. Barbara Nawrot
Polish Academy of Sciences
Lodz, Poland

Publications:

* ***Am. J. Pathol. (2010)***

MIPROTRAN: TRANSFER OF MISFOLDED PROTEIN AS A PATHOGENETIC MECHANISM IN NEURODEGENERATIVE DISEASE

"After the funding period has ended, we will continue with our collaborations as we have discovered that we complement each other on a scientific level. By continuing the collaborations, we will more efficiently get the results and knowledge that will help us to improve the treatment for patients with neurodegenerative diseases".

Main achievements of the consortium

To document the uptake and infectivity of different high molecular weight forms of α-synuclein (α-syn), we have been able to generate different oligomeric forms of α-syn and have labelled them with various extrinsic fluorophores. These labelled forms of α-syn have been exposed to cultured cells and we have documented the subcellular localization of the generated α-syn oligomers. Oligomeric α-syn forms have been injected into the brain of model animals and their uptake was quantified using different imaging methods. To document cellular response to toxic α-syn aggregates and clearance of the aggregated α-syn, structurally characterized α-syn oligomers has been degraded with calpain. In addition, hGFAP-tTA transgenic mice have successfully been bred with α-syn responder mice and the expression of human a-syn has been detected via Western blot analysis, conventional immunohistochemistry and double immunofluorescence staining in spinal cord, brain stem and cerebellum of double-transgenic mice. Since hGFAP-syn mice express the human a-syn relatively high, especially in substantia nigra, this line is kept and bred to homozygousity for study of toxic spread to adjacent neuronal cellin this PD relevant region.

The advantages of the transnational collaboration to each one of the partners

The transnational collaboration has not only given us several opportunities to combine different analysis methods to increase the level and quality of our results, it has also given us the opportunity to increase our joint and individual scientific knowledge of cellular response to toxic α-syn aggregates. Thus, we have acquired knowledge that will help us to improve the treatment for patients with neurodegenerative diseases. The collaboration has also given the research fellows a chance to increase their abilities within scientific communication and research collaboration.

Project Partners

Prof. Dr. Patrik Brundin
(Project Coordinator)
Lund University
Lund, Sweden

Prof. Dr. Ronald Melki
Centre National de la Recherche Scientifique
Gif-sur-Yvette, France

Prof. Dr. Mathias Jucker
University Tübingen
Tübingen, Germany

Prof. Dr. Olaf Riess
University Tübingen
Tübingen, Germany

Publications:

* *PNAS (2009)*
* *Parkinsonism relat. D. (2009)*
* *Science (2010)*
* *Nat. Rev. Mol Cell Bio (2010)*

PARKCDNF: DEVELOPMENT OF AN EXPERIMENTAL THERAPEUTIC STRATEGY USING THE NEWLY IDENTIFIED GROWTH FACTOR CDNF FOR TREATMENT OF PARKINSON'S DISEASE

"The consortium will continue along its lines with regard to the development of an experimental therapeutic strategy using CDNF for treatment of Parkinson's disease".

Main achievements of the consortium

The consortium aims at developing an experimental strategy for the treatment of Parkinsins's disease using the newly identified growth factor CDNF. The major achievements within the first half of the funding period are that the CDNF protein stability measured at 37oC showed no signs of degradation during 2 weeks (Tuominen) the chronic infusion of CDNF in 6-OHDA lesion model of Parkinson's disease in rats resulted in restoration of the functional balance of the nigrostriatal neural circuit and was more efficient than GDNF (Tuominen, Saarma) the first toxicity studies a single stereotactic injection of CDNF in common marmorset monkeys did not reveal any clinical nor neuropathological abnormality (Fuchs) CDNF knockout mice were generated and conditional CDNF knockout mice were crossed to nestin-Cre mice resulting in a viable mouse line. Thus, an ideal in vivo system is established allowing a detailed characterization of the role of CDNF in the dopaminergic system (Saarma) that information on the protein structure/fold of CDNF and MANF revealed some highly surprising protein family relationships suggesting a unique and non-canonical way to promote neurotrophic and neuroprotective effects (Saarma).

The advantages of the transnational collaboration to each one of the partners

The consortium represents a joint effort to promote CDNF as a novel neurorestorative treatment for Parkinson's disease.The consortium works multidisciplinarily on the characterization of CDNF as an endogeneous player in the development of the nigrostriatal system, as a pharmacological potent growth factor and on the optimal root of application and saftety concerns with regardto the future use in humans. At the end of the PARKCDNF project funding, the consortium envisions to be ready to enter the clinic (phase I trials). The concortium is closely collaborating and on its way to achieve the promised milestones. The advantages of the transnational collaboration are to gather a group of experts in the field to trustfully collaborate in the European dimension.

Project Partners:

Prof. Dr. Kerstin Krieglstein
(Project Coordinator)
Albert-Ludwigs-University
Freiburg, Germany

Prof. Dr. Mart Saarma
University of Helsinki
Helsinki, Finland

Prof. Dr. Eberhard Fuchs
German Primate Center
Göttingen, Germany

Prof. Dr. Raimo Tuominen
University of Helsinki
Heksinki, Finland

Prof. Dr. Olle Lindvall
Lund University Hospital
Lund, Sweden

Publications:

* ***Dev. Neurobiol. (2009)***

HETEROPARK: SYNTHESIS AND VALIDATION OF ANTIPARKINSONIAN DRUGS TARGETING GPCR HETEROMERS

"Heteropark is a truly trans-disciplinary Consortium and merges the complementary expertise of 4 research groups, granting immediate advantages to the single units.We will continue the collaboration under the same dynamics aftertheend of the funding period"

Main achievements of the consortium

Confirmation of neurotransmitter receptor heteromers in rodent and primate brain samples Demonstration in Parkinsonian models of changes in the amount of receptors and in the degree of heteromers present in brain samples.Selection of targets for Parkinson's disease based in both proven heteromerization and proven presence in the brain of parkinsonian models.Design and synthesis of new compounds to be tested in vitro and in vivo in rodent and primate models of Parkinson's disease.The advantages of the translational collaboration to each one of the partners.

The advantages of the transnational collaboration to each one of the partners

Heteropark is a truly trans-disciplinary Consortium and merges the complementary expertise of 4 research groups, granting immediate advantages to the single units.German partner – This group has a long-lasting expertise in design, synthesis and development of chemical compounds potentially active as agonist/antagonists of receptor homomers/heteromers. Spanish partner (Barcelona) – This group has developed a Sequential Resonance Energy Transfer (SRET) technique to detect receptors heterotrimers in vitro in living cells. Italian partner – This group has a strong expertise in the 6-OHDA rodent PD model.Spanish partner (Pamplona) – This group has the advantage of knowing that anti-parkinsonian and/or neuroprotective drugs have been previously tested in a rodent PD model. Primates are scarce and should be only used as a final step before reaching clinical trials in humans.

Project Partners:

Prof Dr. Rafael Franco
(Project Coordinator)
Universitat de Barcelona
Barcelona, Spain

Dr. Marie-Therese Armentero
IRCCS Neurological Institute
C. Mondino
Pavia, Italy

Prof. Dr. Christa E Mueller
University of Bonn
Bonn Germany

Dr. Jose Luis Lanciego
Fundacion para la Investigacion
Medica Aplicada (FIMA) Pamplona,
Spain

Publications:

* ***J Psychopharmacol OnlineFirst, published on May 20, 2010***

mGluRpatho: GROUP III METABOTROPIC GLUTAMATE RECEPTORS (MGLURS): FROM NEW MOLECULES TO THERAPEUTIC DEVELOPMENT FOR THE TREATMENT OF PARKINSON'S DISEASE

"The project will continue after the end of the funding period to improve our knowledge of the role of glutamate overactivity in animal models of Parkinson's disease, the conformation of mGlu receptor subtypes and their differences. The specificity of each team is necessary to cover a complete figure of the molecules synthesized from the cellular to the behavioral level in rodent models of PD".

Main achievements of the consortium

The aim of our project is to discover and characterize functionally new ligandsthat could compensate for glutamate overactivity and therefore slow the progression of the disease in addition to counteract motor symptoms. The main achievement of the consortium at mid part of the project has been to design, virtually screen and synthesize a number of orthosteric ligands (binding to the glutamate site) characterized pharmacologically on cloned receptors of the different subtypes. The best ligands (LSP1-2111, LSP4-2022) which demonstrate a 20 times more efficient activation of mGlu4 compared to mGlu8 receptors were made availableto all partners of the project. They have been found to be neuroprotective against in vitro models of excitotoxicity with lesser effects in in vivo experimental models of parkinsonism. These orthosteric ligands counteract Parkinsonian motor symptoms and reduce the expression of L-DOPA-induced dyskinesia. This highly multidisciplinary project may have major implications in the development of novel pharmacological strategies for neuroprotective and neurorestorative treatment of Parkinson's disease. This will lead to the identification of the cellular and molecular processes underlying the expression of parkinsonian symptoms and avoid long-term L-DOPA-induced dyskinesia.

The advantages of the transnational collaboration to each one of the partners

The combination of five different teams experts in chemistry, pharmacology, behavior,quantitative morphology and molecular biology enable us to achieve a complete picture of "candidate" molecules for PD treatment that have agonist action at mGluR4 and lesser action at mGluR7 or mGluR8, from their chemical structure-based design to their physiological action. Analyzing the functional and cellular impact of treatments activating these receptors is essential to identify the best pharmacological anti-glutamate strategy alternative to deep brain stimulationin PD treatment

Project Partners:

Prof. Dr. Marianne Amalric
(Project Coordinator)
CNRS Aix-Marseille Universite
Marseille, France

Prof. Dr. Francine Acher
CNRS Universite Descartes Paris V
Paris, France

Prof. Dr. Gilberto Fisone
Karolinska Institute
Stockholm, Sweden

Prof. Dr. Ferdinando Nicoletti
I.R.C.C.S., Pozzilli, Italy

Publications:

* ***J. Med. Chem. 2010, 53 JPET November 25, 2009***
* ***Neuropharmacol (2011, in press)***

FamPD: IDENTIFICATION OF NEW GENES CAUSING FAMILIAL FORMS OF PD

"The three partners will definitely continue with further collaborations since these partners probably have the best combined PD family material in Europe as well as large cohorts of PD patients and controls for further analysis on a population level"

Main achievements of the consortium

This project seeks to take a coordinated approach to the genetic analysis of a large number of families with PD which have been identified by the three groups in this consortium over several years, in whom no defects in the currently known genes has been detected. These families belong to different groups, including those with autosomal-dominant and autosomal-recessive inheritance. Accordingly, different approaches are suggested to identify the underlying genetic defects. Currently, all three centers work within the time schedule. The PD families were recruited, known loci and mutations were excluded and chip hybridization for whole genome linkage analysis is almost done. We then will approach an initial analysis of results in order to perform fine mapping of prioritized regions. The last step will be validating sequence variants in additional cohorts of affected and controls. Further, we will evaluate the mutational spectrum to perform genotype-phenotype associations.

The advantages of the transnational collaboration to each one of the partners

The consortium running this project has a long track of successful collaborations. The groups have been publishing together since 1997 and have provided major contributions to the genetic dissection of Parkinson's disease. The key to this success was the systematic collection of clinical data and biomaterial (DNA). The free sharing of these resources enables each partner to analyze one of the world's most extensive cohorts of familial PD with special regard to ones individual expertise (Tübingen = dominantly inherited forms, Paris recessively inherited forms, London = copy number variants).

Project Partners

Prof Dr. Thomas Gasser
(Project Coordinator)
University of Tübingen
Tübingen, Germany

Prof. Dr. Nicholas Wood
University College London
London, United Kingdom

Prof. Dr. Alexis Brice
Institut National de la Santé et de la Recherche Médicale
Paris, France