



European research projects on neurodegenerative diseases of the central nervous system

The first transnational call of ERA-Net NEURON was published on January 2008. The ERA-Net NEURON funding organizations acted with the mission of promoting and encouraging multidisciplinary transnational research that combines basic and clinical approaches. Researchers from 232 laboratories from 12 countries joined forces in 59 consortia that submitted their applications in response to the call. Following a thorough review process, 12 consortia were chosen for funding based on criteria published by the steering committee. The total funding volume is close to 10 million euros. Funding of the projects will commence on February 1st 2009.

The 12 funded projects are briefly described in the following pages.



Funded by the European Commission

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

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ERA-Net **NEURON** was launched in January 2007 and is funded under the ERA-Net scheme in FP6 by the European Commission. The aim of **NEURON** is to promote the development of a European strategy for research in the area of disease related neuroscience. Among the many diseases affecting human health, disorders of the brain are major causes of morbidity, mortality and impaired quality of life. According to estimates by the World Health Organization (World Health Report 2001), more than one billion people suffer from disorders of the central nervous system. In Europe, disorders of the brain account for approximately one-third of the total burden of all diseases. The project envisages creating a group of relevant research funding organizations in Europe and, thereby, gain maximum added value from investment in this field. Sixteen European national research funding organizations from Austria, Finland, France, Germany, Italy, Israel, Luxembourg, Poland, Romania, Spain, Sweden and UK are cooperating under this single umbrella.

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ADtest: Role of proteases and their inhibitors in pathophysiology and diagnosis of Alzheimer Disease

Project Description

Dementias are a major burden to mankind. Due to the demographic shift towards an aging population, the next decades will see an unparalleled rise in the occurrence of dementias in developed countries. The most prevalent dementia by far is Alzheimer's disease, where accumulation of the proteins beta-amyloid and tau in Neurons or their direct vicinity leads to selective death of neurons and subsequent intellectual deterioration. Lately it has become obvious that accumulation of proteins in tissues or cells is the direct result of an imbalance between generation and clearance of potentially-toxic proteins. Currently, there are only very few, non-invasive tests, corroborating the diagnosis of dementias such as Alzheimer's disease, and these tests suffer from a lack of specificity. In addition, therapeutic options to treat Alzheimer's disease are particularly limited and there is only causal therapy available.

Experts from clinical dementia research, neuropathology, disease modelling and structural biology have joined forces in the ADtest consortium to develop and implement novel diagnostic tools for Alzheimer's disease. Furthermore, ADtest will investigate novel pathophysiological mechanisms of Alzheimer's disease focusing on routes of protein degradation. Results from these studies will help to optimize diagnosing Alzheimer's disease with a cost-effective, non-invasive test. Furthermore, ADtest will search for novel diagnostic targets.



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EPITHERAPY: An epigenetic approach towards the recovery of neuronal network plasticity and cognitive function in neurodegenerative disease

Project Description

Dementia is affecting more than 7 million Europeans, a number that is expected to double by the year 2025 thereby causing a huge economical and emotional burden to our societies. The major causes of dementia are neurodegenerative diseases such as Alzheimer's (AD) or Huntington's disease (HD). Despite intensive research no effective cure is yet available. Most recent data (including members of EPITHERAPY) suggest that epigenetic mechanisms, such as acetylation-state of the chromatin, play an important role in the pathogenesis of AD and HD. Moreover, targeting such mechanisms such as inhibition of histone-deacetylases seems to hold great potential for neuroprotection and neurorestoration. To this end the EPITHERAPY consortium proposes to further elucidate the role of epigenetic mechanisms during neurodegeneration using post-mortem human brain samples and mice as a model organism to identify the most suitable epigenetic drug targets for neuroprotection and neurorestoration. The combination of distinct expertise from the EPITHERAPY participants will allow us explore an epigenetic approach towards neurodegeneration on the molecular, synaptic, network, systems and behavioral level. EPITHERAPY will therefore significantly contribute to the development of effective therapeutic strategies to treat neurodegeneration.



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ERMCC-NDEG: The activity-driven ER-mitochondria Calcium Cycle (ERMCC) and protein misfolding in neurodegenerative diseases: finding targets for therapy

Project Description

Neurodegenerative diseases like Amyotrophic Lateral sclerosis and Alzheimer's disease occur mostly without identifiable cause, and are as yet incurable. The project aims to develop a new strategy of neuroprotection by moderation of the endoplasmic-reticulum-mitochondria-calcium cycle (ERMCC) which links functional and structural metabolism in neurons and plays a central role in neuronal development and survival. We will identify the key pathways of the ERMCC in models of ALS and Alzheimer's disease which collates different features of neurodegenerative processes into manifest ERMCC dysfunction. In a series of collaborative experiments in neuron-like cell and neuron cultures, and tissues of animal models of neurodegenerative diseases we use patch-clamp, fluorescent and photoluminescent imaging, neurogenetic and neuroproteomic approaches to identify neurotoxic and neuroprotective properties of the ERMCC. A pathogenic imbalance of the ERMCC function will be reported by mitochondrial calcium overload, ER calcium depletion, fluorescent protein misfolding and activation of cell death pathways. In the established neuronal systems we will identify molecular targets for serial testing of neuroprotective ERMCC modulators which can then be carried on to preclinical testing in follow-up studies. Drugs stabilizing ERMCC function may thus provide neuroprotection for a range of neurodegenerative diseases of different causes.



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FamPD: Identification of new genes causing familial forms of PD

Project Description

Parkinson's disease (PD) is a common and severe neurodegenerative disease that leads to progressive motor impairment as well as autonomic and cognitive disturbances. In recent years, undoubted significant and rapid progress in our knowledge of the causes of PD has been made by in depth analysis of relatively rare forms of inherited PD that share many clinical and pathologic characteristics with the common sporadic form of the disease. These discoveries have provided a starting point and have inspired intense research work in many laboratories world-wide to unravel the molecular and cellular events that lead to the dysfunction and death of dopamine cells, with the aim to identify novel targets for causative or even preventive treatments. Despite this significant progress, it is assumed that many important genes that may cause or contribute to the development of PD still remain to be discovered.

This proposal 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 applying groups 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. Recent advances in the technologies have meant that performing genome wide searches for genetic variants in a large number of patients and families is now rapid, robust and feasible. This project is focused on new genetic discoveries. We anticipate that the finding of new genes will focus future research efforts into new pathways and ultimately provide the field with potential targets for therapeutic interventions.



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heteropark: Synthesis and validation of antiparkinsonian drugs targeting GPCR heteromers

Project Description

This Consortium will perform complementary translational research to propose a new therapeutical approach for Parkinson's disease (PD) with possibilities to initiate clinical trials in 3-5 years. The approach consists of a combination of novel compounds to alleviate PD symptoms and minimize side effects induced by current therapies. The approach includes the design of novel compounds and of a novel therapeutic approach, based on drug combinations and dual drugs, to target G protein-coupled receptor heteromers. The coordinator of the Consortium has discovered the occurrence of trimers formed by dopamine D2, cannabinoid CB1 and adenosine A2A receptors in the striatum, the target organ in PD therapies, and has the expertise to detect trimer alterations in PD. One member of the Consortium has the expertise and capacity to synthesize novel patentable compounds for these receptors and even of dual compounds, which target simultaneously two different receptors. The other two members of the consortium have expertise in developing animal models of PD, one in rat and another one in primates, and validating new therapeutic approaches for PD. Validating novel therapies targeting striatal receptors firstly in rodents and subsequently in primates is what is needed for initiating phase I clinical trials in humans.



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iPSoALS: Modeling sporadic ALS in motor neurons by genetic reprogramming of patient skin fibroblasts

Project Description

Amyotrophic lateral sclerosis (ALS) is a severe and incurable neurodegenerative disease. In ALS motor neurons in spinal cord, brainstem and cerebral cortex are progressively lost and disconnected from their targets. As a consequence patients lose control of voluntary movement and invariably die, most often from respiratory problems. ALS is also a major socio-economic issue. In Europe ALS is now more common than multiple sclerosis, Jacob-Creutzfeld disease and AIDS together and expenses for individual supportive care can exceed 150.000 Euros per year. Almost nothing is known about the disease mechanisms in sporadic ALS, the most common form. This is due to the difficulty to obtain human motor neurons and to study their degeneration in relevant model systems.

To overcome this limitation we propose to generate human motor neurons by a recently described technique of cellular reprogramming. Skin fibroblasts will be obtained from ALS patients and healthy volunteers and will be genetically re-programmed into motor neurons. We will analyze whether patient's motor neurons show changes in survival, growth or metabolic function, try to understand the underlying degenerative mechanisms and investigate whether these latter originate within motor neurons or in cells of their environment. To this purpose we gathered leading teams in ALS genetics, stem cell biology, motor neuron biology and life imaging working at renowned institutes in France, Germany, Israel and Sweden.



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mGluRpatho: Group III metabotropic glutamate receptors (mGluRs): from new molecules to therapeutic development for the treatment of Parkinson's disease

Project Description

Restoring the balance between excitatory and inhibitory circuits in the basal ganglia, following the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta in Parkinson's disease (PD), represents a major challenge to treat Parkinsonian patients and avoid long-term L-DOPA induced dyskinesia. Recent studies have focused on the modulatory action of metabotropic glutamate receptors (mGluRs) on neurodegenerative diseases including PD and subtypes 4 and 7 mGluRs (belonging to group III) are largely expressed in the basal ganglia. The objectives of the project are to gather the expertise of five different international teams and use their individual skills in chemistry, pharmacology, behaviour, quantitative morphology and molecular biology to achieve a complete picture of "candidate" molecules for PD treatment that have agonist action at mGluR4 and 7, from their chemical structure-based design to their physiological action. Analyzing the functional and cellular impact of treatments activating these receptors will be essential to identify the best pharmacological anti-glutamate neuroprotective and neurorestorative strategy alternative to surgery in PD treatment.



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MIPROTRAN: Transfer of misfolded protein as a pathogenetic mechanism in neurodegenerative disease

Project Description

Alzheimer's and Parkinson's diseases (AD and PD) are neurodegenerative disease that start late in life and where the symptoms gradually worsen. It is still largely unknown what causes these diseases. They are characterized by deposits of two proteins (called aggregated amyloid- β protein and α -synuclein) in brain cells. These proteins take on an abnormal shape and become "misfolded". Our recent studies suggest that the changes in protein folding in the brain in AD and PD spread from one cell to another, through a novel and potentially very important mechanism. We base this idea on findings we obtained in animal models of AD and observations we made in two PD patients we grafted with fetal dopamine neurons. Our consortium will take a joint effort to investigate whether and how misfolded proteins move between cells in different cell- and animal models of AD, PD and a related disorder called multiple system atrophy (MSA). We will examine strategies to inhibit the transfer of the proteins between cells and study the cellular defense mechanisms against aggregation of misfolded proteins. Our ultimate goal is to lay the foundations for neuroprotective therapies in AD, PD and MSA, based on inhibiting transfer of misfolded proteins.



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nEUROsyn: Molecular mechanisms underlying synaptic dysfunction in prototypic neurodegenerative diseases related to protein misfolding

Project Description

A novel concept has recently emerged in neurodegenerative disorders: synaptic dysfunction may precede neuronal death by several years and can underlie many important but still reversible symptoms. The aim of this project is to investigate the mechanisms that lead to synaptic impairment and eventual demise of neurons in two prototypic neurodegenerative conditions related to protein misfolding, i.e. Alzheimer disease (AD) and Huntington disease (HD). Both disorders involve production and deposition of abnormal protein fragments which harm neurons. The rationale of the study is that AD and HD share critical cellular changes such as the dysregulation of Ca²⁺ homeostasis and mitochondrial function. The resulting Ca²⁺ imbalance initially results in a "synaptopathy" and eventually progresses to neuronal death. In a series of five complementary and interactive sub-projects based on cellular and animal models, we will monitor alterations of synaptic and dendritic spine remodelling, investigate changes in receptor trafficking at the synapse, explore disturbances in trafficking of different cellular components and study the role of exosomes in neurodegeneration. We will pay special attention to the Permeability Transition Pore, which is another important target of Ca²⁺/mitochondrial dysregulation that may be affected in AD and HD. The study will provide important information for the identification of novel therapeutic targets for treatment strategies in early stages of the pathology.



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PARKCDNF: Development of an experimental therapeutic strategy using the newly identified growth factor CDNF for treatment of Parkinson's disease

Project Description

Parkinson's disease is a neurodegenerative disease of unknown cause. 12-20 new cases per 100.000 inhabitants per year are reported in developed countries such as Europe. Furthermore, no causal therapy for restoring nigrostriatal neuron loss or slowing down the disease progression is available. Potential and promising therapies may therefore lay in the neurotrophic support of old and environmentally challenged dopaminergic neurons. Mart Saarma and Raimo Tuominen have discovered a new conserved dopamine neurotrophic factor, CDNF, and were able to show that CDNF protects and repairs nigrostriatal neurons in rodent models of PD. CDNF is unique and distinct from other already known neurotrophic factors and is therefore an excellent candidate for a therapeutic lead in PD. The consortium represents a joint effort to promote CDNF as a novel restorative treatment for Parkinson's disease. At the end of the PARKCDNF project funding, the consortium envisions to be ready to enter the clinic (phase I trials).



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PhysiolDBS: Physiological mechanisms of Deep Brain Stimulation in Parkinson's disease

Project Description

This consortium is proposed to uncover physiological mechanisms of deep brain stimulation (DBS) in Parkinson's disease as a model neurodegenerative disease. There is a pressing need to do this, because future advances in DBS technology including the development of more intelligent stimulation paradigms or closed-loop stimulation systems, will require a better understanding of the nature of abnormal brain activity, that needs to be modulated, and its interaction with extrinsic electrical stimuli. Because DBS has multiple effects on brain activity from a local cellular level to complex interactions with functional brain networks a collaborative approach of researchers from the fields of cellular physiology, systemic neurophysiology, behavioural and clinical neurosciences is required. We aim at coordinating the already existing, but geographically dispersed, high-level of research expertise in Europe on this topic. Project results will primarily increase our knowledge of Parkinsonian pathophysiology and the interaction of disease related brain activity with electrical stimulation. Some of the consortium outputs, however, may be suitable for patent protection. These spin-offs could be exploited in future cooperations with the medical industry. Therapeutically relevant results of the consortium will be immediately translated into clinical proof-of-principle studies, which will be possible through the close collaboration between basic and clinical scientists.



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ProGen: Protecting against neurodegeneration by somatic gene therapy

Project Description

Alzheimer's disease (AD) is an incurable neurodegenerative dementing disorders of higher age with an enormous socio-economic burden. The lifetime risk for AD between 65 and 100 years is 33% for men and 45% for women. By 2025 about one-third of the European population will be older than 65 years and, thus, be at risk for dementing disorders. Currently, there is neither an effective prevention nor a treatment available. AD is one of the leading causes of disability, and represents the fastest growing area of unmet medical need. The number of demented patients in Europe, currently about 8 million will double to triplicate within the next 20 years. Medicare costs will rise accordingly. Annual costs of over € 130 billion in the EU already today makes AD the third most expensive disease. An intervention that could delay the onset of AD by five years would already cut the number of patients with AD by half.

Here we propose to establish and validate under experimental conditions in animals a gene therapeutic approach that will slow down or even prevent neurodegeneration with high therapeutic efficacy and minimal or no side-effects. The therapeutic approach is based on a new concept that targets critical molecular switches that under neurodegenerative conditions regulate aberrantly activated cell division mechanisms in neurons. Therapeutic tools to prevent neurodegeneration will subsequently be transferred to clinical applications. Principal solutions to be developed in this project can be applied with only minimal modifications to a variety of other neurodegenerative CNS disorders including Parkinson's disease or Amyotrophic Lateral Sclerosis.



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