

Call for Projects Recruitment 2008

“Young Research Team”

**Proposal from the Rhône-Alpes Region
“Parkinson” group to recruit a young research
team specializing in rodent models of
dopamine-dependent behavioral disorders**

**Deadline for project submission:
May/17/2008**

Practical information:

Deadline for project submission in PDF format: midnight,
May/17/2008, address:

contact@fondation-neurodis.org

Deadline for project submission on paper: May/22/2008 (postmark),
5 copies, address:

Fondation Neurodis
Inserm Bâtiment 452B
Centre Hospitalier Le Vinatier
95, Boulevard Pinel
F-69675 Bron cedex

The selected candidates for interviews will be informed on:
May/30/2008

Interviews will be held, by mutually agreed appointment, as of
June/9/2008

Contact:

- ♣ for further technical or scientific information:
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- ♣ for further administrative or financial information:
claire.rigaud-bully@fondation-neurodis.org

Context

The NeuroDis Foundation was set up on August 3rd, 2007 by the French Higher Education and Research Ministry and the French Health Ministry to finance research projects in neuroscience applied to the development of innovative diagnostic and treatment methods for neurological and psychiatric disorders. The Foundation is part of a network of neuroscience research institutes and laboratories and university hospital neurology departments in the Rhône-Alpes and Auvergne Regions of France. Information on the research teams and hospital departments involved in the Foundation and on the research priorities laid down by the NeuroDis Pilot Committee is available at: <http://www.fondation-neurodis.org>

Field and topic of the Call for Projects

As part of its mission, in 2008 the NeuroDis Foundation is financing a 3-year contract to set up a young **behavioral neuroscience** research team, and is recruiting a scientific officer for this by Call for Projects.

The successful applicant will set up and manage a young team conducting a scientific project meeting the Foundation's priority objectives in the area of behavioral disorder in Parkinson's disease, using animal models. Appendix 1 lays out the main lines of the project.

Means available

To carry out his/her research project, the successful applicant will dispose of premises in the Grenoble Institute of Neuroscience (GIN – CR Inserm U836-CEA-UJF-CHU), in a favorable scientific and medical environment, making use of not only behavioral, electrophysiological, neurochemical, cellular and molecular but also clinical investigation tools. GIN's research potential will facilitate interaction between different fundamental and clinical approaches, being situated within the Grenoble University Hospital.

He/she will enjoy:

1. Access to GIN's research equipment, and particularly to all tools for animal experimentation (surgical, stereotactic, electrophysiological, functional neurochemical, etc.) and behavioral investigation (videotracking, etc.). Small-animal imaging and microscopy and videomicroscopy platforms will be available.
2. Networking with the GIN-U836 teams, and particularly with:
 - Marc Savasta's U836 team 10 (Dynamics of Neuronal Networks of Movement), which has for many years been interested in the pathology of Parkinson's disease and the mechanisms underlying the treatment efficacy of high-frequency subthalamic nucleus stimulation in correcting associated motor symptoms. The team has a number of animal models for both motor

and behavioral aspects of the pathology, in rodents and shortly also in primates, which can be used in interaction with the new team to be formed. Clinical investigation is integral to this team, with research topics centered on motor, cognitive, affective and behavioral disturbances of Parkinson's disease and their alterations under dopaminergic drugs and deep-brain stimulation (DBS) of variable targets.

- Christophe Segebarth's U836 team 5 (Functional and Metabolic Neuroimaging), with their small-animal NMR and fMRI equipment.
3. Networking with regional clinical and research teams involved in Parkinson's disease, and particularly Emmanuel Broussolle's (Lyon) and Frank Durif's (Clermont-Ferrand) teams.
 4. A 3-year budget of €442,800, including:
 - the successful candidates salary of €45,600 gross p.a.;
 - a research technician's salary of €30,000 gross p.a.;
 - a doctoral student's grant of €22,000 gross p.a.;
 - a 3-year budget of €50,000 p.a. (i.e., €150,000 in all) to cover operating and equipment costs.

It is also hoped to recruit 2 post-doctoral fellows to reinforce the Lyon and Clermont-Ferrand teams, strengthening their cooperation in fundamental and clinical research.

Application criteria

Applicants should meet the following criteria:

- ♣ Post-doctoral level with at least 2 years' experience in piloting a research project.
- ♣ Experience in an internationally recognized fundamental or clinical research team.
- ♣ Experience of Ph.D. supervision.
- ♣ Fluent English; knowledge of French useful but not mandatory.

Application procedure

The application is to be written in English, comprising:

- ♣ Personal details: surname, first name(s), date of birth, nationality, family situation, work address, telephone number and e-mail address.
- ♣ A resume, meeting the application criteria.
- ♣ A list of scientific publications, research contracts, patents, etc. for the period 2001-2007.
- ♣ A scientific project presented in no more than 5,000 words, describing:
 - o the present state of knowledge;
 - o the scientific objectives;

- o the research methodology, including input sought from other NeuroDis teams and networking with outside research teams;
 - o the performance schedule over 3 years, with expected results;
 - o a provisional 3-year operating budget, including staff and equipment, taking account of the above-mentioned contribution from NeuroDis and the applicant's personal contribution in the form of research contracts
- ♣ A Ph.D. teaching project.

Applications failing to meet these criteria or lacking elements of this application procedure will not be examined.

Project Application examination and assessment

Applications will be examined by a committee of experts both from and outside of NeuroDis. Applicants short-listed after examination of application files will be asked to present their project *viva voce* to the NeuroDis scientific pilot committee. Project performance will undergo annual scientific audit by the NeuroDis Scientific Council, comprising 6 outside experts.

Schedule

April/14/2008: Call for the "Young NeuroDis Team" posted on Neurodis website

May/17/2008: e-mail application submission deadline

May/22/2008: postal application submission deadline

May/30/2008: information to the short-listed candidates

June/9/2008: start of interviews

Appendix 1:

Proposed scientific project:

Title: Behavioral disorders in Parkinson's disease

In the Rhône-Alpes-Auvergne region, several groups are involved in research in Parkinson's disease (PD). Non-motor symptoms, in particular apathy and depression related to dopaminergic depletion and impulse control disorders (pathologic gambling, hypersexuality...) related to dopaminergic treatment can have a higher impact on quality of life than the motor symptoms. These non-motor symptoms have been neglected by clinical and basic research in the past.

Deep brain stimulation of the subthalamic nucleus (STN DBS), if highly successful, allows for arrest of dopaminergic treatment, even in advanced stages of PD. While the dopamine-sensitive motor symptoms are well controlled by STN DBS, such patients who take no or only very little dopaminergic drugs can develop prominent apathy, with or without depression. This apathy is reversible on dopaminergic treatment. Thus STN DBS in PD is a model of pure dopamine-sensitive apathy giving insights into the pathophysiology of motivational and mood disorders. Apathy is observed in as many as 40% of PD patients, and is a frequent symptom in Parkinsonian syndromes, depression, schizophrenia and dementia and a better understanding of pathophysiology and clinical management is warranted.

Continuous treatment with dopamine agonists induces less motor sensitization than the more pulsatile treatment with L-dopa. Motor complications (on-off fluctuations and L-dopa -induced dyskinesia) being more frequent with L-dopa, use of dopamine agonists has been favored in recent years. New dopamine agonists with more potent affinity to the D3 receptor, which has a high density in the limbic system, have been marketed. In this context, clinicians have observed a marked increase in behavioral disorders in PD patients. The dopamine-induced pathological behaviors include impulse control disorders (pathological gambling, hypersexuality, compulsive shopping, punding, etc.) and the dopamine dysregulation syndrome associating impulse control disorders with addiction to dopaminergic medications (Lawrence 2003). These pathological behaviors are more frequent in patients with premorbid mood disorders or alcohol abuse. Lifetime prevalence of pathologic hypersexuality, compulsive shopping and pathologic gambling is 6.1% in PD and increases to 13.7% in patients on dopamine agonists (Voon 2006). The high prevalence of severe psychiatric drug-induced behavioral disorders that can be modulated with dopaminergic treatment gives insight into the pathophysiology of behavioral and mood disorders such as addiction and mania. STN DBS can induce impulsivity with acute increase in stimulation parameters. However, on chronic stimulation, the threshold to induce such behaviors increases, in opposition to

sensitization with dopaminergic treatment (Ardouin 2006). Thus STN DBS allows a treatment of drug-induced behavioral disorders and offers a tool to study the mechanisms of such disorders.

Changes in behavior in PD patients modulated by dopaminergic depletion, dopaminergic treatment or STN DBS raise several issues:

- 1) What factors contribute to individual susceptibility to developing mood and behavioral disorders?
- 2) Is dopaminergic depletion a risk factor for developing apathy?
- 3) What is the relationship between apathy and depression?
- 4) Is dopaminergic depletion a risk factor for developing impulse control disorders and addiction if exposed to dopaminergic treatment?
- 5) Why are the hyperdopaminergic behaviors more frequent with dopamine agonist drugs than with levodopa? What are the respective roles of pulsatile treatment and receptor affinity?
- 6) What is the anatomic-functional substrate of these behavioral disorders? (A9 versus A10 dopaminergic neurons, limbic striatum, interconnections between motor, associative and limbic loops?)
- 7) Can these behaviors be modulated using DBS? Are there new targets to treat such different psychiatric diseases as Obsessive Compulsive Disorders, depression, Gilles de la Tourette syndrome, anxiety disorders, or addiction?

In order to further study these issues raised by clinical observations, the clinical research teams in Clermont-Ferrand (F Durif), Lyon (E Broussolle, S Thobois) and Grenoble (P Pollak, P Krack) involved in PD research and in DBS, and who have already strong collaborations have decided to join forces in studying dopamine-dependent behavior, which is the greatest common denominator in their research interests. To do so, a tight collaboration between clinical and basic research is warranted. Each team has already such clinical/fundamental interactions but joining forces between Clermont-Ferrand, Lyon and Grenoble will allow the whole spectrum of tools available in the region to be used.

The current research efforts of the Lyon, Grenoble and Clermont-Ferrand teams need to be implemented in order to better accomplish the goal of a better understanding on the mechanisms involved in the changes in mood and behavior in PD patients and notably the role of dopaminergic depletion, dopaminergic treatment or STN DBS. To this end, the regional research task force has agreed to present a NeuroDis project involving both animal studies and brain imaging research in human.

1)- Rat models of dopamine dependent behaviors

Rat models of apathy and of hyperdopaminergic behaviors are currently being developed in Grenoble (team of Marc Savasta, Pierre Pollak, Paul Krack) and Clermont Ferrand (team of Frank Durif). Lyon has a principal focus on

imaging studies (PET, SPECT, fMRI) in PD and behavioral disorders (team of Emmanuel Broussolle and Stephane Thobois in collaboration with CERMEP). All the tools (intra- and extra-cellular electrophysiology, microdialysis, molecular biology, imaging including 11T MRI, SPECT and microPET for the rat) to study the mechanisms of behavior in the rat are available. However, there is a lack of specific expertise in rat behavior. For this reason the collaborative group of clinicians and fundamental scientists proposes to call for the creation of an independent group of basic scientists with a particular expertise in dopamine-dependent behavior in rats as modulated by dopaminergic depletion, dopaminergic treatment and DBS. The creation of such a group could boost the research in this field and allow hyper- and hypo-dopaminergic behaviors in the rat model to be rapidly investigated, addressing the above-mentioned issues.

2)- Functional imaging of dopamine-dependent behavior

Several collaborative research studies using positron emission tomography and functional Magnetic Resonance Imaging (fMRI) are on-going or in the pipeline for the next 3 years.

The current research and future research topics of the collaborative group are: 1)- Mechanisms of apathy in Parkinson's disease (PD): A PET 11C-raclopride study in apathetic and non-apathetic PD patients treated with long-term subthalamic (STN) stimulation. 2)- PET 15O-H₂O activation study of mania in PD patients long-term treated with STN stimulation. 3)- fMRI activation study of the Stroop emotional test in PD patients with mood fluctuations in off-and-on medication. 4)- PET 18F-MPPF study of serotonergic changes in the living human brain in PD patients with and without depression. 5)- f-MRI activation study of addiction in PD patients suffering from hyperdopaminergic syndrome.

In order to meet this goal, the present collaborative project of Lyon, Grenoble and Clermont-Ferrand will require financial support for a post-doctoral fellowship by NeuroDis for 3 years. Applicants for this fellowship should be either neurologists or PhD researchers with expertise in PET and/or fMRI in neurology, behavior, and/or Parkinson's disease. The post-doctoral fellow will be located in Lyon at the PET/MRI research center called CERMEP, in the University Hospital campus of East-Lyon, which includes the Pierre Wertheimer Neurological Hospital. The post-doctoral fellow would work with Pr. Emmanuel Broussolle and Dr. Stephane Thobois on the regional PET and fMRI collaborative studies in Lyon, Grenoble and Clermont-Ferrand, and also with Pr. Franck Durif on MRI studies in Clermont-Ferrand, and with Grenoble group for specific fMRI studies conducted in Grenoble. Even when some imaging studies are to be performed in Grenoble or in Clermont-Ferrand, data analysis can be performed at CERMEP in Lyon, to avoid undue traveling.

3) Clinical studies on behavioral disorders

To better clinically characterize behavioral disorders such as apathy, depression-related impulse control disorders (pathologic gambling, hypersexuality, compulsive shopping and eating, compulsive medication use), several collaborative clinical studies are in progress. The studies are: 1) Epidemiology of addictive behaviors in Parkinson's disease and in controls; 2) Building and validation of a non-motor behavioral disorders scale in Parkinson's disease; 3) Building of an autoquestionnaire on behavioral disorder; 4) Clinical change of addictive disorders in Parkinson's disease after DBS-STN: role of dopaminergic treatments and of the intensity and location of the chronic stimulation; 5) Relation between DBS-STN, emotion and depression in sample of Parkinsonians; 6) Postoperative suicide after DBS-STN; and 7) Impact of dopaminergic treatment and DBS-STN on compulsive eating and creativity

In order to accomplish this goal, the present collaborative project of Lyon, Grenoble and Clermont-Ferrand will require financial support for a post-doctoral fellowship by NeuroDis for 3 years. Applicants for this fellowship should be PhD researchers with expertise in psychology and cognition. The post-doctoral fellow will be located in Clermont-Ferrand in the "Neuropsychopharmacology of dopaminergic sub-cortical pathways" university research team. The post-doctoral fellow will work with Pr. Franck Durif and Pierre Michel Llorca in interaction with the clinical team of Lyon and Grenoble

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