

UMR 1214 - Inserm/UPS  
ToNIC  
Toulouse NeuroImaging Center

Toulouse, 3rd of May

To whom it may concerned

As director of the Toulouse NeuroImaging Centre, it is a great pleasure to announce that ToNIC members give their full support to the TMBI enthusiastic and innovative project. This ambitious perspective is in line with the main objective of the lab which is to study human brain, cognition, and main pathologies which may affect it.

The innovation of TMBI is to better organize bottom-up and top-down excellence. Bottom-up excellence goes with the selection and the formation of interdisciplinary students. Top-down excellence is the TMBI support through collaborative projects that do not exist today but that are emerging because TMBI allowed to better define large communities.

***One novel community could be TMeMBI (Toulouse Merging Minds for Brain Implants) that covers all TMBI labs.*** Brain Implants for pathologies and handicaps (main of which are Neurodegenerative diseases, Cerebrovascular diseases, Epilepsy, Trauma, deaf or blind persons, etc.) include for example regenerative medicine, biomaterials, prostheses, drugs, and brain stimulation electrodes. For example, today researchers on fields that seem a priori too far do not collaborate with researchers of the same SFR, even in the same building whereas collaborations could lead to synergies, such as merging expertise on stem cells/biomaterials, on pharmacological and on electrodes. TMBI will foster the communities to collaborate with specific calls asking for large projects needing 3-5 master students that will be supervised by two directors that never collaborated together before. If successful, the students will be allowed to continue for a PhD.

Ambitious projects will be built on our current research and our technical resources. Currently, the two teams of our Centre (iDREAM and DEVIN teams) use and develop structural and functional brain imaging technologies: EEG, TMS, MRI and PET.

The I-Dream Team (*Therapeutic innovation, stimulation and modulation of plasticity and recovery*, led by Dr I. Loubinoux) develops innovating technologies to recover motor and cognitive functions of damaged central nervous system (e.g. by cerebrovascular accident, head trauma, amyotrophic lateral sclerosis, multiple sclerosis, Huntington, Alzheimer, etc...).

For instance, a major issue and an essential target for research activities of this team consists in developing human architectural brain implants onto murine and simian models of neurologic disorders such as stroke that boost recovery. Their originality is to organize the tissue reconstruction and to reconnect with long-distance bridges two areas apart. Non-

invasive imaging techniques are developed to follow in vivo regeneration. Due to strong relationship of ToNIC researchers, physicians of the Toulouse University Hospital (CHU de Toulouse), and animal cognition experts (CRCA, CerCO) a number of translational researches and clinical trials are also developed to characterize mind and brain mechanisms and drugs effect in patients. In parallel, the DEVIN Team (*Development and validation of biomarkers in MRI and in nuclear medicine*, led by Dr P. Péran) develops clinical research projects which mainly concern the development and validation of biomarkers able to show the cognitive decline during normal ageing or different neurological and psychiatric pathologies. Those biomarkers are usable on human in molecular imaging and are entitled to be considered as radiopharmaceutical medication. They are key-elements of research topics developed by ToNIC. Over the last few years ToNIC took advantage of the development of facilities allowing investigating physiopathological mechanisms in molecular imaging on animal and human.

*In the context of the TMBI project, ToNIC will also set up an efficient and innovative tool allowing to develop radiotracers and radiopharmaceuticals available for the entire TMBI community.* This project of "Radiochemical and radiopharmaceutical innovative facilities for new PET imaging probes" (Pi-R<sup>2</sup> project) will also benefit from strong inputs in the field of radiochemistry of the 'Laboratoire de Chimie de Coordination' also member of TMBI.

Three research topics will be developed by ToNIC and partners within the TMBI projects:

**Research topic 1: Development of radiofluorination innovative techniques**, a preliminary step implemented by ToNIC radiopharmacists in partnership with LCC Chemistry and Biology unit (laboratoire de chimie coordination – UPR 8241 CNRS/UPS – led by Pr A. Bousseksou, E. Gras Team). This unit will work on developing new chemical tools using hetero-elements already used in ToNIC, in order to meet the challenges of preclinical and clinical studies.

#### **Research topic 2: Pre-clinical phase.**

Based on the local expertise and relationship in a rich network of clinical and preclinical research in mind and cognition abilities, the I-Dream Team of ToNIC, will develop different translational studies to characterize brain mechanisms (e.g. "*Pharmacological Manipulation of the Noradrenergic System in Memory Reconsolidation: a Translational Treatment Development Study for PTSD*", **Recovery Project**, P. Rouillet/P. Birmes). Together with CerCo (Centre de Recherche Cerveau & Cognition – UMR 5549 CNRS/UPS – led by Dr S. Thorpe) and CREFRE (Centre régional d'Exploration Fonctionnelle et de Ressources Expérimentales – Institut Universitaire du Cancer de Toulouse – US 006 Inserm/UPS – led by Pr Y. Barrera), ToNIC will participate in the validation radiotracers developed on the fluorination platform. Many collaborative projects are under way and others were submitted to national invitations to tender. Among them, the **MarmoCog project** ("*Multimodality approach of the ageing brain pathology in Non-Human Primate*" – Pr Payoux; selected for the first step of call to ANR generic projects) bring together researchers from all mentioned laboratories (ToNIC, CerCo, CREFRE, together with the "Institut de Mathématiques de Toulouse") to develop a non-human primate (NHP) model of the ageing brain pathology. Other projects are led by ToNIC in collaboration with a number of TMBI members (LAAS, CerCo, CREFRE, ENVT) to develop and validate radiotracers allowing marking the metabolic activity of stem cells which are

implanted when using a cellular therapy. (*"Graft of stem cells on nanoprostheses in the brain lesioned rat and marmoset. Follow-up with MRI and PET imaging."* **Innov-in-Stroke Project** – I. Loubinoux; *"3D oriented supramolecular hydrogels for axonal guidance"* **Neuraxe project** – J. Fitreman/I. Loubinoux).

**Research topic 3: Clinical phase.** The provision of innovative and PET-compliant radiopharmaceuticals will allow setting up clinical research projects which will be developed in close interactions between ToNIC, the Toulouse University hospital and the Institute for Neurological, Psychiatric and Sensorial disabilities (CHU de Toulouse), to investigate physiopathological mechanisms from childhood to adulthood, in:

- **Neurology:** Recently, new tools have been developed to assess inflammation in vivo and specifically microglial activation using specific Positron Emission Tomography (PET) radioligands, as well as new methods to assess brain functional and structural integrity using MRI or EEG. Translational clinical research projects that rely on transversal and longitudinal studies or on intervention proof of concept studies are developed in ToNIC in neurodegenerative diseases (*"Does inflammation predict cognitive and functional outcome in cerebral amyloid angiopathy? Cognition, Inflammation & Amyloidopathies"*, **CIA project** – J. Pariente; *"Imaging and modulating brain Amyloid Related Inflammation in patients"*, **ARI/Imaging project** – J. Pariente; *"Effect of the VX-745 on brain Inflammation using PET scan in selected AD patients"*, **VIP project** – J. Pariente; *"Multimodal MRI in patients with parkinsonism for differential diagnosis and disease progression"*, **DOPIANIM Project** – P. Péran/O. Rascol), in patients with severe traumatic brain injury that is responsible of the acute state of unarousable unawareness, named coma (*"Whole brain connectivity changes induced by traumatic coma: combined structural, functional and neuroinflammatory approaches"* - **Coma3D project** – S. Silva; *"EEG high density and connectivity analyses in comatose and post-comatose"*, S. Silva) and in brain-lesioned patients (*"Spasticity post-stroke and drugs"*, P; Marque; *"REsting state MRI CONnectivity in Acute Ischemic stroke : SSRI in Enhancing motor recovery : a placebo controlled study"*, **RECONISE Project**, F. Chollet, I. Loubinoux). Other pathologies are also currently explored in childhood (*"Neurocognitive study of procedural learning and procedural memory in Dyslexia and Developmental Coordination Disorder"*, **DYSTACMAP Project** – Y. Chaix; *"A new treatment with OXYTocin In NeoNates with Prader-Willi syndrome"*, **OXYTINN Project** – M. Tauber/P. Payoux).
- **Psychiatry:** New imaging biomarkers enable tracking neuroinflammation and their relationship with the observed symptoms in psychiatric disorders, such as major depressive episode (*"Cerebral neuroinflammation in major depressive episode : a pilot study"*, **InflaDep project** – PHRCI – A. Yroni) or to explore "in vivo" the physiopathology of neuropsychiatric disorders, such as the glutamatergic system in patients with Tourette's syndrome (*"Exploration of glutamatergic system with PET radiotracer in Gilles de la Tourette patients: pilot study"*, **GlutaTour project** – C. Brefel).

and neuro-oncology: Projects are also developed to explore the impact of radiotherapy on cognitive functions in patients with glioblastoma by the CRCT (Centre de Recherche en Cancérologie de Toulouse – Inserm UMR 1037 CNRS ERL 5294/UPS – Dir. Pr J.-J. Fournié) .

This combined approach provides us a fine-grained description of the mind functioning and brain network dysfunctions. These projects have to be reconsidered in the context of a rich transdisciplinary network in Toulouse : teams involved are supported by the Innovative Radiopharmaceuticals for Oncology and Neurology Laboratory of Excellence (IRON Labex; Coordinator: Payoux, P; [www.labex-iron.com](http://www.labex-iron.com)), the French Clinical Research Infrastructure Network, a national clinical research infrastructure funded by the “Investissement d’Avenir” program to facilitate proof-of-concept trials (F-CRIN, Coordinator: Rascol O, [www.fcrin.org](http://www.fcrin.org)), the NeuroToul Toulouse Centre of Excellence in Neurodegeneration (Coordinator: Rascol O), which is part of the European Network of Centres of Excellence in Neurodegeneration (COEN, [www.coen.org](http://www.coen.org)), binding together teams in clinical research, biology, imaging and methodology of clinical trials, and FHU HoPeS, a “Fédération Hospitalo-Universitaire” dedicated to research into cognitive, psychic and sensorial disabilities (directed by Prs J. Pariente – C. Arbus). These combined elements make these projects not only feasible but also natural in the history of our teams.

It is obvious that an ambitious project such as TMBI is an exceptional opportunity for the development of Tonic in an exceptional scientific environment

Pierre Payoux.

