Kick-off meeting: STROK@LLIANCE

May 10th, 2017 – 11:00 AM – 4:30 PM

MAISON DE LA CHIMIE
28 Rue Saint-Dominique, 75007 Paris

http://congres.maisondelachimie.com/

Launch of STROK@LLIANCE, the new preclinical platform resulting from the alliance of the public Experimental Stroke Research Platform (ESRP) and the well-established CRO ETAP-Lab.

For half a day, neurologists, neuroradiologists, neurosurgeons, researchers, specialists in preclinical and clinical trials, will give you an overview of stroke etiology, current acute management practices and animal modeling. Next, they will discuss with you during a debate: "The transition from preclinical drug to clinical drug for stroke: What are the essential information for clinicians about pharmacology issues?"

More about STROK@LLIANCE

ESRP (Cyrille Orset, Scientific Leader) is the offshoot of the highly-recognized INSERM unit "Physiopathology and Imaging of Neurological Disorders" (PhIND; **Pr. Denis Vivien**, Head of the unit). **ETAP-Lab** (Nicolas Violle, President and CEO) is a well-established CRO, with more than 25 years of market knowledge. The new platform **STROK@LLIANCE** is fully dedicated to preclinical stroke in order to address mechanisms, diagnostics and therapeutics in stroke.

STROK@LLIANCE manages projects for the pharmaceutical industry with high-skilled specialists ensuring expertise and creativity to provide high-level animal studies in a quality-controlled environment. Taking advantage of **CYCERON** facilities (Caen, France), **STROK@LLIANCE** accesses to cutting-edge technologies such as MRI and proposes fine-tuned behavioral studies.

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Program

11:00 AM: Welcome of participants

11:30 AM: Introduction

- **Pr. Denis Vivien and Dr. Nicolas Violle**

Pr. Denis VIVIEN, Ph.D: Professor of Cell Biology, Caen Medical School, Caen-Normandie University – Professor, Caen University Medical Center, Department of Clinical Research - Professor senior, Institut Universitaire de France IUF (2009) - Head UMR-S U1237 "Physiopathology and Imaging of Neurological Disorders" PhIND, INSERM/EFS/Caen-Normandie Univ., GIP CYCERON - Team A leader "tPA and neurovascular disorders", PhIND.

Dr. Nicolas Violle, Ph.D: Chief Excecutive Officer, ETAP-Lab, Vandoeuvre-lès-Nancy, France.

12:15 AM - 1:15 PM: Lunch

1:15 PM – 3:15 PM: Conferences

- **Fernando Pico: "Etiology of stroke"**

Pr. PICO Fernando, M.D. Ph.D: Head of neurology department and stroke center, Versailles Hospital, France - Paris Saclay and Versailles Saint Quentin en Yvelines University - INSERM LVTS (Laboratory for Vascular Translational Science)-1148, Paris, France.

- **Mathieu Zuber: "Acute management in stroke"**

Pr. Mathieu ZUBER, M.D., Ph.D: Head of Neurology dept., Hospital group Paris Saint Joseph, Neurology and Neurovasc. Service – Professor, Paris Descartes University, PhIND Laboratory, INSERM UMR-S 1237 Univ. Caen-Normandie - GIP CYCERON.

- **Thomas Gaberel: "Stroke: the neurosurgeon's point of view"**

Dr. Thomas GABEREL, M.D. Ph.D: Department of Neurosurgery, University Hospital of Caen, Caen, France – PhIND Laboratory, INSERM UMR-S U1237, Normandie University, Caen, France, GIP CYCERON

- **Denis Vivien: "What is the relevance of preclinical stroke trials?"**
- **Michael Mazighi: "Expectation from pre-clinical research: a clinician's perspective"**

Pr. Mikael Mazighi, M.D., Ph.D.: Professor and Hospital Practitioner, Centre de Recherche et de Formation en Pathologies Neurovasculaires, Fondation Ophtalmologique de Rothschild - Laboratory of Vascular Translational Science INSERM U 1148 - DHU NeuroVasc Paris 7 Denis Diderot and Sorbonne Paris Cité University.

3:15 PM - 3:30 PM: Break

3:30 PM - 4:15 PM: Discussions

"The transition from preclinical drug to clinical drug for stroke: what are the essential information for clinicians about pharmacology issues?"

4:15 PM - 4:30 PM: Conclusions

4:30 PM: End

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ETIOLOGY OF STROKE

Pr. Fernando Pico M.D., Ph.D [1, 2, 3]

(1) Head of neurology department and stroke center, Versailles Hospital, France

(2) Paris Saclay and Versailles Saint Quentin en Yvelines University

(3) INSERM LVTS (Laboratory for Vascular Translational Science)-1148, Paris, France.

Stroke is the leading cause of acquired disability, the second cause of dementia, and the third cause of death in Europe. There is two main type of stroke: ischemic stroke (also called brain infarction) usually caused by the occlusion of a cerebral vessel which represent 85 % of all stroke and hemorrhagic stroke due to the rupture of a cerebral vessel (15 % of all stroke).

There is a huge heterogeneity of brain infarction etiology conversely to myocardial infarction for which ruptured atheromatous plaque account for more than 95 % of all case. For brain infarction, 20 % of cases are due to a cardio-embolic source (mainly atrial fibrillation); 25% are caused by atherothrombosis of aorta, cervical or intracranial arteries; 25 % is related to small vessel disease; and 5% are due to unusual causes such as dissection of cervical arteries (which represent the first cause in young patients (< 45 years old). Of note 25% of brain infarction is considered as “cryptogenic” (no known cause) but recently large studies have demonstrated that occult paroxystic atrial fibrillation is detected by invasive or non-invasive long duration cardiac rhythm monitoring in 15% to 30 % of patients with “cryptogenic” stroke. Regarding hemorrhagic stroke, it is now considered that there are always a cause and that the term “idiopathic” or “primary” brain hemorrhage should not be used. In particular, anti-thrombotic drugs such as antiplatelet or anticoagulant can favor brain hemorrhage but should not be consider as the unique cause. The two leading causes in elderly are hypertensive microangiopathy, responsible for deep brain cerebral hemorrhages, whereas amyloid angiopathy produces lobar (i.e. superficial) brain cerebral hemorrhages. The most important other causes are: structural vascular malformations such as cavernoma, arteriovenous malformation and aneurysm; brain tumors (primary or metastasis); traumatisms; cerebral venous thrombosis; infective endocarditis; and hemorrhagic transformation of a brain infarction.

A comprehensive search of stroke etiology is of paramount importance for specific curative and preventive treatments.

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ACUTE MANAGEMENT IN STROKE

Pr. Mathieu Zuber, M.D., Ph.D [1, 2, 3]

(1) Head of Neurology dept., Hospital group Paris Saint Joseph, Neurology and Neurovascular service

(2) Professor, Paris Descartes University

(3) PhIND Laboratory, INSERM UMR-S 1237 Univ. Caen-Normandie - GIP CYCERON

The well-known adage “time is brain” resumes the degree of emergency when stroke occurs.

In ischemic stroke (80% of all patients) due to arterial occlusion, urgent reperfusion is crucial for prognosis. Intravenous tissue plasminogen activator (tPA) within a narrow time window (i.e. <4.5h) has been for a long time the unique treatment. Since 2015, endovascular therapy (thrombectomy) using stent retrievers has been proved to be effective as an adjunctive treatment to intravenous tPA. Making the procedure available for all ischemic stroke patients is a challenging issue for the future. In intracranial haemorrhages, clinical trials recently reported that early intensive blood pressure reduction can be a safe and feasible strategy.

In all stroke patients, rapid admission in a specialized stroke unit is required, for both evaluation and treatment by a trained multi-professional team. Inpatient management includes dysphagia screening, monitoring of vital functions, prophylaxis for venous thromboembolism, prevention of stroke complications, and adequate of antithrombotic prescriptions.

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STROKE: THE NEUROSURGEON'S POINT OF VIEW

Thomas GABEREL, M.D., Ph.D [1, 2]

(1) Department of Neurosurgery, University Hospital of Caen, Caen, France

(2) PhIND Laboratory, INSERM UMR-S U1237, Normandie University, Caen, France – GIP CYCERON

Stroke is often believed to be only ischemic, and exclusively managed by neurologists. However, some subtypes of stroke could require the intervention of a neurosurgeon. First, 15% of stroke cases are hemorrhagic strokes, which include aneurysm and arteriovenous malformation rupture. Hemorrhagic strokes require the intervention of a neurosurgeon in several situations: (1) cerebellar hematoma requiring surgical evacuation; (2) intraventricular hemorrhage requiring the insertion of an external ventricular drainage; (3) aneurysm or arteriovenous malformation rupture, for which exclusion of the malformation are required. Secondly, massive ischemic stroke can require the realization of a decompressive craniectomy, which corresponds to the removal of the skull bone to decompress the brain. The neurosurgeon has an important place in the management of some subtypes of stroke, and the procedures performed have to be improved. It subsequently required the development of preclinical model of these subtypes of stroke, to investigate innovative surgical strategies.

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WHAT IS THE RELEVANCE OF PRECLINICAL STROKE TRIALS?

Pr. Denis VIVIEN, Ph.D [1, 2, 3, 4, 5]

(1) Professor of Cell Biology - Caen Medical School - Caen-Normandie University

(2) Professor - Caen University Medical Center - Department of Clinical Research

(3) Professor senior at Institut Universitaire de France IUF (2009)

(4) Head of PhIND Laboratory, INSERM UMR-S 1237 Univ. Caen-Normandie - GIP CYCERON

(5) Team Leader "tPA and neurovascular disorders" - UMR-S U1237 - GIP CYCERON

Stroke includes ischemic and haemorrhagic cerebral vascular injuries and is one of the main cause of acquired disabilities worldwide, with an increasing incidence due to the population ageing. This last decade, it is true that all the therapeutic strategies validated in experimental stroke models failed in clinic. However, it should be keep in mind that the only treatment approved so far by the authorities, rtPA-induced thrombolysis (Alteplase®), was validated in 1995 in an experimental model of stroke in rabbits by the group of Del Zoppo prior its use in Human. This means, that without this pre-clinical study, no stroke treatment should be available. Also important, these last two years, the possibilities of stroke treatment were significantly improved based on positive clinical trials published, with a clear beneficial effect of the combination of rtPA with endovascular thrombectomy (Mr-Clean). Another very important point is to consider the number of pre-clinical studies demonstrating the absence or the side effects of a putative new treatments. The last point which should be consider is that animal models are not only needed to test new drugs, but they are required to understand the mechanisms of diseases and thus the identification of molecular targets for the development of new therapeutics and diagnostics. In conclusion, especially for acute diseases such as stroke, we need animal models not only to understand the disease and thus identify new targets for drug development but also to invalidate and possibly validate new drug candidates prior translation to clinic. We all agree that we have to improve our strategy and do our best to be more successful. It is why, thanks to STROK@LLIANCE, we created a network dedicated to the design of pre-clinical studies to improve the clinical relevance of experimental studies in animals.

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Expectation from pre-clinical research: a clinician's perspective

Pr. Mikael Mazighi, M.D., Ph.D. [1, 2, 3]

(1) Professor and Hospital Practitioner - Centre de Recherche et de Formation en Pathologies Neurovasculaires - Fondation Ophtalmologique de Rothschild

(2) Laboratory of Vascular Translational Science, INSERM U 1148

(3) DHU NeuroVasc Paris 7 Denis Diderot and Sorbonne Paris Cité University

Acute ischemic stroke therapy has reached a new stage with the thrombectomy era. Pharmacological environment of the endovascular procedure is one of next challenges. In this perspective, evidences from pre-clinical research are needed to define the new therapeutic targets. Identifying the most relevant animal models, developing new biological diagnostic markers and prognostic imaging tools to refine the therapeutic targets are key steps. But first of all, pre-clinical research will bring the new concepts that will change clinical practice of tomorrow for acute ischemic stroke patients.

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