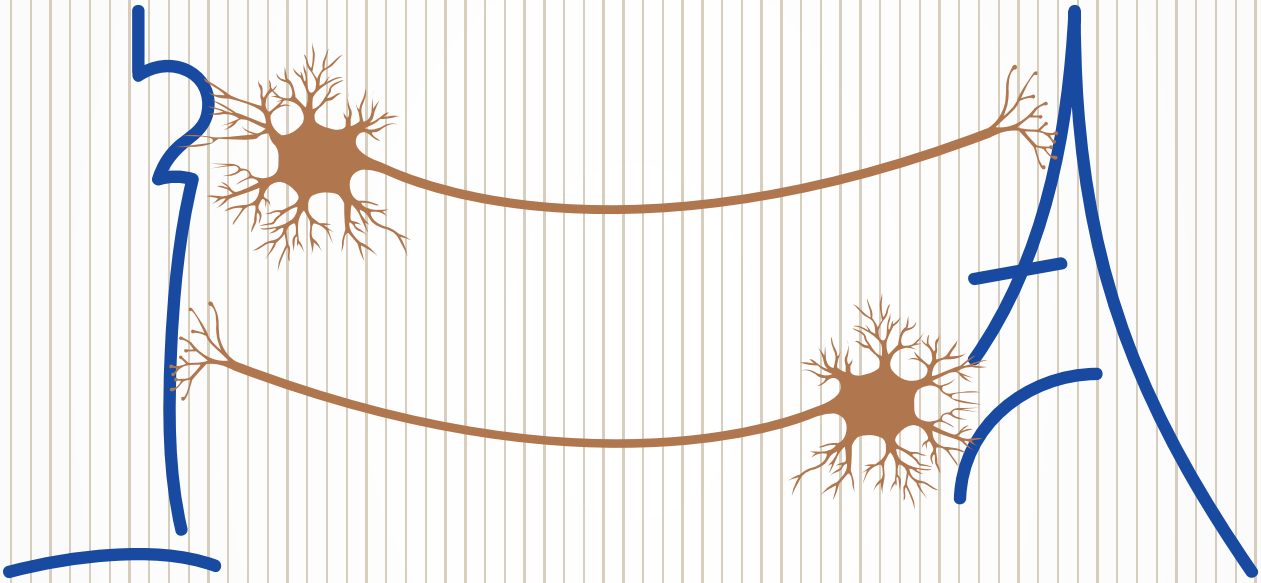
FIOCRUZ

AVIESAN

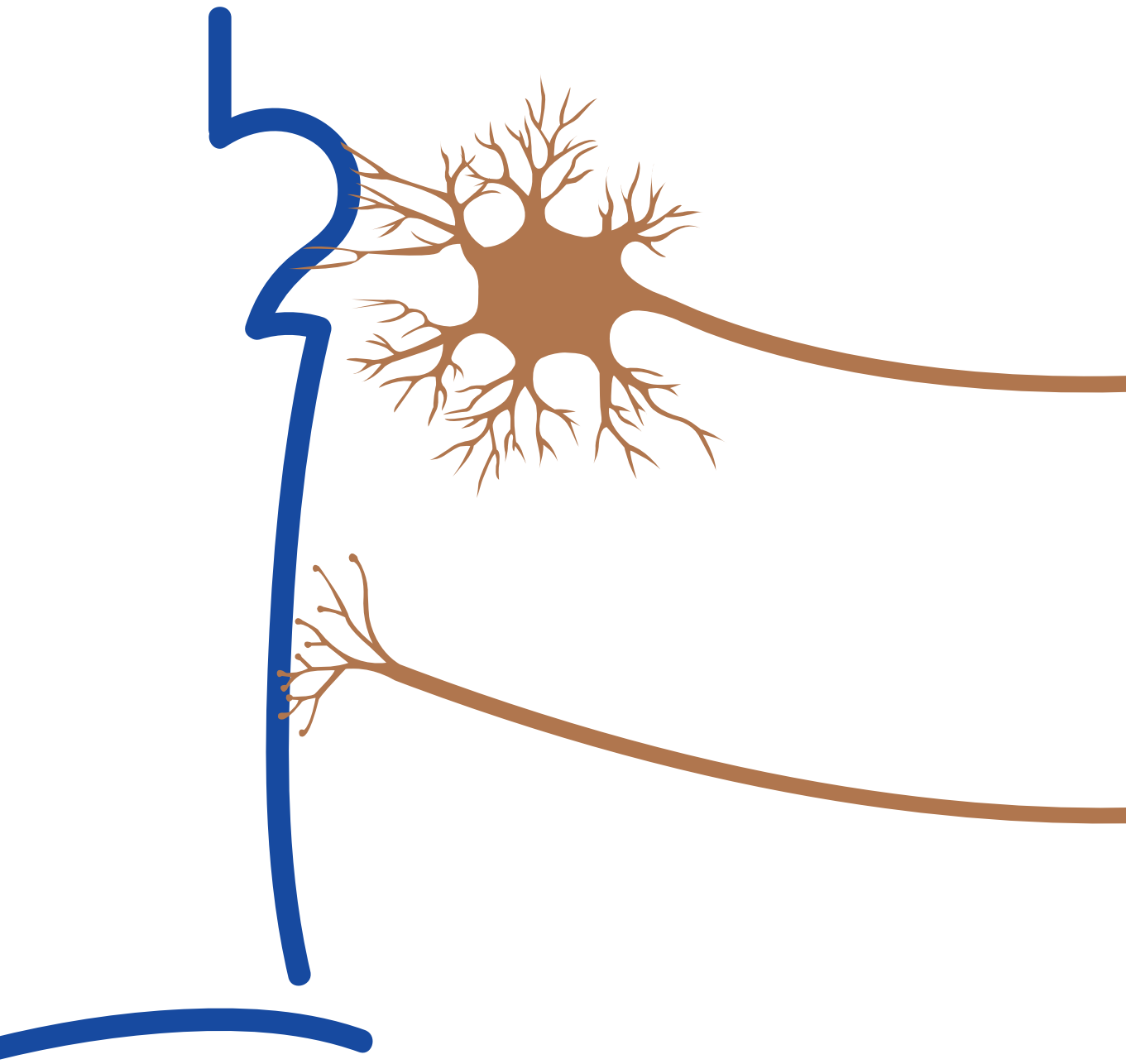


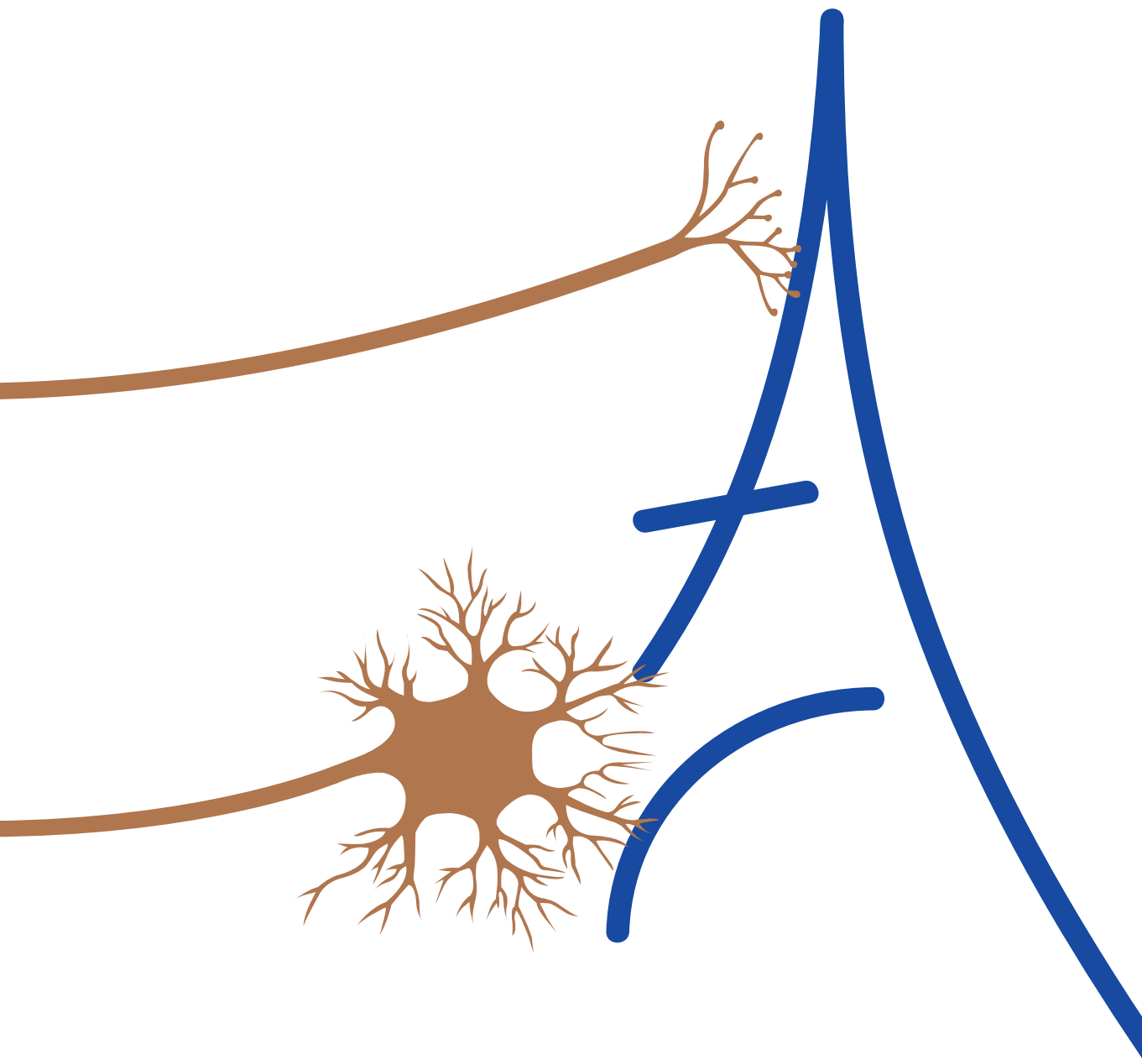
SEMINAR ON NEUROSCIENCE

SEMINÁRIO SOBRE NEUROCIÊNCIA

BRAZIL - FRANCE | BRASIL - FRANÇA

Annals / Caderno de resumos





May 5th, 2014

Venue: Emmanuel Dias Auditorium, Arthur Neiva Building

9:00 | Opening Ceremony

Paulo Gadelha, President of Fiocruz; Rodrigo Stabeli, Fiocruz Vice-President for Research and Reference Laboratories; Paulo Buss, Coordinator of the Fiocruz Center for International Affairs in Health; Brice Roquefeuil, Consul général de France à Rio de Janeiro; Philippe Ahrets, Director of International Affairs, Inserm; Etienne Hirsch, Director of the Multi-Organism Institute of Neuroscience.

10:30 – 12:00 | Session 1: Neuroscience in Brazil and in France: general scenarios

Chairpersons: Sidarta Ribeiro (Brain Institute, Federal University of Rio Grande do Norte, Natal); Vivaldo Moura-Neto (Brain Institute of the State of Rio de Janeiro)

Speakers: Etienne Hirsch (CNRS/Inserm/UPMC); Cecília Hedin-Pereira (President of the Brazilian Society of Neurosciences and Behavior); Wilson Savino (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

13:30 – 15:30 | Session 2: Neurodegenerative Diseases

Chairpersons: Roland Liblau (Inserm/UPS/CNRS/CHU Toulouse); Wilson Savino (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Speakers:
Neurodegenerative disorders a challenge for the society: Where do we stand for Alzheimer's disease?
Frédéric Checler (IPMC/CNRS/Inserm, Valbonne)

Possible role of calcium-calmodulin signaling in psychiatric disorder
Frederico R. Ferreira (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Gene signatures and functional genomics in infectious and neurodegenerative diseases
Milton O. Moraes (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Translational research in biotherapies of the central nervous system: addressing the needs for a better integration between basic and clinical science
Philippe Hantraye (CEA/CNRS, Gif sur Yvette part Fontenay aux Roses)

16:00 – 18:00 | Session 3: Neuroimmunology and Neuroinflammation

Chairpersons: Ricardo Godoy (Fiocruz-Rondônia, Porto Velho); Fabrice Chrétien (Institut Pasteur, Inserm, CNRS, Paris)

Speakers:
Glial reaction and neuroinflammatory processes in Parkinson disease
Etienne Hirsch (CNRS/Inserm/UPMC, Paris)

The effects of neurotrophins and neuropeptides on HIV-1 replication in human primary macrophages
Dumith Chequer Bou-Habib (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Neurology, neurophysiology and neuroimmunology of autism
Leonardo de Azevedo (Fernandes Figueira National Institute of Mother, Child and Adolescents Health, Fiocruz, Rio de Janeiro)

Neurons as targets for T cells in the nervous system
Roland Liblau (Inserm/UPS/CNRS/CHU Toulouse)

May 6th, 2014

Venue: Emmanuel Dias Auditorium, Arthur Neiva Building

9:00 – 12:00 | Session 4: Infectious and non-infectious environment

Chairpersons: Claudio Tadeu Daniel-Ribeiro (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro); Manoel Barral Neto (Gonçalo Muniz Institute, Fiocruz-Bahia, Salvador)

Speakers:
Sepsis induced brain dysfunction (SiBD): the role of microglia
Fernando Bozza (Evandro Chagas National Institute of Infectology, Fiocruz, Rio de Janeiro); Fabrice Chrétien (Institut Pasteur, Inserm, CNRS, Paris)

Cerebrovascular dysfunction in experimental cerebral malaria
Leonardo Moura Carvalho (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Changes of cognition in cerebral malaria
Hugo Caire de Castro Faria Neto (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro)

Overview of the infectious disorders affecting the brain in the French territories including French Caribbean
Annie Lannuzel (CHU, Pointe à Pître, Guadalupe)

14:00 – 17:00 | Session 5: Stem Cells and therapeutic approaches for neurological/ neuromuscular diseases

Chairpersons: Gillian Butler-Browne (Myology Research Center, UPMC, Inserm, CNRS, Paris); Samuel Goldenberg (Carlos Chagas Institute, Fiocruz-Paraná, Curitiba)

Speakers:
Adult neurogenesis: a new chapter in memory
Nora Abrous (Inserm, Institut Magendie, Bordeaux)

Cell therapy in neuromuscular diseases
Ingo Riederer (Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro); Vincent Mouly (Myology Research Center, UPMC, Inserm, CNRS, Paris)

Stem cells, iPS and their use to understand neurological disorders
Delphine Bohl (Institut Pasteur, Paris)

Human pluripotent stem cells: their application for drug Discovery
Cécile Martinat (Inserm/UEVE, I-STEM, AFM, Evry)

17:00 | Closing Ceremony

Etienne C. Hirsch
Institut du cerveau et de la moelle épinière, INSERM UMR1127, CNRS UMR 7225, UPMC, Hôpital de la Salpêtrière, 75013 Paris, France

Etienne Hirsch is a neurobiologist involved in research on Parkinson's disease and related disorders. He obtained his PhD in 1988 from the University of Paris VI (Pierre et Marie Curie). He is currently the director of the French Institute for Neurosciences, Cognitive sciences, Neurology and Psychiatry, the associate director of CRICM, head of "Experimental therapeutics of Neurodegeneration" at the CRICM at Pitié-Salpêtrière hospital in Paris and councilor for Neuroscience, Neurology and Psychiatry at the French Ministry for higher education and research. His work is aimed at understanding the cause of neuronal degeneration in Parkinson's disease and is focused on the role of the glial cells, the inflammatory cytokines and apoptosis but also on the consequences of neuronal degeneration in the circuitries downstream to the lesions. He is member of several advisory boards including, French Society for Neuroscience (past-President), Scientific Advisory board at INSERM. He obtained several prizes including Tourette Syndrome Association Award in1986, Young researcher Award, European Society for Neurochemistry in 1990, Grand Prix de l'Académie de Sciences, Prix de la Fondation pour la recherche biomédicale « Prix François Lhermitte » in 1999, Chevalier de l'ordre des palmes académiques in 2009, Prix Raymond et Aimée Mande of the French National academy of Medicine in 2011, Member of the French National Academy of Pharmacy in 2011. He is author of more than 200 peer reviewed articles.

Glial reaction and neuroinflammatory processes in Parkinson disease

Both epidemiological and genetic studies support a role of neuroinflammation in the pathophysiology of Parkinson's disease (PD). Indeed, both prospective and retrospective epidemiological studies indicate that the long term use of anti-inflammatory drugs and especially ibuprofen reduces the risk od developing Parkinson's disease. On the other hand genome wide analysis also indicate that one haplotype the immune related gene HLRdr is associated with a higher risk to develop the disease. Furthermore, post mortem studies confirm the involvement of innate as well as adaptive immunity in the affected brain regions in patients with PD. Indeed, activated microglial cells and T lymphocytes have been detected in the substantia nigra of patients concomitantly with an increased expression of pro-inflammatory mediators. Preclinical investigations conducted in various animal models of PD indicate that inflammatory processes are instrumental in neuronal cell death even though they are unlikely to be a primary cause for neuronal loss. Neuroinflammatory processes in PD are rather involved in self-perpetuating deleterious events that lead to protracted neuronal degeneration. In line with this, recent data indicate that glucocorticoid receptors are important in curtailing microglial reactivity, and deregulation in their activity in PD could lead to sustained inflammation-mediated degeneration. Altogether, neuroinflammatory processes might represent a target for neuroprotection in PD.

Frédéric Checler
IPMC, UMR7275 CNRS-UNS

Frédéric Checler received his PhD in Cellular and Molecular Pharmacology from University of Nice-Sophia-Antipolis (1983). His honors include: Top 1% researcher in the world "Biology and Biochemistry" (ISI WOK field of ranking at the end of 2011); the BioMerieux award (1997); 1999 MHRI Kearney Fellow Award, Mental Health Research Institute; the Charles-Louis de Saulces de Freycinet Award, French National Academy of Science (2002); the Grand Prix Jaffé of the French Academy of Sciences (2013); Medal of the Departmental council; Medal of the University of Nice-Sophia Antipolis (2013). He has been recently elected « foreign corresponding member of the Brazilian Academy of Sciences ». He published over 250 articles in international journals, books, monographs, editorials, and reviews. He also attended 213 Invitations in International meetings and 96 invited seminars. Dr. Checler was President of the scientific committee of the European League against Alzheimer's disease (LECMA, 2005-2010), and has been a Member of the steering committee of the French Alzheimer plan launched by President N. Sarkozy. He has been Chief Editor or editor of J. Neurochem and currently European Editor of Current Alzheimer Research and senior editor of Scientific Reports. He formerly or still belongs to the J. Biol. Chem.; Journal of Alzheimer disease: American Journal of Neurodegenerative Disease editorial boards. He supervised 63 Masters, Doctoral, and Post-doctoral students.

Neurodegenerative disorders a challenge for the society: Where do we stand for Alzheimer's disease?

With the expansion of mean lifetime in occidental countries, age-related disorders have become, besides cancers, one of the major causes of death. These neurodegenerative diseases are not only devastating public health problems but appear as major societal and economical burdens.
This communication will first review the dramatic figures of several of these neurodegenerative disorders and will underline the important economical efforts recently launched to circumscribe them. Several fundamental advances recently delineated for some of them, with special emphasis on Alzheimer's disease, will also be described and their prospective will be discussed. Clearly, both fundamental and clinical approaches have led to significant advances in the understanding of molecular dysfunctions taking place in these diseases. This should be reinforced by the development of international collaborations and networks that are clearly necessary to fight these neurological disorders.

Frederico Ferreira

Laboratory on Thymus Research, Oswaldo Cruz Institute, Fiocruz

Researcher Frederico Ferreira is graduated in Biological Science at Federal University of Uberlandia, 2000, and has MSc degree in Genetic and Biochemistry by the same University. He joined to the Psychopharmacology Laboratory at Medical School of Ribeirão Preto for PhD. His project was aimed to investigate molecular targets involved on neurobiology of depressive disorder, and pharmacological treatment. Frederico has post-doc training at The Salk Institute for Biological Science in Molecular Neuroscience, CA, EUA, and in Molecular Neurophysiology at The Saarland University, ZA, ALE. PhD. Ferreira moved to Oswaldo Cruz Institute (IOC) as assistant researcher since 2013, working on the Thymus Research Laboratory.

Possible role of Calcium-calmodulin signaling in psychiatric disorder

Major depressive disorder (MDD) is one the most severe and a disabling psychiatry illness. Its neurobiology, however, is not completely understood. Imipramine is a prototypic antidepressant drug that acts primarily by inhibiting serotonin and noradrenalin reuptake. How this mechanism is translated in its therapeutic effects, however, is still unknown. Chronic imipramine treatment increases mRNA expression of calmodulin 1 (CaM1) in rat hippocampus, and polymorphisms on genes of the CaM1/Calmodulin-dependent protein kinase (CaMK) signaling pathway are associated with susceptibility to MDD and resistance to tricyclic antidepressant treatment. Thus, restoring intracellular Ca2+-CaM1 homeostasis could be involved in the beneficial effects of this drug. Therefore, the present talk will present selected data supporting the evidence that intracellular calcium homeostasis could be involved in the effects of antidepressants drugs such as imipramine.

Milton Ozório Moraes
Hansen's Disease Laboratory, Oswaldo Cruz Institute, Fiocruz

Milton Ozório Moraes graduated in biological sciences from the Federal University of Rio de Janeiro (UFRJ), earned a master's degree also in biological sciences (biophysics) from the same institution and a Ph.D. in cellular and molecular biology from the Oswaldo Cruz Foundation (Fiocruz) and has been formally trained in molecular biology and immunology since undergraduation in Biology. Dr. Moraes's research interests are focused on the human immune response to mycobacteria or other intracellular pathogens (Leishmania, T.cruzi) as well as the genetic determinants of these immunological responses. He has been collaborating with researchers in Brazil to study aspects of infection that could lead to new diagnostic or prognostic methods and could understand the pathophysiology of these diseases. He has developed a molecular method to leprosy diagnosis that is routinely used in Referral Centers in Brazil. Also, other technical procedures are set up in his lab ranging global gene expression, high- medium throughput genotyping, genotype-phenotype studies are searching for biomarkers. He has been interacting with partners in Mozambique, India, Canada, France, Netherlands and USA, being part of a network to study the genetic basis of the immune responses in leprosy and tuberculosis among other projects. Dr. Moraes has been supervising Masters, Ph.D. students and pos-docs from Brazil and other countries in South America and Africa. He currently works at Fundação Oswaldo Cruz (Fiocruz) as tenure researcher, where he has a position of Assistant Dean of Graduate programs, leads a research group for functional genomics and genetic epidemiology and also manages a gene expression facility. Milton also teachs molecular biology at State University of Rio de Janeiro.

Gene signatures and functional genomics in infectious and neurodegenerative diseases

Genomic analyses have been pinpointing several pathways, genes and specific polymorphisms as associated with different diseases. An overall analysis of these data indicates that same pathways are used for infectious and other chronic diseases. Genetic and molecular studies in mycobacterial diseases indicate that particular SNPs are associated with certain diseases and an improvement in the genotype-phenotype correlation is assisting the production of a road map of the pathological responses.

Philippe Hantraye

Molecular Imaging Research Center MIRCen, Life Science Division of the CEA, Fontenay-aux-Roses

Philippe Hantraye, Beside my doctoral fellowship held from 1984 to 1987 in the Laboratoire de Physiologie Nerveuse, CNRS, Gif /Yvette (Dir. Robert Naquet) and the Service Hospitalier Frédéric Joliot, CEA, Orsay. (Dir. Pr. André Syrota), I held sequentially various positions including a post-doctoral fellowship (1986-1987) in the Laboratory of Medical Cell Research, University of Lund, Sweden (Dir. Pr. Anders Björklund), a visiting fellowship in Neurobiology (1990-1992) at Harvard University (Neuroregeneration Laboratory Boston and Southborough Primate Center , Massachusetts, USA. Dir: Drs. Ole Isacson & Roger Spealman), and a visiting fellowship (1993-1994) in the CNRS URA 1414 unit (Ecole Normale Supérieure, Paris. Dir. Dr. Alain Prochiantz). From December 2000, I have been in charge of two research units located at Service Hospitalier Frédéric Joliot (Orsay). The CNRS URA CEA CNRS 2210 unit (Neurodegenerative diseases) and the Isotopic Imaging, Biochemistry and Pharmacology Unit, a research laboratory of the CEA/SHFJ involved in the development of medical imaging (PET, MR Imaging, MR Spectroscopy). From January 2004, I am the director of the Molecular imaging research center (MIRCen), a 8500 m2 preclinical integrated center belonging to the CEA, developed in joint venture with the French National Medical Research Council INSERM and dedicated to the design, testing and validation of drug, cell and gene-based therapies for neurodegenerative disorders, cardiac, hepatic and infectious diseases.

Translational research in biotherapies of the central nervous system: addressing the needs for a better integration between basic and clinical science

Translational Neuroscience provides a closer interaction between basic and clinical neuroscientists to expand understanding of brain structure, function and disease, and translate this knowledge into clinical applications and novel therapies against neurodegenerative diseases like Parkinson, Huntington or Alzheimer's disease. In comparison with more classical therapeutic strategies such as drug-based approaches, gene therapies and cell grafting procedures are among the most challenging to develop and validate for a clinical translation. Particular issues associated with the development of gene- and cell-based therapies include the choice of the viral vector or the cell type to be administered, the GMP production of those therapeutic agents, the determination of the number and location of the injection sites requested to achieve therapeutic efficacy in the patients, as well as specific observations demonstrating the safety and stability of the gene expression and/ or cell- differentiation in the long-term. Examples of such translational research developments for Parkinson's and Huntington's diseases will be given to illustrate the main achievements and the specific requirements of these translational research projects, both at the preclinical and clinical levels.

Dumith Chequer Bou-Habib
Laboratory on Thymus Research, Oswaldo Cruz Institute, Fiocruz

Education/training: Medicine, Federal University of Espírito Santo, Brazil; 1976. Master of Science, Federal University of Rio de Janeiro, Brazil; 1981. Doctor of Science, Federal University of Rio de Janeiro, Brazil, 1991. Postdoctoral, Center for Biological Evaluation and Research, Bethesda, MD, US-FDA, 1995. Line of research: Immunopathogenesis of HIV-1 infection, with emphasis on endogenous and exogenous factors that modulate the HIV-1 replication in human peripheral cells, such as cytokines, neuropeptídes, ligands of toll-like receptors and co-pathogens.

The effects of neurotrophins and neuropeptides on HIV-1 replication in human primary macrophages

The human immunodeficiency virus type 1 (HIV-1), the causal agent of acquired immunodeficiency syndrome (AIDS), infects immune cells, and its replication is modulated by a number of endogenous factors that interact with HIV-1-infected cells. The nerve growth factor (NGF) and other neurotrophins, and the neuropeptides vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) can also affect HIV-1 virus particle production upon binding to their receptors on the membranes of infected cells. These molecules exert opposite effects on HIV-1 replication, as NGF and other neurotrophins enhance and VIP and PACAP reduce viral production in HIV-1-infected human primary macrophages. In this seminar, we will present the main effects of these two groups of mediators on the HIV-1 replicative cycle, as well as the mechanisms that underlie their abilities to modulate HIV-1 production in infected immune cells.

Leonardo C. de Azevedo

Research Assistant at Maternal-Child Hospital - Department of Pediatrics – Neurology Division – IFF – Fiocruz

Universidade Federal Fluminense – RJ - Brazil, M.D., 1968, Medicine. Hospital dos Servidores do Estado - RJ, 1969-70, Residency in Pediatrics. University of Pennsylvania – Philadelphia - USA, Fellowship, 1973-75, Pediatric Neurology. Federal University of Rio de Janeiro, M.sC., 1987, Pediatrics. Federal University of Rio de Janeiro (UFRJ), Ph.D., 2000, Morphological Sciences (Neurobiology/Neuroscience). Positions and Employment: 1978-1986, Instructor in the Pediatric Residency Program (Neurology) and Head of Pediatric Neurology Division (Department of Pediatrics - Children's Hospital - UFRJ). 1987-2012, Instructor in the Pediatric Neurology Residency Program and Head of Pediatric Neurology Division (Department of Pediatrics – Maternal-Child Hospital – Fiocruz - Ministry of Health). 1987-1995, Assistant Professor at Children's Hospital - UFRJ. 1996-2014, Associate Professor at Children's Hospital - UFRJ. 2012-2014, Research Assistant at Neurology Division and Laboratory of Neurobiology and Clinical Neurophysiology – Department of Pediatrics – Maternal-Child Hospital – IFF - Fiocruz – Ministry of Health.

Neurology, Neurophysiology and Neuroimmunology of Autism

In autistic children with intact intellectual and verbal functions, the main findings were: allergic inflammation detected by high serum IgE levels and cutaneous tests; possible involvement of CD38 receptor in the regulation of oxytocin secretion and complex social behavior; incapacity to process idiomatic expressions identified via EEG and ERPs; and reduced right hemisphere activation, latent hyperconnectivity in the left hemisphere and reduced interhemispheric interaction revealed by resonance-like EEG responses to the rhythmic photic stimulation.

Roland Liblau
Inserm/UPS/CNRS/CHU Toulouse

MD, PhD. Education: 1990: Medical Doctor degree and Medical Thesis, Paris.1991: Certification, Neurology Specialty Board. 1995: PhD, in Immunology, Paris. Medical Activity: 1983-1989: Residency program in Neurology, Paris. 1994-2001: Head of the CSF analysis Laboratory, Salpêtrière Hospital, Paris. Since 2001: Professor of Clinical Immunology, Toulouse. Research Activity: 1989-1991: PhD student, Pasteur Institute (Dr M.A. Bach). 1991-1994: Post-doctoral position with Pr H. McDevitt, Stanford University, USA. 1996-2002: Head of the Neuro-Immunology Research Team, INSERM CJF97-11 then INSERM U546, Paris. Since 2003: Head of the Autoimmunity and Immunoregulation Research Team, INSERM U563, Toulouse. Since 2007: Chairman of the Department of Immunology and Infectious Diseases, INSERM U563. Since 2011: Director of the Pathophysiology Research Center of Toulouse Purpan (CPTP-INSERM U1043-CNRS U5282).

Neurons as targets for T cells in the nervous system

The CNS is confronted to a double challenge regarding its interactions with the immune system. On the one hand it should allow the immune system to fight invading pathogens and on the other it should prevent inflammatory damage given its vital functions and poorly regenerative capacity. A series of mechanisms, collectively referred to as 'immune privilege', ensures that immune reactions are kept minimal within the CNS. However, activated T cells readily penetrate the CNS parenchyma in numerous inflammatory, infectious or degenerative neurological diseases. The consequence for CNS neurons of their encounter with activated T cells is a question that we have addressed recently using experimental rodent models. I will present our efforts to understand how cytotoxic CD8 T cells and helper CD4 T cells can target neuronal antigens and thereby contribute to CNS tissue damage. Intriguingly, some autoreactive T cells recognize several autoantigens but the functional significance of such 'cross-reactivity' is not fully understood. We have identified, in mice, autoreactive CD4 T cells recognizing both MOG and NF-M and have investigated their pathogenic contribution using animals deficient for one or the other self-antigens. Shedding light on the mechanisms by which T cells promote CNS tissue damage may allow the design of more refined therapeutic strategies for immune-mediated neurological diseases, including multiple sclerosis.

Fabrice Chrétien

Institut Pasteur, Inserm, CNRS, Paris

MD, PhD. Histology and Neuropathology Professor in Paris Descartes University. Neuropathologist specialist in post mortem neuropathology and pathology of brain tumors. Head of Neuropathology department (Saint-Anne Hospital, Paris). Head of the Histopathology and Animal models Unit in Institut Pasteur Paris, a research unit working on experimental neuropathology and more specifically central nervous system and muscle injury as well as mechanisms of tissue regeneration. F. Chrétien coordinates a task force for the study of neurological consequences of sepsis (in human and in animal models) that associates both scientists and clinicians: neurologists, neurosurgeons and intensivists expert in the field of sepsis and septic associated encephalopathy. Since more than two years they are associated with FioCruz and Pr Fernando Bozza. Since January 2014, F. Chrétien is partner of the national F-CRIN network of excellence TRIGGERSEP that support experimental studies and clinical trials on innovative therapeutic targets in sepsis.

Sepsis induced brain dysfunction (SiBD): the role of microglia

Sepsis induced brain dysfunction (SiBD) is a major public health problem as it affects 500 000 patients/year in Europe and is associated with high mortality and long-term psycho-cognitive dysfunctions. SiBD is considered to result from a neuroinflammatory process, whose mechanisms are still not elucidated. In addition to astrocytes, microglia is a key element of neuroinflammation. When activated, microglial cells undergo morphological changes and become pro-inflammatory cells releasing mediators that are known to be neurotoxic. Pro-inflammatory mediators are also able to promote astrogliosis or endothelial activation and damage the BBB. Our experimental studies in a canonical mouse model, using genetically engineered mice, show that microglial cells undergo morphological and functional changes very early after sepsis induction leading to mitochondrial dysfunction and oxidative stress.

Fernando Augusto Bozza
National Institute of Infectious Disease (INI-IPEC), Fiocruz

Senior Scientist actively involved in basic and clinical research studies. Head of Critical Care Lab. of the National Institute of Infectious Disease (INI-IPEC), FIOCRUZ and Head of the Lab of Inflammation and Metabolism, National Institute of Science and Technology for Structural Biology and Bioimaging – INBEB. Chairperson of Brazilian Research in Intensive Care Network (www.bricnet.org). My research interest is focused on the host immune response and metabolic adaptation to severe infections. I've been working on the mechanisms involved in the propagation of the inflammatory response in brain associated to severe infections and its relation to cognitive decline.

Neuroinflammation is emerging as the central mechanism in the pathogenesis of many neurodegenerative diseases, including Alzheimer's disease (AD), multiple sclerosis, HIV, and prion disease. There has been a growing interest by the scientific community on the impact of systemic inflammation on the development of acute and chronic brain damage. Systemic inflammation or infection worsens outcome of neurological disease in humans and in animals. Sepsis, defined as the systemic inflammatory response to infection, results frequently in neurological disorders ranging from confusion to coma and death. Also, sepsis can produce endothelial activation, blood brain barrier breakdown, cerebral edema, and release of endogenous danger signals and inflammatory mediators by the brain. The mechanisms responsible for altered mental status during systemic inflammation are not well understood. As a central hypothesis of the work we believe that systemic inflammation may determine acute brain damage, often characterized by acute brain dysfunction (delirium), modifications of the BBB, metabolic and phenotypic changes in brain tissue, which can lead to transient or permanent cognitive decline. Sepsis is actually a major public health problem in high and middle-low income countries. We will present here a panel of experimental and clinical evidences about mechanism and consequences of severe infections in acute and long term brain functions.

Leonardo José de Moura Carvalho
Malaria Research Laboratory, Oswaldo Cruz Institute, Fiocruz

Graduation: Pharmacy-Biochemistry, Universidade Federal de Juiz de Fora (1990). PhD: Immunology, IOC-Fiocruz (2000). Researcher, IOC-Fiocruz. Associate Professor, La Jolla Bioengineering Institute, San Diego-USA. Academic Editor, PLoS One ; Member: ASTMH, Braz. Soc. Protozool., PTHE and NIGMS Study Sections (NIH-USA). Selected publications: Ong et al., PLoS Pathog. 2013 9(6):e1003444. Orjuela-Sanchez et al., Antimicrob Agents Chemother. 2013 57(11):5462-71. Cabrales et al., Am J Pathol, 2010 176(3):1306-15. Inventions: US Patent Application 2011/0077258 A1. Italian Patent Application 2013/TO2013A000283. Funding NIH R01-AI082610.

Cerebrovascular dysfunction in experimental cerebral malaria

In experimental cerebral malaria (ECM), vascular occlusion, constriction and low nitric oxide bioavailability result in reduced cerebral perfusion and oxygenation. Intravital microscopy of the pial microcirculation revealed impaired arteriolar responses to Acetylcholine and NMDA. Vasoconstriction was reversed with L-arginine, BH4 or glyceryl-trinitrate. Vascular dysfunction is a target for ECM treatment.

Hugo Caire de Castro Faria Neto
Immunopharmacology Laboratory, Oswaldo Cruz Institute, Fiocruz

Universidade Estadual do Rio de Janeiro, Rio de Janeiro, Brazil, M.D., 1988, Medicine. Instituto Oswaldo Cruz, Molecular and Cellular Biology Program, Ph.D., 1992, Pharmacology. University of Utah, Program in Human Molecular Biology and Genetics, PostDoctoral Training, 1994-1995, Molecular Biology. Positions and Honors: Assistant Scientist, Department of Physiology and Pharmacodynamics, Fiocruz, (1992-1994). Postdoctoral Fellow, Program in Human Molecular Biology and Genetics, University of Utah, (1994-1995). Internship Physician, General Clinics, Hospital Universitario Pedro Ernesto, (1998). Member for the Scientific Advisory Committee at the Oswaldo Cruz Institute, Fiocruz, (1997-2001). Associated Scientist, National Council for Scientific and Technological Development (CNPq) - level 1A, (1996). Senior Scientist, Department of Physiology and Pharmacodynamics, Fiocruz, (2004). Head, Laboratory of Immunopharmacology, Department of Physiology and Pharmacodynamics, Fiocruz, (2004). Chairman for the Animal Welfare Committee at the Oswaldo Cruz Foundation, (2003-2006). Professor of Pharmacology, Estacio de Sa University, (2006). Vice-Director of Research, Technological Development and Innovation at the Instituto Oswaldo Cruz, Fiocruz, (2013). Other Experience and Professional Memberships: Consulter ad-hoc (referee) for the financial agencies FAPERJ, FAPESP and CNPq. Committee Member of The Institutional Program of Scientific Initiation Fellowships (Brazil). Board of the PhD program in Cell and Molecular Biology, Fundacao Oswaldo Cruz. Member of the Institutional Research Board, Fundacao Oswaldo Cruz. Member of the Board for the Intensive Care Society of Rio de Janeiro Editorial Board member for SHOCK journal.

Changes of cognition in cerebral malaria

Cerebral malaria (CM) is the most severe manifestation of Plasmodium falciparum infection in children and non-immune adults. Previous work has detected a persistent cognitive impairment in children who survived an episode of CM that was mimicked in animal models of the disease. Potential therapeutic interventions to this condition have not been investigated and are urgently needed. HMG-CoA reductase inhibitors (statins) have been widely prescribed for the treatment of cardiovascular diseases. In addition to its effect on the inhibition of cholesterol synthesis, statins have been associated with pleiotropic immunomodulatory effects. We will show results about the effect of lovastatin during experimental cerebral malaria and its therapeutic effect on cognitive impairment. Six days after infection with Plasmodium berghei ANKA (PbA) mice displayed clear signs of CM and were treated with lovastatin. Intravital examination of pial vessels of infected animals showed a decrease in functional capillary density and an increase in the rolling and adhesion of leukocytes to the endothelium that were reversed by treatment with lovastatin. Brain levels of MDA, IL-1β, TNF-α, MCP-1 and IL-12 levels were also increased in PbA-infected mice, but reduced to non-infected control levels after treatment with lovastatin. In addition, oedema and ICAM-1 expression were reduced in brains of lovastatin-treated PbA-infected mice. Fifteen days post-infection cognitive dysfunction was detected by different memory and cognition tests in animals rescued from CM by chloroquine treatment, but cognitive dysfunction was absent in animals treated with lovastatin-chloroquine combination. In summary, lovastatin treatment prevents neuro-inflammation and blood brain barrier dysfunction in animals with CM, effects that were associated with prevention of the cognitive sequel in animals rescued by antimalarial treatment.

Annie Lannuzel

CHU, Pointe à Pitre, Guadalupe; INSERM U1127 – ICM paris, France

MD, PhD, studied Neurology and Neurosciences in Besançon and Paris (France). After a PhD on the neurotoxicity of HIV, she joined in 1997, as an assistant, the University Hospital of Pointe à Pitre in Guadeloupe (French.West.Indies). She is currently, head of the department of Neurology; teacher at the University Antilles-Guyane and affiliated to the Brain and Spinal Cord institute (ICM) in Paris (Inserm, CNRS, UM 75, U1127). Her research activities are mainly focused on atypical parkinsonian syndromes unusually frequent in Guadeloupe. Her work has shown that atypical forms of Parkinson observed in Guadeloupe are tauopathies and constitute a new subtype of PSP. Experimental work supported the hypothesis that the abnormally high frequency of atypical parkinsonian syndromes in Guadeloupe could be related to consumption of fruits and plants of the Annonaceae family. Her current projects include the clinical and epidemiological characteristics of ALS in the F.W.I.. Studies on atypical parkinsonism are extended to neighboring Islands. A new animal model of intranasal administration of annonacin is under development in collaboration with Prediger RD (Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis, Brazil).

Overview of the infectious disorders affecting the brain in the French territories including French Caribbean

Most viral infections and some bacterial infections can result in acute encephalitis or myelitis. Infectious encephalitis is mainly caused by viruses with herpes simplex virus (HSV) being the most frequently isolated (42% of cases) in France followed by Varicella-Zoster Virus (15%), Mycobacterium tuberculosis (15%), and Listeria monocytogenes (10%). Arboviral infection (dengue and chikungunya) causing encephalitis, myelitis and stroke have recently emerged or reemerged in the French West Indies and Reunion Island. Bacteria, especially mycoplasma pneumoniae and leptospira, fungi and parasites are also potential etiological agents for acute encephalitis. Neurological manifestations of retrovirus infection have decreased in France with follow-up of HIV-infected patients and anti-retroviral therapy. However, neurological manifestations of HTLV, in particular myelopathy/tropical spastic paraparesis (HAM/TSP), remain a public health issue in the French West Indies.

Nora Abrous; Montaron MF; Tronel S; Koehl M
Inserm, Institut Magendi, Bordeaux

Dr Nora Abrous is Head of the Neurogenesis and Pathophysiology team at the Neurocenter Magendie in Bordeaux, France. She obtained a PhD in Neuroscience at the University of Bordeaux (1990) and, following two years of postdoctoral work in the University of Cambridge, UK, she obtained a tenure track at the Institut National de la Santé et de la Recherche Médicale (Inserm). Abrous's early primary research interest was the study of neuronal plasticity in the context of grafting embryonic dopaminergic neurones in animal models of Parkinson's disease. She then studied the adult brain's ability to create new neurons, with a particular focus on the role of adult-born neurones in memory processing and in the appearance of age-related memory disorders. Dr Abrous is currently managing a dozen of persons. She is the Principal Investigator of several ANR grants, one of them labelised by the "Fondation Plan Alzheimer". In 2011, Dr Abrous was awared a "Prime d'excellence" by INSERM.

Adult neurogenesis: a new chapter in memory

The discovery of a continuous renewal of neurons in adult mammalian brains, in particular in the adult hippocampus, has been a breakthrough in the field of plasticity and memory, as it has introduced a new actor that could sustain memory processes. Here I will review our current knowledge on the role of these adult hippocampal new neurons in memory. In particular I will provide evidence showing that adult-born neurons are required for learning and memory processes, such as building allocentric space representations and performing spatial pattern separation. In addition I will highlight that an alteration of the production of new neurons during aging or after early life insults leads to memory impairments and that these effects can be reversed by either behavioral or pharmacological manipulations. I will also show that learning exerts a complex influence on the development of the new neurons and that this "epigenetic" specification is long lasting, depend upon the level of cognitive demand and upon NMDA receptors. An alteration of these learning-evoked responses determine the learning abilities of the animals both when young adult or senescent. Taken together, these data highlight the importance of this unique form of plasticity in forming memories and open new avenues for treating memory disorders.

Ingo Riederer
Laboratory on Thymus Research, Oswaldo Cruz Institute, Fiocruz

Professional Status: Associate Researcher. Academic degrees: Post-doc at Université Pierre et Marie Curie (ParisVI) / Institut de Myologie, UPMC/PARISVI, Paris, France (2004 – 2008). Ph. D. degree in Cellular and Molecular Biology (2001) - Oswaldo Cruz Foundation – Rio de Janeiro - Brazil. M.Sc. degree in Medical Biochemistry (1997) – Federal University of Rio de Janeiro - Brazil. Bachelor degree in Biological Sciences (1994) – Santa Úrsula University - Rio de Janeiro - Brazil.

Cell therapy in neuromuscular diseases

Ingo Riederer; Gillian Butler-Browne; Vincent Mouly; Wilson Savino

Therapeutic trials using myoblast transplantation to treat neuromuscular pathologies were unsuccessful due to the limited migration, reduced proliferation and early cell death of the injected myoblasts. By transplanting human myoblasts into immunodeficient mice, we demonstrated that engrafted cells are preferentially located in areas enriched in laminin and macrophages. We are now investigating how both elements can provide a niche that can favour these muscle progenitor cells engraftment.

Vincent Mouly
Myology Research Center, UPMC, Inserm, CNRS, Paris

Vincent Mouly, Research Director at CNRS. PhD in Virology in 1988 at the Pasteur Institute (direction MY Fiszman). Permanent position at CNRS (CR2) in 1990. Nominated CR1 in 1992, then Research Director in 2008. Actually group leader Within the Center for Research in Myology. Research interests: Regeneration, Pathophysiology and therapy of human striated muscle, using cellular modela. 110 publications in peer-reviewed journals. Member of the Academic Board (Commission for Research) of l'UPMC, project manager for the vice-president for research at UPMC. Member of the scientific board of DIM Biothérapies, AFM, SFTGC, and UPMC Stem Cell Initiative.

Cell therapy in neuromuscular diseases

The proliferation of human progenitors is generally limited, and this includes muscle progenitors. Although this limit in proliferation is not reached during normal ageing, the number of progenitors decreases (perturbation of self-renewal). In contrast, this limit is reached in some dystrophic situations, and the inflammatory context that is triggered during repeated cycles of degeneration-regeneration further amplifies the resulting deficit in progenitors. It is thus essential to better understand the mechanisms and parameters involved in muscle regeneration, in order to optimize therapeutic strategies such as cell therapy. These parameters include cell to cell cross-talk, including via secreted molecules (secretome), which orchestrate tissue regeneration. In parallel to these research themes, the team has carried out with clinicians from Tenon Hospital in Paris a first clinical trial of autologous cell therapy for patients suffering from oculo-pharyngeal muscular dystrophy (OPMD), and the results of this clinical trial will be discussed.

Delphine Bohl
Pasteur Institut, Paris

During my PhD thesis (1992-1997) and first years as a permanent researcher at the Pasteur Institute (Paris, France) in the laboratory of Dr Heard, my achievements were essentially in the field of gene therapy and the development of methods to regulate the delivery of therapeutic proteins, in particular for the treatment of thalassemia. In 2002, I explored model systems in which gene therapy would be used to reprogramming stem cell fate. My work led to the identification of transcription factors capable of inducing motor neuron differentiation of neural stem cells. In 2008, I decided to focus my interest on the applications of the iPSc technology to model human neurodegenerative disorders. A human iPSc model was generated to study a fatal lysosomal storage disorder, the Sanfilippo B syndrome, a disease for which treatment by gene therapy to the brain was developed in the laboratory. Since 2011, my projects focus on the characterisation of pathological defects in motor neurons derived from iPSc of patients with a fatal adult motoneuron disorder, Amyotrophic Lateral Sclerosis.

Stem cells, iPS and their use to understand neurological disorders

Human induced pluripotent stem cells (iPSc) obtained by reprogramming technology has emerged as a powerful tool for regenerative medicine, modeling of diseases and new drug development. In particular, the generation of iPSc from the somatic cells of patients with uncurable diseases and their subsequent differentiation into affected cells has permitted the construction of disease models that contain patient-specific genetic information. Since the initial description of this technology in 2007, iPSc models have been established for patients with genetic as well as sporadic forms of neuropsychiatric disorders and neurodegenerative diseases. Several studies revealed the impressive capacity of iPS cell research to elucidate pathological phenomena. However, we are clearly just beginning to explore the value of human iPSc. The technology offers promises but many hurdles remain to be solved. In the future, it will be necessary to develop new tools and technologies to reveal relevant phenotypes and generate novel pathophysiological insights.

Cécile Martinat
Inserm/UEVE, I-STEM, AFM, Evry

Cécile Martinat is a senior researcher recruited by Inserm in 2007. She has been working for more than 10 years in the field of pluripotent stem cells, and has acquired a large expertise in the use of human pluripotent stem cells for pathological modeling of neurodegenerative disorders. She has been working since 2005 at I-STEM (INSERM/UEVE UMR 861) where she manages a group dedicated to the use of Human Embryonic Stem Cells and human induced pluripotent stem cells for modeling monogenetic diseases. In particular, the C.M. group recently demonstrated that human embryonic stem cells carrying the causal mutation for Myotonic Dystrophy Type 1 (DM1) can be used to identify new pathological mechanisms, especially implicated in the neuritogenesis and synaptogenesis as well as drug screening. In parallel to DM1, her group is also interested in the development of a new cellular model for spinal muscular atrophy using human-induced pluripotent stem cells both to unravel new physiopathological mechanisms and also therapeutic strategies based on drug screening.

Human pluripotent stem cells: their application for drug discovery

The lack of existing models of pathologic tissues has rendered many important questions in disease pathogenesis inaccessible. Human embryonic stem cells derived from affected embryos during a pre-implantation diagnostic (PGD), as well as the technical development to obtain human induced pluripotent stem cells generated from patients, offer the unique opportunity to have access to a large spectrum of disease-specific cell models. Disease-specific pluripotent stem cells capable of differentiation into the various tissues affected in each condition could undoubtedly provide new insights into the pathological mechanisms by permitting analysis in a human system. These new disease-specific cell models are applicable for a wide systemic mechanistic analysis ranging from functional studies at the cellular level to a large-scale functional genomics screening. As a proof of principle, we demonstrated that PGD-derived hES cells and derivatives which, express the causal mutation implicated in the Myotonic Dystrophy type 1 (DM1), may mimic molecular defects associated to the pathology, such as the nuclear aggregation of mutant RNA. By taking advantage of this pertinent cellular model, we identified, through a genome-wide analysis, two early developmental defects in genes involved both in myogenesis as well as in neurite formation and establishment of neuromuscular connections. These neuropathological mechanisms may bear clinical significance as related to the functional alteration of neuromuscular connections associated with DM1. In parallel to these functional pathological studies, we developed two different approaches to identify new therapeutic strategies. The first one was based on a high content screening approach. A pilot drug screening experiment has been successfully conducted in order to identify new molecules which, due to their ability to disrupt the nuclear mutant RNA aggregation, might represent new therapeutic strategies. The second strategy used a genomics screening based on gene knockdown approach. This analysis allowed the identification of a potentially druggable target protein, inhibition of which tends to normalize molecular defects associated to DM1 leading to the development of a clinical trial.


Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

CNRS

UPMC
SORBONNE UNIVERSITÉS

cea

aviesan
alliance nationale
pour les sciences de la vie et de la santé

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

IOC
Instituto Oswaldo Cruz

Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz

GOVERNO FEDERAL
BRASIL
PAÍS RICO É PAÍS SEM POBREZA