

SCIENCE RESEARCH FOR THE FUTURE

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This annual report covers the period from October 2022 to September 2023.

The most complex organ in the human body; the brain manages our social behavior, our emotions and our actions. It is the brain that makes us aware of the world around us, of ourselves and of others. But despite considerable progress achieved in science and technology, our understanding of how the brain works is still very patchy, and treating brain disorders remains a major challenge for the health of humanity.

Paris Brain Institute was established in 2010, and was created as a collaborative, interdisciplinary research model that promotes innovation and groundbreaking discoveries. This environment, in which patients, researchers, clinicians, engineers, technicians, business leaders and students work side by side, has become a Europe's leading center for research into the central nervous system.

With drive and ambition, the Institute's teams work tirelessly to achieve a single objective: to transform fundamental discoveries into therapeutic solutions, so they can be accessed by patients and by society as quickly as possible.

PARIS
BRAIN
INSTITUTE

Changes

PROF. GÉRARD
SAILLANT

President of Paris Brain Institute



OVER THE PAST YEAR, Paris Brain Institute has continued to pursue its commitment to a process of transformation - one that brings with it challenges and opportunities for the future. To prepare for these changes, the entire community within the Institute embarked in 2023 on an in-depth review and analysis to develop a multi-year strategic roadmap to 2030. This roadmap has been designed to support robust research - basic research as well as clinical and translational research - and to enable an ambitious innovation and training policy. This approach comes at a pivotal time in the Institute's development, with several major institutional deadlines looming, and at a time when its scientific maturity means it can now pursue more extensive research projects, increase its sphere of influence in France and around the world, and consider investing on an even larger scale. Four major cross-disciplinary projects, financed by generous sponsorship support, have been selected. These projects focus on identifying early markers of neurodegenerative diseases, the mapping and functional characterization of brain cells, the development of new deep brain stimulation (DBS) strategies for Parkinson's disease based on circuits preserved in different genetic forms and, finally, neuroinflammation, its role and potential for developing new therapies for brain diseases. High-level research requires access to cutting-edge equipment. Our teams have been working hard this year to prepare for the imminent arrival of a state-of-the-art 7-Tesla MRI scanner, an exceptional piece of equipment that the Institute is proud to be able to make available to its staff and to the neuroscience scientific community. Another major milestone was the selection of the Institute's next Executive Director by an ad hoc committee. She will officially take office in January 2025. January 2025 will also see changes in the

composition of the Joint Research Unit (UMR), with a reorganization of the scientific teams to cover new research themes and provide a better response to the contemporary challenges faced by neuroscience.

On the cusp of its fifteenth anniversary, the Institute's ambition is clear: to continue its progress as one of the world's leading neuroscience research institutes.

The Institute is fortunate to be able to count on its partners and donors to help it succeed in its ambition to scale up. Their unwavering commitment helps to guarantee the continuity and stability of funding for our teams and gives our scientists the freedom to carry out ever more innovative and ambitious work, exploring possibilities never before considered. Their engagement - your engagement alongside us - is essential if this momentum is to be maintained. This is what spurs us on to always go further. I hope we can continue to share this exciting adventure and to work together to shape the future of neuroscience.

Supporting the Institute's transformation and accelerating innovation

CORINNE
FORTIN

Secretary General of Paris Brain Institute



IN 2023, BUOYED BY THE MOMENTUM GENERATED IN 2022 by the implementation of a resource development plan, the strengthening and consolidation of increasingly demanding areas of expertise, and its commitment to the IHU France alliance, Paris Brain Institute has firmly established its position as a major player in scientific and medical research, helping to invent tomorrow's medicine to serve and support patients.

Our "Innovation 2030" plan - conceived as an embryonic biocluster - has given renewed impetus to the Innovation Directorate, which has been equipped with a new acceleration hub providing new tools to boost the future industry value of projects developed at the Institute.

At the same time, the Institute worked alongside Dassault Systèmes, Inria, six other IHUs and four startups (including two from Paris Brain Institute) to set up the MediTwin project, which aims to develop personalized digital twins over the next five years; digital tools designed to improve the patient care pathway from diagnosis to therapy.

Finally, the Institute has obtained Sésame Filières France 2030 funding from the Île-de-France Region to the tune of €2 million for its Neuro@7T project. This will enable it to build a sector for the development of new solutions, particularly biomarkers, based on imaging data from our state-of-the-art 7 Tesla MRI scanner, equipment funded by sponsorship and the Île-de-France Region, which will be implemented at the Institute in June 2024.

These successes are a recognition of our expertise, in our research teams and in our support functions and core facilities,

all of which are essential links in the chain of excellence in research.

Ethics, scientific integrity, openness and agility have also guided the development of our data governance policy, adopted in early 2023, which guarantees the rigorous management of data originating from the Institute's studies, the integrity of its research and the widest possible access to results. I warmly welcome the continuing reinforcement of technical and regulatory support for research and, more broadly, the growing professionalism of our functional and administrative departments, which are supporting increasingly demanding research.

And so, we are moving forward with ambition and confidence, and with a constant focus on providing a flexible platform to support research and scientific progress, for the benefit of patients.



PROF. ALEXIS BRICE

Executive Director of Paris Brain Institute

In recent months, Paris Brain Institute has embarked on an ambitious development trajectory. What form does this take?

This period has been one of wide-ranging reflection on the future of the Institute. We have been working, in particular, on the scientific and medical strategy for our research center, which should guide our actions up to 2030. This roadmap will enable us to initiate a number of ambitious and transformative projects, for which the Institute is fortunate to be supported by an invaluable corporate partner. These projects draw on the Institute's rich scientific resources, creating synergies between groups of researchers who bring complementary expertise to the table. This work also has provided a framework for the development of the IHU 2024-2030 roadmap (for University-Hospital Institutes). Alongside these activities, we

received a visit in October 2023 from the French High Council for Evaluation of Research and Higher Education (HCERES), which evaluation was very positive.

Changes in the Institute's governance also took place in 2023. The next Executive Director of Paris Brain Institute has been appointed and will take over as Head of the Joint Research Unit (UMR) in January 2025, and I would like to welcome her in advance to the helm of this fine Institute. I would also like to extend a special thank you to Bassem Hassan and Catherine Lubetzki for their dedication and inspiring vision in their roles as Scientific and Medical Directors for the Institute. The Management Committee welcomed Brian Lau as the new Scientific Director and Director of Platforms, and as Deputy Director of the UMR from January 1, 2024, and Jean-Christophe Corvol, who is now acting Medical Director.

What can we learn from the Institute's scientific activities over the last few months?

Well, we have covered quite a lot of ground! We have selected the two new team leaders: I am delighted to announce that Dafni Hadjieconomou has been with us since September 2023 and is working on the physiology of the plasticity of the brain-gut axis, and that Nikolas Karalis joined us in January 2024 and is studying the combinatorial neuromodulation of mental states. These two brilliant young researchers were recruited through our international call for applications, launched in 2021, which resulted in more than 250 applications, a mark of the Institute's international reputation.

Another highlight in our scientific success is the arrival of Kaj Blennow from the University of Gothenburg (Sweden), who will be supporting us as a visiting professor. Kaj will be working with the Institute's teams to share his valuable expertise in biomarkers for Alzheimer's disease.

Lastly, the Institute welcomed the five young PhD students recruited as part of our International PhD program, launched in 2023 with the C-BRAINS academic and industrial neuroscience network to select the best young talent from abroad.

Clinical research is a core discipline for the Institute. What action was taken in this area?

Our clinical research projects have been stepped up significantly this year, but we need to go even further. We are currently working to put in place mechanisms to facilitate the secondary use of data and samples, in order to optimize the valuable information obtained from clinical trials.

In 2023, we selected the successful candidates from our call for applications for interface contracts. These contracts for clinicians involved in research allow them to devote more of their time to research. Three clinicians were chosen for this first cycle, and a new call for applications is planned for 2024.

What are the highlights of the year in terms of innovation?

Firstly, the progress we have made in setting up the Brain & Mind biocluster. This is a major project and a source of enormous hope for the research and development of therapies in the field of neurological, psychiatric and sensory organ disorders. It is also a unique collaborative effort, bringing together a community of around fifty partners in the Île-de-France Region.

We also rolled out our Innovation 2030 plan, creating the first technological development and innovation unit, GENOV, for gene therapy, and selecting the two

winners of our NeurAL Neurosciences Acceleration Launchpad.

How has the Institute continued to develop its international partnerships?

We have nurtured a huge number of new partnerships this year! This increased international reach is one of the indicators of the success of our partnership policy, which expanded significantly in 2023, with a growing number of joint projects. These are described in this report, but I would like to highlight two of them here: our partnership with the Montreal Neurological Institute (Canada) on two joint projects in the fields of nervous system development and function, and our partnership with the UK's Dementia Research Institute (UK-DRI), which has also joined us in the CURE-ND alliance. The aim of this work is to stimulate and increase the impact of translational research with a view to finding a technological or therapeutic application. A project was funded in 2023 in the field of biomarkers for Alzheimer's disease. We are also enthusiastic about our partnerships with the Latin American Brain Health Institute in Chile and the Indian Institute of Technology in Delhi.

Is there a specific challenge for the year ahead?

It promises to be an exciting year. Paris Brain Institute is fully committed to preparing for future transformations, which are essential if it is to enter a new phase in its development and respond effectively to the growing challenges in the field of neuroscience and nervous system disorders. Guided by a clear vision and a strategic approach, our commitment remains unchanged: to work every day for the health of everyone.

OCTOBER 22



FRANCE'S ANNUAL SCIENCE FESTIVAL: GETTING THE WORD OUT ABOUT OUR RESEARCH

As it does every year, the Institute played an active part in the France's annual Science Festival, a major event that provides a superb opportunity for outreach and for talking about science to the general public. An Open Brain Bar meeting was organized on the influence of the brain on our diet, along with a conference on brain-computer interfaces.

➔ SEE p. 57

ROUTE DU RHUM: PARIS BRAIN INSTITUTE SPONSORED BY A BOAT

Transatlantic sailor Francis Joyon set off on the famous Route du Rhum yacht race aboard his iconic trimaran, Idec Sport, flying the colors of Paris Brain Institute.



NOVEMBER 22

THE LINK BETWEEN SLEEP AND CREATIVITY

Following her thesis work on the link between sleep and creativity, Célia Lacaux, from the MOV'IT team, won the NOMIS & Science Young Explorer Award, giving her an opportunity to write a paper on her work for the journal *Science*. In this article, she shows that the transition between wakefulness and sleep represents a gateway to creativity. This discovery, which touches on one of the most essential human capacities, has far-reaching implications for humanity.

➔ SEE p. 26



SOCIETY FOR NEUROSCIENCE (SFN) CONFERENCE

The 2022 annual conference of the Society for Neuroscience (SFN), the leading international meeting place for people involved in research in this field, was held from November 12 to 16. A delegation from the Institute attended the conference to present the recent work carried out by its teams.



DECEMBER 22

JOINT PARIS BRAIN INSTITUTE/ YALE UNIVERSITY WORKSHOP

A workshop on new approaches to neurovascular imaging in humans and rodents was held on December 16 at the Institute, as part of the partnership with Yale University that has now been in place for several years.

➔ SEE p. 42



LAUNCH OF THE EPICA PROGRAM

December saw the launch of the Epica program, a new training program in partnership research in the health sector, led by Paris Brain Institute, Institut Pasteur, the Imagine Institute and the startup Caméo, with the support of Banque des Territoires-Caisse des Dépôts.

➔ SEE p. 56

SPOTLIGHT ON A CONTROVERSIAL AREA OF THE CORTEX

The dorsomedial prefrontal cortex/dorsal anterior cingulate cortex is an area of the brain that is the subject of numerous theories and controversies. A review of the state of the art explains these theories in more detail, along with their convergences and disagreements, and suggests future pathways towards a better understanding of the function(s) of this region.

➔ SEE p. 27



TEAM EVALUATIONS BY THE SAB AND THE HCERES

At the end of January, the Paris Brain Institute's Scientific Advisory Board (SAB) held three days of sessions to evaluate the research teams and the plan for the next Joint Research Unit (UMR) (from January 1, 2025). The SAB's recommendations were then fed into the documents submitted as part of the evaluation of the UMR by the French High Council for Evaluation of Research and Higher Education (HCERES).

➔ SEE p. 20

BRAIN TUMORS: THE ROLE OF CELL SENESCENCE REVEALED

In a study published in *Nature Communications*, scientists from the Institute have shown *in vitro* that eliminating senescent cells - cells that have stopped dividing - could modify the ecosystem of brain tumors known as "glioblastomas" and slow their progression.

➔ SEE p. 24

ADOPTION OF THE DATA GOVERNANCE POLICY AND THE SCIENTIFIC INTEGRITY POLICY

In January, the Institute drafted both its Data Governance Policy and its Scientific Integrity Policy. These documents are designed to guarantee the rigorous management of data originating from the Institute's studies, the integrity of its research and the widest possible access to the results.

➔ SEE p. 68



JANUARY 23



DELPHINE OUDIETTE AND STÉPHANIE BAULAC AWARDED ERC FUNDING

The European Research Council (ERC) has awarded two of the grants in its highly competitive award procedure to two researchers from the Institute: Delphine Oudiette (Inserm) (Consolidator Grant) and Stéphanie Baulac (Inserm) (Proof of Concept Grant). Three other researchers from the Institute also received a Starting Grant in September 2023.

➔ SEE p. 14

BRAIN ACTIVITY IN LANGUAGE PROCESSING: A MARKER OF CONSCIOUSNESS

To explore the language-processing abilities of patients suffering from disorders of consciousness, scientists at the Institute have developed an auditory test and have compared the brain activity of healthy volunteers with that of patients. The scientists have shown that this simple auditory test could have diagnostic and prognostic value in terms of probing the state of consciousness and its recovery in non-communicative patients.

➔ SEE p. 28



A CONFERENCE ON ARTIFICIAL INTELLIGENCE (AI) AND BIG DATA

The IHU France alliance - of which Paris Brain Institute is a member - the Council of State and the French Data Protection Authority (CNIL) organized a conference on February 10, 2023, to attempt to address the ethical issues surrounding the use of AI and big data in research and medical practice, and the prospects offered by these new tools. According to the IHU, big health data should become a "collective good" for research.

FEBRUARY 23

MARCH 23



INAUGURATION OF THE "INVINCIBLE ÉTÉ" SPACE

On March 30, 2023, Paris Brain Institute opened its "Invincible Été" space in the very heart of its laboratories, in recognition of the support and extraordinary commitment of Olivier Goy, the Institute's ambassador and major donor, who suffers from Charcot-Marie-Tooth disease.

A LOOK BACK AT THE FRANCE BRAIN BEE 2023

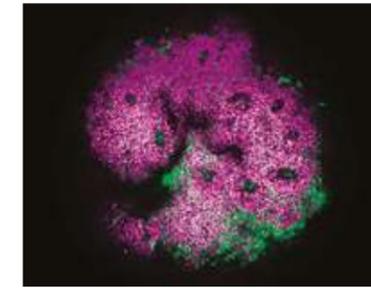
The latest France Brain Bee neuroscience Olympiad was held at the Institute. Open to secondary school students, this event – a spin-off of the International Brain Bee Championship created in 1998 – encourages younger generations to learn more about neuroscience and pursue careers in research.



THE ORIGINS OF ALZHEIMER'S DISEASE COULD BE IN NEURODEVELOPMENT

The Brain Development team has shown the amyloid precursor protein's role in neurodevelopment. In certain individuals, subtle disruptions to this mechanism could cause vulnerabilities that only become apparent in adulthood, after decades of biological stress.

→ SEE p. 23



JUNE 23

APRIL 23

MULTIPLE SCLEROSIS AND COVID-19

A cohort study conducted at Paris Brain Institute revealed that the risk of severe Covid-19 was higher in people with primary-progressive MS (PPMS) than in those with relapsing-remitting MS (RRMS), suggesting a relationship between Covid-19 severity and severity of the disability. Furthermore, anti-CD20 therapy was also associated with an increased risk of severe Covid-19 in RRMS or incipient PPMS patients.

→ SEE p. 30

A WELCOME FOR KAJ BLENNOW

Through the support of the Alzheimer Research Foundation and Fondation Sorbonne Université Chaire Axa, Paris Brain Institute is delighted to be welcoming Prof. Kaj Blennow, a world leader in the field of biomarkers for neurodegenerative diseases, for a three-year appointment as a visiting professor at its laboratories. This recruitment marks the first step in an ambitious program designed to put France on the international stage in clinical research into biomarkers of Alzheimer's disease.

→ SEE p. 22



SPINOCEREBELLAR ATAXIAS: WIDE VARIABILITY IN THE AGE OF ONSET OF SYMPTOMS

Spinocerebellar ataxias form a very heterogeneous group of hereditary diseases, with some forms being difficult to study because they are so rare. At the initiative of the Basic to Translational Neurogenetics team, an international consortium has demonstrated significant heterogeneity in the age of onset of symptoms, ranging from birth to 75 years for the same gene, suggesting the presence of modifying factors in addition to the causal gene.

→ SEE p. 24



LAUNCH OF PARIS BRAIN INSTITUTE AMERICA

In July 2023, Paris Brain Institute obtained charity status for Paris Brain Institute America, a New York-based organization designed to support research projects between Paris Brain Institute and major research institutions in North, Central

and South America. The launch of Paris Brain Institute America was celebrated with a charity dinner at the French Consulate in New York on October 4, 2023, in the presence of actors Michelle Yeoh and Jean Reno, patrons of the Institute.

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JULY 23

MAY 23

BRAIN & MIND, A NEUROSCIENCE BIOCLUSTER

The Brain & Mind project, led by Paris Brain Institute, the FondaMental Foundation and the Institut de la Vision, has been selected as the winner of the second wave of the biocluster call under the "France 2030" plan. This project will bring together more than 50 scientific, medical and industrial partners with the aim of creating an internationally renowned innovation ecosystem in neuroscience and mental health in France.

→ SEE p. 51



THE NEURAL PROGRAM SELECTS ITS FIRST TWO WINNERS

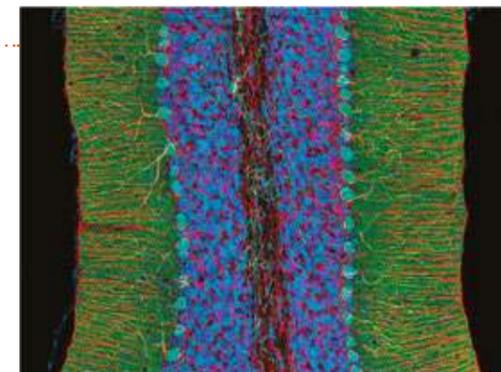
Launched in 2023 by Paris Brain Institute with the support of the Fondation Anne et Claude Berda, the NeurAL (Neuroscience Acceleration Launchpad) neuroscience seed program identifies, ratifies and supports the most promising startup projects. In April, the program awarded its first prize to the IGHOR project (development of new candidate molecules for the treatment of glioblastoma) and its second prize to CicaNEURO (development of a drug candidate with neuroprotective properties that can be applied in Parkinson's disease).

→ SEE p. 48

ACQUISITION OF A HIGH-THROUGHPUT SEQUENCER

Paris Brain Institute has acquired a NovaSeq X Plus high-throughput sequencer, developed by Illumina. This latest-generation technology will support the existing equipment making up the iGenSeq genotyping and sequencing core facility.

→ SEE p. 40



USING ARTIFICIAL INTELLIGENCE FOR DIAGNOSIS

Various algorithms have been proposed for computer-assisted diagnosis of dementia in Alzheimer's disease based on anatomical MRI of the brain. These approaches achieve a high degree of accuracy when applied to research datasets. The researchers showed that the performance of the algorithms was significantly reduced when applied to routine clinical data.

→ SEE p. 32



AUGUST 23



HOW OUR TASTES INFLUENCE OUR CREATIVITY

Published in the journal *American Psychologist*, a study by researchers in the FrontLAB: Frontal Functions and Pathology team, has shown how individual preferences influence the speed at which new ideas emerge, as well as their degree of creativity. This work also shows that these preferences determine which ideas we decide to use and communicate to others.

➔ SEE p. 27

SEPTEMBER 23



WELCOME ABOARD!

In September, the Institute welcomed Dafni Hadjieconomou from Imperial College London as the new head of the Gut Sense Lab team.

➔ SEE p. 20

BRAIN TO MARKET SUMMER SCHOOL

From September 11 to 15, the Open Brain School - Paris Brain Institute's training arm - organized the ninth edition of this unique course in neuroscience and entrepreneurship, which fosters innovation in the field of health. The 2023 event, which focused on Alzheimer's disease, attracted 50 international participants.



SUPPORT FROM THE PARAYRE CHAUFOUR FOUNDATION FOR THE INTERNATIONAL BIG BRAIN THEORY

Thanks to the generous support of the Marie-Françoise Parayre Chaufour Foundation, Paris Brain Institute has launched its first Big Brain Theory international appeal, an ambitious program to encourage international scientific innovation, in partnership with Mission Lucidity in Belgium.

➔ SEE p. 79



846

staff, including 83% scientific, medical and paramedical staff (as at September 30, 2023)



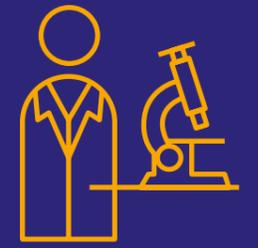
45

nationalities



25

research teams selected by a Scientific Advisory Board



11

dedicated technical facilities and biobank



88

ongoing trials in the CIC, including 13 promoted by Paris Brain Institute



573

patients included in trials by the Neuroscience CIC



586

publications in scientific journals in 2023 (calendar year)



13 clinical research facilities (iCRINs)



16

training programs at the Open Brain School with over 300 participants (2,000 since it began)



95,134

active donors between October 1, 2022 and September 30, 2023



62

new industry contracts



58

active patents, including 8 new patent requests filed and 4 copy-righted software programs



29

startups hosted in the iPEPS incubator, including 5 new startups

ACHIEVEMENTS

Paris Brain Institute's research teams have won prestigious awards and funding, a recognition of the excellence of our scientists' work.

→ HONORS AND AWARDS

Full members of the Académie nationale de médecine



ALEXIS BRICE
Executive Director of Paris Brain Institute



MARIE VIDAILHET
(Sorbonne University/AP-HP)
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

2022 NOMIS & Science Young Explorer Award



CÉLIA LACAUX
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

→ COMPETITIVE EXAMINATIONS

Research associates (CRCN) (Inserm)



MATHIEU BARBIER
Basic to Translational Neurogenetics team



NIKOLAS KARALIS
Neural Circuits and Brain Dynamics team



SARA BIZZOTTO
Genetics and Pathophysiology of Epilepsy team



JÉRÔME MUNUERA
Experimental Neurosurgery team

University Professors-Hospital Practitioners (PU-PH)



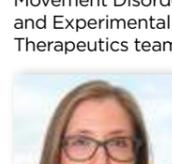
BENEDETTA BODINI
Repair in Multiple Sclerosis: from Biology to Clinical Translation team



NADYA PYATIGORSKAYA
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team



CÉLINE LOUAPRE
Repair in Multiple Sclerosis: from Biology to Clinical Translation team



YULIA WORBE
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

University Lecturers-Hospital Practitioners (MCU-PH)



PAULINE LALLEMAND
Basic to Translational Neurogenetics team



LAURA MARIE-HARDY
Sensory Spinal Signaling team

→ GRANTS AND FUNDING

European Research Council (ERC) Starting Grants



THOMAS ANDRILLON
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team



SARA BIZZOTTO
Genetics and Pathophysiology of Epilepsy team



DAFNI HADJIECONOMOU
Gut Sense Lab team

European Research Council (ERC) Consolidator Grant



DELPHINE OUDIETTE
(Inserm)
Mov'It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team



STÉPHANIE BAULAC
Genetics and Pathophysiology of Epilepsy team



25,5 MILLION EUROS:

total competitive, national and international funding obtained between October 1, 2022 and September 30, 2023

16 ANR

grants won in the same period, a success rate of 30%, including 4 ANR Early Career Scientist grants

anr [©] agence nationale de la recherche

Paris Brain Institute's scientific and medical strategy is based on a transdisciplinary, synergistic approach combining basic and translational research, clinical expertise and support for cutting-edge technology platforms. This structure enables the Institute to meet the challenges involved in understanding the nervous system and the diseases that affect it, and to build a strong international reputation with growing visibility.

1

RESEARCH

Research teams

Paris Brain Institute brings together 25 research teams affiliated to one or more of the Institute's five fields, following a multidisciplinary approach that fosters flexibility as the key to scientific and medical success. The list below summarizes all the teams and the competitive funding they obtained between October 2022 and September 2023.

ARAMIS: Algorithms, Models and Methods for Images and Signals of the Human Brain



Olivier Colliot (CNRS),
Stanley Durrleman (Inria),
FACE Foundation, ANR-PRC,
ANR-JCJC, DIM C-BRAINS

ALS: Causes and Mechanisms of Motor Neuron Degeneration



Séverine Boillée (Inserm)
ARMC (2), ARSLA

Cognitive Control – Interoception – Attention



Philippe Fossati
(AP-HP/Sorbonne University),
Liane Schmidt (Inserm)
Fondation John Bost pour la Recherche

Brain Development



Bassem Hassan
(Inserm)
Fondation Fyssen,
ARSEP

Structural Dynamics of Networks



Nicolas Renier
(Inserm)
Fondation
Schlumberger

Dynamics of Epileptic Networks and Neuronal Excitability



Stéphane Charpier (Sorbonne University),
Mario Chavez (CNRS),
Vincent Navarro
(AP-HP/Sorbonne Université)
ANR-PRC, MSCA-PF

FrontLAB: Frontal Functions and Pathology



Richard Lévy
(AP-HP/Sorbonne Université)
Fondation pour
la Recherche sur
Alzheimer, Fondation
Claude Pompidou

Genetics and Development of Nervous System Tumors



Emmanuelle Huillard (CNRS),
Marc Sanson
(AP-HP/Sorbonne University)
AP-HP Grant (3), FRM Grant (2), RIF,
Sorbonne University (2), Fondation
de France Grant, ARTC, CRNO, Inserm-
Equipement Grant, ANR-JCJC, ARC,
Ligue contre le cancer (2)

Genetics and Pathophysiology of Epilepsy



Stéphanie Baulac (Inserm),
Éric Leguern
(AP-HP/Sorbonne University)
SEED4EU+, ANR-JCJC, ERC Starting grant,
ERC Proof of concept

Repair in Multiple Sclerosis: from Biology to Clinical Translation



Catherine Lubetzki
(AP-HP/Sorbonne University),
Bruno Stankoff
(AP-HP/Sorbonne University)
ANR-PRC (2), Fondation Hippocrène

Alzheimer's Disease and Prion Diseases



Marie-Claude Potier (CNRS),
Stéphane Haïk (Inserm, AP-HP)
InVs-Institut de veille sanitaire, ANR-CoEN,
Fondation Jérôme Lejeune, ANR-PRC,
DIM C-BRAINS, France Alzheimer, AFM

Cellular Mechanisms of Sensory Processing



Nelson Rebola (CNRS),
ANR-PRC

Motivation, Brain and Behavior



Mathias Pessiglione (Inserm),
Sébastien Bouret (CNRS),
Jean Daunizeau (Inserm)
NIH-conference, ANR-JCJC, DIM C-BRAINS,
FRM Grant (2)

Mov'it: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics



Marie Vidailhet
(AP-HP/Sorbonne University),
Stéphane Lehéricy
(AP-HP/Sorbonne University)
SFRMS, ANR-JPND, BPI France funding,
ERC Starting Grant, Horizon Europe,
ERC Consolidator grant, ANR-ERA NET
E-RARE, Ville de Paris, FRC

Experimental Neurosurgery



Brian Lau (CNRS),
Carine Karachi (AP-HP/Sorbonne University)
FRM Grant, Sorbonne University,
Association France Parkinson

Basic to Translational Neurogenetics



Alexandra Durr
(AP-HP/Sorbonne University),
Giovanni Stevanin
(Inserm/EPHE)
BRAIN-TEAM Health Network, Fondation
pour la Recherche sur Alzheimer, ANR-PRC,
France Alzheimer, Fondation Allianz-Institut
de France, Spastic Paraplegia Foundation

Neurophysiology of Repetitive Behaviors



Éric Burguière
(CNRS)
DIM C-BRAINS,
ANR-PRC

Cellular Physiology of Cortical Microcircuits



Alberto Bacci (Inserm)

Gut Sense Lab



Dafni Hadjieconomou
(Paris Brain Institute)
ERC Starting Grant

Molecular Physiology of Synaptic Bioenergetics (Diane Barrière Chair)



Jaime De Juan-Sanz
(CNRS)

Molecular Pathophysiology of Parkinson's Disease



Olga Corti (Inserm),
Jean-Christophe Corvol (AP-HP/
Sorbonne University)
NeurATRIS, ANR-France 2030-PEPR,
FRM, ANR-France 2030-AMI biocluster,
DIM C-BRAINS

PICNIC - Physiological Investigation of Clinically Normal and Impaired Cognition



Laurent Cohen
(AP-HP/Sorbonne University),
Lionel Naccache
(AP-HP/Sorbonne University),
Paolo Bartolomeo (Inserm)
FRM Grant, Fondation de France Grant,
Pediatric Epilepsy Research Foundation,
MSCA-SE, Templeton World Charity
Foundation

Myelin Plasticity and Regeneration



Brahim Nait Oumesmar
(Inserm),
Violetta Zujovic
(Inserm)
ARSEP (5), FRC, FRM Grant, ANR-PRC

Sensory Spinal Signaling



Claire Wyart
(Inserm)
Académie des
Sciences, ANR-PRC,
MSCA-PF, HFSP

Experimental Therapeutics of Parkinson's Disease



Etienne Hirsh (CNRS),
Stéphane Hunot (CNRS)
NEB - NATURALIA ET BIOLOGIA,
France Parkinson, ANR-PRC

GLOSSARY

AFM: French Muscular Dystrophy Association
ANR-JCJC: French National Research Agency (ANR) – Early Career Scientist
ANR-ERA-NET E-Rare: ANR Transnational co-funding on rare diseases
ANR-PRC: ANR Collaborative Research Projects
ANR-France 2030-AMI biocluster: ANR Call for Expressions of Interest
ANR-CoEN: ANR Network of Centers of Excellence in Neurodegeneration
AP-HP: Paris Public Hospital Network
ARC: Association for Cancer Research
ARMC: Grant for Research on Brain Diseases
ARSEP: French Association for Multiple Sclerosis Research
ARSLA: French Association for Amyotrophic Lateral Sclerosis Research
ARTC: French Association for Brain Tumor Research
BPI: Public Investment Bank
CRNO: French Neuro-oncology Research Center
DIM C-BRAIN: Major Research and Innovation Field – Cognition and Brain Revolutions: Artificial Intelligence, Neurogenomics, Society
ERC: European Research Council
FRC: French Foundation for Brain Research
FRM: French Foundation for Medical Research
HFSP: Human Frontier Science Program
MSCA-PF: Marie Skłodowska-Curie Actions – Postdoctoral Fellowships
PEPR: Priority Research Programs and Equipment
NIH: National Institute of Health
RIF: Île-de-France Region
SFRMS: French Sleep Research and Medicine Society

Basic and clinical research, a synergy underpinning the Institute's model

Since it was first established, Paris Brain Institute has developed a scientific and medical strategy focused squarely on the patient. The strength of its model lies in the synergy between cutting-edge basic and clinical research, strengthened by the unique environment of Pitié-Salpêtrière Hospital's University Medical Department (DMU) for Neuroscience.

PERSPECTIVES **Jean-Christophe Corvol, Acting Medical Director, and Brian Lau, who was appointed Scientific and Platforms Director and Deputy Director of the Joint Research Unit (UMR) on January 1, 2024, review the short- and long-term prospects for basic and clinical research.**

What do you consider to be the highlights of the past period in terms of medical and scientific momentum?

◉ **Brian Lau:** This is a period of significant change for the Institute, particularly in the composition of its teams. The arrival of Kaj Blennow as a visiting professor to support our work on Alzheimer's disease is a huge boost. We also welcomed Dafni Hadjieconomou and Nikolas Karalis, our new young team leaders, who will broaden the Institute's range of research activities. The platforms have also been strengthened through the recruitment of new managers.

◉ **Jean-Christophe Corvol:** On the clinical research side, it is very encouraging to see that our partnership with the Neuroscience DMU is growing stronger. The recent arrival of Danielle Seilhean as head of this department is a significant development in this respect. The Neuroscience Clinical Investigation Center (CIC) has also been successful in obtaining ISO 9001 certification: a guarantee of quality and excellence for the clinical research work carried out at the facility.

How does the Institute attract scientific talent, specifically from younger generations?

◉ **J-CC:** We encourage young doctors to engage with the Institute's research teams. Interface contracts provide an excellent boost to appeal. They give physicians in the Neuroscience DMU, who are often young and talented, the opportunity to allocate some of

their time to research as part of a team at the Institute. Three of these contracts were awarded in 2023, and a second call for applications is already planned.

◉ **BL:** The international PhD program, launched in 2023 with the C-BRAINS consortium, will train five young foreign scientists. This is a fantastic opportunity for our teams to recruit top talent and increase our international visibility.

How will the scientific and medical policy continue to be developed in 2024?

◉ **BL:** The year 2024 will focus on preparing for the changes to the Institute's UMR in 2025. We will be consolidating the strategic plan up to 2030, which is based on groundwork laid by discussions within the five research fields and targeted working groups in 2023. This will be done in consultation with our new Executive Director, whose arrival is scheduled for 2025. We will also be launching the first major cross-disciplinary projects. Three of these projects will focus on basic research, with another aimed at developing international partnerships. Two other projects will focus on clinical research – one of them in cooperation with Yale University.

◉ **J-CC:** We will also be launching a second call for clinical research infrastructures (iCRINs) in 2024. These systems, which play a central role in our medical policy as interfaces between the Institute and the Neuroscience DMU, are already recognized and firmly established. It is extremely pleasing to note that, after nearly 15 years, the Institute has now achieved the maturity to transform the existing picture and implement large-scale projects on a long-term basis.

Jean-Christophe Corvol and Brian Lau



A year of evaluation and preparation

Between the end of 2022 and the end of 2023, the Institute faced two major deadlines. At the end of 2022, the recruitment process was launched for the new Executive Director, who will take up her post in January 2025. In January 2025, changes will also be made to the composition of the Joint Research Unit (UMR), bringing together all the Institute's research teams. In view of this new scientific configuration, an initial assessment of the UMR has been carried out by the international Scientific Advisory Board (SAB).

The 27 candidate teams each prepared a project and presented these to the SAB at the end of January 2023. The SAB's recommendations were implemented throughout the year for the purposes of the UMR's evaluation by the French High Council for Evaluation of Research and Higher Education (HCERES), the independent public authority responsible for evaluating all higher education and research entities. The final HCERES report will be published in 2024.

Outreach of scientific activities

Alongside these two organizational milestones, the scientific teams have continued their research work. The Institute has maintained a high publication volume, with a total of 586 publications in 2023, including 222 in journals with an impact factor of more than 7. Of these articles, 16 are in the top 1% of the most-cited papers of 2023 in their discipline, while 45 are in the top 5%. Five of the Institute's researchers have also been awarded prestigious competitive grants from the European Research Council (ERC).

The Institute's international visibility and recognition have also enabled it to forge collaborative relationships with world-renowned experts such as Kaj Blennow. Kaj is a pioneer in the field of Alzheimer's disease biomarkers and is now working closely with the Institute's scientists as a visiting professor. The development of new detection tests is under way, and work already completed will be presented in 2024 at various national and international conferences.



Nicolas Karalis and Dafni Hadjieconomou

Lastly, Paris Brain Institute welcomed two new team leaders, selected following an international recruitment process: Dafni Hadjieconomou, who joined us in September 2023 to focus on the brain-gut axis, and Nicolas Karalis, who arrived a few months later, to delve deeper into the fundamental principles underlying the organization of neuronal circuits.

Interface contracts: fostering clinical research

A call for applications for interface contracts was launched in January 2023. This scheme makes it possible for clinicians to devote 50% of their time to research, as part of one of the Institute's teams, for a period of three to five years. The aim is to enable clinicians involved in research to develop ambitious research projects because they have this protected research time available. Three recipients have been selected: Céline Louapre for her project "Therapeutic strategies to promote remyelination in multiple sclerosis: development of electrophysiological tools and translational therapeutic trials", Mehdi Touat for the project "New therapeutic strategies to overcome glioblastoma resistance to chemotherapy and immunotherapy", and Raphaël Le Bouc, who is working on the project "Towards a neurocomputational characterization of motivational processes and their dysfunction in neurobehavioral disorders". Their contracts began in late 2023.



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Young scientists at the heart of our scientific strategy

For several years now, Paris Brain Institute has been making a special effort to recruit young scientific talent, through a number of initiatives. At the end of 2022, the Major Research and Innovation Field (DIM) C-BRAINS, in cooperation with Paris Brain Institute, launched a call for applications for the international PhD program, with the aim of funding 13 PhD contracts. Five of those contracts will be funded by Paris Brain Institute, in order to raise its international profile and attract high-potential foreign researchers to its laboratories. These five young researchers - who hail from Germany, Brazil, England, the Netherlands and China - will start their PhDs at the Institute in fall 2023. This program offers them an attractive three-year remuneration package, help with living arrangements in the Paris Region, an operating budget and a broad range of training courses.

In addition to these grants, the Institute has, for some years now, been offering a range of services specifically geared towards young scientists. For example, two masterclasses were organized in 2023. The first was designed to prepare participants for applying for competitive ERC funding, providing coaching for eight participants as part of the Open Brain School. The second aimed to help young researchers, post-doctoral researchers and students take the competitive examination to qualify as Inserm or CNRS research associate (normal grade).

Finally, in June 2023, the Institute organized a workshop for young scientists, open to researchers from the Institute, led by an editor from the scientific journal *Nature Neuroscience*, on publication strategy and improving article preparation.



DAFNI HADJIECONOMOU,
head of the new Gut Sense Lab team,
who joined Paris Brain Institute on September 22, 2023.

What does your team at Paris Brain Institute study?

► We will be focusing our research on the mechanisms involved in brain-gut communication. First, we will study how intestinal neurons integrate changes in lifestyle habits (diet, exercise) and their impact on how our metabolism is regulated. This project received support in 2023 from the European Research Council, which awarded us one of its starting grants.

What do you hope to discover?

► We know that communication between the brain and the gut plays a key role in metabolic regulation, but the mechanisms involved are still not clearly understood. There is still much we need to discover about the brain networks, cells and key molecules involved in this phenomenon. Our work could also be useful in understanding conditions such as Parkinson's disease, as some recent discoveries have indicated that this pathology might have an intestinal origin.

Why did you choose Paris Brain Institute as the place to build your team?

► I'm delighted to have been selected as a new team leader at Paris Brain Institute, because it's a place where basic and clinical research can coexist, creating an environment that fosters synergies between teams. There are also excellent technology platforms that we can draw on to advance our research.



THREE QUESTIONS FOR...

KAJ BLENNOW,
visiting professor for a three-year tenure at the Institute

As part of a program financed with the support of the French Alzheimer Research Foundation and Fondation Sorbonne Université (AXA Chair), supported by the AXA Research Fund, Paris Brain Institute began its collaboration with Kaj Blennow as visiting professor in April 2023. A pioneer and world leader in the field of biomarkers for neurodegenerative diseases, he leads the clinical neurochemistry laboratory at Sahlgrenska University Hospital in Gothenburg, Sweden. At the Institute, he is developing a project to study and research biomarkers of Alzheimer's disease in cerebrospinal fluid and blood, to better

understand the natural history of the disease and improve diagnostic accuracy. He is working with Nicolas Villain in Marie-Claude Potier's team and with team co-director Stéphane Haïk, Director of the French National Center of Reference for Prion Diseases, to analyze new biomarkers of neurodegeneration. He is also working with the Memory Institute (Institut de la mémoire et de la maladie d'Alzheimer) (IM2A), the ARAMIS laboratory at Paris Brain Institute, headed by Olivier Colliot, and the Biochemistry Department at Pitié-Salpêtrière Hospital, run by Foudil Lamari.

FOCUS ON...



Cellular and molecular neurobiology

The primary objective of the teams working in this field is to identify the genetic, molecular and cellular mechanisms underlying brain function during development and aging. This fundamental knowledge is essential for understanding major brain functions and neurological and psychiatric diseases, and for developing new therapeutic targets.



Research field manager: Stéphanie Baulac, Inserm Research Director, Team Leader

THE ROLE OF PERIPHERAL IMMUNE CELLS IN NEURODEGENERATION

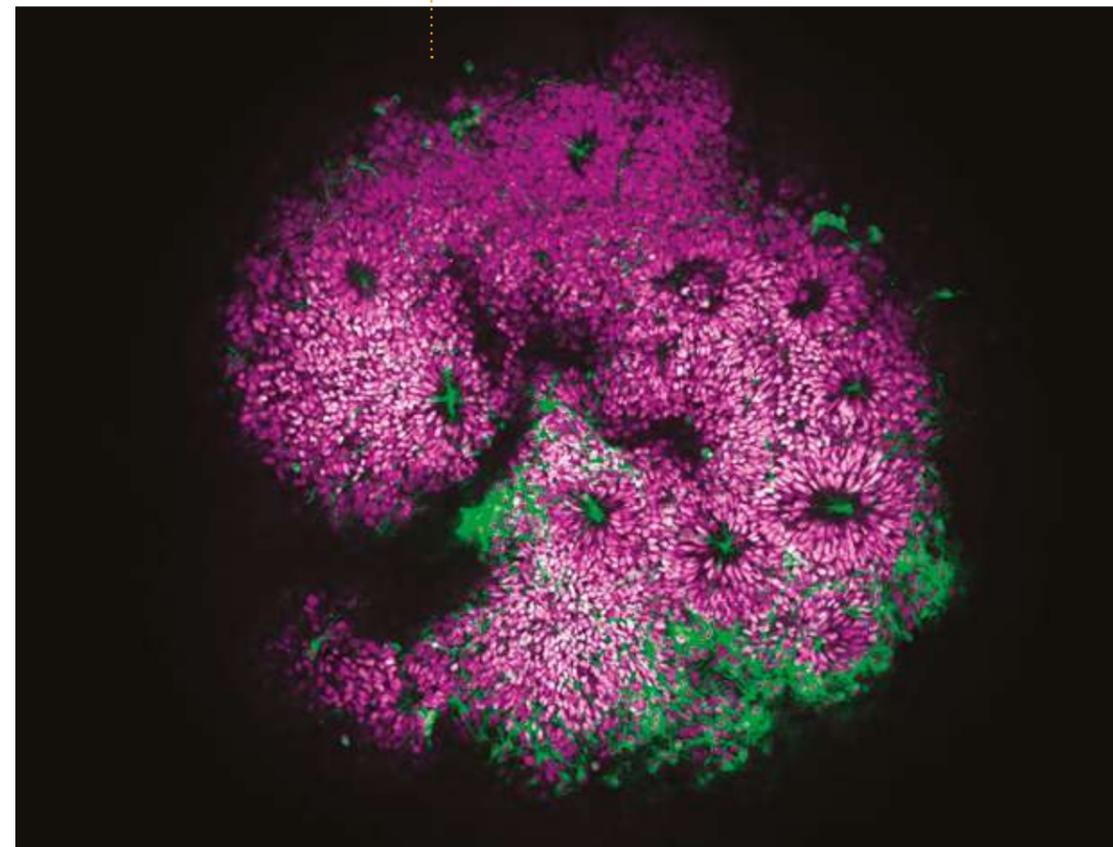
During neurodegeneration, the body reacts by triggering an inflammatory process, mobilizing various immune cells. These include brain-resident microglial cells, which are directly activated. In some cases, inflammation also recruits monocytes, macrophages and lymphocytes, "peripheral" immune cells that are present in other parts of the body. While these cells were thought to act only after infiltrating the central nervous system, recent data suggest that some of them may also act earlier, on the periphery, and may modify the course of neurodegenerative processes. After having shown that microglial cells and peripheral macrophages respond very differently to the motor neuron degeneration, and modifying these macrophages, at the periphery, can slow down amyotrophic lateral sclerosis (ALS) disease progression, researchers at Paris Brain Institute have been invited by *Nature Neuroscience* to conduct a literature review comparing existing and emerging evidence of the role of peripheral immune cells in ALS and other neurodegenerative diseases. In ALS, macrophages can directly act at the periphery on the neurodegeneration of the central nervous system. A comparable situation has also been demonstrated for Alzheimer's disease, where peripheral macrophages play an important role in eliminating amyloid deposits in the cerebral vasculature.

Berriat F. *et al. Nat Neurosci.* 2023
ALS: Causes and Mechanisms of Motor Neuron Degeneration team

COULD ALZHEIMER'S DISEASE HAVE A NEURODEVELOPMENTAL ORIGIN?

While neurodegenerative diseases are generally diagnosed between the ages of 40 and 60, scientists believe that the decline of certain neuronal connections and populations begins much earlier, several decades before the first clinical signs appear. This loss of connectivity is itself a reflection of anomalies at a molecular level, present from childhood or even before. Scientists at the Institute have this year demonstrated that some of these early mechanisms involve the amyloid precursor protein (APP). The role of this protein is to regulate neurogenesis - the differentiation of stem cells into different nerve cell lines. Analysis has shown that in certain individuals, subtle disruptions to this mechanism could cause vulnerabilities that only become apparent in adulthood, after decades of biological stress.

Shabani K. *et al. Science advances.* 2023
Brain Development team



BRAIN TUMORS: THE ROLE OF CELL SENEESCENCE REVEALED

Glioblastomas are the most common malignant tumors occurring in the adult brain. They survive and recur after conventional treatment, which consists of surgery followed by a radiation therapy and chemotherapy protocol. In a recently published study, researchers at the Institute examined the role of senescent cells - cells that have stopped dividing - in the progression of glioblastoma. In particular, they demonstrated *in vitro* that the use of molecules targeting and killing senescent cells had the effect of modifying the tumor ecosystem and slowing its progression. Modulating cellular senescence could therefore be an interesting therapeutic approach to complement conventional treatments for glioblastoma.

Salam R, Saliou A. *et al. Nat Commun.* 2023

Genetics and Development of Nervous System Tumors team

Cortical organoid under confocal microscopy (magenta: all cells; white: progenitor cells; green: immature neurons)

SPINOCEREBELLAR ATAXIAS: WIDE VARIABILITY IN THE AGE OF ONSET OF SYMPTOMS

Spinocerebellar ataxias form a very heterogeneous group of hereditary diseases, which differ as much in their genetic origin as in their clinical manifestations and course. They are characterized by degeneration of the cerebellum - the region at the back of the skull that plays an essential role in motor control. Patients exhibit progressively worsening gait and balance disorders. While the better-known ataxias are caused by a specific type of mutation (triplet repeat expansions), there are also forms of the disease resulting from other genetic changes. However, the study of these non-expansion-related ataxias has proven problematic because they are so rare, making it difficult to establish correlations between genetic variations and the resulting symptoms. At the initiative of a team from Paris Brain Institute, an international consortium has collected genetic and clinical data from 756 individuals with variants in one of the seven genes associated with spinocerebellar ataxias without known repeats. One of the most astonishing results was the very wide heterogeneity in the age of onset of symptoms, which ranged from birth to age 75. Despite this variability, disease progression was generally slow. This suggests the presence of genes or other modifying factors in addition to the causal gene: it is very important that this is studied so we can provide the best possible advice to people carrying this gene.

Cunha P. *et al. The American Journal of Human Genetics.* 2023

Basic to Translational Neurogenetics team

COMPETITIVE EXAMINATIONS

SARA BIZZOTTO has been successful in the competitive examination to qualify as an Inserm research associate. Her work within the Genetics and Pathophysiology of Epilepsy team focuses on the cellular processes that form the human brain.



MATHIEU BARBIER was also successful in the competitive examination to qualify as an Inserm research associate. His research in the Basic to Translational Neurogenetics team aims to better understand the molecular mechanisms underlying frontotemporal lobar degeneration (FTLD), in order to predict and treat FTLD.



Integrative neurophysiology

The teams specializing in neurophysiology study the mechanisms and neuronal interactions underlying sensory processing, cognition and motor control. Their main objective is to characterize the activity of synapses – areas between neurons where information is exchanged – and of microcircuits and whole-brain networks. This research also seeks to understand how and why behavior – or movement-linked neuronal activity malfunctions in pathological conditions such as an epileptic seizure or a motor block during gait in Parkinson’s disease.



Manager for the research field: Brian Lau, replaced by (from January 1, 2024) Claire Wyart, Inserm Research Director, Team Leader

CEREBRAL BLOOD VOLUME, VISUAL INFORMATION PROCESSING AND GAZE CONTROL

To better understand how the brain enables us to perform different sets of tasks, we need to be able to record neuronal activity simultaneously on a number of spatio-temporal scales. Unfortunately, these recordings are sometimes complex to carry out. Scientists at the Institute have succeeded in recording neuronal activity (on a small spatial scale) and variations in cerebral blood flow (on a large spatial scale). In an attempt to investigate variations in the correlation between the two phenomena, they conducted a study combining functional ultrasound imaging of cerebral blood volume and recordings of neurons in the visual and medial frontal cortex during a gaze-control task. The results of their work showed that neuronal activity and cerebral blood volume were indeed statistically correlated, but only during task execution, and not at rest or before commencing the task. The links between variations in neuronal activity and neurovascular changes during motor activities lasting several minutes are not yet fully understood.

Claron J. *et al. Cell reports. 2023*
◉ Mov’It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

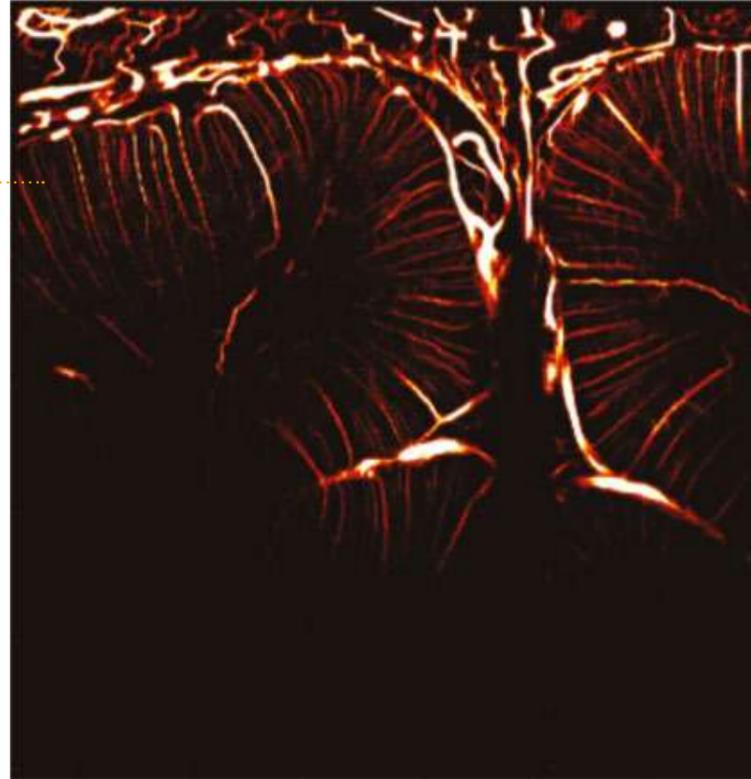


Image of brain vasculature in animals

NEW MAPPING OF NEURONS INVOLVED IN LOCOMOTION

Walking is a complex mechanism involving both automatic processes and volitional control. Gait disturbances can have multiple, sometimes extremely subtle, causes in the motor cortex, brain stem, spinal cord or muscles. Recent work at the Institute has shown that walking is controlled by a region classically known as the “mesencephalic locomotor region”, which controls the vigor and speed of movement and transmits the nerve message to the spinal cord via control neurons located in the brain stem. This new mapping, carried out in zebrafish, could ultimately contribute to our understanding of the movement control circuits that are deficient in Parkinson’s disease.

Carbo-Tano M. *et al. Nat Neurosci. 2023*
◉ Sensory Spinal Signaling team

EPISODIC MEMORY ENCODING AND RETRIEVAL

The brain is traversed by electrical waves of varied and specific frequencies, which differ according to the tasks performed or the state of consciousness (wakefulness, sleep, etc.). When in active stand-by mode, our brains emit primarily fast waves, known as “beta” waves (from 12 to 30 Hz). During intense intellectual and mental activity, we see the appearance of specific gamma waves (around 40 Hz). While alpha waves (8 to 12 Hz) predominate during light relaxation or wakefulness, theta waves (4 to 8 Hz) appear during deep relaxation and REM sleep. Research carried out in 2023 on memory encoding and retrieval concludes that gamma oscillations are coupled to the peak of the theta rhythm during memory encoding and to the trough of the theta rhythm during memory retrieval. Furthermore, the degree of theta-gamma phase opposition is associated with memory performance.

LSA di Chanaz. *et al. Current Biology. 2023*
◉ FrontLAB: Frontal Functions and Pathology team

A GATEWAY TO THE POSSIBLE

Every night, we cross a bridge between wakefulness and sleeping. We know little about this bridge – the period when we are falling asleep – because this transition between states is brief and we can barely remember it. Numerous artists and inventors, such as Salvador Dalí and Thomas Edison, were fascinated by this period and considered it a true source of creative inspiration. Following her thesis work on the link between falling sleep and creativity, Célia Lacaux, a PhD student from the MOV’IT team, won the NOMIS & Science Young Explorer Award, giving her an opportunity to write a paper on her thesis work for the journal *Science*. In this article, she shows that the transition between wakefulness and sleep offers a gateway to creativity. This discovery, which touches on one of the most essential human capacities, has far-reaching implications for humanity.

Lacaux C. *Science. 2022*
◉ Mov’It: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

NIKOLAS KARALIS,

who was recently recruited by the Institute as a team leader, was successful in the competitive examination to qualify as Inserm research associate, and has been awarded ATIP-AVENIR certification under the Inserm/CNRS ATIP-AVENIR grant program. His work will focus on the effect of the combination of neuromodulators and body signals, such as breathing and heart rate, on internal states such as sleep, hunger, fear and happiness.



JÉRÔME MUNUERA was also successful in the competitive examination to qualify as Inserm research associate. His work in the Experimental Neurosurgery team aims to identify and understand the neurocognitive mechanisms of reward and its interaction with motivation and learning processes.

Cognitive neuroscience

The aim of research in this field, where psychology intersects with biology, is to identify the brain circuits behind mental processes and how they are impaired by disease, treatment and rehabilitation. In more detail, the teams study how the brain encodes language, attention, consciousness, motivation, decision-making, cognitive biases, behavioral control, creativity, reasoning, mood, emotion and the effects of social influences.

To shed light onto the hidden neurocognitive foundations of these mental processes, the teams combine behavioral testing, mathematical modeling and brain imaging. They apply these tools to investigate cognition in healthy people, and in patients with disorders such as depression, apathy, dementia, aphasia, and impaired planning, reasoning and behavioral control. Findings from this field of research offer an understanding of neurological and psychiatric disease through the lens of behavior and brain imaging, which has implications for the development of novel treatment strategies.

HOW DO OUR TASTES INFLUENCE OUR CREATIVITY?

The more we love an idea, the faster we bring it to life. But to be creative, you need to have a knack for ideas that are extraordinary. New behavioral study and a computational model, which reproduces the various components of the creative process, researchers have been able to describe how individual preferences influence the speed at which new ideas emerge, along with their degree of creativity. These preferences determine which ideas we decide to use and communicate to others.



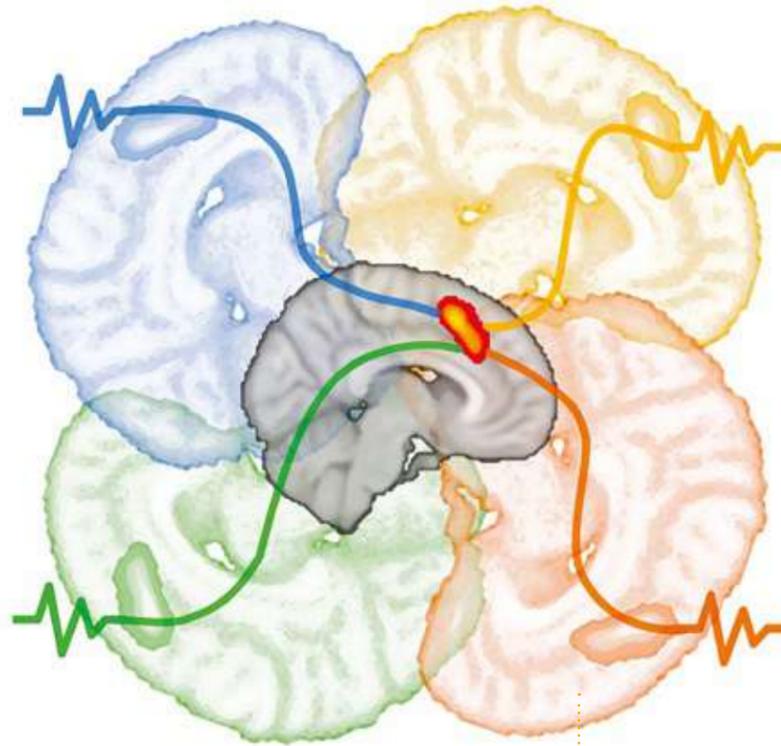
Manager for the research field:
Liane Schmidt, Inserm Research Associate, Team Leader

Lopez-Persem A. *et al. Am Psychol.* 2023
FrontLAB: Frontal Functions and Pathology team

DORSOMEDIAL PREFRONTAL CORTEX/DORSAL ANTERIOR CINGULATE CORTEX: AVENUES FOR FUTURE RESEARCH

The dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (dmPFC/dACC) is an area of the brain that is the subject of many theories and controversies, in relation to its function and its precise anatomical limits. Over the past few decades, this region has been associated with more than 15 different cognitive processes, some of which appear to be unrelated, such as body image and cognitive conflict. Several major theories have emerged to explain its main function. Researchers at Paris Brain Institute have made a review of the state of the art that explains these theories in more detail, along with their convergences and disagreements, and suggests future pathways towards a better understanding of the function(s) of this region.

Clairis N. *et al. Brain.* 2023
FrontLAB: Frontal Functions and Pathology team



Representation of the dorsomedial prefrontal cortex/dorsal anterior cingulate cortex (center) and the various theories (four colors) surrounding its function and the cerebral signal it represents

MARION ROUAULT, who was promoted to CNRS research associate in 2022 in the Motivation, Brain and Behavior team, has been awarded Early Career Scientist funding from the French National Research Agency (ANR) for her work on the brain mechanisms involved in self-confidence and their effects on learning and decision-making.



COMPETITIVE FUNDING

ANATOMY AS A BASIS FOR THE STUDY OF BRAIN FUNCTION

Anatomically-based identification of functional networks, namely long-distance fiber connections, appears to be a promising approach for identifying the anatomo-functional patterns involved in cognitive tasks in healthy brains. Researchers at the Institute have concluded that these specific patterns of anatomical white matter disconnection could predict the recovery of brain-injured patients and their cognitive recovery after procedures such as transcranial magnetic stimulation (TMS).

Kaufmann B.-C. *et al. Brain.* 2023
PICNIC - Physiological Investigation of Clinically Normal and Impaired Cognition team

RAPHAËL LE BOUC

has been awarded an interface contract under an initiative launched by the Institute in 2023 to enable doctors in the Neuroscience DMU to dedicate 50% of their time to research as part of an Institute team for a period of three to five years. Raphaël conducts research on cognitive functions such as procrastination and decision-making in the Motivation, Brain and Behavior team.



INTERFACE CONTRACTS

BRAIN ACTIVITY IN LANGUAGE PROCESSING, A MARKER OF CONSCIOUSNESS

A team from the Institute has carried out a study to explore the language processing abilities of patients suffering from consciousness disorders. The team recorded brain activity using electroencephalograms (EEGs) in healthy volunteers and at patients' bedsides as they listened to two types of auditory stimuli: real words (for example, "apricot") or pronounceable pseudowords (such as "logatome"). In healthy volunteers, this test enabled them to isolate two successive cerebral responses, the second of which seems to be specific to awareness of the word's meaning. In 19 patients, ten of whom were in a minimally conscious state and nine in a vegetative state (also known as "unresponsive wakefulness syndrome"), the test identified this second response in some of the individuals tested. Virtually all patients with this response improved in the following months. These very encouraging results suggest that this new test could have diagnostic and prognostic value in terms of probing the state of consciousness and its recovery in non-communicative patients.

Ben Salah A. *et al. Ann Neurol.* 2023
PICNIC - Physiological Investigation of Clinically Normal and Impaired Cognition team

Clinical and translational neuroscience

From the laboratory to the patient's bedside and *vice versa*, the main objective of the teams in this research field is to promote the development of translational research into neurological and psychiatric diseases. Their scientific approach aims to understand the physiology and pathophysiology of the brain, using human diseases as models. The objective is to provide innovative tools for the clinical assessment of symptoms, diagnosis, for identifying biomarkers of progression, and the design of new therapies. This research requires the creation of patient cohorts with clear characterizations in terms of their phenotypic and biological features, using molecular biomarkers, brain imaging or electrophysiological criteria. These approaches make it possible to study molecular and cellular pathological mechanisms and promote targeted, personalized medicine.



Manager for the research field:
Jean-Christophe Corvol, PU-PH
 AP-HP/Sorbonne University,
 Team Leader, Acting Medical
 Director of the Institute

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: SEARCHING FOR WAYS TO IMPROVE MANAGEMENT AND TREATMENT

The diagnosis of primary central nervous system lymphoma (PCNSL) is based on brain biopsy in a compatible brain imaging context. The clinical course of PCNSL is extremely heterogeneous and the prognosis is poor. In fact, two thirds of patients present with a relapse or a resistance to treatment, and only one third of patients are fully responsive. To aid the diagnosis and prognosis of PCNSL, scientists at Paris Brain Institute have sought to define patient profiles based on analysis of the DNA, RNA and epigenetic changes of tumor cells, as well as the clinical and radiological findings observed. A joint analysis of these data identified four specific profiles associated with a prognosis that was more or less severe, and rapid progression. This work represents a promising pathway for improved stratification of prognosis and the introduction of faster, more targeted therapy.

Hernández-Verdin I. *et al. Ann Oncol.* 2023
 • **Genetics and Development of Nervous System Tumors team**

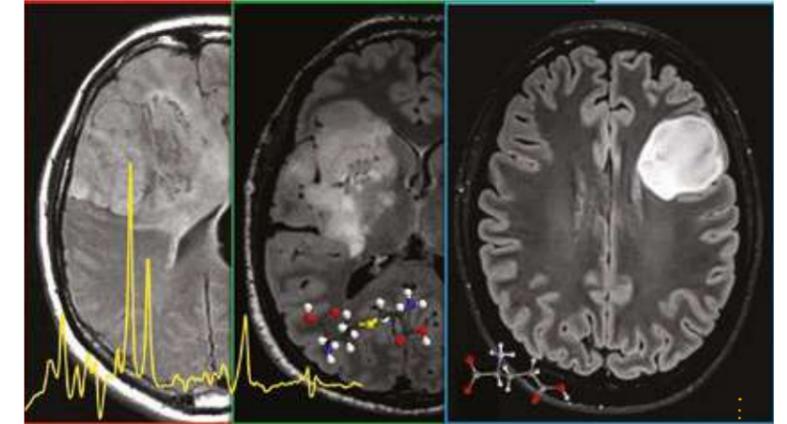


Anonymized MRI of a patient with central nervous system lymphoma

THE EFFECTS OF DEFERIPRONE IN PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disorder that specifically affects the dopamine-producing neurons in the substantia nigra in the brain. Previous research has shown that there is too much iron in the substantia nigra of Parkinson's patients, and that this build-up could be partly responsible for the loss of neurons. Deferiprone is a drug that binds iron and increases iron elimination. In cooperation with Lille University Hospital, the promoter of the study, and the French clinical research network for Parkinson's disease (NS-PARK/FCRIN), the Institute's team was involved in setting up and running a therapeutic trial testing deferiprone in Parkinson's patients in the early stages of the disease. The results of this study showed that this molecule reduced the amount of iron in the substantia nigra, but unfortunately this effect was not associated with a benefit for disease progression compared with the placebo. The reasons for this failure are still to be determined and are the subject of further research.

Devos D. *et al. N Engl J Med.* 2022
 • **Molecular Pathophysiology of Parkinson's Disease team**



Three glioma subtypes distinguished by MRI according to the presence or absence of IDH gene mutation

REFINING THE DIAGNOSIS AND TREATMENT OF GLIOMAS USING MRI SPECTROMETRY

Non-invasive identification of brain tumor subtypes is important for optimizing treatment strategies. In glioma tumors, tumor cells can exhibit a mutation of the IDH1 gene and deletion of segments of chromosomes 1 and 19. This combination of genetic abnormalities is associated with a more favorable prognosis, and results in the accumulation of two oncometabolites - D-2HG and cystathionine - in tumor cells. Work carried out at the Institute in 2023 on 31 individuals with and without these mutations validated a magnetic resonance spectroscopy method, a non-invasive MRI technique, for detecting and quantifying oncometabolites present in the brain. This research confirms that it is possible to diagnose gliomas using a simple MRI scan, and paves the way for tailored therapies for patients identified in this way.

Branzoli F. *et al. Radiology.* 2023
 • **Genetics and Development of Nervous System Tumors team**

ANTI-CD20 THERAPY, MULTIPLE SCLEROSIS AND COVID-19

Some individuals with multiple sclerosis (MS) treated with immunosuppressants are at increased risk of developing a severe form of Covid-19. However, it is still unclear whether this severity was associated with the immunosuppressive therapies administered, such as anti-CD20, or with the severity of their neurological disabilities. A cohort study conducted at Paris Brain Institute revealed

that the risk of severe Covid-19 was higher in people with primary-progressive MS (PPMS) than in those with relapsing-remitting MS (RRMS), suggesting a relationship between Covid-19 severity and severity of the disability. Furthermore, anti-CD20 therapy was also associated with an increased risk of severe Covid-19 in RRMS or incipient PPMS patients, suggesting that this treatment plays

a role in the severity of Covid-19 infection in patients with limited disability.

Januel E. *et al. JAMA Netw Open.* 2023
 • **Repair in Multiple Sclerosis: from Biology to Clinical Translation team**

CÉLINE LOUAPRE and MEHDI TOUAT

have been awarded interface contracts under an initiative launched by the Institute in 2023 to enable doctors in the Neuroscience DMU to dedicate 50% of their time to research as part of an Institute team for a period of three to five years.

Céline Louapre will be developing her research on multiple sclerosis, particularly on the contribution of new technical developments in MRI to analysis of the pathophysiological mechanisms of this disease.

Mehdi Touat will be conducting research on brain tumor genetics, translational oncology, and mechanisms of glioma resistance to chemotherapy and immunotherapy in the Genetics and Development of Nervous System Tumors team.



Computational modeling in neuroscience

Mathematical and computational modelling of brain mechanisms on a varying scale is essential to our understanding of healthy and pathological brain function. Teams in this field are developing exploratory methods, including network science, signal and image processing, machine learning and artificial intelligence, to interpret and analyze data from neuroscience research to enable better diagnosis and prognosis of neurological and psychiatric diseases.



Manager for the research field:
Jacobo Sitt,
Inserm Research Director

CORRELATION ANALYSIS OF VARIED AND HETEROGENEOUS BIOLOGICAL DATA

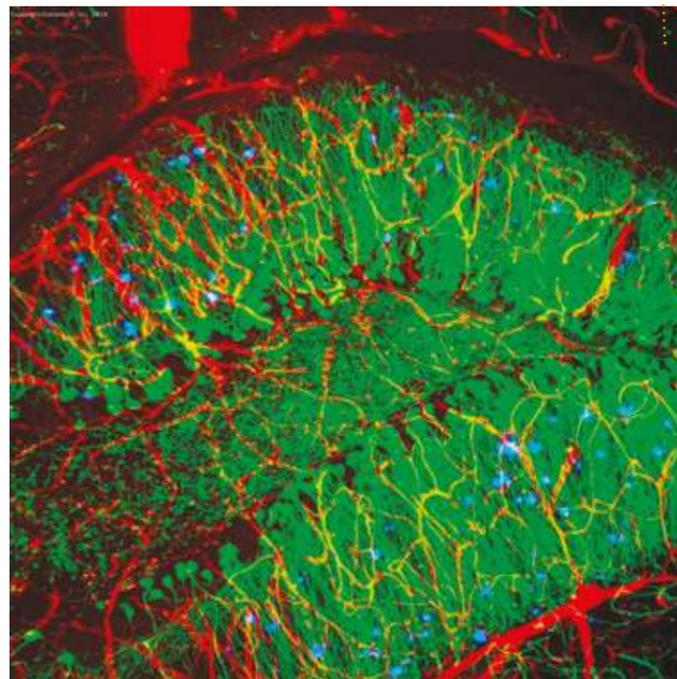
The transient inflammatory states observed in MS patients result in the production of molecules by immune cells. These generate valuable genomic, transcriptomic and metabolomic data - known as "multi-omic" data - but their volume and diversity make them difficult to analyze. This is why we use data fusion to analyze them, seeking to exploit the synergies among them, a process that provides better results than an individual analysis. This year, one of the Institute's teams developed a statistical program enabling the simultaneous analysis of numerous data to identify the factors responsible for the disease and to set new therapeutic targets.

Girka F. *et al. Information Fusion. 2023*
Myelin Plasticity and Regeneration team

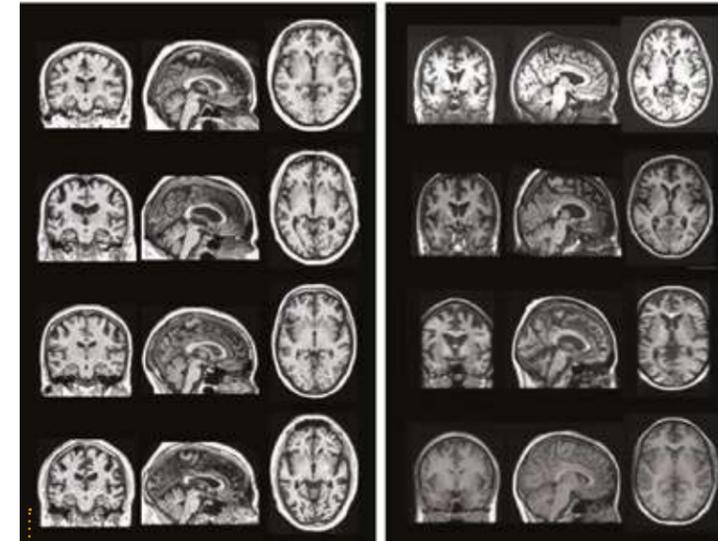
PREDICTING INDIVIDUAL TRAJECTORIES OF ALZHEIMER'S DISEASE PROGRESSION

Anticipating the progression of Alzheimer's disease is crucial for evaluating secondary prevention measures designed to modify the trajectory of the disease. However, it is difficult to predict the natural progression of the disease, especially as many functions decline at different ages and rates in different patients. By analyzing the neuropsychological assessments and imaging biomarkers of 4,600 patients, scientists have developed a statistical model that predicts the progression of the disease in a given person at a given time during the course of the disease.

Maheux E. *et al. Nat Commun. 2023*
ARAMIS - Algorithms, Models and Methods for Images and Signals of the Human Brain team



Brain showing hallmarks of Alzheimer's disease (plaques in blue)



Comparison of MRI images from research and routine clinical use

USING ARTIFICIAL INTELLIGENCE FOR DIAGNOSIS

Various algorithms have been proposed for computer-assisted diagnosis of dementia in Alzheimer's disease based on anatomical MRI of the brain. These approaches are highly accurate when applied to research datasets, but their performance on real-life routine clinical data had not yet been evaluated. Researchers and statisticians at the Institute have therefore carried out the relevant tests. It was found that the performance of the algorithms was significantly lower when applied to routine clinical data than when applied to research data. There are therefore still challenges to be overcome before computer-aided diagnosis systems for dementia can be transposed to routine clinical practice.

Bottani S. *et al. Med Image Anal. 2023*
ARAMIS - Algorithms, Models and Methods for Images and Signals of the Human Brain team

PREDICTING STROKE OUTCOMES WITH MRI IN THE ACUTE PHASE

Advances in artificial intelligence, and particularly with machine learning, could be applied to acute stroke imaging to build powerful predictive models to supplant traditionally used biomarkers. Recent work at the Institute has sought to evaluate the performance and interpretability of a machine-learning model based on MRI results acquired on day 1 after a stroke. These results could point the way to patient categorization strategies for neuroprotective and rehabilitative therapies, to optimize patient recovery.

Moulton E. *et al. J Cereb Blood Flow Metab. 2023*
Mov'it: Movement, Investigation, Therapeutics. Normal and Abnormal Motor Control: Movement Disorders and Experimental Therapeutics team

NINON BURGOS, a CNRS researcher in the ARAMIS team, has been awarded Early Career Scientist funding from the French National Research Agency (ANR) for her work on the individual analysis of medical images to improve differential diagnosis and strengthen personalized medicine.



COMPETITIVE FUNDING

Research and treatment: the Institute's actions focused squarely on the patient

Paris Brain Institute's clinical and translational research activities, which have historically been a core part of its mission and underpin its status as a university teaching hospital, are structured around the Neuroscience Clinical Investigation Center (Neuroscience CIC), the clinical research facilities (iCRINs) within the hospital departments at Hôpital Pitié-Salpêtrière, national and international networks of experts and in-house multidisciplinary teams. This synergy between these complementary and collaborative structures makes it possible for the Institute to conduct outstanding clinical research, serving patients and society as a whole.

Complementary, collaborative structures

A PIVOTAL YEAR FOR THE NEUROSCIENCE CIC

The Neuroscience CIC is a clinical research platform located on the first floor of Paris Brain Institute. The facility is responsible for coordinating and organizing clinical trials, and numerous patients suffering from neurological and psychiatric diseases come to the CIC every day to take part in this research.

After the upheavals of the Covid-19 period, which led to changes in its organization, the CIC's activities have returned to full capacity over the past year. In 2023 the teams strengthened the CIC's quality approach, providing a guarantee of the ethics, safety and quality of the data collected and the scientific excellence of the clinical research conducted there. An internal audit was carried out in September 2023 with a view to obtaining ISO 9001 certification. The activities have become more structured, with the consolidation of the CIC's management team, comprising three people dedicated to coordinating clinical trials, overseeing quality and the management of clinical research staff and, finally, the structure's financial management. *"This year saw the culmination of work to formalize our organization so that we can meet the scientific challenges of the future. A structure that brings*



together research units and clinical units, with such support from our institutions, is unique," emphasizes Céline Louapre, Joint Director of the CIC.

Through the support of Paris Brain Institute and the AP-HP, the possibility of conducting night-time monitoring when required for a clinical trial became a reality at the CIC in September 2023. In early-phase trials - which account for half of the therapeutic studies undertaken in the CIC - this means that the volunteers included can be monitored for 24 hours after administration of the drug.

The CIC has also embarked on a project to create a dedicated website. This has become essential to the visibility of the teams' activities for all concerned: healthcare professionals, sponsors, patients, healthy volunteers and institutions. The site is due to be launched in 2024.

In April 2023 the CIC organized a half-day retrospective on its 12 years of clinical research since it was first established at Paris Brain Institute. The aim was to promote the work carried out and the benefits for patients. The CIC's activities are the intermediary stage between research and the evolution of care. This retrospective highlighted the work done every day by the research teams at the CIC and its impact on healthcare.

CLINICAL RESEARCH FACILITIES (iCRINs)

The aim of Paris Brain Institute's clinical research facilities (iCRINs) is to

develop interactions and the sharing of expertise between the Neuroscience Department (DMU) at Pitié-Salpêtrière Hospital (AP-HP) and the Institute's research teams. The funding allocated to these facilities is intended to meet the specific needs of each clinical department in developing its clinical research activities. There are 13 iCRINs.

OPTIMIZING THE PROMOTION OF CLINICAL TRIALS AT THE INSTITUTE

Clinical trials conducted at the Institute are coordinated by the Research Involving Human Subjects (RIPH) Support Unit for the Institute's research teams, and by Neurotrials for industrial partners. In both cases, the same team provides support with procedures that are the responsibility of the sponsor: administrative activities, help with writing and revising the research protocol and essential documents, regulatory submissions, compliance for the processing of personal data in liaison with the Data Protection Officer (DPO), performing the implementation visit, monitoring the study investigation site, closure of the investigation site, and archiving of documents and data, etc. The RIPH Support Unit has grown over recent years, with an increasing number of studies being taken on: since the unit was set up in 2019, three studies have been completed,

13 are in progress and six are being prepared.

THE STRENGTH OF NATIONAL CLINICAL RESEARCH NETWORKS

The CIC is part of three national clinical research networks, which enable the national coordination of multi-center clinical trials, making it possible to improve the efficiency and quality of trials carried out for therapeutic and pathophysiological clinical research purposes. Paris Brain Institute hosts two of these networks - F-CRIN4MS for multiple sclerosis (coordinated by Céline Louapre) and Act4ALS-MND for amyotrophic lateral sclerosis and motor neuron diseases (coordinated by Gaëlle Bruneteau). Finally, the Institute is heavily involved in the NS-Park network for Parkinson's disease, hosted by the Toulouse University Hospital, for which Jean-Christophe Corvol is one of the coordinators.



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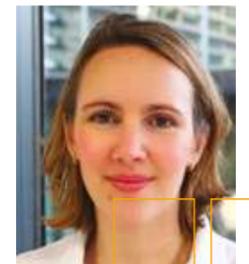


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This year saw the culmination of work to formalize our organization so that we can rise to the scientific challenges ahead. A structure that brings together research units and clinical units, with such support from our institutions, is unique.

Céline Louapre, Joint Director of the CIC



AMANDINE DIETRICH, Healthcare Supervisor at the Neuroscience CIC

What is your role as a healthcare supervisor?

► My role is to ensure effective, coordinated and compliant management of clinical research activities, while guaranteeing the quality of care provided to study participants. It's a role at the intersection between research and treatment. In operational terms, I manage a multidisciplinary paramedical team of around twenty people (clinical research nurses, laboratory technicians, neuropsychologists, care assistants, medical secretaries, etc.), to organize and optimize clinical research

activities. I'm also responsible for the CIC's quality policy, working in tandem with the clinical trials coordinator.

What projects are you planning to work on in the coming months?

► Of course, we need to be prepared for the arrival of new protocols. We're working to maintain compliance with the ethical, legal and regulatory requirements in force, and to meet the quality obligations of the ISO 9001 standard. The creation of the CIC's website is also a major milestone for the visibility of our activities.

The 13 iCRINs at Paris Brain Institute

Strokes



Charlotte Rosso
(AP-HP/Sorbonne University)

Orthopedic Surgery



Hugues Pascal-Moussellard
(AP-HP/Sorbonne University)

Alzheimer's Disease



Richard Lévy
(AP-HP/Sorbonne University)

Parkinson's Disease and Movement Disorders



David Grabli
(AP-HP/Sorbonne University)

Neurosurgery



Carine Karachi and Alexandre Carpentier
(AP-HP/Sorbonne University)

Neurogenetics



Alexandra Durr
(AP-HP/Sorbonne University)

Neuro-oncology



Ahmed Idbaih
(AP-HP/Sorbonne University)

Adult Psychiatry



Bruno Millet
(AP-HP/Sorbonne University)

Multiple Sclerosis



Bruno Stankoff and Catherine Lubetzki
(AP-HP/Sorbonne University)

Amyotrophic Lateral Sclerosis (ALS)



François Salachas
(AP-HP/Sorbonne University)

Neurological Intensive Care



Sophie Demeret
(AP-HP/Sorbonne University)

Sleep



Isabelle Arnulf
(AP-HP/Sorbonne University)

Cranial Trauma



Éléonore Bayen
(AP-HP/Sorbonne University)

Key clinical trials in 2022-2023

Antisense messenger RNA (mRNA) therapies modulates the expression of certain target proteins in the central nervous system by administering fragments of genetic material capable of specifically suppressing the expression of certain genes. Among these therapies, Tofersen has produced good results in certain genetic forms of amyotrophic lateral sclerosis (ALS). In 2023, the Neuroscience CIC has been inspected by the health authorities validating the quality of the Tofersen study. This drug can currently be used on a compassionate basis (expanded access), pending marketing authorization.

In cooperation with an industrial partner, Paris Brain Institute has conducted a clinical trial, the only one of its kind in the world, to measure the effect on neuroinflammation of ocrelizumab, a drug already indicated for relapsing forms of multiple sclerosis (MS). This study relies on the expertise of the research team led by Bruno Stankoff and Catherine Lubetzki in positron-emission tomography (PET) neuroimaging and the CIC's rigorous monitoring of patients included in its clinical trials. The 55 volunteers recruited will be monitored for two years. The aim is to observe the effects of the drug on disease mechanisms and physiology, to understand why some patients may not respond to treatment. The results are expected by 2025.

Another study being conducted at the CIC in cooperation with an industrial partner tested the effect of a monoclonal antibody targeting alpha-synuclein (α -Syn), the protein that builds up pathologically in patients with Parkinson's disease, on the motor symptoms associated with this pathology. Initial results show a significant slowdown in the progression of the disease. New studies will be set up to continue the development of this compound, which is still in the trial phase.

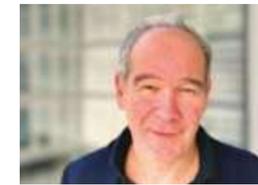
A world first in the field of spinocerebellar ataxias, a phase I trial, which is intended to include between five and ten patients, began in September 2023. The aim of this trial is to test protocols for targeted therapies using antisense RNA (asRNA).



Encouraging people to get involved in clinical research

In recent years, Paris Brain Institute has successfully run a number of programs designed to encourage exchanges between clinicians and researchers:

- The STARE educational program that gives third-year medical students an introduction to neuroscience research;
- The DÉCLIC immersion program, developed in cooperation with the Neuroscience DMU at Pitié-Salpêtrière Hospital, which offers the Institute's research personnel the opportunity to undertake a placement in a clinical department;
- "Paramed Days" at Paris Brain Institute for paramedical staff from the Neuroscience DMU, with the aim of supporting the development of paramedical research.



ADULT PSYCHIATRY ICRIN with Bruno Millet, Manager of the iCRIN and Professor of Psychiatry at Pitié-Salpêtrière Hospital

The mission of the Psychiatry iCRIN is to develop new forms of therapy for psychiatric disorders. Its activities are focused on three key areas.

The first, based on the "digital phenotype", aims to combine machine-learning approaches with different types of sensors to determine a patient's condition and measure changes in real time, not just during consultations. The Redress trial, carried out in cooperation with Ad Scientiam, was part of this project. Its objective was to detect early non-response to antidepressants using smartphone-based tests. The results are currently being analyzed.

The second area of focus is the development of new non-invasive (transcranial magnetic stimulation) and invasive (deep-brain stimulation) neuromodulation methods. In this sphere, the Psychiatry iCRIN has supported the implementation of the ORBITOC trial, which aims to measure the therapeutic potential

of magnetic stimulation of the orbitofrontal cortex in obsessive-compulsive disorder.

Lastly, the iCRIN is working on the development of new therapeutic trials. Clinical teams have completed a trial in post-traumatic stress disorder. It involves the use of a drug treatment, propranolol, and exposure to the traumatic event to reduce the emotional charge of the memory. The results are encouraging and are expected to be published in the coming months.

"Many other projects are under development," stresses Bruno Millet, "such as pharmacogenetic approaches to depression and the development of new digital patient monitoring tools. The iCRIN enables us to recruit clinical research associates and is an invaluable resource in setting up our studies."

FOCUS ON..

1,114 patients included in clinical trials, 573 in the CIC and 541 in the 13 iCRINs.

88 trials under way in the CIC, including 22 new studies launched in 2023. 39 are sponsored by institutional partners and 49 by industrial partners.

102 trials under way in the iCRINs, 78 sponsored by institutional partners and 24 by industrial partners.

13 trials are currently sponsored by Paris Brain Institute.

1,994 visits by patients to the CIC and 1,832 to all iCRINs.

These figures cover the period from October 1, 2022 to September 30, 2023.

Technological excellence to serve research and patients

The 11 core facilities at the Institute give its teams, as well as teams at other research institutes and at industrial partners, access to state-of-the-art equipment, and to expertise in acquiring, interpreting and using data from specialists in these technologies. They offer researchers the opportunity to explore and understand brain mechanisms under normal or pathological conditions, on the basis of a single neuron or the whole brain.

<p>iGenSeq</p> <p>▶ Sara Baldassari</p>	<p>iGenSeq, the ISO 9001- and GIS IBISA-certified genotyping and sequencing core facility, specializes in genome analysis techniques (DNA and RNA) to detect mutations or variations in the expression of disease-associated genes. iGenSeq is part of the France Génomique network.</p> <p><i>ISO 9001:2015 (excluding provision of equipment and animal DNA and RNA genotyping)</i></p>	<p>▶ Yannick Marie</p> 
<p>ICV</p> <p>▶ Philippe Ravassard</p>	<p>The Cell Engineering and Vectorology core facility is organized around four technology platforms.</p> <p>Cell culture - cell models and tools for their culture.</p> <p>Cytometry - multiparameter flow cytometry, cell sorting and characterization of cytokines and chemokines.</p> <p>Vectorology - production of viral vectors for gene transfer.</p> <p><i>The Vectorology core facility is ISO 9001:2015-certified (excluding provision of equipment)</i></p> <p>IPs - human-induced pluripotent stem cells (iPSC).</p>	<p>▶ Laetitia Strehl</p>  <p>▶ Laetitia Strehl and Jérôme Van Wassenhove</p>  <p>▶ Blandine Bonnamy</p>  <p>▶ Stéphanie Bigou</p> 
<p>Ephys</p> <p>▶ Nelson Rebola</p>	<p>The Ephys platform specializes in electrophysiology and offers a wide range of technology approaches such as functional screening of cell excitability, functional characterization of iPSC-derived human neurons and exploration of drug effects.</p>	<p>▶ Carine Dalle, Charlotte Deleuze and Delphine Rousset</p> 
<p>Histomics</p> <p>▶ Brahim Nait Oumesmar</p>	<p>The Histomics platform provides scientific teams with all the infrastructure required for histological tissue analysis: from standard analysis (cutting, staining, immunohistochemistry) to advanced analysis such as image analysis using artificial intelligence or spatial transcriptomics.</p>	<p>▶ Annick Prigent</p> 
<p>ICM.Quant</p> <p>▶ Frédéric Darios</p>	<p>The ICM.Quant platform offers access to multiple cutting-edge imaging technologies and essential scientific know-how in electron microscopy, light microscopy and image analysis.</p>	<p>▶ Olivier Renaud</p> 

<p>PhenoParc</p> <p>▶ Philippe Ravassard</p>	<p>The PhenoParc platform specializes in the development of preclinical functional exploration protocols that are essential for effective, preclinical applied research.</p>	<p>▶ Sophie Nunes-Figueiredo, Nadège Sarrazin and Morgane Weissenburger</p> 
<p>CENIR</p> <p>▶ Stéphane Lehéricy</p> <p>▶ Nathalie George</p> <p>▶ Marie-Laure Welter</p> <p>▶ Carine Karachi</p> <p>▶ Marie-Odile Habert</p> <p>▶ Pierre Pouget</p>	<p>The CENIR neuroimaging core facility comprises six technology platforms.</p> <p>MRI neuroimaging</p> <p>MEG-EEG</p> <p>PANAM - physiology and movement analysis center</p> <p>STIM - neuroimaging analysis software</p> <p>PET-MRI</p> <p>PA-MRI for imaging experimental disease models for translational research projects</p>	<p>▶ Eric Bardinet</p>  <p>▶ Laurent Hugueville</p>  <p>▶ Jean-Charles Lamy</p>  <p>▶ Sara Fernandez Vidal</p>  <p>▶ Eric Bardinet</p>  <p>▶ Mathieu Santin</p> 
<p>PRISME</p> <p>▶ Mathias Pessiglione and Philippe Fossati</p>	<p>PRISME specializes in the study of brain function and normal and pathological human behavior.</p>	<p>▶ Karim N'Diaye</p> 
<p>Data Analysis Core</p> <p>▶ Violetta Zujovic</p>	<p>The Data Analysis Core platform specializes in biomedical computing. It provides targeted data analysis methods, from experimental study design to data analysis.</p>	<p>▶ Stephen Whitmarsh</p> 
<p>DNA & Cell Bank</p> <p>▶ Alexis Brice</p>	<p>The DNA & Cell Bank is a Biological Resource Center (BRC) platform specializing in the collection, processing, conservation and provision of samples from patients and controls.</p>	<p>▶ Sylvie Forlani</p> 
<p>RnD Unit</p> <p>▶ Charly Rousseau</p>	<p>The purpose of the RnD unit is to provide equipment and advice to develop innovative and unique tools not available on the market.</p>	<p>▶ Pierre Tissier</p> 

Core facilities in continuous development

In 2023, a new research and development facility (RnD Unit) has been added to the technology offering available to Paris Brain Institute's research teams. Core facility teams have also been boosted, with the recruitment of several operational managers.

Creation of the RnD Unit

Paris Brain Institute's RnD Unit core facility was created in January 2023 with the aim of developing new, innovative and non-commercial tools based on the needs and ideas of scientists, to remove technological barriers to the advancement of research. With its highly qualified engineering staff (electrical, mechanical, prototyping, design) and fast response times, the facility can provide teams with prototypes within very short lead times. The facility's role relies on rapid manufacturing techniques such as 3D printing and laser cutting, which are well suited to customized production. For example, in cooperation with a research team and a neurosurgeon, the RnD Unit facility has developed a tool capable of reducing intracerebral electrode implantation time by 60%. A patent has been filed for this innovation.

The RnD Unit's electronic development laboratory



Flow cytometry, a new area of expertise for the cell engineering facility

In 2023, the Institute supplemented its available technologies within the cell engineering core facility by integrating the IHU ICAN flow cytometry platform. This technology qualitatively and quantitatively characterizes populations of cells or particles present in a suspension and sorts them according to various parameters. The system will be used by many of the Institute's basic and clinical research teams to gain a better understanding of cell mechanisms in the healthy brain and in pathological conditions. It is the tool of choice for studying resistance to treatments, and is also used in neuroimmunology research to study inflammatory diseases of the central nervous system such as multiple sclerosis.

Sésame Filières funding awarded - Neuro@7T

The MRI sector development project, coordinated by Stéphane Lehericy, was selected in 2023 as part of the Île-de-France Region Sésame Filières call for projects. With expertise in pathological signal detection that is unique in the Paris Region, and support for healthcare research, this program aims to foster the emergence of an original healthcare sector for the deployment of new digital technologies and methodologies to aid diagnosis and treatment in the fields of neuroscience and neurological and psychiatric pathologies. The sector will develop and apply more intelligent treatment plan solutions that are directly usable by researchers, clinicians involved in research and hospital doctors for the benefit of patients, based on imaging data for diagnosing and monitoring major brain and spinal cord pathologies. It will develop new biomarkers of pathological processes, enabling more accurate assessments of the effect of therapeutics.



Analysis and sorting of a sample using flow cytometry on the ICV platform



SIMOA® equipment

Large-scale investment to upgrade technological equipment

In 2023, Paris Brain Institute invested four million euros in state-of-the-art equipment, including:

- a latest-generation DNA sequencer, the Novaseq +, housed within the iGenSeq platform, which substantially reduces the time and cost of whole-genome sequencing, accelerating advances in genetic research;
- equipment acquired as part of the Histomics platform, the GeoMx Digital Spatial Profiler (DSP) for spatial transcriptomics, which can localize more than 20,000 RNA targets and 150 proteins in tissue;
- a Juno system, on the DNA & Cell Bank platform, which now enables systematic genotyping of DNA samples before they are made available to research teams;

• SIMOA® technology equipment, acquired with the support of Fondation Claude Pompidou, for research coordinated by the team of Marie-Claude Potier together with our visiting professor Kaj Blennow on Alzheimer's disease, to enable ultrasensitive detection of biomarkers in blood samples.

NeurATRIS program

NeurATRIS is a translational research facility for innovative therapies in the neurosciences, awarded 28 million euros over ten years as part of the French Government's 2012 Investissements d'Avenir investment program. Paris Brain Institute is one of five partners, along with CEA Paris-Saclay, Groupe Hospitalier Henri Mondor - UPEC, Institut des Biothérapies pour les maladies rares (BIRD) and Inserm. The NeurATRIS program has contributed 3.5 million euros to the development of four Paris Brain Institute platforms.

FOCUS ON...

NEW EXPERTISE

To provide a state-of-the-art service, investments in core facility equipment have been combined with expanding our teams. New experts have joined the Institute:

Olivier Renaud
Operational Manager of ICM.Quant

Charly Rousseau
Scientific Manager of the new RnD Unit platform

Stephen Whitmarsh
Operational Manager of the Data Analysis Core platform



STEPHEN WHITMARSH, Operational Manager of the Data Analysis Core (DAC) facility on January 2023

What does the Data Analysis Core platform do?

▶ The Data Analysis Core facility (DAC) supports researchers in analyzing and managing their data. The omics division analyses genetic and genomic data from cells in patient cohorts and from cells at different stages of brain development. The statistics & methodology division provides advice on the design of protocols and analysis to maximize discoveries and insights in research studies. The image analysis division exploits machine learning and artificial

intelligence to analyze images, from sub-cellular to whole-brain scale. The data management & open science division helps organize and share valuable research data from unique patient cohorts.

What are the challenges of data analysis?

▶ The DAC provides expertise that responds to a technology-driven field. This requires constant exchange in working groups, steering committees, and international conferences. Increasingly multimodal and multi-cohort studies require coordination within and between platforms and an effort in optimizing data management within the Institute.

What were last year's major successes?

▶ Following the success of our tool for whole-tissue transcriptomic analysis, we developed an online data exploration tool for single-cell transcriptomics. A new image analysis division provides algorithms for image processing and cell segmentation for spatial transcriptomics. With the neuroimaging facility, we are developing artificial intelligence approaches to reduce biases (linked to age, gender or the technical specificities of imaging tools) to better understand the effects of disease on brain anatomy. Finally, we implemented the institute's Data Policy in a new Data Management Plan template.

THREE QUESTIONS FOR...

International partnerships

Paris Brain Institute's international reach is reflected in a vast network of some 300 partnerships worldwide. These collaborative relationships make it possible to pool progress and to pursue joint research, training and knowledge transfer projects.

CURE-ND (FRANCE, GERMANY, BELGIUM, UNITED KINGDOM)

A European network of excellence in neurodegenerative diseases, the CURE-ND (Catalysing a United Response in Europe to Neurodegenerative Diseases) consortium brings together Paris Brain Institute, the UK Dementia Research Institute (UK-DRI), Germany's DZNE and Belgium's Mission Lucidity (VIB, UK-Leuven, UZ Leuven, imec). Three major meetings took place involving scientists from the consortium in 2023: a clinical workshop organized at Paris Brain Institute in February attended by around 100 persons, a special CURE-ND session as part of the *British Neuroscience Association's* annual international conference in Brighton (UK) in April, and a workshop for early career researchers (ECRs), held in Leuven in May.

CURE-ND clinical workshop at Paris Brain Institute



UK-DRI (LONDON, UNITED KINGDOM)

A joint call for tenders between Paris Brain Institute and the UK-DRI funded a shared project involving Marie-Claude Potier, Frances Wiseman and Natalie Ryan. In addition, a Centres of Excellence Network in Neurodegeneration (CoEN) project was undertaken by Marie-Claude Potier, Nicolas Villain and Henrik Zetterberg on the exploration of a specific mutation of the amyloid precursor protein (APP), which generates amyloid peptides that do not aggregate - unlike what happens in Alzheimer's disease - in neuronal models derived from induced stem cells.

TESTIMONIAL

THE BIRTH OF A CROSS-CHANNEL PARTNERSHIP

Marie-Claude Potier is a CNRS Research Director and Head of the Alzheimer's Disease and Prion Diseases team at Paris Brain Institute. In April 2023, at a clinical workshop organized as part of the CURE-ND consortium, she spoke with Natalie Ryan, principal investigator at the University College London Dementia Research Institute. This meeting was the catalyst for a new research project.



Marie-Claude Potier



Natalie Ryan

Natalie Ryan and I found that our research questions were very much complementary. In particular, our discussions focused on amyloid angiopathy. This cerebrovascular disease is fairly common in the elderly, and is comparable to certain symptoms of Alzheimer's disease. It is characterized by a pathological deposition of amyloid peptides in blood vessels, which can lead to cerebral hemorrhage. We came up with the idea of finding a specific blood signature for these peptides to identify the patients most at risk. Natalie is developing a rapid MRI imaging method to detect this type of bleeding in patients. This will be invaluable for testing the effectiveness of the biological analysis we hope to develop at Paris Brain Institute. This blood test would be the first of its kind in the world. In addition to the prospect of better care for at-risk patients, it would also offer great hope for people with trisomy 21, who are currently excluded from therapeutic trials in Alzheimer's disease because of an increased risk of hemorrhage.



« Conversations on Consciousness » at the Columbia University

Baulac, Inserm Research Director at Paris Brain Institute;

Joint Paris Brain Institute-Yale University workshop at Yale (May 2023), on translational research in epilepsy and neuroinflammation in brain diseases;

Cross-disciplinary project on "Monitoring neuroinflammation": a new collaborative research program developed during the December 2022 workshop has been funded through support from a sponsor. This project investigates the markers and mechanisms of neuroinflammation implicated in neurodegenerative diseases, with a focus on multiple sclerosis and movement disorders;

Clinical exchange program: this program enables researchers from both institutions to work as part of the partner's team, dealing with cases and learning about the local approach to diagnosis and treatment.

COLUMBIA UNIVERSITY (NEW YORK, UNITED STATES)

The partnership between Paris Brain Institute and Columbia University continued in 2023. In particular, this cooperation took the form of neuroscience internships within the Institute's teams for Columbia University students. "Conversations on Consciousness", two debates with the Institute's researchers, also took place during the students' four-week stay.

STANFORD UNIVERSITY (CALIFORNIA, UNITED STATES)

We continued to welcome undergraduates from Stanford University for immersion internships with Paris Brain Institute (Stanford University Bing Overseas Studies Program - Paris).

YALE UNIVERSITY (NEW HAVEN, UNITED STATES)

In 2023, we continued our partnership with Yale University, initiated with the aim of establishing an ongoing clinician exchange program. Several major events were organized:

"Cerebral vascular imaging" workshop at the Paris Brain Institute (December 2022): fifteen brain imaging experts from the USA and Paris shared their latest scientific advances and discussed potential joint projects;

Mini-symposium on "Somatic mosaicism in neurological diseases" at Yale (May 2023), with a talk by Stéphanie

MONTREAL NEUROLOGICAL INSTITUTE - MNI (CANADA)

The cooperation agreement between the two institutions has been extended. A call for tenders to develop collaborative projects has been launched, and two joint pilot projects have been selected for 2023, led by:

Julia Sliwa (Paris Brain Institute) and Justine Cléry (MNI): "Identifying neuronal circuits and mechanisms to understand social relationships";

Laurent Cohen (Paris Brain Institute) and Roberto Zatorre (MNI): "Reading text and music: brain specialization and cross-modal interactions".

In addition, Paris Brain Institute welcomed a delegation from the MNI to discuss the organization of a joint Big Brain Theory call for projects in 2024, the development of projects on neurodegeneration, open science and organoids.

SAME-NEUROID (POLAND, FRANCE, GERMANY, NETHERLANDS)

SAME-NeuroID is a Horizon Europe Twinning project launched in October 2022 by Paris Brain Institute, Łukasiewicz PORT - Polish Center for Technology (Poland), the Erasmus Medical Center (EMC, Netherlands) and the Max Planck Institute of Psychiatry (MPI, Germany). The aim is to establish standardized protocols for modeling and researching neuropsychiatric disorders (SAME-NeuroID) at Łukasiewicz PORT.

Following the project kick-off meeting in Wrocław (Poland) in January 2023, a number of events took place throughout the year, including:

- organization of a workshop on "Implementing human stem cell models and cortical organoids for neuroscience research" in Paris in April;

- a visit to Paris Brain Institute by a delegation from Łukasiewicz PORT in May. The event provided an opportunity to explain how the Institute operates and to foster exchanges such as the participation by students in the Brain to Market Summer School in September 2023.

INDIAN INSTITUTE OF TECHNOLOGY - DELHI (NEW DELHI, INDIA)

Paris Brain Institute is involved in the new Franco-Indian Campus set up by Sorbonne University (SU, Paris) and the Indian Institute of Technology Delhi (IITD, New Delhi, India), selected in November 2022 following the French Embassy in India's call for proposals on life sciences for health.

This campus, entitled "Integrated Health" and coordinated by SU, aims to develop academic and scientific cooperation between the two institutions, by promoting the creation of joint master's programs, student mobility at master's and doctoral level, and the establishment of scientific partnerships between researchers from both countries.

Researchers from Paris Brain Institute are fully involved in setting up this Franco-Indian campus. One of the Institute's research professors, H el ene Cheval, is involved in coordinating scientific and academic interactions and exchanges between SU and IITD. On the training side, the iMIND international master's program is one of the starting points for the creation of joint training courses. In just over a year, joint research projects have emerged from meetings with IITD, specifically involving Paris Brain Institute scientists Rahul Gaurav and Liane Schmidt. In addition, the close liaisons between researcher Violetta Zujovic and members of IITD's Humanities and Social Sciences Department in the organization of workshops and seminars has added to Paris Brain Institute's involvement and openness to important societal issues, such as gender inequality and gender bias in research.

TREND IN AFRICA & BIORTC (ABUJA, NIGERIA)

TReND in Africa is an organization that contributes to the advancement of neuroscience education and research in Africa. Since its creation in 2011, it has played a significant role in building a community of African neuroscientists and developing innovative solutions, adapting to limited resources with low-cost technologies. Paris Brain Institute pledged in 2023 to contribute to the development of neuroscience in Africa. Initial discussions have focused on setting up collaborations on best research practices, student exchanges, training opportunities and the organization of workshops.

Latin American Brain Health Institute - Universidad Adolfo Ibanez au Chili

LATIN AMERICAN BRAIN HEALTH INSTITUTE/ADOLFO IBANEZ UNIVERSITY (SANTIAGO, CHILE)

A long-term collaboration on dementia and brain health (RedLat) has been launched between Paris Brain Institute and the Latin American Brain Health Institute - Adolfo Ibanez University in Chile. The launch meeting for this partnership was held in Santiago in July 2023. A cooperation agreement was also signed in 2023.



JACOBO SITT,

Inserm Research Director at Paris Brain Institute

What was the starting point for cooperation with research institutes in South America?

► Several researchers at Paris Brain Institute have already established collaborative scientific links with colleagues in South America. We saw the potential to take this to a different scale, on an institutional basis. The Institute wanted to develop new partnerships with countries in the Southern Hemisphere. This year, we signed an agreement with the Latin American Brain Health Institute, which brings together laboratories from Mexico to Argentina.

What are the benefits and challenges of these partnerships?

► There is a great deal of complementarity between

our work and the activities of research institutes in Latin America. There is a real interest in sharing our data, for example. Our studies in France are mainly based on genotypes typical of Europe and the United States, but we have a lot to learn about the pathophysiology of neurological and psychiatric diseases in people from other parts of the world, in terms of both genetics and environment. It is also a challenge to find the best way to share data. From a methodological point of view, we also have much to share in terms of know-how and interdisciplinary approaches, including the development of new biomarkers, statistical methods, neuroimaging protocols and computer modeling.

What is happening next?

► We need to find resources to foster partnerships between our institutes and set up joint calls for projects. Funding opportunities for collaborative projects between Europe and South America are limited. So we need to develop the tools to provide the necessary resources for these exchanges. Then we need to showcase the potential of these international partnerships, to demonstrate just how important they are for both continents.

THREE QUESTIONS FOR...

Paris Brain Institute's Innovation department is focused on accelerating the delivery of therapeutic solutions that can benefit patients and society as a whole.



INNOVATION

Accelerating innovation to benefit patients

Since its inception, Paris Brain Institute has nurtured a strong ambition for innovation, driven by the research excellence of its laboratories. Its goal is to accelerate the creation and transfer of knowledge, skills and techniques, to support the rapid development of solutions for patients.

Promoting research discoveries

FOUR NEW PATENT APPLICATIONS

As of September 30, 2023, the Institute has a portfolio of 58 active patents. Over the last annual budget year, it filed four new patent applications and protected three new software programs. Two of these patents relate to vectors for gene therapy and two to artificial intelligence algorithms for imaging analysis. Two software applications have been developed in partnership with the company Humans Matter, a company specialized in cognitive design. The softwares will be integrated on their platform used by speech pathologists for brain-injured patients rehabilitation.

INCREASINGLY ACTIVE INDUSTRIAL PARTNERSHIPS

The Institute fosters a large number of active industrial collaborations, with 62 new partnerships signed in 2023, totalling €3 million. In parallel, the MediTwin project was launched in 2023 by a consortium between the IHU France alliance and four of their start-ups, including two from Paris Brain Institute (Qairnel and Neurometers), Inria and Dassault Systèmes. The aim of this project is to develop personalized virtual twins of organs, metabolism and cancerous tumors, to enable better diagnosis and treatment. For five years, from 2024 to 2029, the MediTwin consortium partners will work together to develop digital tools designed to improve the patient care pathway, from diagnosis to therapy. Paris Brain Institute will bring its expertise in the detection of Alzheimer's disease, vascular dementia and epilepsy, and in the analysis of data from patient cohorts.



Driving the development of products and services for patients

A HEALTH INNOVATION PLAN FOR 2030

In 2022, Paris Brain Institute published its 2030 Health Innovation Plan. That was when the Research Applications Department (DAR) became the Innovation Department, endowed with a new "acceleration" hub providing new tools to boost the future industry value of projects developed at the Institute. The first tools deployed through this new mechanism include a "GENOV" gene therapy technological development and innovation unit, created in late 2022 to accelerate the market introduction of concrete solutions to the most pressing healthcare needs. GENOV has seen positive business growth, with a number of contracts signed in its first year of operation.

The NeurAL program, a launchpad to identify and endorse the most promising startup projects and help them get off the ground, was launched in March 2023, with support from the Fondation Anne et Claude Berda. This is the first seed program to support R&D projects in the neurosciences. It aims to ensure that the technological development of such projects is sufficiently solid to benefit from significant seed funding, leading to the creation or acceleration of startup companies. It identifies and endorses some of the most promising scientific projects, helps them to minimize risk in their startup phase and in developing their business models, guiding them in building sound business strategies. This initiative was born out of the realization that France lacked the capacity to bring together leading technical and industrial expertise in the complex field of neuroscience.

NEUROTRIALS: OPTIMIZING THE PERFORMANCE OF CLINICAL TRIALS SPONSORED BY INDUSTRIAL PARTNERS

The Institute's roadmap for the professional application of clinical research tools to support industrial partners led to the creation of a dedicated unit, Neurotrials, in 2018. This unit, which currently pools its resources with the RIPH Support Unit, operates on behalf of industrial sponsors in the management of clinical trials/studies (regulatory management, medical/scientific advice, medical writing, quality assurance, study management, etc.).

It continued to expand in 2023, bringing the number of collaborations with industrial customers on clinical trials and medical, scientific and regulatory consulting to around 15 since its creation in 2019. Thanks to the integration of this unit into the Institute's ecosystem, and more broadly into the Neuroscience DMU, Neurotrials is leveraging unique scientific and technical know-how to offer its industrial partners the academic expertise coupled with optimal operational efficiency required for industrial clinical development.



FRANÇOISE PIGUET,
Director of the technological development and innovation unit
GENOV



What is GENOV?

GENOV is a technological development and innovation unit specializes in gene and cell therapy for neurodegenerative diseases and rare diseases known as "storage disorders" in children and adults. Gene therapy makes it possible to treat patients with a single administration of a medicated gene carried by viral vectors (inactivated, non-infectious viruses) delivered to the relevant cells in the brain. To optimize these therapeutic strategies, we are working on improving injection methods to make them as minimally invasive as possible, while effectively targeting the brain and spinal cord.

How did the first year of operation go?

This has been a very important year for GENOV. Our team has succeeded in establishing several proofs of concept for new treatments in the preclinical phase (cell therapy, gene therapy). Our work has also validated new vectors, enabling efficient targeting of the brain after intravenous injection, and demonstrated the efficacy of an ultrasound technique for opening the blood-brain barrier. In addition, we have exceeded our expectations by establishing collaborations with a number of industrial partners for cell and gene therapy trials.

What are the challenges for the coming year and beyond?

Even though we've had some great successes this year, we need to keep up our efforts. We will, of course, continue to work on the structure of viral vectors to regulate the level of drug gene expression once present in cells. The development of an intracerebral injection system under MRI with real-time visualization of diffusion of the therapeutic product in the brain is another area on which the team will be focusing its work. We will also be setting up clinical trials based on approaches we have developed for diseases such as metachromatic leukodystrophy and mucopolysaccharidosis. The team has also set itself the goal of forging more collaborative relationships with major industrial groups, to further develop our operations. And, of course, we will continue to patent new therapeutic methods.

Each year, NeurAL intends to select projects in the fields of therapeutics, medical technologies and digital solutions, from world-renowned academic research institutions focusing on neuroscience and nervous system disorders. In addition to personalized support, the two winners selected in 2023 received funding to help develop their projects.

◊ The aim for the **IGHOR project** is to develop and test a new chemical entity for the treatment of glioblastoma, specifically targeting a hormone receptor. This project was awarded the sum of €250,000, along with the Anne and Claude Berda Individual Prize for Innovation (€10,000).

◊ The **CicaNEURO project** is developing two new chemical entities for the treatment of neurodegenerative disorders. Through a chemical process the team transformed antibiotics into neuroprotective and anti-inflammatory molecules with a first in class lead compound targeting Parkinson's disease. It was awarded a grant of €100,000.



THE "SLEEPING BEAUTIES" PROGRAMME: THERAPEUTIC POTENTIAL TO EXPLORE

Launched in 2018, the "Sleeping Beauties" programme, performed in collaboration with leading academic medicinal chemists, enables the in vitro screening and early-stage development of molecules of therapeutic interest in the field of nervous system diseases. In 2023, this collaborative effort made it possible to explore the cellular toxicity and efficacy of over 300 molecules. This work has been carried out within six translational research projects focused on Alzheimer's disease, Parkinson's disease and glioblastoma.

In addition, the integration of three new in vitro models, two of which developed by Dr. Brahim Nait Oumesmar's team at the Institute, paved the way for the evaluation of 80 new molecules for the treatment of multiple sclerosis. This collaboration demonstrates the Institute's lasting commitment to discovering new therapies for patients.



62
new industrial agreements

58
active patents

8
therapeutic molecules under development

29
startups incubated, including 5 in 2023

1
digital health startup acceleration program

INNOVATION AT THE INSTITUTE

THE BRAIN & MIND BIOCLUSTER: BUILDING A NEUROSCIENCE INNOVATION HUB

In May 2023, the French President announced that the Brain & Mind biocluster had won the second call of the "France 2030" plan's call for expressions of interest. The aim of this call was to create world-class clusters of excellence bringing together business, healthcare, research and breakthrough innovations - with the ambition of transforming the French biomedical research landscape.

THE CARE LAB: DESIGNERS WORKING TO HELP PATIENTS AND THEIR CAREGIVERS

Established in 2015 by Paris Brain Institute and AP-HP, and located in the heart of Pitié-Salpêtrière Hospital, the Care Lab is a specialized neurology and psychiatry laboratory created with the aim of co-constructing, designing, prototyping and field-testing innovations (technologies, products, services). In 2023, the Care Lab team has stepped up its efforts to improve quality of life for patients. A project proposed by caregivers in the Epilepsy Department at the AP-HP's Pitié-Salpêtrière Hospital has been finalized. Therapeutic education tools have been jointly developed and made available in hospital services - receiving patients with epilepsy and multiple sclerosis. The Strokecare program with the partner

Humans Matter continued, with three new solutions under development. Lastly, four startups have been supported, including the company Diampark. This support, with collaboration from the hospital's "Parkinson's" unit, has led to the development of DigiPark, a digital medical device designed to support patients with Parkinson's disease and their carers, and Motiv'Park, a therapeutic education game designed specifically for the same patients.



THE CARE LAB, an innovation laboratory dedicated to neurology and psychiatry

Positioned in a unique open-innovation ecosystem within the Neuroscience DMU at Pitié-Salpêtrière Hospital, the Care Lab is a team of three designers whose mission is to develop concrete solutions with an immediate impact on improving patients' lives. The model is based on close cooperation between patients, healthcare professionals and innovation players, from needs assessment and idea generation through to market entry.

An approach based on design thinking

The originality of Care Lab's approach lies in the application of design thinking to the healthcare sector. This user-centered methodology is based on co-creation, creativity and iteration. The Care Lab team applies this method throughout the design process, from idea to prototype generation, in collaboration with the Institute's Information Systems Department and R&D Unit. The organization of creativity workshops in medical departments, along with the program open to student designers, are essential levers for identifying painpoints, needs and proposing solutions to integrate into the patient's care pathway.



Leveraging feedback for innovation

The Caregiver Initiative program offers healthcare professionals in the Neuroscience DMU the opportunity to submit ideas that could be selected for co-development with the support of the Care Lab. The aim is to develop these new innovative solutions, and through industrial partnerships, company startups creation or in-house development, bring these new technologies to as many patients and health professionals as possible. The Care Lab therefore draws strength and inspiration from the ecosystem

development and intellectual property teams, and by the iPEPS startup incubator.

Successful synergies with industrial partners

Finally, the Care Lab is forging successful collaborative links with industrial partners, particularly Humans Matter as part of the specific program "Strokecare" dedicated to patients suffering from brain injuries. It is this synergy between the various players that helps to uncover innovative solutions tailored to patients' specific needs.

FOCUS ON...

THE CARNOT LABEL, ESSENTIAL SUPPORT FOR PARTNERSHIP RESEARCH

Established in 2006, the Carnot Label was designed to address the need for partnership-based research. Namely, it supports public research organizations to develop and carry out research in partnership with socio-economic players, primarily industry (from SMEs to large corporations). The aim is to prepare for the industrial and economic future by supporting all companies in their innovation and transformation strategies.

By 2023, the Carnot network encompassed 39 institutes. The 35,000 research professionals within the Carnot institutes, representing 20% of the human talent pool involved in public research, implemented 55% of the R&D contracts outsourced by companies to public research organizations.

In 2020, the four-year renewal of its Carnot Label enabled Paris Brain Institute to finance Carnot Maturation projects, the Skills Build-up program, Carnot Training and scientific resourcing initiatives, including conferences organized at the Institute, editors days, etc.

2024 will be an important year because of the upcoming renewal process.



Supporting new startups

iPEPS: 10 YEARS ON

Over the past 10 years, Paris Brain Institute's business incubator, iPEPS, has supported over 70 startups, helping them to raise funds (over €600 million), recruit (over 1,000 jobs created) and improve patients' lives (15 products launched on the market).

A ceremony was held in late 2022 to celebrate this decade of success with incubated startups, Institute management and incubator partners.

NEW STARTUPS INCUBATED

Five startups joined the iPEPS incubator in 2023, gaining access to a unique environment dedicated to the technological development and accelerated growth of healthcare startups:

Actipulse Neuroscience® is a brain technology company developing a non-invasive brain stimulation platform to treat a range of central nervous system disorders at home. It is currently in phase III of a pivotal study for the treatment of major depressive disorder. The

teams are also conducting trials for the treatment of brain tumors.

Callyope is developing a voice-based remote monitoring solution to prevent psychiatric relapse. Its voice analysis technology can be used to assess the severity of symptoms in severe depression, bipolar disorder and schizophrenia.

AiiNTENSE is a digital platform to support medical decision-making and the management of patients with neurological or post-resuscitation pathologies.

Qairnel is a spin off startup that emerged from research by Stanley Durrleman and Igor Koval, two researchers at Paris Brain Institute who have developed and patented a methodology for predicting the progression of Alzheimer's disease in a diagnosed patient. It is developing a digital solution, Clinique du Docteur Memo, which aims to identify symptoms early, offering patients a personalized and coordinated pathway with a specialist team, and proposes inclusion in appropriate clinical trials, thanks to artificial intelligence algorithms.



Ziwig uses molecular biology and artificial intelligence to identify new biomarkers in saliva. This individual information, combined with real-life data on its Multi-Omics platform, can be used to diagnose numerous diseases, predict the effectiveness of treatments, track the course of diseases and disorders, create new services and digital therapeutics, and accelerate research and clinical trials.



A SECOND ROUND FOR THE IMPACT SANTÉ MENTALE PROGRAM

The result of an innovative public/private partnership*, "IMPACT Santé mentale" aims to develop or accelerate innovative solutions to address gaps in mental healthcare for young adults and adults. It is based on a call for collaborative, partnership-based projects, open to e-health startups proposing solutions built around priority themes such as access to care, patient management, follow-up and continuity of care in non-hospital settings.

Building on the success of the first, the members of the IMPACT initiative launched the second round of the program in early 2023 to promote innovation in mental health. The focus was on three themes: prevention, follow-up and care for psychiatrists and their patients, and continuity of patient care in non-hospital settings.

The five startups selected in 2023 (Healthy Mind, O-Kidia, Callyope, Sémia and Shifters) were given nine months of unprecedented support from the initiative's partners, including mentoring, coaching, networking and specific modules (health data, assessing the impact of solutions, mental health from several angles, etc.) and access to experimental sites.

* The project partners are PariSanté Campus, Fondation Université Paris Cité, AP-HP, Otsuka, Eisai, France Biotech and France Assureurs. Other partners have joined the project: Groupe VYV and MGEN, the FondaMental Foundation, Groupe Hospitalier Universitaire Paris psychiatrie & neurosciences and Paris Brain Institute's iPEPS.



BRAIN & MIND BIOCLUSTER
A project with a huge social, medical and economic impact

Thanks to a public investment of almost €100 million from France 2030, the Brain & Mind biocluster, announced in May 2023, will roll out large-scale innovation projects supported by multidisciplinary technology platforms. At the initiative of the FondaMental Foundation, Institut de la Vision and Paris Brain Institute, the project aims to take a fresh look at the development of therapeutic and preventive approaches

for both adults and children. The aim is to create an internationally renowned ecosystem for innovation in neuroscience in the Paris region and nationwide. It brings together a community of over 50 scientific, medical and technology partners in the fields of neurology, psychiatry and sensory impairment. Brain & Mind will be headed by Alexis Genin, formerly Director of Innovation at Paris Brain Institute.

Alexis Génin, previously the Institute's Director of Innovation, now leads the Brain & Mind biocluster



Brain & Mind
Paris Region Neuroscience Cluster

Since its creation, one of the core missions of Paris Brain Institute has been to share knowledge with experts, patients and their families, and with citizens interested in its research and progress. This commitment is reflected in our range of training courses, and in a major communications drive aimed at the general public to make neuroscience accessible to everyone.

3

TRAINING & OUTREACH

Education and training

Because passing on and sharing knowledge are part of its core missions, Paris Brain Institute has a proactive approach to its training offer, having developed new programs for a variety of audiences. The Institute's training offer is built around three areas: neuroscience and technology, clinical neuroscience, and neuroscience and innovation.

Neuroscience and technology

The partnership agreement between Paris Brain Institute and Educ'ARTE, the ARTE Group's video-on-demand platform for teachers and students, has been renewed for the 2022-2023 school year. The aim is to continue to promote neuroscience to young people and raise their awareness of the issues involved. The partnership includes an educational project on neuroscience for school classes, and the provision of educational fact sheets and videos. In October 2022, Paris Brain Institute offered a masterclass on the theme "What is the impact of cognitive science research in schools?". Once again this year, the relevance of this project has been praised by the teaching staff and various bodies within the educational community.

The training of future scientists continues at university level through the iMIND international master's program.

Clinical neuroscience

Paris Brain Institute is committed to fostering links between hospitals and its research teams. With this in mind, two programs have been launched at the Institute. The first, the STARE (Stage d'Initiation à la Recherche) research internship program, gives young clinicians an opportunity to work in the Institute's research laboratories. In 2023, 20 new medical students took part in this program and spent two weeks working with the Institute's teams and platforms. In parallel, DÉCLIC program, launched in 2022, offers six researchers from the Institute the chance to spend a week in the neuropathology and neuro-oncology departments of Pitié-Salpêtrière Hospital in Paris.

Neuroscience and innovation

MEDTECH GENERATOR AND ACCELERATOR (MGA) SIA PROJECT

This program, with which a consortium comprising Paris Brain Institute, the Imagine Institute and Institut de la Vision won a call for proposals in 2020, ended in December 2023 and was aimed at accelerating the launch and growth of new startups by offering dedicated innovative support, targeting medical technologies for neurological diseases and genetic and/or rare diseases. As part of the project, 12 e-learning modules were offered to program winners and to other participants. Over 130 people have been able to access the modules. These training courses covered soft skills development as well as key entrepreneurship topics such as intellectual property, regulatory issues and financing.

EPICA PROGRAM

In 2023, Paris Brain Institute developed the Epica project with the Imagine Institute, Institut Pasteur and the startup Cameo, supported by Banque des Territoires-Caisse des Dépôts. Launched at the end of 2022, the program's aim is to offer stakeholders involved in partnership-based innovation in the healthcare sector in France professional training in the methods, techniques and attitudes needed to conduct partnership research projects. It consists of six months of courses and e-learning modules, along with work-based learning in pairs within startups and healthcare establishments. The pairs are made up of students from the public and private sectors, and the process is designed to facilitate the sharing of practices and cultures. This program has been funded for five years, and should be welcoming its first participants in 2024.



IMPROVING CREATIVE PROCESSES THROUGH THE INSTITUTE'S MASTERCLASSES



In addition to its range of training courses for scientists and clinicians, whether at the start of their careers or those with more experience, Paris Brain Institute is committed to offering programs covering non-technical, neuroscience-based skills, aimed at a wider audience. The Institute's annual masterclasses are intended for experts seeking innovation, professionals in the fields of design or artistic creation, managers, consultants, trainers or other project managers wishing to sharpen their creative processes using neuroscience. Last March, the 2023 masterclass was held on the theme of "creativity and neuroscience".

The program included an exploration of the various creative processes at work in the brain, the discovery of scientific tools for understanding and measuring creativity, identifying obstacles to creativity and the conditions that foster creativity.

This program is the result of a unique alliance between two areas of expertise: cutting-edge science and innovative teaching methods. Scientific coordination was provided by creativity researcher Emmanuelle Volle and her team, and other top-level international figures also took part in the courses.

FOCUS ON..

THREE QUESTIONS FOR...

HÉLÈNE CHEVAL, Manager of the Master 2 iMIND program



The iMIND course has been around for a few years now. How would you sum up the experience?

► iMIND is the result of a collaboration between Sorbonne University and Paris Brain Institute. In four years, we have succeeded in developing an attractive master's program (50 applications this year), with original, high-quality teaching in the field of neurodegenerative diseases. We started with six students in 2019 and have now reached our target of 15 students.

What are the advantages of the collaboration between Paris Brain Institute and Sorbonne University for this international Master's program?

► This course has been designed to enable students to benefit from the cutting-edge research carried out at Paris Brain Institute. Many of the Institute's researchers teach on the Master's program, as do the platform engineers. Two of them are also joint directors of teaching units. Paris Brain Institute also offers scholarships for international

students coming to France for the first semester of their Master 2 course.

What's new and what's in store for iMIND?

► As part of the 4EU+ Alliance, in which Sorbonne University participates, we have developed a close partnership with the Molecular Biosciences master's program at the University of Heidelberg (Germany). As an indicator of the quality of this partnership, we have obtained funding to run a summer school in 2024.

This will be open to doctoral and post-doctoral students, with the aim of developing scientific collaborations. We hope to make this a recurring event. Further exchanges with foreign universities are under discussion and we hope to see these finalized in the near future.

Sharing our knowledge for the common good: a key mission

As a key player in the neuroscience landscape, the Institute is actively involved in communicating knowledge to the general public. Providing a range of reliable and accessible sources of information about the brain, how it works and its diseases, gives everyone the keys to a better understanding of current advances in research and, more broadly, sheds light on the growing impact of neuroscience on society.

A stronger, enhanced events offering

Between October 2022 and 2023, the Institute expanded its range of events for the general public, including national events (Annual Science Festival in October 2022, Brain Awareness Week in March 2023) and lecture series organized by the Institute. As pandemic restrictions eased, it was possible to organize an open day during Brain Awareness Week, which saw over 400 people visit the Institute.

To boost audience figures, the quarterly lectures have been renamed "Les Matinales", and they are all now open to the general public through live online access. The premium in-person offer for donors remains unchanged. Lastly, the monthly "Science, Art & Culture" lectures once again featured prestigious figures from the scientific, artistic and cultural worlds. All of these lectures are available on Paris Brain Institute's YouTube channel.



FOCUS

RAISING AWARENESS ON WORLD ALZHEIMER'S DAY

To mark World Alzheimer's Day on September 21, 2023, Paris Brain Institute teamed up with a platform which has a large audience to highlight advances in Alzheimer's research. Two articles and two video interviews were produced and posted online on the Lefigaro.fr website, featuring two of the Institute's scientists, Ninon Burgos and Nicolas Villain, to discuss issues around the disease.

These activities were combined with a digital campaign run by the fundraising teams.



Digital communications and online visibility

Visits to the Institute's website show an excellent uptake (over 1.1 million visitors in 2022, an increase of 19%).

2023 saw the continuation of the project to redesign the website, which will be redeveloped over the course of 2024 for launch in the summer of that year.

There is significant momentum on our social media channels. The Institute has a growing audience on various platforms (Facebook, X, LinkedIn, Instagram, YouTube). Engagement is up by 28% in 2023 compared to 2022, with all five accounts attracting a community of over 90,000 followers.

Lastly, in terms of audiovisual content production, our major video events are growing, with regular content being produced and gaining visibility. Various concepts are developed and published on a regular basis: "Comprendre en 2 minutes" videos, focusing on a quick explanation of a pathology or a team, or "Just Published" formats, presenting recently published research work explained by the scientists themselves.



An increasingly strong media presence

Over the past year, our media presence has been developed significantly, to amplify the reach of the Institute's research work and promote its leadership and innovative approach.

2023 saw a sharp increase in the presence of Paris Brain Institute and its experts on radio, TV, web media and in the traditional press, with a 57% increase in coverage over that period - around 1,200 media coverage opportunities. The Institute has maintained a high profile in the English-language media: the results achieved by the research teams have appeared

in *The Washington Post*, *BBC Future*, *Scientific American*, *Newsweek*, *Nature mag*, *New Scientist*, *MIT News*, etc., and in specialist economics, culture and society media. Exclusive new connections have been forged with journalists from a wide range of backgrounds, so that the Institute can offer them quality scientific information tailored to their target audiences - indirectly reaching an audience of several million people.

Paris Brain Institute is built around a partnership between a public joint research unit (CNRS, Inserm and Sorbonne University) and a private foundation with recognized charitable status, Paris Brain Institute Foundation, working with the AP-HP Paris Public Hospital Network. The Institute's governing bodies reflects the strength of this partnership.



GOVERNANCE

Governing bodies

Board of Directors

The Board of Directors is made up of 15 members divided into four colleges. The Board governs the affairs of the Institute through its deliberations. It decides on the strategic direction proposed by the Executive Director, votes on the budget and approves the Foundation's accounts.

COLLEGE OF FOUNDERS AND MEMBERS OF THE BOARD

- President – Gérard Saillant, Honorary Professor of Orthopedic and Trauma Surgery
- Vice-President – Jean Todt, UN Secretary-General's Special Envoy for Road Safety
- Treasurer – Serge Weinberg, President of Weinberg Capital Partners
- Jean Glavany, Former Minister
- Jean-Pierre Martel, Attorney

COLLEGE OF QUALIFIED PERSONS

- Richard Frackowiak, Emeritus Professor at University College London
- Philippe Ménasché, Professor of Thoracic and Cardiovascular Surgery
- Élisabeth Tournier-Lasserre, Professor of Medical Genetics at Université Paris-Cité

COLLEGE OF FULL MEMBERS

- André Le Bivic, Director of the CNRS's National Institute of Biological Sciences (INSB)
- Didier Samuel, President and CEO of the French National Institute for Health and Medical Research (Inserm)
- Bruno Riou, Dean of the Faculty of Medicine at Sorbonne University
- Nicolas Revel, CEO of Paris Hospital Administration (AP-HP)

COLLEGE OF FRIENDS OF THE FOUNDATION

- Martine Assouline, Co-founder Assouline Editions
- Maurice Lévy, Chairman of the Supervisory Board of Publicis Groupe
- Christian Schmidt de La Brélie, CEO of Klesia

GOVERNMENT COMMISSIONER

- Jean-Marie Paulot

Board committees

SCIENTIFIC ADVISORY BOARD

Consisting of leading international neuroscience experts, the Scientific Advisory Board (SAB) has the task of advising Paris Brain Institute and providing the necessary support in defining its overall strategy.

- President – Prof. Dimitri Kullmann, Clinical & Experimental Epilepsy, UCL Queen Square Institute of Neurology, UK
- Prof. Adrienne Fairhall, Department of Physiology and Biophysics, Department of Physics and Department of Applied Mathematics, Washington University, USA
- Prof. Tamas Gabor, Department of Physiology, Anatomy and Neuroscience, University of Szeged, Hungary
- Prof. Magdalena Goetz, LMU Department of Physiological Genomics, Helmholtz Center Munich, Institute Stem Cell Research, Germany
- Prof. Masud Husain, Wellcome Trust Principal Fellow – Nuffield Department of Clinical Neuroscience – University of Oxford, UK
- Prof. Sabine Kastner, Princeton Neuroscience Institute, USA
- Prof. Giovanna Malluci, Department of Clinical Neurosciences, University of Cambridge, UK
- Prof. Eve Marder, Victor and Gwendolyn Beinfeld Professor of Biology, Brandeis University, USA
- Prof. Elizabeth Phelps, Department of Psychology, Harvard University, USA
- Prof. Carmen Sandi, Laboratory of Behavioral Genetics, Brain Mind Institute, EPFL de Lausanne, Switzerland
- Prof. Erin Schuman, Department of Synaptic Plasticity, Goethe University Frankfurt, Germany
- Prof. Mikael Simons, Institute of Neuronal Cell Biology (TUM-NCB), Technical University Munich, German Center for Neurodegenerative Diseases (DZNE), Germany

AUDIT COMMITTEE

- President – Serge Weinberg, Treasurer of Paris Brain Institute Foundation
- Elli Chatzopoulou, Inserm Representative
- Jean Glavany, Former Minister
- Jean-Pierre Martel, Attorney

APPOINTMENTS AND WAGES COMMITTEE

- President – Serge Weinberg, Treasurer of Paris Brain Institute Foundation
- Elli Chatzopoulou, Inserm Representative
- Jean Glavany, Former Minister
- Jean-Pierre Martel, Attorney

COMMITTEE FOR COORDINATION OF PARIS BRAIN INSTITUTE PARTNERSHIP

- President – Gérard Saillant, President of Paris Brain Institute
- André Le Bivic, CNRS Representative
- Elli Chatzopoulou, Inserm Representative
- Bruno Riou, Sorbonne University Representative
- Erik Domain, AP-HP Representative

ETHICS AND PROFESSIONAL CONDUCT COMMITTEE

The mission of Paris Brain Institute's Ethics and Professional Conduct Committee (Cometh) is to guide reflection on ethical and professional conduct issues raised by scientific and medical research programs, and to help all those involved in research at Paris Brain Institute to comply with the principles governing ethics and professional conduct by facilitating reflection on own practices and contributing to general thinking based on pioneering experiences. Cometh hosts monthly ethics and professional conduct training sessions for new recruits.

FOUNDERS OF PARIS BRAIN INSTITUTE

- Gérard Saillant, Honorary Professor of Orthopedic and Trauma Surgery, President of Paris Brain Institute
- Jean Glavany, Former Minister of Paris Brain Institute Friends Committee
- Jean Todt, UN Secretary-General's Special Envoy for Road Safety, Vice-President of Paris Brain Institute
- Maurice Lévy, Chairman of the Supervisory Board of Publicis Groupe, Co-Chair of Paris Brain Institute Friends Committee
- Yves Agid, Honorary Professor of Neurology and Neuroscience
- Olivier Lyon-Caen, Professor of Neurology, former Director of the Nervous System Diseases Division at Pitié-Salpêtrière University Hospital
- Luc Besson, Film director
- Jean-Pierre Martel, Attorney
- Louis Camilleri, Former CEO of Ferrari
- Lindsay Owen-Jones, Honorary Chair of L'Oréal and of Paris Brain Institute Friends Committee
- David de Rothschild, Honorary Chairman of the Supervisory Board of Rothschild & Co
- Michael Schumacher, Former Formula 1 Driver
- Serge Weinberg, President of Weinberg Capital Partners, Treasurer of Paris Brain Institute

Management Committee (CODIR)*

The senior management team implements the policy developed by Paris Brain Institute's Board of Directors. The Executive Director, appointed by the Board of Directors, leads the five-member management committee.



◉ **Prof. Alexis Brice**
Executive Director of Paris Brain Institute and the Joint Research Unit (UMR)



◉ **Corinne Fortin**
Secretary General of Paris Brain Institute and the Joint Research Unit (UMR)



◉ **Brian Lau**
Scientific Director and Deputy Director of the Joint Research Unit (UMR)



◉ **Jean-Louis Da Costa**
Director of Communications and Development



◉ **Prof. Jean-Christophe Corvol**
Medical Director (acting)

The Support Function Management Committee (CODIS) also leads institutional and interdisciplinary projects and has the following members:

- ◉ **Alexis Brice** – Executive Director
- ◉ **Corinne Fortin** – Secretary General
- ◉ **Pierre Couraud** – Deputy Secretary General
- ◉ **Jean-Louis Da Costa** – Director of Communications and Development
- ◉ **Géraldine Farjot** – Director of Innovation
- ◉ **Pierre Georges-François** – RIPH Unit Manager
- ◉ **Mathilde Gibert** – Director of Legal Affairs
- ◉ **Géraldine Gouzer** – Director of Scientific and Medical Affairs
- ◉ **Sylvain Gugliermi** – Director of the Procurement, Equipment and Logistics Department
- ◉ **Laurine Lenoir** – Director of the Organization and Quality & Risk Management Division
- ◉ **Frédérique Lesaulnier** – Data Protection Officer
- ◉ **Cécile Proust** – Director of Human Resources
- ◉ **Antoine Souquière** – Director of Information Systems
- ◉ **Marc Thévenot** – CFO

* as at March 1, 2024



CODIR Committees

SCIENTIFIC AND MEDICAL STEERING COMMITTEE (COPIL)

The Scientific and Medical Steering Committee (Copil) is a consultative body on all matters related to the Institute's scientific and medical strategy. It provides opinions to the Management Committee (CODIR). Additionally, it has decision-making authority on funding allocations for internal calls for proposals. It brings together five researchers representing the Institute's scientific fields.

- ◉ **Stéphanie Baulac**,
Head of cellular and molecular neurobiology
- ◉ **Céline Louapre**,
Head of Clinical and translational neuroscience
- ◉ **Liane Schmidt**,
Head of cognitive neuroscience
- ◉ **Jacobo Sitt**,
Head of computational modeling in neuroscience
- ◉ **Claire Wyart**,
Head of integrative neurophysiology

TEAMS COUNCIL

The Teams Council, comprising the senior management team and all team leaders, meets once a month. It is consulted on scientific policy, budgetary matters, and resources to be allocated for the UMR.

GENDER EQUITY COMMITTEE

The Gender Equity Committee (GEC) performs an advisory and monitoring role for Paris Brain Institute's governing bodies, and takes action to promote gender equity. The work of the GEC is supported by the Gender Equity Movement (GEM) initiative, a collective of Paris Brain Institute staff who have come together to raise awareness of gender bias and inequities and propose measures to address them.

Following the adoption of the Institute's gender equality charter in 2021, the GEC developed an action plan and continued its work on awareness raising, monitoring statistics and indicators measuring gender distribution at all professional levels, together with communication campaigns and initiatives. Paris Brain Institute's workplace gender equality index has

progressed in recent years, achieving 75 in 2020, 91 in 2021, 89 in 2022 and 90 in 2023, out of a maximum score of 100.

The GEM has been organized into working groups for planning a biennial international workshop and developing a website, journal club, scientist mentoring program and broader educational activities.

Staff representative bodies

SOCIAL AND ECONOMIC COMMITTEE

The task of the Social and Economic Committee (CSE) is to represent the Paris Brain Institute Foundation's staff in dealings with management and relay any individual or collective questions raised concerning the application of labor regulations (Labor Code, pay, working hours, health and safety, etc.).

The role of its Health, Safety and Working Conditions Committee (CSSCT) is to oversee compliance with legal and regulatory requirements, help protect the health and safety of staff and implement measures to improve their well-being, analyze occupational risks, be available for consultation by the employer and assist in reviewing working conditions.

LABORATORY COMMITTEE

The role of the Laboratory Committee is to advise the UMR's management on scientific, budgetary and human resources policy, and on all other matters related to UMR operations. Members are elected by the Institute's public sector staff. They represent the various categories of staff: researchers and teacher-researchers, technical and administrative staff, doctoral students, and permanent and contracted civil servants.

The research conducted at Paris Brain Institute is underpinned by sound, diversified financial resources, and by support teams that pool all the expertise needed to help researchers in the design and implementation of their projects.

5

SUPPORTING
RESEARCH

Technical and regulatory support: a key factor in supporting research

In 2023, the Institute continued the work carried out over the past few years to strengthen its overall support system for scientific teams. The success of this approach is reflected in the Institute's continued efforts to support the professional application and consolidation of in-house technical, regulatory and organizational expertise.

Optimizing project success through the Regulatory and Technical Support Unit (CART)

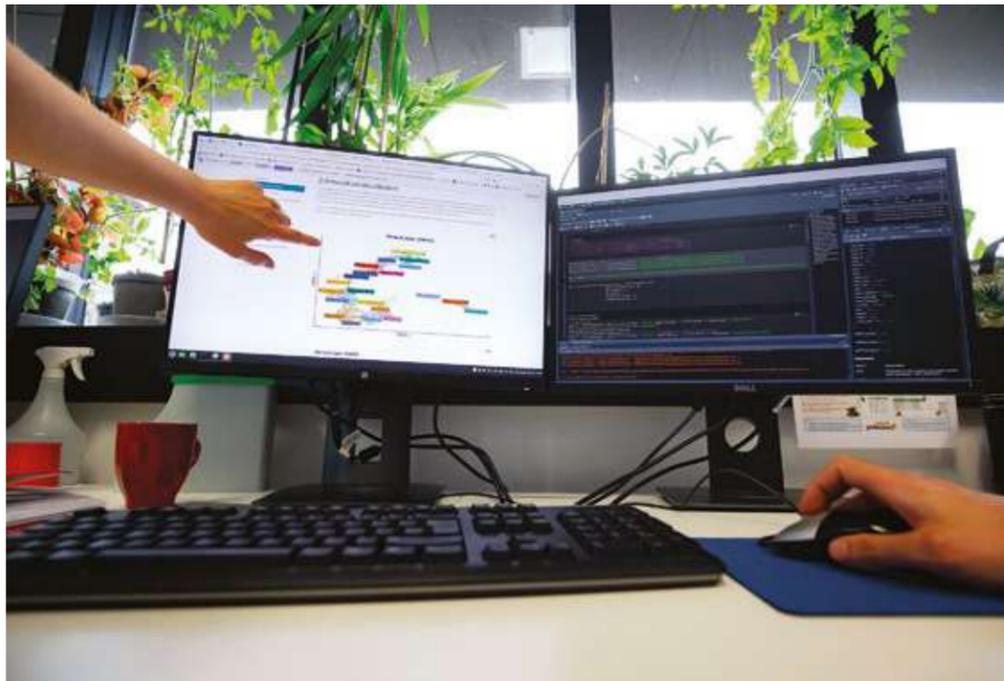
Created in 2022, the Regulatory and Technical Support Unit (CART) provides the Institute's research teams with regulatory support and technical solutions to help them navigate the legal, regulatory and IT constraints associated with their projects. This advisory, consultancy and guidance unit incorporates a number of complementary skills: the Data Protection Officer (DPO), providing support for studies involving personal data, the Scientific Integrity Officer, the Legal Department, the RIPH Support Unit (research involving humans, support for clinical studies promoted by Paris Brain Institute), the Information Systems

Department (DSI), the Organization, Quality and Risk Management Department (ROQ), and the Data Analysis Core platform (structural support in bioinformatics, statistics and methodology, image analysis and data management ●).

In 2023, the CART designed and implemented an updated version of the Data Management Plan (DMP) template to help researchers meet expanding data management and regulatory compliance requirements. In particular, the new model allows for more intuitive organization based on the life cycle of research data, in line with the data policy and requirements of the French National Research Agency (ANR), the European Research Council (ERC) and a growing number of scientific journals.



See box on page 40



Further training day on animal welfare



Preparation of the Institute's Data Governance Policy

In 2023, the Institute developed its Data Governance Policy. Research data are a real driving force for academic research. Management of these data requires rigorous organization and handling throughout the research project cycle, not only to ensure the reliability, quality and reproducibility of the research, but also to promote the reuse (and reusability) of the data.

At Paris Brain Institute, the research ecosystem (teams, platforms and facilities) uses, manipulates and generates vast quantities of digital and non-digital data, and relies on the development of software programs of varying complexity, ranging from short scripts to more elaborate applications. Data collection and production must respect the legal framework established to protect individuals with regard to the processing of their personal data, to preserve data quality and integrity, and observe the intellectual property rights of all third parties.

The data management policy therefore aims to ensure the integrity of research and the widest possible access to results, maximizing their value for

scientific progress. It covers all digital and non-digital research data, and applies to all staff working at Paris Brain Institute.

Animal welfare: renewed accreditation and a stronger team

In August 2023, the Institute secured a renewal of its accreditation for establishments using animals for scientific purposes, issued by the French Ministry of Agriculture every six years. This accreditation demonstrates the Institute's animal model compliance. In addition, the Institute is permanently committed to updating the skills of its staff in the use of animals for scientific purposes. Further training days on animal welfare, offered by the animal sciences provider, were held in 2022 and 2023, and open to the 280 people who use animals for research purposes. Each new employee also receives training on arrival, including a focus on regulations and a reminder of the specific well-being requirements for the species he or she will be working with. The regulatory affairs team, which assists the teams in this field, thereby guaranteeing the quality of the research and the welfare of the animals, will be expanded in 2022 and 2023 to include four people.

Supporting the growth of the Institute and its staff

One of the great strengths of Paris Brain Institute lies in the range and depth of the skills of its staff, and their ability to work collaboratively. This collaborative approach to research fosters exchanges between researchers, doctors, clinicians, engineers and administrative staff, helping to break down barriers in scientific research and find innovative solutions.

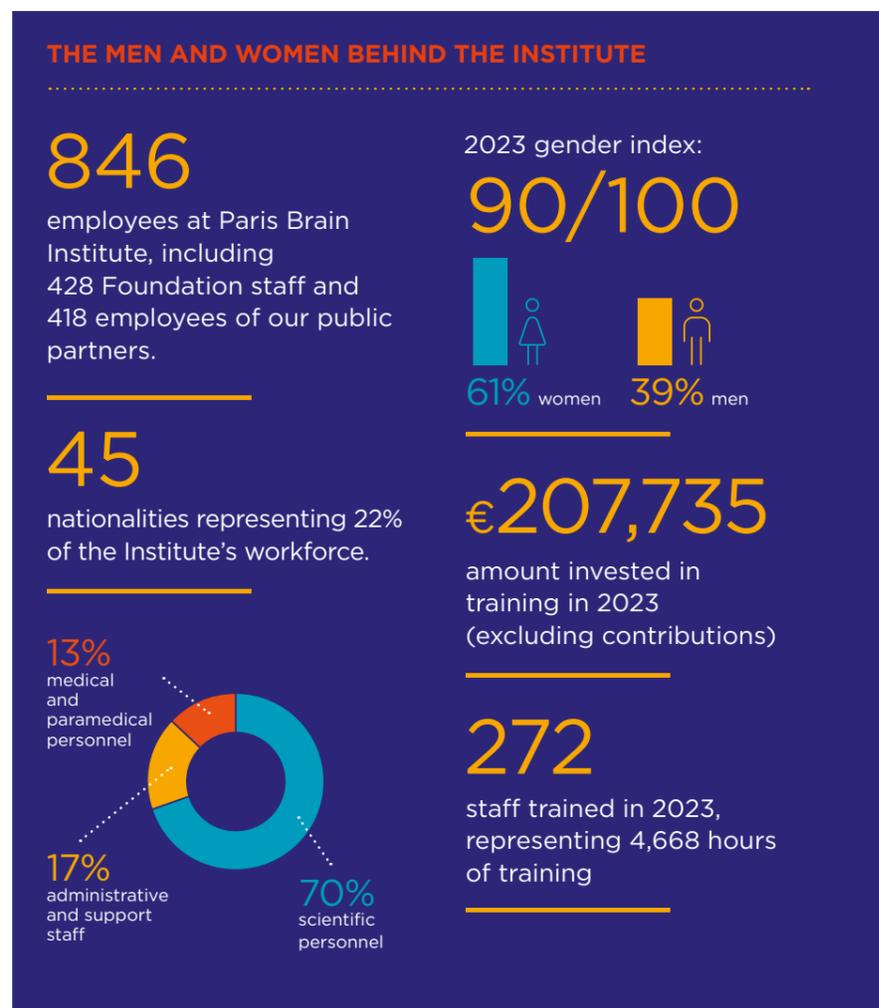
The Institute's Human Resources Department supports, guides and promotes this diversity of disciplines, skills, nationalities and sectors (public-private).

Given the Institute's growth in its financial resources and its workforce, the Human Resources Department pays particular attention to providing career development pathways and ensuring a responsible and collaborative working environment, in line with the Institute's values of integrity, fairness and inclusion.

A fast-growing Institute

The increase in staff numbers is a natural consequence of the Institute's growth, having diversified its activities and having seen significant increases in its funding since it was first established. In three years, the Foundation's workforce has grown by 27%. The Institute's active recruitment policy, which includes the creation of two new research teams in 2023, is part of this momentum. Clinical and translational research activities are also expanding rapidly.

"The diversification of professions, combined with the increase in both basic and clinical research activities at the Institute, data management obligations, the emergence of new technologies and the acquisition of new equipment, heralds major changes in neuroscience research. This is pushing us to anticipate our human talent and new skills needs even more effectively, so that we can adapt and remain competitive and innovative", explains Cécile Proust, Human Resources Director.



as at 30 September 2023

Managing careers and supporting employees

Paris Brain Institute's maturity has enabled it to create new positions and hire more and more employees, which in turn implies an increased focus on career development. This task is made more complex by the fact that the Institute's staff, who can come from public, private or business sectors, have a wide range of different statuses.

Paris Brain Institute sees the development of its staff's skills and expertise as a major asset. A very substantial budget is therefore allocated for training in order to meet the specific needs of the various occupations within the Institute. Our five pillars are: regulatory trainings, neuroinformatics, linguistics, management and soft skills.

A responsible working environment

Health, well-being and the quality of working conditions are among our priorities at the Institute. The results of the Quality of Life at Work survey, conducted every two years and most recently in March 2023, show that 90% of employees enjoy working at the Institute. The questionnaire also brought to light specific requests from employees (for example individual workspaces) that we have strived to meet.

Improving parity within teams, and more broadly gender equity, is one of the Institute's main focus points. The Institute has a dedicated Gender Equity Committee, that has defined a specific action plan. Training initiatives, to raise awareness and improve gender equity, are being carried out at the Institute, in particular through the "Leadership, communication and human skills development" training course.

“ The major changes taking place in neuroscience research at Paris Brain Institute are pushing us to anticipate our human talent and new skills needs even more effectively, so that we can adapt and remain competitive and innovative. **”**

Cécile Proust,
Human Resources
Director

NATHALIE ELIAS, HR Development Manager

With over 15 years of experience in human resources development in the public and private sectors, Nathalie Elias joined Paris Brain Institute in September 2023 to manage recruitment, training and careers in general, including the implementation of an employment and career path management framework.



What is the goal of an employment and career path management framework?

▶ The aim of this approach is to introduce employment and career path management. It is an essential factor in providing optimum support for employees' career development and responding more effectively to the Institute's needs. It also means we can be more responsive to employee requests to maintain skills and acquire new ones.

More specifically, what are the challenges of this kind of framework in a research context?

▶ We're in the midst of a process of rapid evolution and transformation of scientific careers. The Human Resources Department must be able to support employees through these major changes through customized training, but also through recruitment to attract talents with specific skills. Our goal is to make the Institute as attractive as possible and to enable research progress.

How will this project be rolled out at the Institute?

▶ As a first step, we'll meet the managers to map the jobs and expertise requirements. Second, we will draw up career paths and skills development plans for each professional category. To support this process, we'll roll out new training management tools.

THREE QUESTIONS FOR...

RESSOURCES HUMAINES

•••

Lastly, as part of its efforts to prevent psychosocial risks, the Institute organizes conferences to sensitize on these issues, making an occupational psychologist available to all employees once a week on site, and setting up a harassment prevention unit.

Huge cultural and linguistic diversity

The Institute's appeal is also growing internationally. International staff represents more than 20% of the Institute's workforce, a figure that is rising with the expansion of several international partnerships and programs, such as the international PhD program with DIM C-BRAINS, which began in 2023.

To meet their specific needs as effectively as possible, the international office assists these employees with all aspects of their relocation to France (finding ac-



commodation, opening a bank account, etc.), and with the specific taxation and social security requirements of the French authorities, for example. The Institute also aims to support the creation of a network of international staff, by organizing events to facilitate their integration.



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FINANCE

Financial report: rigor and transparency central to our action

Funding for research projects came from multiple sources, with a resolute focus on the long-term prospect of gaining knowledge and achieving major breakthroughs within the field of neuroscience. The balance sheet presented here covers the period from October 1, 2022 to September 30, 2023.

INCOME STATEMENT BY NATURE AND FUNCTION (ISNF) AND EXPENDITURE STATEMENT (ES)

INCOME BY NATURE

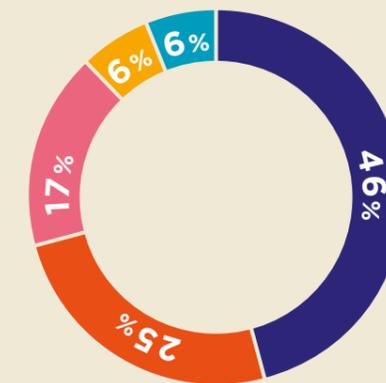
Income amounted to **€86.4 M**, including **€66.9 M** in income for the fiscal year and **€19.5 M** in carryover of resources allocated and not used in previous years. Income for the fiscal year consisted of fundraising revenue (€31 M or 46%), which includes donations (€14.7 M or 47%), bequests and gifts (€7.7 M or 25%), and sponsorship (€8.6 M or 28%).

It also includes:

- Income from core facilities activities (€10 M) and research collaborations with industrial partners (€1.2 M);
- Public and private grants (€16.6 M);
- Funding of the IHU Program (€3.9 M);
- Miscellaneous income (€4.2 M) (rental, re-invoicing of charges, financial revenue).

Income breakdown

- Fundraising revenue
- Public and private competitive funding of research projects
- Revenue from core facilities activities and collaborations with industrial partners
- Funding of the "IHU program"
- Miscellaneous income (rental, re-invoicing of charges)



ALLOCATION BY FUNCTION

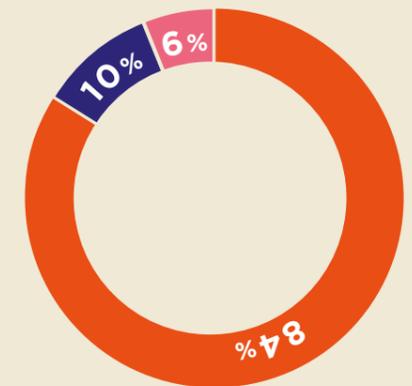
Overall expenses amounted to **€83.9 M**: **€57.7 M** used and **€26.2 M** to be used subsequently from the allocated resources. An amount of **€47.8 M** was allocated to **social missions**, representing **84%** of total ISNF allocations.

Paris Brain Institute social missions include:

- Research programs;
- Core facilities;
- Scientific leadership and implementation of international alliances;
- Incubation of innovative businesses.

Breakdown of allocations

- Social missions
- Fundraising and communication costs
- Operating costs



Funding for research projects is primarily dedicated to nervous system diseases and spinal cord injuries. Core facilities (neuroimaging, vectorology, genotyping and sequencing, cell culture, histology and bioinformatics) support these projects.

Fundraising and communication costs are expenses incurred to collect funds from individuals (donations and bequests), companies and private foundations (patronage and sponsorship initiatives), as well as communication

RAHUL GAURAV, a beneficiary of the international program

Rahul Gaurav, a research engineer in the Mov'it team, started to work at Paris Brain Institute eight years ago. From the moment he arrived, he was supported by the international office. Rahul shares his experience here.

The international office was a huge help.

This service really helps us to integrate, both with the French authorities and within the various departments of the Institute. The international office also organizes events to help us get settled in France and meet other international staff working with us at the Institute. The people in charge of this service really understand the specific problems faced by international staff and are committed to providing them with the best possible support.



I was really touched by their support and the kindness of the people I met there. I got the impression that there's a real desire to help people, beyond purely job-related assistance.



TESTIMONIAL

initiatives. They represent a total of €5.6 M, or 10% of total ISNF allocations.

Operating costs are expenses incurred in support of research (general administration, finance, human resources, legal, IT and logistics) and represent **6%** of total ISNF allocations, and thus €3.6 M.

ALLOCATION OF PUBLIC FUNDRAISING RESOURCES

Public fundraising resources amounted to €31 M. For every €100 raised from the public, €77 was used to finance social missions and investments, €20 was used to cover the costs of fundraising and communication and €3 was used to cover Paris Brain Institute operating costs.



BALANCE SHEET*

Assets (M €)	2022	2023
Net fixed assets	60	65
Realizable and available assets	86	86
Total	146	151

Liabilities (M €)	2022	2023
Equity	53	49
Fiscal year profit/loss	-2,8	2,5
Dedicated funds	25	31
Debt	42	42
Deferred income	29	26
Total	146	151

* As at September 30

Total investments made by Paris Brain Institute since inception amount to €62 M, allocated primarily to core facilities supporting research.

Investments for the fiscal year October 2022-September 2023 amount to €7.7 M (including variation in assets in progress) and include investments in scientific materials and equipment (€3.7 M, including €1.2 M for a latest-generation sequencer and €0.7 M for a scanning fluorescence microscope).

Net fixed assets amount to €65 M. As of September 30, 2023, cash holdings amount to €43.2 M, including €19.6 M allocated to earmarked funding. Paris Brain Institute equity stands at €51.5 M (including the profit for the fiscal year of €2.5 M). This includes €32.8 M in net position, supplemented by investment grants of €18.7 M. The non-expendable endowment held by Paris Brain Institute totals €1.2 M. At fiscal year-end, dedicated funds (funds still to be invested in multi-year programs) amount to €26 M.

RESERVE POLICY

When it was established in 2006, Paris Brain Institute Foundation had an endowment of €11.7 M, including €1.2 M in non-expendable endowments. Thanks to tight budget management, the Foundation has balanced its expenses and income for the past seven years prior to 2023, thus avoiding any need to draw on its reserves, which total €30 M as at September 30, 2023. These reserves contribute to building assets that can be used for the development of scientific research, as is the case for any non-profit foundation with recognized charitable status. However, since the Foundation is still young, there is currently no reserve policy aimed at setting a target reserve amount. Instead, the Board of Directors ensures each year that reserves allow for short-term coverage of capital commitments (primarily payroll and building costs, including the repayment of property loans). In addition, the investment policy applied by the members of the Board of Directors is extremely prudent. Paris Brain Institute's cash holdings are invested in marketable securities (capitalization contracts taken out with leading banking institutions, which are 100% capital-guaranteed euro funds) and capital-guaranteed term deposits.

VOLUNTARY IN-KIND CONTRIBUTIONS

VOLUNTEERING

Paris Brain Institute was supported by volunteer hours during the 2023 fiscal year, primarily for communication initiatives. The total volume of these hours is evaluated at 0.8 FTE, or, on the basis of an hourly minimum wage, a total amount of €25,000.

IN-KIND PATRONAGE

Paris Brain Institute was also supported by in-kind patronage and patronage in skills in connection with its communication and fundraising activities, namely:

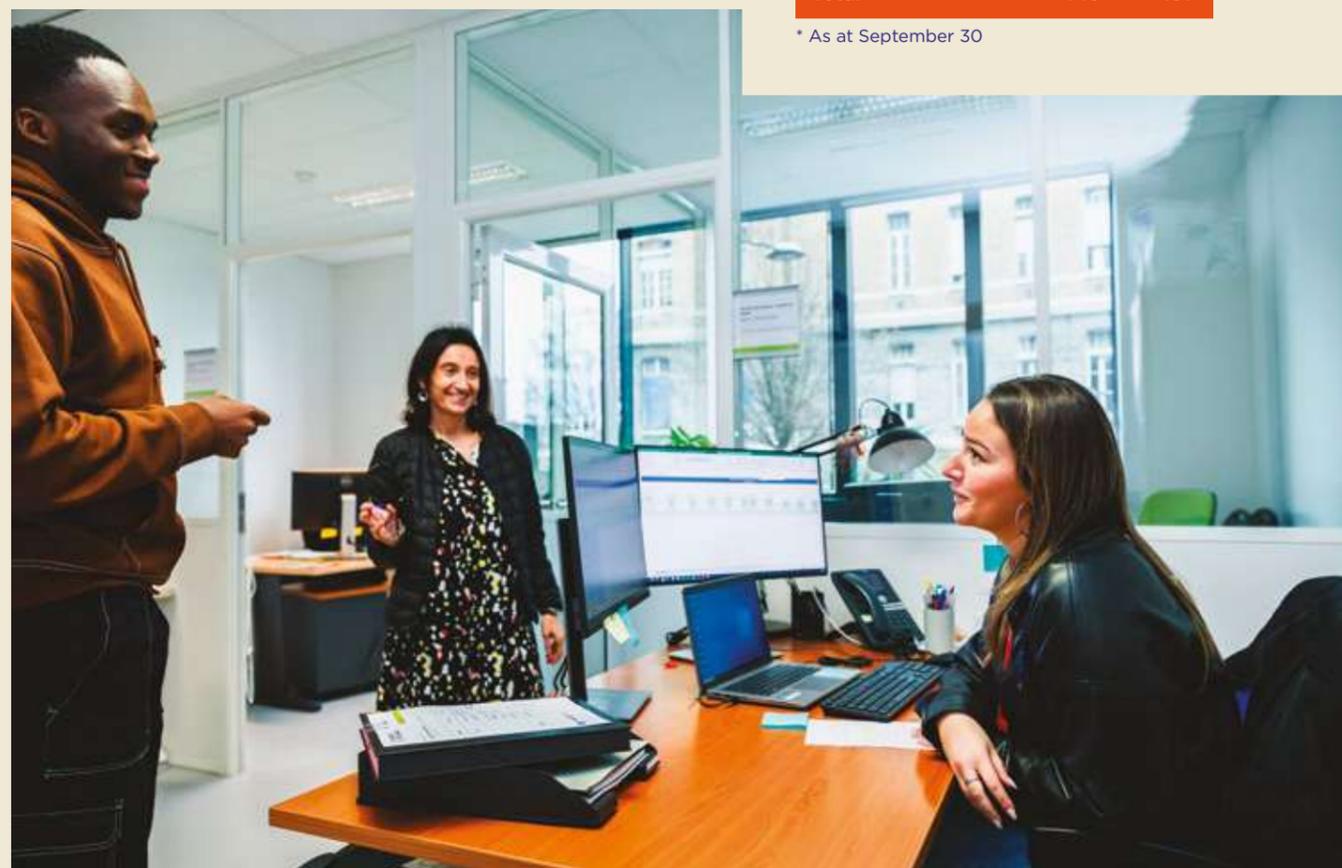
- Media space with: Richard Mille, France TV, Altice Média Publicité, TF1, Radio France, 366, Canal+, Amaury Média, beIN SPORTS, Bayard Média, RTL, NRJ, Groupe Barrière, JC Decaux and Klesia;
- Donated products and services: Publicis Groupe, Orrick Rambaud Martel, Anacofi, Air France, IDEC, Orange and Willkie Farr & Gallagher LLP.

To maintain its standards of excellence, Paris Brain Institute has internal and external control procedures in place to guarantee effective and efficient management. It holds Trusted Donations Charter Committee certification and uses independent auditors.



TRUSTED DONATIONS

On November 3, 2010, Paris Brain Institute was granted certification by the Trusted Donations Charter Committee, which was renewed in October 2022. For over 20 years, this Committee has acted as a professional regulator for public fundraising initiatives. Its actions are based on three commitments: certified organizations must adhere to codes of ethics, implement a stringent policy towards donors, and accept ongoing monitoring of their commitments.



INCOME STATEMENT BY NATURE AND FUNCTION (IN EUROS)

Income and expenses by nature and function	Fiscal year oct. 2022 - sept. 2023	
	Total	Including public support
INCOME BY NATURE		
1. Resources collected from the public	30,950,866	30,950,866
1.1 Donations free of equivalent compensation		
1.2 Patronage, donations and bequests	30,948,679	30,948,679
<i>Personal donations</i>	14,720,305	14,720,305
<i>Bequests, donations and life insurance policies</i>	7,656,481	7,656,481
<i>Patronage</i>	8,571,893	8,571,893
1.3 Other revenue from public support	2,187	2,187
2. Resources unrelated to public support	19,375,690	
2.1 Donations free of equivalent compensation		
2.2 Corporate patronage		
2.3 Financial contributions free of equivalent compensation	3,940,226	
2.4 Other revenue unrelated to public support	15,435,464	
<i>Services rendered</i>	10,011,890	
<i>Partnerships</i>	1,226,823	
<i>Other revenue</i>	4,196,752	
3. Grants and other public funding	16,491,412	
4. Reversals of provisions and impairments	116,716	0
5. Use of allocated resources from previous fiscal years	19,486,644	2,049,788
Total	86,421,329	33,000,655
EXPENSES BY FUNCTION		
1. Social missions	47,773,866	21,311,142
1.1 Carried out in France	47,773,866	21,311,142
<i>Actions directly carried out</i>	47,773,866	21,311,142
<i>Payments to a central body or other bodies acting in France</i>		
1.2 Carried out abroad	0	0
<i>Actions directly carried out</i>		
<i>Payments to a central body or other bodies acting in France</i>		
2. Fundraising costs	5,547,031	5,547,031
2.1 Cost of public appeals	4,674,417	4,674,417
2.2 Costs related to canvassing	872,614	872,614
3. Operating costs	3,624,507	732,640
4. Provisions and impairments	837,155	0
5. Income tax		
6. Carryover of fiscal year allocated resources	26,161,181	5,409,841
Total	83,943,739	33,000,655
Surplus or deficit	2,477,590	0

EXPENDITURE STATEMENT (IN EUROS)

Allocations by function	Fiscal year oct. 2022 - sept. 2023	Resources by nature	Fiscal year oct. 2022 - sept. 2023
Allocations for the fiscal year		Resources for the fiscal year	
1. Social missions	21,311,142	1. Resources collected from the public	30,950,866
1.1 Carried out in France	21,311,142	1.1 Donations free of equivalent compensation	
<i>Actions directly carried out</i>	21,311,142	1.2 Patronage, donations and bequests	30,948,679
<i>Payments to a central body or other bodies acting in France</i>	0	<i>Personal donations</i>	14,720,305
1.2 Carried out abroad	0	<i>Bequests, donations and life insurance policies</i>	7,656,481
<i>Actions directly carried out</i>	0	<i>Patronage</i>	8,571,893
<i>Payments to a central body or other bodies acting in France</i>	0	1.3 Other revenue from public support	2,187
2. Fundraising costs	5,547,031		
2.1 Cost of public appeals	4,674,417		
2.2 Costs related to canvassing	872,614		
3. Operating costs	732,640		
Total allocations in the income statement	27,590,813	Total resources	30,950,866
4. Provisions and impairments	0	2. Reversals of provisions and impairments	0
5. Carryover of fiscal year allocated resources	5,409,841	3. Use of allocated resources from previous fiscal years	2,049,788
Resource surplus for the year		Deficit of public fundraising for the year	
Total	33,000,655	Total	33,000,655

Philanthropy: supporting the Institute, as a partner in its progress

The Circle of Friends is a recognition program for major donors and corporate partners, offering them a unique opportunity to learn about the work of the scientists at Paris Brain Institute. The members of the Institute's scientific and medical community would like to express their sincere gratitude to the philanthropists, companies, foundations, endowment funds and associations that continue to make a substantial commitment to the Institute, for their unwavering trust and generosity.

An ever-growing community of corporate partners

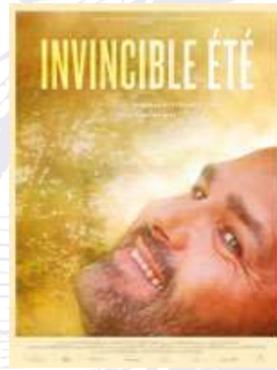
The faith and support of corporate partners is a powerful driver of success, making it possible for our research teams to commit to high-level work over the long term. Our scientists and experts are immensely grateful for the continued support of the Fondation d'entreprise Air France, Bolloré SE, the Fondation Bettencourt Schueller, the Fondation OCIRP, the Fondation Sucres et Denrées, the Fonds de dotation Janssen Horizon endowment fund, the Rousselet Group and UNIM. Boston Scientific SA, Accuracy and the Fonds Saint Michel also renewed their generous annual support in 2023. Donations from our long-standing partners also continued in 2023. These include watchmaker F.P.Journe, the SCPI Pierval Santé sharing fund, managed by Euryale and led by Crédit Mutuel Nord Europe, which also supports the Institute, alongside La Française AM, through the SCPI LF Avenir Santé, sharing fund.

Klesia, a long-standing partner of Paris Brain Institute, is renewing its multiyear commitment

Through the support of KLESIA Prévoyance, IPRIAC and CARCEPT Prévoyance, the Klesia Group is one of Paris Brain Institute's major historical patrons, having committed its support at a time when the Institute was just an idea and the building had not yet even been constructed. The Group renewed its three-year commitment in 2023.

Olivier Goy's unprecedented contribution in support of ALS research

In December 2020, at the age of 46, Olivier Goy, entrepreneur and co-founder of the fintech platform October, was diagnosed with amyotrophic lateral sclerosis (ALS). He decided to make his battle with this disease a public one, launching a film project, *Invincible été* (Invincible Summer), to tell his story, bring visibility to this condition and raise funds to support ALS research at Paris Brain Institute. Through his network and the entire community he has built around him, Olivier Goy generated almost €800,000 in donations for the Institute in 2023, from 1,300 new donors.



of the Paris Brain Institute Friends Committee. 80% of the fund's capital gains will be used to support Paris Brain Institute, with 20% going to its subscribers. Managed by Impact Partners, The Brain Fund aims to strengthen the Institute's long-term financial resources. In 2023, it completed an initial round of financing of €25 million from institutional and corporate investors, family offices and entrepreneurs.

"The success of this first financing campaign is a sign that the model is attractive to subscribers who wish to actively support Paris Brain Institute's mission, while at the same time making a low-yield investment", explains Eddie Misrahi.

Establishment of Paris Brain Institute America

In 2023, Paris Brain Institute started the process of creating a sister organization in the United States: Paris Brain Institute America (PBIA). Led by its President Martine Assouline, founder of the eponymous publishing house, PBIA aims to support large-scale research projects carried out by Paris Brain Institute in part-

nership with major research institutions in North, Central and South America. The launch of Paris Brain Institute America was celebrated with a charity dinner at the French Consulate in New York on October 4, 2023, in the presence of actors Michelle Yeoh and Jean Reno, ambassadors of the Institute.



From left to right : Zofia and Jean Reno, Jean Todt and Michelle Yeoh, Maurice Lévy, Gérard Saillant and Martine Assouline

Inauguration of the Diane Barrière Chair of Molecular Physiology of Synaptic Bioenergetics

The Diane Barrière Chair of Molecular Physiology of Synaptic Bioenergetics, named as a tribute to the mother and businesswoman who ran the Barrière family corporate group until her death at age 44 following a plane crash, focuses on mitochondrial dysfunction as the main cause of epilepsy.

ing the rules that control how neurons communicate with each other will help the scientific and medical community to better understand not only how our brains work, but also how synaptic dysfunction can be implicated in different nervous system pathologies," explains Jaime de Juan-Sanz, Director of the Diane Barrière Chair.

Using state-of-the-art optical techniques to study bioenergetics in firing synapses, in combination with metabolic and genetic manipulations, the team is working to develop a detailed molecular understanding of the role of synaptic mitochondrial metabolism in the control of neuronal function in health and disease. *"Understand-*

To mark the inauguration of the Chair, Prof. Gérard Saillant, President of Paris Brain Institute, paid tribute to Diane Barrière, a woman he knew and cared for when she was a quadriplegic suffering from third-degree burns: *"We can only hope that Diane's energy, tenacity and intelligence will support the*



Jaime de Juan-Sanz, Director of the Molecular Physiology of Synaptic Bioenergetics team

work of our researchers and enable them to discover more about the role of mitochondria."

PARIS BRAIN INSTITUTE AMBASSADORS

- ▶ Michelle Yeoh, actor,
- ▶ Jean Reno, actor,
- ▶ Guillaume de Tonquédec, actor

The Fondation Anne et Claude Berda: innovation and entrepreneurship to drive advances in neuroscience

The goal of the Fondation Anne et Claude Berda is to contribute to the treatment of brain diseases, by supporting innovative research projects, particularly those with significant development potential and societal impact. This is why the Fondation has decided to support Paris Brain Institute's NeurAL program, a first-of-its-kind program in France that brings together leading technical and industrial expertise to "de-risk" R&D projects and help them through the crucial stages leading to business creation.



Performance by Chun Wing Lam, Paris Opera dancer, during the Art-Science Breakfast

of those taking part, a total of over €1.2 million was raised for the Institute, and will be used primarily to enable researchers to have access to latest-generation technological equipment. The Fondation NRJ - Institut de France, founded by Jean-Paul Baudécroux, has made a substantial commitment to the Institute to enable the acquisition of an STED (Stimulated Emission Depletion) microscope. This equipment is the first of its kind in France and will enable the Institute to become a reference center for this technology.



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2023 Art-Science Breakfast: restoring movement in patients with Parkinson's disease

On October 18, 2023, in partnership with the Paris+ par Art Basel contemporary art fair and with the generous support of François Henrot, patron of the event, the Art-Science Breakfast was held at the Café de l'Homme in Paris. Carine Karachi presented her work on restoring movement in patients with Parkinson's disease. Thanks to the support of the Fondation NRJ - Institut de France and the incredible generosity

"In line with its values, HALTRA Communities is funding this key research project in the hope of bringing a positive, long-term impact to multiple sclerosis patients. We are honored to contribute to this vital work to advance understanding of neuronal death in multiple sclerosis, and proud of the progress made to date. Congratulations to the research team!", say Matthieu and Pauline Baumgartner.

Paris Brain Institute is expanding its horizons thanks to support from the Fondation Marie-Françoise Parayre Chauffour

Through the support of the Fondation Marie-Françoise Parayre Chauffour, a Belgian foundation committed to supporting medical research, Paris Brain Institute is launching its first international call for Big Brain Theory (BBT) projects, in partnership with Mission Lucidity in Belgium. The Big Brain Theory program was created in 2016 by Paris Brain Institute to fund innovative, interdisciplinary and high-risk research projects involving the Institute's teams. After three project cycles supporting 33 research projects, Paris Brain Institute is extending this program to include its international partners in order to fund original multidisciplinary projects carried out with the best experts available.

CIRCLE OF FRIENDS OFFICE

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cercle@icm-institute.org

Launch of the ENERGY-SEP HALTRA project

HALTRA Communities joined the Circle of Friends in November 2022 with a view to becoming a long-term patron. It is funding the ENERGY-SEP HALTRA project, a three-year research project aiming to gain a better understanding of the mechanisms leading to neurodegeneration in patients suffering from multiple sclerosis, the main cause of clinical disability. This study focuses specifically on exploring energy deregulation, a key and potentially reversible mechanism recently implicated in neuronal death.

PARIS BRAIN INSTITUTE FRIENDS COMMITTEE

The Friends Committee is a group of outstanding philanthropists who are not only generous donors but are also actively involved in the development of Paris Brain Institute*:

- ▶ Lindsay Owen-Jones, Honorary President of Paris Brain Institute Friends Committee
- ▶ Gérard Saillant, Founding Member and President of Paris Brain Institute
- ▶ Jean Todt, Founding Member and Vice President of Paris Brain Institute
- ▶ Martine Assouline et Maurice Lévy, Joint Chairs of Paris Brain Institute Friends Committee
- ▶ Jean-Luc Allavena, Cédric de Bailliencourt, Frédéric Banzet, Alexandre Barrière, Jean-Charles et Natacha Decaux, François Henrot, Jean-Philippe Hottinguer, Véronique De Kepper, Richard Mille, Eddie Misrahi, Margaux Primat, Christian Schmidt de La Brélie, Serge Weinberg

FRÉDÉRIC BANZET JOINS THE FRIENDS COMMITTEE

Frédéric Banzet joined the Friends Committee in January 2023. He was a member of PSA Group's Supervisory Board and CEO of Citroën. In 2022, he was appointed President of Établissements Peugeot Frères, the family group's holding company. This holding company is the second-largest shareholder in Stellantis, a substantial historic asset. "I'm deepening my commitment today, because it's urgent. While treatments exist for many cancers, and most of our limbs can be repaired, no one can yet cure the brain diseases that are the most important cause of the 21st century!", explains Mr Banzet.

TRIBUTE TO FRANÇOIS THOMÉ

The women and men of Paris Brain Institute wish to pay tribute to celebrated lawyer François Thomé, who passed away on March 17, 2023. Since the creation of Paris Brain Institute, François Thomé has been committed to working alongside our scientists to combat diseases of the nervous system. For more than ten years, he was also an active and loyal member of the Friends Committee.



* As of September 30, 2023

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And nine anonymous donors and partners.

Individual giving: vital support for research

Since its creation 10 years ago, the role of the public fundraising team has been to provide financial support for all research conducted at the Institute. Whether through basic research, clinical protocols, funding allocated to research teams, or the acquisition of new equipment, the funds raised each year from thousands of donors help to advance brain research.

Charitable giving on the rise

In 2022/2023, the fundraising team conducted 42 public appeal campaigns throughout the year, including mailouts, digital campaigns, and telemarketing campaigns. In total, our efforts raised €10.5 million in donations, marking an increase of 5.51% on the previous year.

This year, the Institute was supported by 95,134 dedicated donors, of which almost 29,000 were new supporters. Despite challenging economic conditions, donations from the general public continue to grow year on year, proving that brain research remains a major interest and key issue even when finances are tight for many.

This remarkable generosity of the public is the result of a carefully managed fundraising strategy, but also of a desire to diversify our sources of donations by leveraging innovative channels such as the introduction of regular donations through direct debit, enabling us to make a long-term commitment to the Institute's scientific strategy. In 2023, the Institute was supported by 10,609 regular direct debit donors.

Paris Brain Institute would like to thank all donors who give the Institute's researchers the means to pursue their ambitions, whatever the amount they contribute.

Donor-focused events

To thank the thousands of donors who have supported us, the Institute is committed to keep them informed of the advancements their donations have directly facilitated. To do this, four "Les Matinales" lectures are organized annually and hosted by the Institute's researchers. For each of these events, nearly 200

registered donors are welcomed to the Edmond and Lily Safrá auditorium located on-site at the Institute. The program covers a broad range of topics (including neurodegenerative diseases, rare diseases, cognition, etc.) and different aspects of research (basic, clinical and applied). These lectures are also streamed live on the Institute's YouTube channel.

Additionally, one-off events are organized regularly for donors, with the aim of reporting updates on ongoing works and the latest scientific breakthroughs. One example of this was an evening event held in November 2022, "Inside the Minds of the Researchers", a panel discussion hosted by journalist Mélanie Gomez featuring three pairs of researchers working on Parkinson's disease, brain tumors and obsessive-compulsive disorder (OCD).

Finally, *Synapse*, the quarterly scientific magazine for donors, provides clear and accessible content that focus on specific aspects of research, along with the latest news from researchers and the Institute in general.



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Engagement as a driver of progress

Celebration events, charity races, artistic events, in memoriam donations... Many private individuals organize fundraising campaigns in support of the Institute. It provides donors with an online fundraising platform for this purpose: jecollecte.institutducerveau-icm.org.

One of these generous initiatives is supported by a group, deeply committed to our cause: the Amour Amour Amour association. Since 2019, this association, founded by Delphine and Christophe Gusman, has utilized its network and channeling its energy to raise funds for brain tumor research. With the sale of products bearing the Amour Amour Amour label and the organization of various events including sporting and cultural activities, the association has already raised nearly €200,000. Paris Brain Institute extends its heartfelt gratitude to the association's generous donors for their incredible support, and the members of its board for their unwavering belief and determination.



Guillaume de Tonquédec, ambassador and Discoverers of Hope (Découvreurs d'Espoir)

Since 2019, actor Guillaume de Tonquédec has generously lent his support to the Institute, championing the message of hope for our major annual fundraising campaign. As ambassador for the "Découvreurs d'Espoir" campaign, Guillaume de Tonquédec lends unparalleled visibility to the dedication of researchers and their efforts in the field of neurological and psychiatric diseases. In November 2022, he invited his friend and co-star, actress Valérie Bonneton, to join him in this endeavor. Paris Brain Institute extends its heartfelt gratitude to Guillaume de Tonquédec for his continued, loyal support, and Valérie Bonneton for her generous participation in the campaign.



CHRISTOPHE GUSMAN, co-founder of the Amour Amour Amour association

The Amour Amour Amour association was founded as a tribute to Julien Gusman, my son, who passed away from brain cancer in May 2018 at the age of 26. As his family and friends, we didn't want his incredible battle be in vain. We wanted to help all those who are bravely fighting cancer, especially the youngest patients, and we also wanted to support research. When we visited the Institute, we were amazed by the advanced equipment. The level of precision is impressive, but so is their cost of acquisition, underscoring the significance of every donation made to Paris Brain Institute, regardless of the amount. Excellence comes at a price. We are committed to continuing our fundraising efforts to help research.

TESTIMONIAL

Support from bequests and life insurance policies

With a growing awareness that the fight against brain diseases is a major public health challenge requiring long-term support, generous donors are increasingly opting to donate all or part of their estates to Paris Brain Institute by leaving gifts in their wills or naming the Institute as a beneficiary in their life insurance policies.



Carole Clément, Testator Relations Officer

Bequests and life insurance donations received by the Institute amounted to €4.9 million in the period from October 1, 2022 and September 30, 2023, an increase of over 100% compared to 2022. Each year, these funds make a growing contribution to the financing of scientific research. As a non-profit foundation with recognized charitable status, the Institute is fully exempt from inheritance tax.

To raise awareness of Paris Brain Institute and the possibility of making a bequest, communication campaigns have been launched for donors (through *Synapse* magazine and dedicated e-mailing campaigns) and the general public. The year 2023 saw two highlights: a TV and a radio commercials, and a press commercial in targeted magazines.

Carole Clément, Testator Relations Officer, is available to speak with anyone considering passing on assets to the Institute and seeking advice on how to proceed or simply wishing to find out more. A meeting can also be arranged with the Institute's legal expert, a specialist in notarial law, who can offer guidance and address specific requirements. Any discussions are completely

Visual for a communication campaign on bequests to the Institute



FRANÇOISE S. has chosen to leave a legacy to Paris Brain Institute and her niece



I started thinking about my estate after my mother died. As I had no children of my own, I wanted to pass everything on to my niece, but inheritance tax seemed extremely high. Then I read in a magazine about the option of a universal bequest to an association, where a bequest can be paid to a loved one net of fees and taxes. I chose Paris Brain Institute because several people close to me have been affected by these illnesses: my mother had Alzheimer's disease and I have a friend who has amyotrophic lateral sclerosis (ALS). The Institute is therefore my universal legatee and will pay a sum to my niece. To be useful and to be of service - that's really the aim of the path I've chosen.



confidential and non-binding, and follow a rigorous code of ethics and conduct. Testators can also arrange a visit to the Institute to find out more about its research. These meetings are very much appreciated, as they provide an invaluable opportunity for people considering gifting their assets to discuss possible options.

TESTIMONIAL

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RICHARD MILLE



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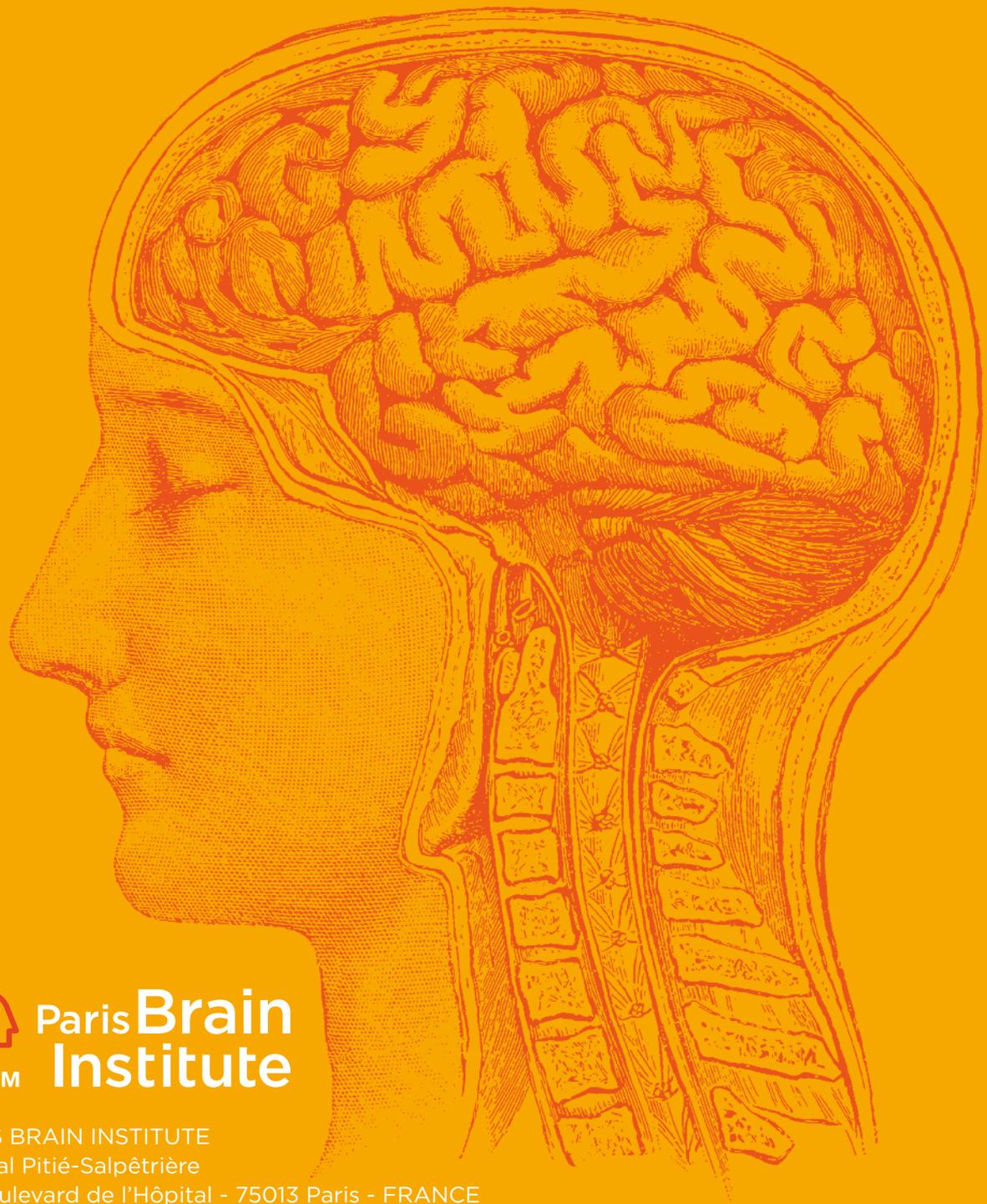
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Hôpital Pitié-Salpêtrière
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