Research evaluation

EVALUATION REPORT OF THE UNIT

ICM – Institut du cerveau et de la moelle épinière

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Sorbonne Université,
École pratique des hautes études – université Paris Sciences & Lettres – EPHE-PSL
Institut national de la santé et de la recherche médicale, Inserm
Centre national de la recherche scientifique, CNRS

EVALUATION CAMPAIGN 2023–2024
GROUP D

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High Council for evaluation of research and hgher education

In the name of the expert committee[1]:

Vania Broccoli, Chairman of the committee

For the Hcéres [2]:

Stéphane Le Bouler, acting president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, evaluation reports are signed by the chair of the expert committee and countersigned by the Hcéres chair.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson: Mr. Vania Broccoli San Raffaele Scientific Institute Italie (President)

Experts :

Mr. Simon THORPE, Centre de recherche cerveau et cognition, Toulouse, France. (HCERES Expert Panel, Vice-President)

Ms. Elli LEADBEATER, Centre for Ecology, Evolution and Behaviour, UK. (HCERES Expert Panel)

Ms. Frederique LIEGEOIS, Developmental Neurosciences Department, UCL GOS Institute of Child Health, UK. (HCERES Expert Panel)

Ms. Elisa ZANIER, Laboratory of Traumatic Brain Injury and Neuroprotection, Milan, Italy. (HCERES Expert Panel)

Mr. Alexandre REYMOND, Centre for Integrative Genomics, Faculty of Biology and Medicine of the University of Lausanne, Swiss. (Expert)

Ms. Annalisa BUFFO, Department of Neuroscience Rita Levi-Montalcini, University of Turin, Italy. (Expert)

Mr. Mikael SIMONS, Biology of Glia and Neuro-inflammation, Munich, Germany. (Expert)

Mr. Juan BURRONE, Mental Health, King's College London, UK. (Expert)

Mr. Thomas KUNER, Interdisciplinary Centre for Neurosciences, *University of Heidelberg,* Germany. (Expert)

Ms. Claudia VERDERIO, Institute of Neuroscience, University of Milano-Bicocca, Italy. (Expert)

Mr. Federico CALEGARI, Centre for Regenerative Therapies, Dresden, Germany. (Expert)

Mr. Pieter MEDENDORP, Cognition & Sensorimotor Neuroscience, Radboud University, Netherlands (Expert)

Mr. Alexander DITYATEV, German Centre for Neurodegenerative Diseases, Germany. (Expert)

Mr. Pietro FRATA, UCL Queen Square Institute of Neurology, London UK. (Expert)

Mr. Léon TREMBLAY, Institut des Sciences Cognitives Marc Jeannerod, Lyon, France. (Representative of CNRS, section 25)

Mr. Denis VIVIEN, Université Caen Normandie, Caen, France. (Representative of Inserm, CSS4)

Ms. Sylvie RAISON, Institut des Neurosciences Cellulaires et Intégratives, Strasbourg, France. (Representative of CNU 69)

Mr. Orestis FAKLARIS, Platform manager, Bio-Campus, Montpellier, France. (Representative of supporting personnel)

HCÉRES REPRESENTATIVE

Ms. Nadia Soussi-Yanicostas

REPRESENTATIVE(S) OF SUPERVISING INSTITUTIONS AND BODIES

- INSERM : Mr. Franck Lethimonnier,
- CNRS : Mr. Bernard Poulain,
- Sorbonne University: Ms. Anne-Genevieve Marcelin and Mr. Alain Chedotal.

CHARACTERISATION OF THE UNIT

- Name: Institut du cerveau
- Acronym: ICM
- Label and number: UMR 7225 ; UM 75
- Composition of the executive team: Alexis BRICE, directeur

SCIENTIFIC PANELS OF THE UNIT

SVE : Sciences du vivant et environnement
SVE5: Neurosciences and Nervous System Disorders

THEMES OF THE UNIT

The mission of the Institut du Cerveau et de la Moelle épinière (ICM) is to advance the scientific knowledge and therapies for diseases of the nervous system, both neurological and psychiatric, by performing cutting-edge fundamental research and develop new strategies for diagnosis and clinical treatments.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

ICM was created in 2011 and is located at the Pitié-Salpêtrière Hospital site in the heart of Paris. Since 2014, Mr. Alexis Brice has acted as Executive Director up to the entire reporting mandate, while this position will be taken presumably by Ms. Stephanie Debette for the next contract. The institutional stakeholders of ICM are INSERM, CNRS, Sorbonne University and Pitié-Salpêtrière (AP-HP). Its privileged location and strong ties with AP-HP offer to ICM a unique environment which facilitates disease-oriented research, preclinical and clinical activities, with the ultimate goal to conduct translational research from the bench to the bedside.

RESEARCH ENVIRONMENT OF THE UNIT

ICM Foundation owns a 22,000-square-meter building hosting the research labs, core facilities, clinical infrastructure, an incubator for start-ups and on-site administration and legal offices. During the report period, the Institute includes 25 research teams organised in five scientific areas: molecular and cellular neuroscience, neurophysiology, clinical and translational neuroscience, cognitive and computational neuroscience (this last domain added in 2019). The ICM provides eleven technological core facilities with the goal to support the research teams and promote technological innovation and development.
ICM is involved in multiple networks and initiatives (IHU, CIC, iCRINs, BBTs, NeurATRIS, CATI, Carnot, Findmed) that foster interdisciplinary research, scientific cross-fertilisation and technological transfer. The Open Brain School is a training centre at ICM which develops and supervises innovative educational programs and initiatives for students, researchers and clinicians.

UNIT WORKFORCE: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	76
Senior lecturers and equivalent	23
Researchers and equivalent	103
Research support staff	282
Sub-total for permanent research staff	**484**
Non-permanent teacher researchers and researchers	1
Non-permanent research support staff	1
Post-docs	161
PhD	294
Sub-total non-permanent staff in active employment	**457**
Total staff	**1004**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'autres'.

Name of employer	EC	C	PAR
APHP	36	6	25
AUTRES	5	8	32
CNRS	0	34	6
ICM	21	3	174
IHU-A-ICM	3	0	7
Inserm	0	57	56
Sorbonne Université	43	11	15
Total staff	108	119	315

GLOBAL ASSESSMENT

The ICM is an exceptional research centre. Since its creation in 2011, it has become one of the world's leading research centres in Brain Research. It houses 130 PIs covering a full range of research topics, from fundamental research to clinical applications. They are backed by eleven well-equipped technical platforms and over 240 support staff. The 25 research teams that were evaluated by the HCERES panel are all at least excellent, with ten of them being rated at excellent to outstanding. This excellence is reflected in the fact that ICM has recruited sixteen new permanent INSERM, CNRS or INRIA researchers in the period 2017–2023, with another 4 recruits in 2023.

The ICM's ability to raise research funds is quite exceptional. For example, in the last year alone, it obtained a phenomenal 84.8 M€ of funding. During the evaluation period, its researchers obtained a large number of competitive grants, including no less than eight ERCs (with 5 new ones in 2023), eighteen Marie-Curie fellowships and 121 ANR projects. But it has also profited from its almost unique status as a public private foundation, which has allowed it to raise over 110 M€ in donations over the evaluation period. Indeed, in the last year, the 23.8 M€ of donations provided 28% of all the finance. Since the utilisation of these additional funds is largely at the discretion of the governing board, this gives the ICM a remarkable advantage over other research institutions in France. The ICM looks set to improve its financial success even more in the coming years, with other large-scale funding initiatives likely to come on stream in the near future, including the IHU project.

Globally, the ICM's scientific output is excellent, with a total of 3123 publications and a remarkably large proportion in top-ranking journals. This is certainly impressive and it remarks the ICM capacity to pursue high-quality, original and cutting-edge science making good use of the extraordinary resources at current disposal of the Unit.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

A first recommendation related to ICM's teaching and training activities. In response, the ICM implemented an international Master on Neurodegenerative diseases (iMIND) with the participation of major European Institutions and an International PhD program. ICM is also planning to launch an International post-doc program. These initiatives further expand the ICM's significant commitment to the area, which resulted in the training of 317 PhD students and 193 post-docs during the present contract. A second recommendation solicited more mentoring activities for all the research personnel, from PhD students to junior group leaders. On this aspect, ICM robustly reinforced its onboarding program with more engaging welcome activities (as the Expat Lunch and French classes). A third recommendation echoed concerns of the mid-tier researchers about internal career progression and independence. In this regard, ICM established a PI mentoring program to support Junior PIs for a period of 2–3 years. Of note, ICM has promoted thirteen PIs as new team leaders for the next contract, confirming the ICM's active policy to promote internal career development. A fourth recommendation highlighted the concerns of insufficient space, precarious employment conditions and gender balance active policies. Regarding this aspect, ICM created the 'CDI de chantier' for technical personnel, with stabilisation of 46% of ICM personnel in 2022 (up from 44% in 2018). ICM established active Gender Equity policies for most of its selection processes, strongly improving the gender ratio within all the ICM's managing bodies. A fifth recommendation revolved around the scientific recognition of the personnel in the technical platforms and original data archiving. In response, ICM drafted an official note based on the Avesian rules for authorship policy guidelines. They also implemented a Data working group to issue procedures for data archiving and related services. Data storage is ensured by both local infrastructure and cloud-based services. A sixth recommendation dealt with some internal complaints about the lack of sufficient information about institutional decisions. In response, ICM created working groups on specific institutional questions. Moreover, ICM better defined COPIL responsibilities and promoted a weekly Newsletter and monthly 'Lunch and Learn' meeting for regular updates. The last recommendation solicited ICM to fully implement its translational mission with the goal to develop disease-modifying therapies with clinical and societal impact. With this goal in mind, ICM created thirteen clinical research platforms in 2019. The Neurocatalyst program funded seven projects focusing on medical devices and drug repurposing. Two more supporting Units were created for research on human subjects (RIPH) and phase 1/2 a clinical trials (Neurotrials). Competitive internal funding was implemented to finance early and innovative projects between two or more teams and externally evaluated by the Scientific Advisory Board (SAB).

B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The ICM's ambition is to be a leading and attractive international centre at the forefront of biomedical research and technology aimed at advancing our understanding of the molecular, cellular and network mechanisms underlying brain development, function, behaviour and diseases. ICM aims to accelerate innovation in diagnosis and treatments of neurological disorders by organising and running world-class clinical research, infrastructure and early clinical trials. ICM research is supported by a strong technological transfer program to maximise business development and industrial partnership s. The scientific program, framework and objectives are outstanding, promoting strong integration between fundamental and translational research, numerous clinical studies and exceptional capabilities to attract resources and competitive funding.

Assessment on the unit's resources

Public stakeholders of ICM are CNRS, INSERM, Sorbonne University (SU) and Pitié Salpétrière Hospital (AP-HP) that supervise general governance of the institute together with the ICM foundation private entity. The close partnership between these funding bodies are an excellent asset and provides a multidisciplinary ecosystem for pursuing excellence in science, medicine and education. The privileged ICM location at the AP-HP campus facilitates the synergy between researchers and clinicians, accelerating the translation of research discoveries into innovative clinical treatments. During the present contract, ICM recruited sixteen new permanent CRCN researchers at INSERM, CNRS and INRIA and 22 of its clinician researchers were promoted to PU-PH. ICM hosted 317 PhD students of which 130 have graduated, and 193 Post-docs. All early career researchers (PhDs and Post-doc) published at least one article in a peer-reviewed journal each year confirming the functional organisation of the structure for education and training.

Assessment on the functioning of the unit

The ICM's general governance is well-structured, with clearly delineated responsibilities between the different governance bodies. The executive committee is the main decisional board of ICM which is assisted by the COPIL (Comité de Pilotage, Steering Committee), the key advisory body for Institutional scientific and medical strategies, composed by representatives of the five scientific disciplines. Direction meets with the team and laboratory councils on a regular basis, and a general assembly is organised once a year together with all the working personnel. ICM runs several committees to properly supervise scientific and operative internal policies. The overall organisation of ICM is outstandingly structured and defined with supervising bodies (executive committee, scientific and medical steering committee), team council, laboratory council, general assembly) and operative committees (gender equity, ethics and deontology, tech transfer, health, safety and environment, Scientific Advisory Board – SAB) that cover all the aspect of the life of the Institute.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

ICM is actively promoting multidisciplinary research across multiple scales on the development, structure, function of the nervous system in humans and animal models to elucidate physiological and pathological mechanisms. The teams are organised according to five scientific domains (Cellular and molecular neuroscience, Neurophysiology, Cognitive neuroscience, Clinical and translational neuroscience, Computational modelling in neuroscience) which facilitates internal communication and the swift identification and management of operative and organisational needs. This richness in scientific projects, approaches and models at ICM provides an outstanding environment to pursue cutting-edge research and technical development. In particular, complementary research in humans and animal and cellular models facilitates the integration between fundamental and translational research in order to accelerate the development of new tools and strategies for innovative treatments and diagnosis of the patients. A major strength of ICM is the scientific and physical integration between fundamental and applied research with complementary preclinical and clinical projects where scientists and clinicians can actively cooperate, creating a vibrant cross-fertilising environment. ICM is a key and leading partner in strategic national, European (Cure-ND alliance) and international networks (Yale Uni., UC San Francisco, Columbia Uni., Weizmann Institute, Mc Gill Uni.) that brings together major research centres in order to accelerate scientific discoveries and implement medical innovation.

Weaknesses and risks linked to the context

The integration between the fundamental and clinical research domains remains heterogeneous between medical sectors. There is a strong and powerful integration in research on Multiple sclerosis, brain cancer, epilepsy and Parkinson's disease. Multidisciplinary research programs on Huntington's disease and ataxia are growing. For other neuropathologies as neurodevelopmental disorders, Alzheimer's disease and Amyotrophic Lateral Sclerosis (ALS) this integration is yet to be consolidated. Relative few clinical trials have started based on medical products or therapeutic strategies made in ICM.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them.

Strengths and possibilities linked to the context

ICM has been highly successful in obtaining competitive and prestigious funding by local, national (e.g. 120 ANR AAPG projects and 13 ANR Jeunes chercheurs), and European bodies (8 ERCs, 15 postdoctoral MSCA fellows and five doctoral MSCA networks). In the present contract, ICM obtained more than 400 grants, receiving around 12 to 18 M€ in grants per year. ICM has also successfully renewed the Carnot and IHU (Institut Hospitalo-Universitaire) funding programs in 2019. Moreover, ICM has implemented an outstanding asset for public-private R&D, business development and start-up initiatives obtaining a significant financial return. These revenues represent around 25% of the overall annual income that provides essential resources to ICM for launching new initiatives and infrastructural upgrading. As such, ICM stands out as an impressive example of successful fundraising based on its strengths in cross-disciplinary research, R&D services and business development. These results exemplify the strong visibility and reputation that ICM has gained in preclinical and clinical applications, disease-oriented research and human studies. Indubitably, ICM offers an outstanding multidisciplinary environment with high-level technological platforms where fundamental and clinical research can flourish. Noticeably, ICM sustains a continuous effort to identify and explore new emerging and cross-disciplinary fields in biomedicine where to expand its leadership. Good examples of this are its recent commitments on neuroinformatics, computational modelling and the establishment of the Care Lab for the development of devices and software for patients with neurologic and psychiatric care issues.

Weaknesses and risks linked to the context

The centre has significantly grown both in terms of new personnel, teams, infrastructure (iCRINs), technical platforms and start-up incubators. Given this, lack of space might raise significant concerns in the near future, creating some problematic issues for the research and clinical activities and the wellbeing of the personnel during work activities.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage.

Strengths and possibilities linked to the context

ICM has devoted significant efforts to appoint operating committees that, with the support of scientific and management offices, supervise human resource management, safety (Pole HSE), environment (Green team), ethical protocols (Ethical and deontological committee-Cometh) and data as well as scientific heritage protection. This organisation assures full compliance with rules and directives defined by the stakeholders, but also stimulate additional actions to further implement innovative management choices (e.g. mapping ICM carbon footprint, greentips, limiting waste in energy consumption) and identify and prevent major risks to the ICM scientific and management assets. In particular, ICM has diligently followed the recommendations of the previous review round (2018) by implementing a Gender equity Committee (GEM) which issued an action plan to promote equal gender representation throughout the operating boards at ICM. This action has improved gender balance within the ICM governance at all levels (from the COPIL to the Team leaders). More broadly, GEM has been proactive in raising awareness and promoting best practices to prevent conscious and unconscious inequity also by managing regular training sessions for researchers and managers and poser campaigns. As such, the ICM management and organisational structure are outstanding and should facilitate a timely intervention and contribute to guaranteeing an environment respectful for the needs of the working personnel.

Weaknesses and risks linked to the context

Although ICM has undertaken a set of initiatives for the smooth enrolment of new personnel, several non-French scientists newly recruited at ICM had faced important challenges in dealing with all the administrative compliance, lodging issues and necessary paperwork feeling insufficient support from the ICM management. This aspect needs to be revised internally in order to improve the support to the new recruitment that is essential for the overall attractiveness of ICM and its international standpoint.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

ICM offers an exceptional ecosystem where fundamental and clinical projects can synergize to accelerate transformative research from the bench to bedside and vice versa. ICM established a strong research infrastructure with highly competitive technological and clinical platforms. These initiatives have strengthened the ICM's competitive edge, giving the Institute a strong international reputation and attractiveness. ICM members have obtained very prestigious grants and numerous invitations to top-notch meetings, confirming the strong contribution of ICM to the international neuroscience research.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

ICM has developed into a highly international institute with a strong international component between senior researchers (24%), post-doc (58%) and PhD students (33%) as for 2022. As such, ICM plays a key role for research and training at the international level. To promote its international reputation, ICM is a founder member of the CURE-ND consortium with tight links with world-leading neurological institutes (McGill, Columbia, UC San Francisco, …). In Europe, ICM reinforced its synergies with leading institutions including KV-Leuven, the German DZNE network and UK-DRI. A laudable action is the development of new alliances with emerging institutions in Eastern Europe (Lukasiewicz PORT) and India (Institute of Technology Delhi), expanding its attractiveness in these areas. ICM has implemented valuable initiatives to create a welcoming, stimulating and collaborative environment. For instance, the 'Ajites' young researcher group animates multiple scientific and recreational activities that foster inclusivity between the ICM community (e.g. happy hours, theatre, photography context, etc.). Scientific life at the ICM is very rich with regular seminars presented by international scientists (167 during the reporting period), internal seminars, 'Neuroscience lunches' for clinicians, 'Brain fuel' talks by early career scientists and a yearly institutional retreat. ICM researchers have been extremely successful in obtaining competitive funding with more than 400 grants in the present contract, among which eight ERC, one ATIP-Avenir label, 120 ANR, five MSCA and 21 EU collaborative projects. A grant office is operating at ICM to organise individual coaching and masterclasses for competitive grant calls. ICM runs eleven state-of-the-art technological platforms with cutting-edge instrumentation that assure timely acquisition of transformative technologies in very competitive and dynamic scientific domains (spatial transcriptomics, MRI 7T imaging, etc.). Importantly, ICM has promoted the stabilisation of its engineering and technician staff in the platforms with permanent positions to ensure high professional standards over time. ICM has also created thirteen clinical research facilities (iCRINS) to strengthen translational research on neurological disorders and promote integration with the Salpêtrière Hospital infrastructure. With these initiatives, ICM is building a strong and dynamic supportive ecosystem to assist at best the research and clinical projects reaching and also going beyond in some instances to the highest international standards.

Weaknesses and risks linked to the context for the four references above

ICM has recently launched a PhD international program to recruit excellent students abroad. This is a very valuable initiative that increases international visibility. However, for the moment this is the first initiative of this kind and its continuation has not been yet confirmed for the next years. Along this line, ICM lacks an International recruitment program for Post-doctoral fellows to maximise its attractiveness for researchers worldwide. Finally, ICM is missing an MD/PhD program that would be strategic to sustain the integration of young clinicians into the research programs.
The centralised management infrastructure is not yet fully configured in terms of accessibility and support management for a safer and long-term archiving of research data generated by teams and clinical studies. Internal IT management at ICM seems to be not as responsive and effective as researchers would need. These

difficulties seem caused by the high-turnover and insufficient number of the IT personnel staff. This hurdle is known by the ICM direction which is taking action to mitigate these dysfunctions.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of ICM is outstanding from both quantitative and qualitative points of view. The centre published a total of 3123 articles or reviews during the period. 2985 of the publications involved at least one of the 25 research teams, with 22% of the publications involving multiple teams. Around 40% of the original research articles publications involved a member of ICM in a leading position, as first, last or corresponding author. Impressively, 310 publications were in journals that figure in the top 1% of the best journals in the field (6 papers in Nature, 33 in other Nature journals (Nature Neuroscience, Nature Medecine, Nature Genetics), eleven in Science, 40 in the Lancet and other Lancet journals such as Lancet Neurology and three each in Cell and the New England J. Medicine. Indeed, over a third of the ICM's publications are in journals that figure in the top 5% of the best journals in the field, a remarkable achievement. The ICM's scientific production is also well cited. Roughly 25% of the publications are in the top 10% in terms of citations rates for the year of publication, which is well above average.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

ICM published 310 articles in the top 1% of the best journals in the field, including papers in Nature journals (39), Science (11), Lancet and other Lancet journals (40), Cell (3) and New England J. Medicine. Over a third of the ICM's publications are in journals that figure in the top 5% of the best journals in the field. As such, ICM's publication production is highly remarkable for both the quality and quantity. Importantly, these publications are homogeneously spread between the different scientific domains where ICM is active, including fundamental science, human studies and translational/clinical research. Scientific production is largely proportionate to the size and number of PIs in the teams, with very few exceptions. It is notable that some of the smallest teams with the youngest leaders have published studies of great impact in their respective fields in top-notch scientific journals. The vast majority of the PhD students published at least first author of one peer-review original article during their training.

The scientific quality of the research performed at ICM is also demonstrated by the invitations to organise or present at distinguished international conferences (FENS, SFN, Gordon Conferences, EMBO, Fondation des Treilles, IBRO, etc.). However, there is a significant variability in the number and quality of publications between the different teams. This imbalance is partially justified considering the number of articles compared to the size of the teams and their relative numbers of PIs. Moreover, clinical groups tend to have a higher number of publications. It is important to highlight that the three newly hired team leaders (teams 9, 19, 20) have already produced a good number of publications, some in highly renowned journals as Cell and Neuron, confirming the high-quality selection operated by ICM in the last recruitment rounds. ICM has detailed clear authorship guidelines in order to assure that the contribution of young career scientists, engineers and technicians in publications is appropriately acknowledged through publication authorship. Importantly, all young researchers published at least one article during their training at the ICM. Scientific production is articulated in 42% in the field of basic neuroscience and 58% in clinical neuroscience. ICM filed 37 new patent applications in the reporting period, reaching a portfolio of 61 active patent applications. Seven licences have been negotiated and signed by ICM, two for the exploitation of a patent, two for the exploitation of a product issued from a research collaboration and three for the exploitation of a software developed by researchers.

ICM has drafted an official 'Data Policy' document drafted by the internal Data Committee, which is responsible for establishing and regularly updating the data policy regulation to be reviewed by the board of directors. The

document outlines the rules for the management and best practices for sharing data, records and digital tools. ICM is adherent to current regulations and legislation, including the General Data Protection Regulation, the French law of 6 January 1978 relating to information technology and the European and national regulation relating to clinical research. Detailed guidelines cover all the steps for maximising data sharing according to the FAIR principles while preserving the compliance with intellectual property right procedures. ICM is actively promoting Open Access (OA) publications through internal procedures and guidelines. This effort has enabled ICM to have published a very consistent fraction of its articles (75%) in OA format in the reporting period, with a strong increase in respect to the previous contract (57%). This fraction of OA articles is particularly impressive considering the high number of ICM total publications and contributing researchers. Published articles in OA should be also be accessible through the HAL repository, with the recommendation to be also uploaded to PubMed Central (NIH Open archive). ICM has also made available OA open-source software programs for neuroimaging data analysis, mouse brain imaging and RNA datasets. Of note, ICM organised the 'Neuro Openscience Workshop' in 2019, a symposium devoted to discuss all aspects of Open science in research.
The level of scientific production is uniformly excellent across all the teams, with some teams demonstrating an exceptional ability to publish very high quality research. This explicitly remarks the good operate of ICM in finalising its exceptional manpower and financial resources into top-quality science and research performance.

Weaknesses and risks linked to the context for the three references above

There are no major weaknesses to be reported.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

ICM has developed an exceptional infrastructure and organisation to foster research valorisation and business development through strong liaisons with industrial partners and the promotion of internal clinical and medtech applications. ICM has been spectacularly active in organising and formalising the diffusion of the knowledge the institute has accumulated to the general public (see further details in the corresponding sections).

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

ICM has established an exceptional string of initiatives and infrastructures to foster research valorisation and business development and accelerate industrial exploitation of medtech and clinical applications. Importantly, these operations have created a coherent and highly attractive ecosystem for industrial partners. In fact, ICM has signed 250 agreements with socio-economic partners including research collaborations, research services for industry, partnership agreements and license agreements during the reporting period. To further strengthen this liaison, ICM is sponsoring the development of common laboratories with industrial partners, setting up 4 of them during this mandate. ICM is one of the five Carnot Institutes on human health and has elaborated multiple initiatives to accelerate entrepreneurship and commercial partnership (e.g. Innovation and Tech Transfer Offices, iPEPS incubator, The Care and Living labs, Neurotrials). ICM Innovation and Tech Transfer Offices have developed strong policies for IP protection, project scouting, research mentoring, collaboration with industrial parties, and inventor incentives. The institute's strong involvement in the R&D sector is exemplified by the iPEPS incubator for start-ups, the iCRIN infrastructures and The Care Lab, as well as Neurotrials and acceleration programs (TIDU and NEURAL). With these assets, ICM is a shining example of successful interaction with the society and business world.
ICM has a portfolio of 61 active patents (37 in the reporting period), 7 of which have been licensed. ICM has incubated 57 start-ups and 6 of them have been co-founded by ICM researchers in the evaluation period. The

undeniable success of this coherent plan is proven by the remarkable revenues in 2022 (in the frame of several million euro) that become available to ICM to finance more initiatives, creating a virtuous economical loop.
ICM is actively communicating its research initiatives and achievements to the general public through press releases for national media (20 yearly), press articles on lay journals (1000 yearly) and social media (400 news item of which 230 were in English) and a recently renovated institutional website. In addition, ICM has developed a strong science outreach program with a variety of initiatives differentiated for target groups (lay public, patients, kids, students, fundraising) and supervised by a well-structured and resourceful team (24 members). ICM organised numerous public conferences during both the 'Brain Awareness Weeks' and during the year with regular cycles exploiting innovative communication ways (Open Brain Bar). All these conferences remain then accessible through the ICM's YouTube channel, providing a valuable resource for long-term outreach and visibility.

Weaknesses and risks linked to the context for the three references above

The reviewers did not detect significant weaknesses.

ANALYSIS OF THE UNIT'S TRAJECTORY

ICM strives to invigorate its research and technical staff with close attention to generational turnover through both the promotion of internal younger researchers (13 leaders emerging from the teams) and the recruitment of external researchers. Following this policy, four new teams were created during the evaluation period, while other seven new teams will emerge for the new mandate with several new team leaders. As a result of this extensive reorganisation, the ICM scientific staff will be structured in 26 teams during the new mandate. Four of the five scientific disciplines are almost equally represented as primary research topics between the 26 teams. The exception is clinical and translational neuroscience, which is somewhat less represented. However, the field is considered the second topic for 9 teams.
ICM has also completed the hiring of two new groups' leaders from abroad (UK and Switzerland) in the fields of cognitive neuroscience and the gut-brain axis. For this selection, ICM received 259 applications worldwide, confirming its highly attractive status as a research centre. ICM's generous start-up packages for the new team leaders is a very positive decision which should facilitate the recruitment of young and emerging talents with an offer compatible with those of other world-leading centres. It is notable that gender ratio among team leaders has strikingly improved in 2022 with 40% female team leaders, compared to only 30% female team leaders in 2017.
To fulfil ICM's ambition to house leading cross-disciplinary research, the Big Brain Theory program is an indispensable asset which funds early and risky projects between different teams. The decision to open this funding to projects in collaboration with partner institutions is particularly valuable in order to strengthen international partnership and research output.
ICM has been very clear that, given its strategic location and its multidisciplinary nature, its key mission is to bridge fundamental and clinical research to translate research innovations into clinical products. Towards this fundamental but challenging objective, ICM will further increase its efforts to cross-fertilise preclinical and clinical research and promote clinical trials. Strategic and precious initiatives in this direction are the expansion of the clinical research infrastructure (CIC and iCRINs), the 'protected research time' program for MDs, the Neurotrials Unit, the Car and Living Labs, the drug development program and the Neuroinformatics centre.
ICM plans to continue investing in the cutting-edge technologies and equipment necessary to maintain competitive technological platforms. For instance, the acquisitions of 7 T-MRI, Novaseq+, STED and 2-photon microscopes and GeoMax for spatial transcriptomics will certainly strengthen the competitive edge of the Institute.
ICM is a trailblazer in business development and industrial partnership, having constituted a very attractive and thoughtful ecosystem for the biomedical and medtech private sectors. ICM is very well aware of this and will further consolidate this position by developing the early pharmacology centre dedicated to Phase 1b and 2a industrial trials, the hospital Living Lab, the partnership with Station F and the acquisition of new space in the Chevaleret building for the development of Medtech projects. These ongoing initiatives will certainly expand the offer and attractiveness of ICM for the private sector and further sustain its internal business development program.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

ICM has been very successful in further increasing its income in terms of fundraising, national programs and competitive grants and has attracted new talents to strengthen its scientific community. However, this impressive

expansion has saturated the physical space available at the ICM building, with some difficulties already visible for the teams. These will probably worsen in the future given the arrival of the team of the new Director, the new Brain & Mind Biocluster funding and the programmed expansion of the computational modelling scientific area. Hence, it is urgent to identify and make available additional space where ICM can allocate some of its infrastructure and personnel. Although this is already an open discussion between ICM stakeholders, a timely program to alleviate these difficulties must be implemented soon. If a reasonable strategy will be to facilitate the turnaround of the teams at ICM, the panel recommends that the total size of ICM should not be diminished, but contrarily expanded to assure that its global leadership and attractiveness in very competitive domains like translational and clinical medical research are preserved or even reinforced in the next future.
Although many instruments and guidelines for internal communication have been implemented at ICM, the panel received numerous complaints regarding some opacity in sharing the institutional decisions. The panel recommends ICM to elaborate initiatives to communicate information actively and efficiently between the organisational levels. For instance, for better communication of top-down decisions, it recommends drafting 'minutes' of the COPIL and team council meetings that can be distributed to the interested personnel. With the same spirit, the panel recommend ICM direction to put in place initiatives to facilitate bottom-up discussions and initiatives to favour a positive interaction and fruitful exchange of ideas and opinions between the institutional boards, team leaders, PIs and research personnel. Along this line, a more transparent process governing the interaction between the SAB and ICM and following decisions would prevent some distress between teams/group leaders, facilitating their acceptance and active collaboration.
A particular note of the panel is dedicated to the PIs (group leaders), some of whom face difficulties to obtain sufficient internal and external visibility and recognition. This is particularly relevant at the ICM, given its size and multi-level organisation. To alleviate this issue, ICM should introduce additional initiatives, including a dedicated space on the website centred on the activities of individual PIs. In addition, direct involvement of PIs in the management of the Institute and its governmental bodies should be further incentivised.
Given the enduring expansion of ICM and its multidisciplinary nature, it would be advisable to stimulate initiatives within each of the scientific domains to facilitate their internal development and organisation. Independent retreats for each of the five scientific areas would be helpful to foster the internal community and facilitate scientific exchange between groups with homogenous interests.
A general concern that was heard by the panel from all levels is the insufficient support from the IT management, both in terms of service and interaction. These dysfunctions appear to be severe, since they challenge the ongoing experimental program of the teams. ICM is aware of this, but stronger initiatives are urgently needed to mitigate these hurdles. The panel collected the requests from several team/group leaders to increase the administrative support since they feel overwhelmed by these duties. Although ICM has an exceptional number of staff dedicated to support services, thanks to very generous funding from the Foundation, the panel recommends actively exploring additional ways to help support researchers and mitigate this burden.
An ongoing problematic issue is the exceedingly long and complex procedure necessary to initiate clinical trials or even clinical studies. Although, this is a general problem in France and elsewhere, it is particularly problematic at the ICM where clinical studies are one of its major strengths. The opinion of the panel is that until this problem has been fixed, ICM will not fulfil its full potential to efficiently transfer new research knowledge into innovative medical products.
ICM has pursued an excellent policy to assure highly up-to-date and expert personnel within the core facilities. ICM could also invigorate 'in-house' training for the whole ICM research personnel in order to spread core technical expertise. At the moment, few facilities (e.g. DAC) run these activities. ICM technical staff have a range of employers with different conditions (INSERM, CNRS, SU, APHP, IHU-ICM or ICM foundation). It is quite a complex scene, with different remuneration, vacations, health care, etc. Facility directors should consider the possibility of salary bonuses that can be given at the end of the year, depending on the yearly objectives. Directors, with the support of the unit administration and HR office, should plan in advance of the yearly interview of the staff and write the corresponding report thereafter.

Recommendations regarding the Evaluation Area 2: Attractiveness

The panel recommends maintaining the scientific richness and multidisciplinary methodologies that ICM direction has been successfully implemented over the last years. The complementary between world-class fundamental research, innovative preclinical applications and first in-human studies have created a thriving and accomplished ecosystem that has few equivalents on the world stage. To further increase its ability to attract excellent talent, ICM should continue to promote international calls for PhD students and initiate a similar hiring for postdoctoral researchers with a regular annual basis. Additionally, the institutional support for facilitating the arrival and integration of the non-French scientists can be further reinforced with additional initiatives and mentoring. Finally, it would be strategic for ICM to activate an MD/PhD program to further consolidate the initiatives to strengthen the integration between research and clinic and train the future generation of clinician researchers.
Following the departure of Nathalie Cartier, ICM lacks a team devoted to advanced methods and applications of gene therapy and editing for neurological diseases. The panel recommends that the ICM plans a future recruitment in this area, given the high impact of these technologies in the development of disease-modifying therapies for neurological diseases.

Finally, through the Neurocatalyst program, ICM has initiated a drug-repositioning project to identify new indications for drugs already in clinical use. The panel recommends exploring more initiatives to rapidly integrate this approach in the ongoing research of the teams and in timely acquisition of equipment, expertise and cellular models to maximise the success of this enterprise.

Recommendations regarding Evaluation Area 3: Scientific Production

No specific recommendations, the achieved level is outstanding. Nevertheless, the ICM should aim to make all its future scientific production open access.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

No specific recommendations, ICM has established an exceptional program of integrated and world-class initiatives for research valorisation, business development, industrial partnership and science communication to general audience.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: **Cellular physiology of cortical microcircuits**

Name of the supervisor: Alberto Bacci

THEMES OF THE TEAM

This team focused on several interrelated themes: 1/Plasticity of perisomatic inhibitory synapses and their role in network synchronisation and information transfer across cortical layers, 2/Connectivities of parvalbumin-expressing (PV+) basket cells and interneurons expressing high levels of cannabinoid receptor type 1, 3/Dendritic inhibitory synapses, including those originating from somatostatin-expressing Martinotti cells with target specificity in cortical layer 2/3, which provided over-inhibition in an established mouse model of Down syndrome, 4/The role of perineuronal net (PNN) accumulation around PV interneurons in the organisation of visual thalamic input to these cells in the cortical area V1.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended focusing on main methods and most promising aims, methods and projects to increase scientific productivity and to reduce administrative load. The team fully addressed the recommendations: The administrative load of PI has been reduced. The group established several cutting-age methods such as in vivo whole-cell recordings, in vivo 2-photon Ca2+ imaging in awake mice, high-density electrophysiological recordings using Neuropixels probes. The group published thirteen papers in excellent journals, including Cell Reports, PLOS Biology, eLife, and J. Neuroscience.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	1
Senior lecturers and equivalent	1
Researchers and equivalent	2
Research support staff	2
Sub-total for permanent research staff	6
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	5
PhD	7
Sub-total non-permanent staff in active employment	12
Total staff	18

EVALUATION

Overall assessment of the team

This excellent team made tremendous technical progress in transition from synaptic biophysics and cell biology towards more in vivo systems approach, built up set-ups, established cutting-edge methods and collected necessary expertise, which culminated in the publication of several seminal studies in its field. Its scientific production is excellent and likely to become outstanding next years. Its ability to attract funding is outstanding (>4,2 M€ from ANR, FRM, EU, ERA-Net, BBT, Fondation J. Lejeune, DIM). The team is internationally recognised and has trained five postdoctoral fellows and 6 PhD students (4 obtained their PhD, and 2 others are still in the process). Two lab members obtained prestigious MSCA fellowships. Thus, the group shows excellent attractiveness.

Strengths and possibilities linked to the context

The team produced thirteen papers that were published in highly visible international journals (e.g. PLOS Biology, eLife, Cell Reports), including several papers defining the connectivity scheme, the plasticity properties, and functional roles of basket cells in several cortical areas and two translational studies characterising GABAergic inhibition in mouse models of DS and early-life insult, leading to adult depressive and anxiogenic phenotypes. The contribution of the team to its field is excellent. The team is very attractive, its size and expertise are excellent, including three permanent researchers and five post-docs. The team has recently integrated a new PI (from UCSF) to implement neurophysiological and optical recording in freely behaving mice. The team work is well supported by research grants, including 3 European grants (ERA-NET Neuron, two MSCA). The results are well presented at national and international conferences (e.g. France Neuroscience, FENS, SfN, Gordon Research Conferences; in total: 13 oral presentations). There are a lot of teaching activities done by the PI (e.g. Master 2 – M2 P7 at Univ. Paris Cité ; Neurophysiology – L3 – at Ecole Normale Superieure; M2 course at Sorbonne University) but also by the other researchers of the team. For three years (Jan 2016 – Dec 2018), the PI of the team was the Scientific Director of the ICM, and hence was responsible for the development of the scientific strategy and activities of the ICM, so it is difficult to overestimate his organisational contribution to the ongoing research in the team and ICM in general. Also other senior team members actively participate in the scientific life of the ICM. The lab benefits from various local, national and international collaborators (e.g. ERA-Net NEURON Consortium DevInDS, MSCA ITN 'Serotonin and Beyond', Laboratoire d'Excellence de Biologie pour la Psychiatrie in Paris). As the team is studying how cortical circuits are altered in a mouse model of Down syndrome and in a mouse model of anxiety and depression induced by early-life insult, it is highly plausible that it will contribute to the development of new treatments of these conditions in the next funding period. Also the group actively participated in the public communications, in particular on the World Down Syndrome Day.

Weaknesses and risks linked to the context

Although several excellent studies have been published, even higher productivity can be expected for a team with such accumulation of researchers with permanent contracts and postdocs. The team is getting a deep insight into dysregulation of inhibitory transmission in animal models of human diseases but does not convert it into patentable products and made no visible transition towards markets. However, the planned research ensures that the team is on the way to increase its translational research. A more advanced/specific tool than chondroitinase ABC should be used for targeting of the extracellular matrix (ECM) to elucidate the ECM functions.

Analysis of the team's trajectory

On the basis of published data and established methodologies, the team will continue to explore the morpho-functional, connectivity and plasticity properties of GABAergic connections that are different in distinct cortical areas, resulting in the formation of cortical area-specific circuits. These differences are especially evident when comparing primary sensory with higher-order cortical areas. Interneurons expressing cannabinoid receptor type 1 (CB1) or parvalbumin will be in the focus of research. The accumulated knowledge on the organisation of cortical circuitries will enable the team to study specific inhibitory circuit dysfunctions in animal models of intellectual disabilities, and anxiety and depression resulting from early-life insult. The plans are outstanding in terms of novelty, technical excellence and potential impact, and the team developed all necessary technologies to implement them. The personnel and financial resources are in line with the proposed project.

RECOMMENDATIONS TO THE TEAM

It may be useful to increase 'industrial' motivation and intelligence with regular seminars on new patents and start-ups emerging in the neuroscience field (success stories), and on the importance of patenting to foster knowledge transfer. Additional options could be to invite colleagues working in the pharma industry to present their translational research that already resulted in clinical development of new products, organise visits to clinical settings and inviting doctors to talk about diseases relevant to the team's research.
It could be beneficial to enhance collaboration with computational neuroscientists to interpret how differences between cortical circuitries reflect the functional optimisation in solving particular tasks.
As chondroitinase ABC broadly removes perisynaptic, periaxonal and glial forms of ECM, more advanced tools for more specific targeting of perineuronal nets should be used to understand their functional role.

Team 2: **Genetics and physiopathology of epilepsy**

Name of the supervisor: Stéphanie Baulac - Le Guern

THEMES OF THE TEAM

This team focuses on the identification of mosaic cortical mutations causing focal epilepsies. In their report, it is stated that the future development of the team is to be led solely by Baulac with the former co-leader Leguern to become head of the genetic clinical department. This seems an excellent choice. Within the focus of cortical mutations during development and cause of dysfunction, the Baulac team has achieved excellent results and diversified its portfolio including mouse and clinical models. The key aims are i) identification of mutations, ii) reconstruct mosaic cell lineages, iii) disease modelling using organoids and iv) addressing effects of cellular senescence in epilepsy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous reviewers recommended that the team i) increases their involvement in journal editorial boards and ii) promotes property rights/commercialisation of findings. While the current panel members do not necessarily agree that jumping on journal editorial boards is the best investment of time for a team leader, this team leader has successfully addressed both recommendations and is now a member of several journal boards. In addition, and perhaps a clearer sign of success, the team was recently awarded a very competitive and prestigious ERC-Proof of Concept grant.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	3
Senior lecturers and equivalent	
Researchers and equivalent	2
Research support staff	4
Sub-total for permanent research staff	9
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	2
PhD	8
Sub-total non-permanent staff in active employment	10
Total staff	19

EVALUATION

Overall assessment of the team

The team is globally excellent. The team is pioneering an important and challenging research line and producing excellent results across the full spectrum of all that is important: publications, grants, and so on. While the panel considered that, in the future, the team should in the future start exploring new avenues, in terms of 'past performance' there is no doubt that this is an excellent team.

Strengths and possibilities linked to the context

As already mentioned above, the team has an excellent performance and international recognition, a strong publication record, extramural funding and all criteria of success including contribution to scientific networks in this highly relevant topic. These strengths are the result of the profound operative and scientific integration of clinicians and scientists working together within the team. This environment is ideal to foster translational research and to accelerate the exploitation of new clinical tools based on the research and innovation generated in the lab.

Weaknesses and risks linked to the context

One weakness has already been recognised by the team itself: they 'lack electrophysiology expertise', and the panel agrees that this could become a serious issue. It seems plausible that diseases such as epilepsy could, in the not too distant future, be cured/mitigated by neuroprosthetics/brain machine interfaces that use AI to interpret brain activity and compensate in real time. The team has so far been focusing on understanding the developmental malformations resulting in epilepsy. It has been very successful in doing so, and should certainly continue to progress in this area. No doubt. However, it may be wise at this point not to neglect what seems the most likely direction of this field. Implementing in vivo cortical electrophysiology (EEG/arrays/etc.) becomes more important than before and moving some steps in this direction (e.g. in collaboration with other groups, hiring a well-trained senior scientist, etc.) would seem feasible and good long-term investment.

Analysis of the team's trajectory

The Team has delineated a coherent future research plan well in line with its strengths and expertise. Building on its recent achievements, the team will expand its efforts to identify new somatic mutations responsible for epileptogenic cortical malformations in bulk or microdissected autoptic brain tissues. The team has reached an international leadership in these studies with established collaborations with international pioneers in the field. The future research will heavily rely on broad whole-genome sequencing and, thus, it is recommended that the IT management and infrastructure will be reinforced to assure timely data delivery and analysis. Gene discovery for these diseases is currently a good and rewarding investment for the Team. However, once more genes will be identified it will be important to be ready to move to more functional studies, optimised disease models and novel therapeutics. The team is conscious of this and has planned new and original work using human iPSC modelling and novel gene-based therapies. These are very important new avenues for the team that will assure its competitive profile for the future. However, to fully embrace these new developments, the team should promptly incorporate this expertise inside the team and do not relay excessively on external collaborations. The good funding already obtained for the next years assures sufficient resources for the swift development of the proposed research.

RECOMMENDATIONS TO THE TEAM

keep on like this, excellent results, but consider investing in future arising technologies (BMI see weaknesses)

Team 3: **ALS Causes and mechanisms of motor neuron degeneration**

Name of the supervisor: Séverine Boillée

THEMES OF THE TEAM

The team was and will be led by Severine Boilee and focuses on amyotrophic lateral sclerosis. The team's leader is extremely well recognised internationally in this area of research and has recently been promoted internally to DR2 Inserm, equivalent of professor grade. The team is very well known for its contributions on non-neuronal cell types in ALS and has made further very significant advances in this area, as illustrated by their landmark 2020 Nature Neuroscience manuscript. There are also strong collaborations related to clinical research, including genetics and work relying on patients sample biobanking. The team has made in this area contributions that have direct implications on patients, for example, significantly increasing the population receiving access to novel SOD1 gene therapies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recognising significant strength in basic science, the previous recommendations included extending collaborations and activities to include more clinical research, and to set up crucial infrastructure for cell collections from patients. The team has definitely delivered on genetic research. Importantly, this has not only been work related to entirely novel genetic aspects of ALS genetics - which are, of course, welcome - but has also focused on the more in-depth analysis of known genetic defects with the very important result of significantly expanding the current SOD1 ALS patient pool that can and will benefit from a recently FDA-approved ASO treatment. The team has also delivered on reinforcing the clinical links allowing them to collect and carry out research on patient-derived cells, as PBMCs. Results deriving from this are to be expected in the future period.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	3
maîtres de conférences et assimilés	
Senior lecturers and equivalent	4
Research support staff	4
Sub-total for permanent research staff	11
Non-permanent teacher researchers and researchers	1
Non-permanent research support staff	
Post-docs	1
PhD	8
Sub-total non-permanent staff in active employment	10
Total staff	21

EVALUATION

Overall assessment of the team

This is an excellent overall team. Their work is very visible and internationally recognised.
The team has published an outstanding Nature Neuroscience manuscript demonstrating the potential of targeting immune cells in the periphery to modify ALS progression. This demonstrates a continued excellence in this area of research where they are world-leading, and also carries translational relevance, fulfilling the attempt of moving the basic science to clinical relevance. The team has made genetic discoveries with tangible patient treatment impact for SOD1 mutation carriers: a significantly increased number of sufferers will receive SOD1 ASO therapy, which is of outstanding impact. The team has created important infrastructure for collecting patient material and cells, which will be important for work in the future period. The team has also been leading on consortia that will contribute to their current projects. The team has secured numerous grants both national and international (e.g. ERANET) and a significant donation. The group has extended to work with the private sector (e.g. by testing a drug relevant to their area of research with MedDay) and submitted patents on guided ultrasound for spinal cord, underlining its successful attempt to include more translational work.

Strengths and possibilities linked to the context

A major strength has been the ability to continue producing high-level science to remain a world-leading team in the area of non-cell-autonomous ALS mechanisms. The Nat. Neuroscience paper and the numerous invitations to international meetings support this. The team has clear international recognition. The team leader built their early work on cell autonomy in ALS in one of the major ALS labs worldwide (UCSD). They have definitely managed to make this area of research their own and are considered world-leading on this, as supported by the numerous talks given, the organisation of an international meeting on this ('immune cells and the CNS') and the publication of a seminal paper in the subject in Nature Neuroscience in 2020. This is an outstanding contribution to the field. The potential clinical-research synergy is enormous due to proximity to the Salpêtrière hospital, and was definitely under tapped in ALS in recent years. The team has been building resources in cell biobanking that will make this a strength for the next research period. The team has also been excellent in outreach, and has secured a significant donation for research. The team has an excellent publication record. Beyond the work in the immune-ALS area of expertise, the team has also published genetic data identifying a novel common SOD1 cause of ALS which has an exceptional output as it impacts patient care by significantly extending the patient pool eligible to SOD1 gene therapy in France. All permanent members of the team participate in publications. The team has secured 3 M€ in competitive funding from national, European and international agencies including: French Medical Research foundation (450 k€), French ALS association (ARSLA, 229 k€), French Myopathy association AFM (207 k€); ERANET Neuron (235 k€/3y), Thierry Latran foundation (272 k€), American ALS association – ALSA (216 k€/3y). Team Members have given 56 oral presentations (2017–2022), and the 4 team leads have been invited to present at national level (22 talks), and on international level (18 talks). They have organised meetings including the international *'Immune cells and the CNS'* ISN Satellite meeting in August 2017, and a symposium on stem cells and regenerative medicine in December 2022. The team shows an outstanding capacity to train PhD students. They have had ten PhD students, with three currently working as postdocs. The team also trained fifteen master students, with 50% then pursuing a PhD and 6 others either going to the biotech private sector or continuing education in medicine/biology. The 4 PIs participated in teaching activities with lectures to Master programs (M1/M2) or University programs (DU/DIU). The team lead is part of the committee of the neuroscience PhD school. The team has strong connections with industry, as demonstrated by work with medDay Pharmaceuticals, Neurophoenyx. and Carthera. The team has also filed patents for the use of ultrasound-guided spinal cord targeting by immune cells in a collaboration with Carthera.

Weaknesses and risks linked to the context

A challenge for moving the proposed research forward will be the current lack of appropriate models. The role of peripheral immunity is difficult to study with current iPSC-based co-culture systems, and mouse models that could take the group beyond the current SOD1 work are not ideal. These are challenges that the whole ALS community faces, but are extremely relevant to the proposed work.

Analysis of the team's trajectory

The team is on an extremely positive and clear upward trajectory.
It has been able to consolidate and position itself as world-leading in the expanding field focusing on the immune involvement in ALS, and now aims to build on this over the coming evaluation period. The previous evaluation had noted insufficient interactions with clinical resources, and now the team has taken the necessary time to build the experimental research set-up and clinical collaborations. Some of these, such as the collection and access to ALS patients' peripheral cells, will be key in allowing them to deliver in the next phase. The team is also planning to focus on how risk factors and ageing contribute to ALS. This work package aims to further create cohesion between the different areas of research of the group.

RECOMMENDATIONS TO THE TEAM

The team is gearing up to take on numerous lines of research using complex systems. This will require significant funding and the team lead definitely has the credentials, the track record and an innovative research plan to be competitive in ERC application, and should definitely be applying for major ERC, EU or NIH initiatives in the coming period.

Beyond collecting cells from cases for their proposed research, there is no direct involvement of neuropathologists in the group, and emphasis on brain and nerve banking should be a priority given the research themes.

Team 4: Neurophysiology of Repetitive Behaviours

Name of the supervisor: Eric Burguière

THEMES OF THE TEAM

This recently established team focuses on neurophysiological and functional aspects of repetitive behaviours in human and mouse models. They use genetically modified mice to study circuits and features that are relevant for diseases such as Tourette syndrome and obsessive-compulsive disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

It was recommended that the team increase its high-impact publication output and its engagement with industry. The team has published a manuscript in Communications Biology which includes mouse and human data, and has a substantial manuscript in advanced revision stages at Nature Neuroscience. The group has also produced a Science publication which has led to new avenues of research within ICM.
The team has also submitted as co-inventors a patent illustrating its efforts to increase the translational relevance of its work.

An increase in team size was recommended and the team did indeed nearly double in size – if one excludes the three PIs.

Lastly, an increased collaboration with clinicians was encouraged, and indeed collaboration and co-authored papers have been produced, as shown by ten co-signed papers. The PhD students have also been able to carry out both human and animal work supporting the integration of these two aspects of the team, and its alignment with recommendations and ICM goals.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	4
Senior lecturers and equivalent	
Researchers and equivalent	2
Research support staff	1
Sub-total for permanent research staff	7
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	1
PhD	10
Sub-total non-permanent staff in active employment	11
Total staff	18

EVALUATION

Overall assessment of the team

This is overall an excellent team. This recently established team has produced excellent research. They have published twenty original articles as main contributors including very visible and important papers in established journals including a Science manuscript, and have been invited to international meetings including FENS, IBAGS and IBNS. They have been excellent in securing funding with over 2M raised, and have successfully attracted talent and expanded the team with international members. They have also filed one patent with another pending. They have been excellent in developing technology and analysis tools, as the BeatBox set-up. Their set-up of parallel mouse and human work is a perfect fit with the Institute's mission.

Strengths and possibilities linked to the context

The team has strengthened its potential by recruiting an engineer and an increasing number of students (6 PhD students in 2023) and postdocs (4 in 2023). Their work developing both software and hardware for projects as the BEATBox puts them in a good position for future projects. They have also established a good track record for student publications, with over one first author publication on average. The team has had 50 publications, leading on twenty and with ten of them co-signed by Team leaders. They have published an outstanding manuscript in Science, and a very strong paper in Communications Biology (2021) where they exemplify their strength of using a mouse/human parallel approach. The team has secured over 2.2 M€ in competitive grants from 2019, through eleven competitive grants led (as PI) by three different team members. The team has developed the Behavioural and Autonomous operant Box (BEATBox) where mice can be studied for weeks whilst performing their task, and this is based on open source principles. Team members have been involved in internal and external activities to promote gender equality (XX-initiative at ICM) and have led a discussion about climate change ('How Can Neuroscience Help to Turn the Tide of the Climate Crisis?' edition on Frontiers). Team leader and member have filed a patent (Method and Device for physiological signal pre-processing (EP22305177.2, 2022)
The team has had ten masters and PhD students and postdoctoral fellows per year.

Weaknesses and risks linked to the context

The 2020 and 2021 years certainly may have had a stronger impact on smaller groups starting projects and relying on complex experimental settings. With the data generated and in course of publication, more ambitious grant schemes should be tried.

Analysis of the team's trajectory

This team is leaving the ICM. No trajectory.

RECOMMENDATIONS TO THE TEAM

The team should continue to do as it has in the last period. Continue performing high-level science combining mouse models and human-based studies, maintain productivity in publications and links with companies. It would be important to seek more international grant funding.

Team 5: **Network dynamics and cellular excitability**

Name of the supervisor: Stéphane CHARPIER/Mario CHAVEZ/Vincent NAVARRO

THEMES OF THE TEAM

The team #5 is dedicated to investigating the pathophysiological mechanisms of focal epilepsies. They have a specific focus on understanding the cellular, synaptic, and network mechanisms that underlie brain dynamics in various epileptic conditions and during deep brain coma. This team conducts translational research to identify new molecular targets and potential treatments.
In the upcoming term, the team will welcome two new members who bring strong expertise in the cellular and molecular study of synaptic function and neuronal excitability. This addition will broaden the range of experimental approaches used by the team. The new leadership will be under J. C. Poncer and V. Navarro.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1. Regarding teaching duties, it was challenging to significantly reduce S. Charpier's teaching load due to his full-time professorship. Nevertheless, the team managed to maintain a good to high level of research activity, as indicated by the publication report. Additionally, the team's productivity has slightly increased in the past two years.

2. *To enhance team dynamics, it is essential to clearly define the responsibilities of the three PIs. Encouraging strong interactions among all team members and making efforts to achieve gender parity are important goals*. While gender parity has improved, it is unclear why there may be a gender bias in proposed experimental approaches, and this should be clarified. The team has also expanded its office space.

3. The committee recommended maintaining project coherence by focusing on the described research topics. Strengthening interactions with other teams, particularly those focused on the genetics of epilepsies and in vitro studies, can yield valuable results in the field of epilepsy. Collaborations suggested by Hcéres, such as those with the teams of Baulac (genetics, ICM), Poncer (in vitro studies, Institut du Fer à Moulin), and Valero-Cabré (ICM), have been successfully implemented. Furthermore, the addition of the two new PIs in the next contract is expected to further strengthen the team.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Staff categories
Professors and equivalent	3
Senior lecturers and equivalent	2
Researchers and equivalent	4
Research support staff	7
Sub-total for permanent research staff	16
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	9
PhD	12
Sub-total non-permanent staff in active employment	21
Total staff	37

EVALUATION

Overall assessment of the team

This is an excellent overall team. The team's scientific goal focused on deciphering cellular, synaptic, and network mechanisms underlying various pathological states, emphasising the importance of in vivo multiscale electrophysiological studies with advanced signal analysis. Their research seamlessly integrated studies in both patients and relevant animal models, allowing for a translational strategy. The Team shows an excellent scientific production with more than 120 original articles published in high to very high-quality journals (i.e. Brain, Prog Neurobiol) and several reviews in top renewed journals (including science and Nat. Comm.). The international recognition of the team is also shown by the high-rate participation to international meetings. Major achievements of the team also include the contribution of eight patents and the generation of two software packages shared with the community. The team capacity to raise funding is excellent with approximately 2.5 M€ of competitive grants from national and international programs (i.e. Eranet) and over 1 M€ obtained through partnership and collaboration with industrial partners. The team has shown an excellent capacity in recruiting and motivating fourteen PhD and 7 IR and post-doc from France abroad as shown by their publication record.

Strengths and possibilities linked to the context

The team's scientific production is very good to excellent, with publications in reputable journals such as Brain, Progress in Neurobiology, and Annals of Neurology. The PIs are recognised as international experts in their respective fields. Their studies in both patients and relevant animal models have led to significant achievements and include the following. Mesial Temporal Lobe Epilepsy (mTLE): They developed a unique platform for recording neuronal activity in patients with focal pharmaco-resistant epilepsies, revealing heterogeneity within the epileptic focus and repetitive patterns in cortical malformations. Status Epilepticus (SE): The team identified novel biomarkers for diagnosing SE, monitoring recurrence, and predicting recovery, leading to a clinical trial for neuroprotection. They also studied seizures in anti-LGI1 autoimmune encephalitis. Absence Epilepsy: Using a genetic animal model, they uncovered the development of increased excitability and paroxysmal activities in cortical neurons, shedding light on sensory perception alterations during absence seizures. Deep Coma: Studying patients in pharmacologically induced isoelectric states and an animal model, they challenged conventional views by revealing neuronal excitability during brain silence. They introduced a novel EEG marker, the 'resuscitation wave', indicating post-anoxic recovery of cortical activities. The scientific environment within the team is robust and supportive of emerging talent. PhD students and young investigators are highly regarded and demonstrate remarkable productivity, often publishing as first authors in esteemed journals (i.e. Progress in Neurobiology). PhD students have contributed to fifteen papers of which have signed 23 as the first author. This environment fosters the development of the next generation of researchers and contributes to the team's overall success. The teams are very well integrated in the ICM research infrastructure and take advantage of local collaborations.

Weaknesses and risks linked to the context

The team already possesses a high publication track record and a strong scientific capacity for securing funding, but there is room for further improvement in this regard.

Analysis of the team's trajectory

The addition of the Poncer/Renner team is expected to enhance the group's research capabilities (as testified by publication in esteemed journals like Science, Nature Communications, and Cell Reports). Furthermore, adding the Poncer/Renner team establishes a unique setting that allows the new team to do translational research from in vitro analyses (mouse/human), via in vivo mouse recordings to human recordings.
The hypothesis being tested involves compensating for KCC2 down regulation by targeting potassium channels. The research aims to validate this hypothesis through electrophysiology and analysis of tissues from epilepsy patients and mouse models. Additionally, the potential of channel openers in preventing seizures will be explored. Furthermore, the team intends to develop allosteric modulators for KCC2 via molecular modelling and virtual screening. Promising candidates will undergo in vitro and animal testing, offering potential advancements in epilepsy therapeutics.
Preliminary research using calcium imaging in mTLE mouse models suggests a role for certain interneurons in leading pathological activities. Principal neurons with altered KCC2 expression and depolarising GABA signalling may contribute to epileptiform activity. Connectivity studies hint at highly connected 'superhubs' as potential contributors to pre-seizure states. To delve deeper, the team plans to employ unbiased approaches with

transcriptomic analysis to identify cells and circuits involved in pathological activities. Additionally, interventional methods will help establish causal links between specific neurons' activity and seizure emergence, shedding light on their molecular identity. This research spans from vitro approaches to studies in patients and holds great potential for understanding epileptogenic networks. Staff and finances are in line with the proposed project.

RECOMMENDATIONS TO THE TEAM

The panel recommends securing major funding. ERC application should be considered.

The translational potential of the team is unique and should be maximally and systematically taken advantage of. The panel recommends including approaches allowing comparing same recording modalities in vitro, and in vivo in mice and human, as well as incorporating – omics approaches in biofluids and tissues.

Team 6: **Physiological investigation of clinically normal and impaired cognition**

Name of the supervisor: Laurent COHEN/Paolo BARTOLOMEO/Lionel NACCACHE

THEMES OF THE TEAM

The team is devoted to the study of human normal and impaired cognition, using behavioural and multimodal imaging methods (aMRI, fMRI, dMRI, EEG, MEG and SEEG), addressing both fundamental questions and developing clinically useful diagnostic and therapeutic tools. They study both healthy participants (including blind and deaf) and brain-damaged patients with focal or diffuse lesion). The team addresses three main themes (i) language and reading, (ii) attention and mental imagery, and (iii) consciousness and disorders of consciousness (DoC).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation recommended that the team maintains the current outstanding level, and it is clear that they have attempted to do this.
They also recommended fostering integration between the PIs, and this has been reasonably successful, as demonstrated by the existence of several publications involving more than one of the PIs.
Finally, they recommended the recruitment of (permanent) research support staff, and this has been possible in at least one case with the recruitment of a hospital funded EEG technician, who also contributed to a better documentation of clinical outcome measures.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	2
Senior lecturers and equivalent	1
Researchers and equivalent	7
Research support staff	9
Sub-total for permanent research staff	19
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	13
PhD	16
Sub-total non-permanent staff in active employment	29
Total staff	48

EVALUATION

Overall assessment of the team

The Physiological Investigation of Clinically Normal and Impaired Cognition team (PICNIC) is globally excellent. They have an excellent level of scientific production with an average of over 6 publications every year per full-time research position. The team has numerous obvious strengths that include (i) the complementarity between the PIs, (ii) access to patients, thanks to the localisation of the ICM, and (iii) a remarkable level of expertise in the use neuroimaging in brain-damaged patients. They also have an outstanding record for outreach to the public via books and national TV and radio programs. Funding is excellent, and the team has been able to benefit from a lot of support from the ICM. The team is also internationally recognised making it very attractive.

Strengths and possibilities linked to the context

The scientific production of the team is excellent. Among the 165 original research articles published by the team, fourteen are in journals that are in the top 1% in their field. They include Brain (5), Annals of Neurology (3), PNAS, Cognition, Neuroimage… Over half (85) are in the top 10% journals. They also published 22 reviews. For

over half the publications, one of the team is in a leading position, as first, last or corresponding author. The team's production is well cited, with 41 appearing in the top 10% of articles ranked by field-weighted citation rate. Some of these publications benefit from the team's excellent and long-standing collaborations with key players such as Stanislas Dehaene, but there are numerous well-cited publications that only involve members of the PICNIC team. They have also produced several significant book chapters, which have also been well cited. Key findings include (1) the discovery of a new behavioural sign of consciousness and the demonstration of a causal effect of DLPFC tDCS stimulation on conscious states and (2) a demonstration of the involvement of a previously undescribed region in the left fusiform gyrus in visual mental imagery. But the team has also made numerous contributions to understanding of musical reading, functional connectivity in literate and illiterate brains as well as colour and shape perception. The attractiveness of the team is also excellent. This is demonstrated by the fact that the team has attracted many PhDs and postdocs from around the world, including many countries such as Israel, Poland, Argentina and Uruguay. One of the team leaders (Lionel Naccache) has received five different distinctions – the Grand Prize of Medicine and Medical Research of City of Paris, the Eloi Collery Grand Prize of Medicine from the French National Academy of Medicine, the Bernheim Prize, the Pierre Simon Ethical Prize as well as being elected Member of DANA Alliance for Brain Initiatives. He was also nominated as a 'Rising Star of Psychology' by the Association of Psychological Sciences (USA). The team's excellent ability to train students and postdocs is demonstrated by the fact that the fourteen postdocs who worked in the group all have good positions. Likewise, of the nineteen PhD students trained in the team, the 9 who defended their theses have gone on to positions in science. On average, each defended thesis was associated with around 2.5 publications. The team is well funded, with a total of nearly 2.5 M€ of funding, including 1.73 M€ of national funding (5 ANR grants), 0.35 M€ of international funding, and 0.38 M€ from industrial collaboration (4M€ according to the written report). It also offers a wide range of methodologies including structural MRI, functional MRI, and diffusion MRI with white matter tractography surface and intracranial electroencephalography, and magnetoencephalography, as well as behavioural techniques. The team's contributions to society are excellent and, in many cases, outstanding. They have some collaborations with industry, including a project funded by Dassault and a collaboration with a start-up (MyP) L that bought an application (NeoStaff) developed by a team member. Their work on clinical biomarkers of consciousness has led to 4 international patents, with a fifth patent on the use of a local anaesthetic for treating stroke. But above all, the team has been extremely active in promoting science to the public, with no less than 9 books, some of which have been translated into other languages. They are also often present in the media, with high-profile contributions to the radio and television, as well as contributions in the press.

Weaknesses and risks linked to the context

Any weaknesses of the team are relatively minor.
Perhaps the biggest weakness lies in the absence of any female scientists among the PIs.
The team's ability to make clinical data publicly available has been somewhat limited by restrictions on ethical authorisation, but this is something that applies to all researchers working in the area.
They note that while they have succeeded in getting numerous research projects financed, this adds to the administrative load, and that it might be better to concentrate on a smaller number of larger grants.
Finally, their very strong presence in the national media means that they have tended to get more requests than they can handle. But this is hardly a negative point.

Analysis of the team's trajectory

The team's trajectory appears to be extremely positive, with an impressive list of cutting-edge projects that look likely to continue the excellent research that they have maintained over the past evaluation period. The topics under consideration are fascinating, and look set to reinforce the team's international standing as a major centre for research on the brain mechanisms underlying consciousness. Staff levels and finance are perfectly in line with the proposed project.
One particularly interesting and relatively novel approach for the team will be the development of computational whole-brain models based on single patient neuroimaging data.

RECOMMENDATIONS TO THE TEAM

The panel recommends that the team continues with the current approach, which has proven to be very efficient.
Given the stature of the PIs, and their heavy commitments, it seems that applying for ERC funding could be a priority, rather than dispersing their activities across multiple smaller projects. This would also help solve some of the other difficulties faced by the team, including the need for a lab manager.
The panel also encourages the team's ambition to include more computational modelling during the next contract.

Team 7: Algorithms, Models and Models and Methods for Images and Signals of the Human Brain

Name of the supervisor: Olivier COLLIOT/Stanley DURRLEMAN

THEMES OF THE TEAM

The team aims to design computational, mathematical, and statistical approaches for the analysis of multimodal imaging data in brain disorders, with an emphasis on imaging data. The methodological domains of the team are: machine learning, data science, medical image computing, and complex systems. These approaches are applied to clinical research in brain disorders in collaboration with other teams of the ICM, clinical departments of the Pitié-Salpêtrière hospital and external partners. The team works towards two objectives: i) advance the state-of-the-art in the fields of machine learning and data science for health care, ii) build useful digital tools to better understand, diagnose and predict brain disorders and create the next generation of clinical trials.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended increasing the economic valorisation of the research work, maintaining the balance between the number of students and supervisors, and staying focused on giving the many potential research opportunities and collaborations. The team has taken appropriate actions to take all of these into account, with concrete examples of tech transfers (new industry contracts, a spin-off company, dissemination of software), recruiting five new faculty members, and more carefully selected collaborations.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	7
Senior lecturers and equivalent	2
Researchers and equivalent	8
Research support staff	41
Sub-total for permanent research staff	58
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	7
PhD	42
Sub-total non-permanent staff in active employment	49
Total staff	107

EVALUATION

Overall assessment of the team

This exceptional team is esteemed for its rigorous work in methodological and medical fields. Their scientific production is outstanding. Team members play major roles in journals/conferences/outreach and junior researchers won prestigious awards. Resources are outstanding with over 10 ME funding in competitive grants, including ERC, ANR. The team has trained 45 PhD candidates (20 ongoing), twelve PDs and 21 engineers. Trainees continue with as faculty at highly respected institutions. The publication level of doctoral students is outstanding. Their Open Science approach is highly laudable. The team has conducted three industry contracts, worth 1 ME, and created a start-up company.

Strengths and possibilities linked to the context

This is a nationally and internationally well-recognised team (7 PIs>50 trainees), esteemed for its work in methodological and medical fields. The scientific production of the laboratory is exceptional 233 original publications with 103 in first or last position –. The team is exceptional; their work stands out in methodological rigour and innovation as well as medical relevance, as exemplified with well-cited papers in leading journals –

e.g. IEEE journals, Medical Image Analyse, J Neural Eng, NeuroImage, Lancet, JAMA, Brain – . As their portfolio shows, important results are the development of computational approaches to extract biomarkers from MRI and PET data, new complex systems approach to analyse, model and control brain networks, a framework for disease – e.g. Alzheimer – progression modelling with longitudinal data, and tools to integrate high-dimensional and multimodal data. Team members play major roles in journals – as editors of Medical Image Analysis, IEEE or Plos One – and conferences – organisers/chairing MICCAI 2020, SPIE Medical Imaging – and junior researchers won prestigious awards. The team's resources are outstanding with over 10 ME funding in competitive grants over the previous contract period, including ERC, ANR. The team has trained 45 PhD candidates – 20 ongoing – , twelve postdocs and 21 engineers. Trainees continue with as faculty at highly respected institutions – CNRS, Inria – or industry – e.g. IBM, Airbus – . The publication level of doctoral students is outstanding – 3 pubs/thesis – . Their Open Science approach is highly laudable, with emphasis on developing open-source software platforms, and matters of reproducibility and trustworthiness of machine learning. The team has conducted three R&D contracts with industry, worth 1 ME in funding, and created a start-up company – Qairnel – . The team has been very active in outreach, including a dozen presentations to various non-scientific audiences – ranging from general public to members of the Bundestag for instance – as well as numerous interviews for radio. The team is highly involved with the ICM institute as a whole – many collaborations–. The team has great possibilities for societal and economic impact, as they have already shown with tech transfers and open source platforms for clinical imaging and modelling of disease progression.

Weaknesses and risks linked to the context

There are no weaknesses regarding the team of its research. A minor point, as they realise, is that they could explore the opportunities for patenting their findings more. A general risk is the difficulty of recruiting postdocs due to competition with industry. The team will benefit from the creation of the new ICM domain on computational methods for neuroscience, as to which they are now the only team.

Analysis of the team's trajectory

The team has made important advances in the computational and mathematical modelling of patient data which have in turn led to innovative tools for better understanding, diagnosis and predicting brain disorders. The team has developed and disseminated ambitious Open-Source software packages, in particular Clinica, ClinicaDL and Leaspy. They will continue and expand all of this work in the upcoming contract period, except for the work on complex networks for neuro-engineering, which will be continued by a new team, led by departing team member dr. De Vico Fallani. A new research axis on computational pathology will be created. The team's future research entails an efficient strategy to further enhance synergies between team members and maximise the impact of their research. Staffing and finances are in line with their future plans. Their research can be expected to produce a new generation of digital tools for characterising brain disorders across multiple scales and provide new systems to build more efficient clinical trials and assist clinical decisions.

RECOMMENDATIONS TO THE TEAM

It is recommended to maintain the current outstanding level. It's recommended to stimulate the building of a new team in the Computational Neuroscience cluster, in particular a team on NeuroAI.

New Team: NERV - SYSTEMS NEUROENGINEERING TO MODEL AND INTERFACE BRAIN NETWORKS

Name of the supervisor: De Vico Fallani

THEMES OF THE TEAM

The overarching goal of this new team is to consider brain-behaviour problems at the intersection of statistical physics, biomedical engineering, and clinical neuroscience, thereby relying on network science. The team will focus on systems neuro-engineering, developing new analytical tools and technological solutions to understand brain functions and remedy its dysfunction. There are two main research objectives: i – Analysing and modelling brain connectivity networks. For this, the team will develop computational frameworks based on network science to characterise the spatiotemporal complexity of brain networks from multimodal and longitudinal neuroimaging data – mainly EEG, MEG and DTI – , and ii) Improving non-invasive brain-computer interfaces. For this aim, the team will leverage the developments in network science to unveil the brain organisational mechanism of BCI-related tasks and ameliorate the decoding of the user's mental intention. The team will experimentally validate their methods in collaboration with clinicians to provide new insights in brain physiopathology, identify predictive biomarkers, and provide new neurorehabilitation strategies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

EVALUATION

Overall assessment of the team

The team departs from the COLLIOT/DURRLEMAN team, following the award of an ERC grant to the team leader. Being embedded in COLLIOT/DURRLEMAN team, the group already made significant contributions to the field of network neuroscience field, particularly on brain connectivity from different neuroimaging data (i.e. M/EEG, DTI, fMRI). They introduced new methods and frameworks, as published in journals such as Plos Com Biol., Netw Neuroscience or IEEE, and applied to address functional questions in Neuroscience. They also made several methodological developments to development of brain-computer interfaces (BCIs), as published in IEEE journals and Neur-oImage. All this work will continue and expanded upon as focus of their new, independent team, connecting network neuroscience and BCIs.

Strengths and possibilities linked to the context

This is a new and strong, very promising team that has unique expertise in both BCI and network neuroscience, with a clear focus on the future project goals. The team has already published excellent papers in journals such as Plos Comp Biol, Netw Neurosc or IEEE that introduce new theoretical frameworks for assessing brain connectivity from different neuroimaging data (i.e. M/EEG, DTI, fMRI). They also used these frameworks to address neuroscience question, e.g. about the human connectome (in J. R. Soc. Interface) or how the brain organisation is changed in Alzheimer's disease (Sci Reports). Another excellent piece of work was on how brain networks dynamically reorganise when learning to master non-invasive brain-computer interfaces, as published in the journal NeuroImage. The team also published a series of original contributions for detecting the brain-related responses of respiratory deficits in intensive care patients, epilepsy preictal state prediction and neonatal monitoring. The team is in an excellent position to receive funding; the team leader has already received an ERC consolidator. The team has also established connections with various clinical partners and has facilitated access to large cohorts of patients. The also maintains collaboration with outstanding international partners (at Penn University, or at Padua University), which is a testimony of their visibility and impact of their work. The team also has possibilities for socio-economic transfer, and are well positioned to attract excellent students and postdocs.

Weaknesses and risks linked to the context

A threat is to keep focus on own projects giving the many potential research opportunities and collaborations.

Analysis of the team's trajectory

The future team (currently four PIs, one of whom the team leader) will build upon the results obtained in their previous research activity, along two axes:
Axis 1: Analysing, modelling and controlling multiscale brain networks. Within this axis, three PIs will work on multimodal/scale networks. Two PIs will work on statistical models of brain networks, including a PhD project on models to account for global network evolution. Another PI duo will work on topics related to network controllability, which also includes a PhD project.
Axis 2: Improving non-invasive brain-computer interfaces (BCIs). Within this axis, two PIs will work on capturing multilayer brain connectivity processes during BCI tasks as well as identifying spatiotemporal events on brain dynamics associated with motor/cognitive tasks. Another PI duo will work on new classification frameworks that integrate information from multimodal and exploit transfer learning strategies and weight updating in classification for BCIs. This also involves a PhD project. Another PI duo will also work on Neuromodulation. More specifically, they will develop models based on network controllability where stimulus induced changes of brain activity are constrained by the structural brain network in order to identify the driver areas and the type of stimulation needed to favour detectable BCI-related brain patterns. All the involved PIs are well versed and have complementary strengths to embark on these various subprojects in these axes together with their trainees. So staffing is very appropriate for these projects.
Besides the work in these two axes, the team (PIs) and their engineers will also develop and deliver new software and technological solutions, including a multimodal BCI platform, interactive software, and portable and bedside solutions for patients, including the integration of OPM technology. All this will be made accessible by the scientific community.
Altogether, the team is expected to fill in gaps in fundamental questions about systems neuroscience and neuro-engineering, such as how to i) model temporal and multimodal/scale brain networks, ii) identify and quantify brain coordination mechanisms of physio-pathologic states, and iii) intervene to induce specific reorganizational processes. The team is in an excellent position to extract biologically interpretable mechanisms of the brain, which improve the diagnosis and prognosis of neurological diseases and solve the BCI inefficiency problem as compared to state-of-the-art knowledge and techniques. Furthermore, the team's affiliation to Inria represents an important advantage for access to computational/informatics resources, funding opportunities and for the interaction with prominent scientists in the field.

RECOMMENDATIONS TO THE TEAM

The team needs to keep focus on their own projects giving the many potential research opportunities and collaborations. One potential strategy could be to constrain the collaborative projects by work on the human brain.

Team 8: **Molecular Pathophysiology of Parkinson's disease**

Name of the supervisor: Olga CORTI/Jean-Christophe CORVOL

THEMES OF THE TEAM

During the recent period, the research efforts focused on identifying new genes associated with Parkinson's disease (PD) and factors influencing the onset of PD, investigating the molecular and cellular mechanisms underlying PD, with a particular emphasis on mitochondria-related processes. Additionally, they worked on developing cellular models derived from PD patients. Finally, the aim at translating their research findings into clinical applications. Overall, their work aims to advance the understanding of PD genetics, pathology, and treatment by bridging the gap between basic research and clinical practice.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendation of the Hceres committee from the previous report was to take the lead in more of the collaborative studies in which it participates.
The team has acknowledged the recommendations and taken the lead on various ongoing projects within consortia, including GWAS studies on age at onset in the LRRK2 population, modifiers of PRKN-PD phenotype, and GWAS on impulse control disorders.
In addition, the recommendation was to complement their in vitro work with PD animal models
Another advice was to secure larger funds to be able to maintain and further expand their clinical PD registries. Additionally, they have restructured the NS-PARK registry into a well-organised cohort called PRECISE-PD, funded by a 3 Mio € grant from France Parkinson and further supported by a 700 k€ partnership with Biogen.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	1
Senior lecturers and equivalent	
Researchers and equivalent	8
Research support staff	15
Sub-total for permanent research staff	24
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	8
PhD	12
Sub-total non-permanent staff in active employment	20
Total staff	44

EVALUATION

Overall assessment of the team

This is an outstanding team that has made seminal contributions in particular the genetics of PD. The team covers an extremely wide range of topics ranging from genetics to human iPSC work and all the way to clinical trials. This wide range is impressive and the team has demonstrated that they are able to deliver important results. The team has an impressive output with over 350 publications, with more than 60 of them being as leading authors. Among these papers are publications in Lancet Neurology, Brain, Annals of Neurology, American Journal of Human Genetics. Additionally, out of eight recent PhD graduates and two postdoctoral fellows who spent more than two years in the laboratory, eight have contributed to at least one manuscript as the first author or co-author. The PIs are highly visible, participating with talks in a large list of conferences and meetings. In addition, the PIs are strongly connected to international networks. The team is internationally well recognised for outstanding contributions to the genetics and their clinical research of PD. Another impressive aspect of their work is the establishment of patient cohorts, which they are continuously updating. This has been an extremely valuable resource for new genetic discoveries, studies involving biomarkers and for clinical trials.

Strengths and possibilities linked to the context

The translational research of the team ranging from genetics to clinical trials is outstanding. There are not many teams that are able to cover such a wide range. To keep such a broad scope is challenging, and comes with the problem of lack of depth in some of the domains. The team has taken some measure to make sure that sufficient expertise is on board. They have expanded the team by recruiting PhD students and postdoctoral fellows with expertise at the intersection of clinical and basic research. In addition, they expanded their capabilities in bioinformatics and biostatistics to integrate phenomic-genomic data, collaborating both internally within ICM and externally with national and international partners. Furthermore, they adopted cutting-edge tools and methods for comprehensive analysis of mitochondrial function in PD models, including genetically encoded reporters and high-resolution respirometry. Additionally, they advanced the development and utilisation of novel cell models, such as microglia-like cells derived from blood and neurons and organoids generated from induced pluripotent stem cells obtained from PD patients. Their excellence is illustrated by their scientific output (330 original publications, 123 in the top 10% citations, 55 first/last/corresponding author, seventeen signed by students/post-docs/clinical research fellow, examples are: Sambin et al., Mov Disord 2022, Tesson et al., Lancet Neurol 2018, Liu et al. Lancet Neurol 2017; Lieu et al. Nat Genet 2021), their high amount of grant acquisition (4 M€ for basic research, 1.5 M€ for the development of hiPSC models and more than 5 M€ for clinical research projects, examples are: IMI2, JPND, ERAPermed and ERACoSysMed, PRCI) and national funding (ANR-PRC)), their scientific outreach (examples are_ media interviews in television – France 5, BFM TV – , radio – Radio Notre-Dame, Vivre FM, Europe 1 – , newspapers – Midi Libre, les Echos, L'Express, Le Quotidien du Médecin – , or on the web) and their ability to attract talented students (13 PhD students) and PostDocs (8 PostDocs). Another asset is the establishment of patient cohorts (>4,000 index cases familial or EOPD, >2,000 patients with longitudinal data Fibroblats from genetic forms of PD>20,000 patients: NS-PARK cohort), their close interaction with industrial partners (Servier, Sanofi, Biogen, PTC Therapeutics) and their collaboration with national & international consortia (IPDGC, GeoPD, GP2, NS-PARK).

Weaknesses and risks linked to the context

The team has a large number of PIs, but a relatively low number of PhDs/PostDocs. It is not clear how so many topics can be handled. In particular for Aim2 in which cellular models are used for disease modelling, it could be advisable to focus on the most promising projects. The team could also increase their use of computational approaches to integrate their large amount of genetic and molecular information into an integrated model.

Analysis of the team's trajectory

The team formed in 2019 from Alexis Brice's previous group, leverage advancements in genomics, human induced pluripotent stem cell (hiPSC) technology, and machine learning to study genetic aspects of Parkinson's disease. They aim to uncover the genetic landscape of PD, identifying relevant pathways and therapeutic targets, and use this knowledge to create personalised medicine approaches. The team is comprised of experts in genetics (Two PIs), disease modelling and molecular research (Four PIs), and clinical investigation (3 PIs). Philippe Ravassard's was added to the group in 2017, following a recommendation by the SAB. This collaboration focuses on exploring the role of non-coding genetic elements in PD and developing hiPSC-based models to study disease mechanisms. Additionally, one PI expert in viral vector technologies, has joined the team part-time to contribute to the development of tools for studying stress-related responses in PD models. Despite this wide scope and large number of PIs, the team has been very successful in generating a coherent structure that is able to progress along the translational path. The team has acquired sufficient funding to carry out these different lines of research, but might need to increase the number of PhDs/PostDocs to increase the depth of their molecular/cellular analyses.

RECOMMENDATIONS TO THE TEAM

This is an excellent team covering an extremely wide range of topics ranging from genetics to human iPSC work and all the way to clinical trials. Even if the team has demonstrated that they are able to deliver important results in all domains, it is challenging to maintain excellence in all the research areas. In particular, the analyses of the iPSC derived cellular models requires extensive cell biological expertise. One way to meet this challenge would be to focus on the analyses of the most promising genetic variants. Another would be to use a system-wide approach to integrate the different factors into one comprehensive model. Overall, the recommendation is to continue with their translational approach as outlined in the proposal.

Team 9: **Molecular Physiology of Synaptic Bioenergetics**

Name of the supervisor: Jaime DE JUAN-SANZ

THEMES OF THE TEAM

The team develops and implements novel genetically encoded probes to study synapse function. They focus on three lines of research: (i) the role organelles in the control of presynaptic calcium and the modulation of synaptic transmission; (ii) the modulation of protein composition and dynamics at the synaptic cleft; (iii) the role of presynaptic mitochondria metabolism in neurotransmitter release. These are all novel areas of research that require novel tools. The laboratory expertise is very well suited to this research programme.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N/A

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	
Senior lecturers and equivalent	
Researchers and equivalent	1
Research support staff	2
Sub-total for permanent research staff	3
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	3
PhD	3
Sub-total non-permanent staff in active employment	6
Total staff	9

EVALUATION

Overall assessment of the team

This is a young, internationally competitive lab, well recognised for its work on synaptic physiology. In terms of attractiveness, this lab is excellent to exceptional. The strong reputation of the team is evidenced by the PIs election as a Kavli Scholar, his award of both a CNRS and INSERM tenured position and his award of internationally competitive grants such as the ERC-StG. The lab started in 2019 and, in a short period of time, has recruited a large group that currently stands at 9 people. It has also managed to secure an important amount of funding as well as publish papers. Since 2019, it has attracted talented and promising early career scientists from France and abroad. The labs scientific appeal and capacity to raise funding are excellent to exceptional – the PI received a highly competitive ERC starting grant, as well as collaborative grants, fellowships for postdocs joining his lab and PhD studentships. In terms of scientific production, the team is excellent, having published papers where the team lead is a corresponding author, as well as other middle author papers. Although the two corresponding author papers represent results that were mostly produced before starting the lab at ICM (mainly at the Center of Molecular Biology Severo Ochoa), part of the work was carried out at ICM and the project was supervised by the Team lead throughout. More importantly, there is at least one bioRxiv preprint as well as a manuscript in preparation that will likely be a better yardstick for lab output, as they represent work carried out entirely at the ICM. Although it is too soon to assess the impact of this work yet, it does show that the team already shows tangible output and has established a solid platform on which to grow. Overall, this is an excellent to exceptional lab that has managed to do much in a short period of time.

Strengths and possibilities linked to the context

There are many strengths. The team has a strong international reputation and is seen as a dynamic and thriving lab, tackling novel questions in the field of synaptic physiology. The team has carved out a niche in the type of research questions they tackle that will certainly play in their favour when competing for grants. The topics explored require the development of new tools to assess function at the synapse. In this regard, the team is in a unique position, with ample expertise on the development of new genetically encoded probes, which it then implements to answer its research questions. This has already resulted in a total of 7 grants/fellowships/studentships for a total of around €2.5 million (of which ~€2 million are for the lab) over the evaluation period, which includes both international (ERC starting grant) and national (such as Avenir, ANR and BBT grants) funding. The team's ability to raise funding is excellent and is in an upward trajectory. The team has published well, with two papers as corresponding author (in Scientific Reports and Communications Biology) and a joint first author paper in Neuron, as well as contributing authorship in a number of other papers, all of high standing (Nature, J Exp Medicine, Neuron). The team's scientific attractiveness is excellent to outstanding as evidenced by the award of a tenured position in both the CNRS and INSERM and the election as a member of FENS-KAVL, as well as the successful recruitment of people to join the team, including three postdocs, five technicians, three PhD students and 4 MSc students. In addition, the PI is well connected in the field, with important collaborations in place, including leaders in the field of synaptic physiology (e.g.— Thomas Sudhof, Casper Hoongenard, Robert Malenka, Pietro de Camilli, Claudia Bagni) and with others that form part of the SynGO initiative at the Broad Institute of Harvard and MIT. This is important for a number of reasons. First, these collaborations have the potential to elevate the research questions tackled by the team to another level, simply by expanding the toolkit of research techniques used and by bringing together knowledge from diverse top labs in the field. For example, these collaborations will provide alternative systems to primary dissociated neurons for tackling their research questions, which is an important point to consider for future research avenues. Second, ongoing collaborations with leaders in the field of genetically encoded probes (e.g.– Eric Schreiter, Kaspar Podorgski) will keep the team at the forefront of the development of new probes and provide early access to these probes. The team shows an excellent capacity to train PhD students (Anjali Amrapali Vishwanath; Agathe Moret; Lorenzo Calzado-Reyes). Of the three students trained, one student has completed a thesis defence so far, which is the expected number for such a short period of time. Importantly, the thesis was defended in under 4 years and the PhD student published a paper as a first author within that period.

Weaknesses and risks linked to the context

In general, there are very few weaknesses and the points raised here are more comments rather than weaknesses. The first deals with the neuronal systems used. Although dissociated neurons grown in vitro are a very useful system, particularly for testing new probes, it could also represent a weakness if not paired with other, more intact systems (e.g.– in vivo, acute slices). The collaborations that are already in place mitigate this somewhat, but relying solely on collaborations could be risky. In terms of funding, the lab is currently very well funded but many of the grants are ending soon (within the next couple of years) and will require renewing. This also requires planning well in advance of grant deadlines.

Analysis of the team's trajectory

The team has only just started but is doing extremely well. It has done an excellent to exceptional job obtaining funding and recruiting people. Specifically, the current funding situation of the team is excellent, with large grants already in place (particularly the ERC grant, which provides a large fraction of the current lab funds until 2025) and a critical mass of people to carry out the projects. In general, staffing and finances are in line with proposed experiments. The people hired so far (10 in total) and their expertise are well matched to ongoing projects and, importantly, the right collaborations are in place to help drive these projects to a successful outcome. Although papers have already been published, the projects that have been mostly carried out in the team are at the preprint or 'in preparation' stage, which is appropriate for the time that has elapsed. In fact, it shows that the team, despite the COVID19 lockdown, has been very productive. The proposed projects for the coming five years are both interesting and innovative. They focus on the understanding novel aspects of the physiology of presynaptic terminals by (i) understanding how organelles contribute to calcium buffering/signalling (ii) providing spatiotemporal descriptions of molecules in the synaptic cleft and (iii) understanding the impact of mitochondrial metabolism on neurotransmitter release. The team has a bright future ahead.

RECOMMENDATIONS TO THE TEAM

It is recommended that the team continues with its high level of science. The proposed projects are exciting, feasible and the preliminary data is of a very high quality. Although the three main aims of the team all centre on assessing synapse function, each aim is clearly distinct both intellectually and in terms of techniques used. Overall, the project aims were well thought-through and have the potential to uncover novel mechanisms for controlling neurotransmitter release from presynaptic terminals.

More practically, the Team should consider slowly developing the use of more intact systems in the lab to avoid having to depend on others. Being able to move projects from the more reductionist in vitro systems to more

complex in vivo or ex vivo systems will add a competitive advantage to research in the team. In addition, the team should consider implementing other techniques to assess synapse function, such as electrophysiology, and synapse structure, such as EM and super-resolution microscopy. To do this, the team will need to expand, recruiting more people, particularly permanent staff to help grow their exciting research portfolio. ICM should help financially with this important transition. Finally, the renewal of grants is not that far away, particularly considering the long processing times of current funding schemes, and this requires planning to avoid gaps in funding. The team should consider focusing on publishing the current manuscripts 'in preparation' to increase competitiveness for the next round of grant deadlines.

Team 10: **Basic to Translational Neurogenetics**

Name of the supervisor: **Alexandra DURR & Giovanni STEVANIN**

THEMES OF THE TEAM

The DURR/STEFANIN team aimed to better describe and identify causes and modifiers of spinocerebellar and frontotemporal lobar degeneration. Given the high genetic heterogeneity of these diseases, a main focus of the team is to identify causative genes of new genetic variants of these diseases and to establish well-defined phenotype-genotype correlations. The team has assembled very large cohorts of patients coordinating clinical-genetic networks at the international level. The ultimate goal of the team is aimed at deciphering the molecular basis of some of these disease forms developing and studying an array of disease models among which mouse, zebrafish and iPSC-based cellular derivatives. The new knowledge obtained investigating these systems will create the basis to identify new clinical-relevant targets and therapeutic approaches to develop disease modifying treatments.
The new DURR/HUMBERT team will pursue similar goals on Huntington's disease and spinocerebellar degeneration

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended to: 1) enhance the training activity of PhD students and young researchers; 2) recruit more long-term technical personnel; 3) have more focus on the studies related to the disease pathophysiological mechanisms given their high burden in time, manpower and resources.
The team has taken appropriate actions to take all of these aspects into account. First, the team increased in the number of PhD students trained during the present period and 7 students obtained their PhD in the reporting period. Second, the team recruited two engineers on long-term contracts to mitigate the fact that the majority of its PIs have clinical duties. Third, they concentrated their mechanistic studies on fewer models (SPG11 and SPG56) and C9ORF72-FTLD.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	11
Senior lecturers and equivalent	3
Researchers and equivalent	4
Research support staff	39
Sub-total for permanent research staff	57
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	13
PhD	16
Sub-total non-permanent staff in active employment	29
Total staff	86

EVALUATION

Overall assessment of the team

The DURR/STEFANIN team has provided a strong contribution to the understanding of the genetic basis and pathophysiological mechanisms of spinocerebellar and frontotemporal lobar degeneration during the evaluation period. They unquestionably fulfilled the goal they had set for themselves in regard to (i) the identification of new genes associated with neurogenetic conditions, (ii) the refinement of phenotypes and study of diseases progression, (iii) the search for modifiers, and (iv) the establishment of therapies. Importantly, they have been highly successful in identifying genetic variants that contribute to the phenotypic diversity of some of these disorders. These are challenging studies to implement but provide precious insights that contribute to illuminate the pathophysiological basis with an unbiased approach. These achievements were reached thanks to the proactive attitude of the team to play a key role in large international clinical networks. The team has gained an unquestionable international leadership in the field which is also attested by the excellent level of funding gathered during this contract. The scientific production is remarkable both in quantity and quality with 215 articles published in the reporting period, some of which in high-quality specialistic journals such as Brain, Cell Reports, Ann. Neurology, J. Exp. Med., A.J.H.G, and others. The overall assessment of the team is excellent to outstanding.

Strengths and possibilities linked to the context

The reorganisation of the team with the new PI should be regarded has an opportunity. New dynamics and different positive synergies could be set up. With the hiring of Dr. Humbert, the ICM gains a trailblazer in modelling Huntington's disease with an excellent track record. Of note, the two team leaders have already collaborated suggesting that the disruptions inherent to any move could be at least partially mitigated when the laboratory of Dr. Humbert is transferred from Grenoble to Paris. The new team has access to large cohorts, as well as expertise in experimental models and deep phenotyping. This combined with an extensive set up to organise clinical trials should ensure future success.

Weaknesses and risks linked to the context

This team is very strong and successful with no particular weaknesses related to its science, staff composition and funding capacity. The ongoing change of one of the team leaders requires particular attention to create the right conditions for its timely integration in the ICM ecosystem.

Analysis of the team's trajectory (Alexandra DURR & Sandrine HUMBERT)

The new set-up of this team for the next period does not allow us to compare with a previous baseline, but the past individual successes of both PIs should ensure an upward trajectory. The possible synergies between the two PIs are numerous and equally strategic for both sides. This new composition will help to expand the scientific and technical expertise of the team to perform even deeper cellular and molecular studies to better untangle the basis of these diseases. Given the high success of both team leaders in the previous contract, it is expected they will continue to attract good funding to support these studies. The staff size is compatible with the proposed scientific program, maintaining the current genetic studies and further consolidate and enrich the functional studies in the different disease models.

RECOMMENDATIONS TO THE TEAM

This is a strong team with high international scientific leadership in studies on relevant and orphan disorders with high impact in the society and ICM should strive to support its needs. Along this line, ICM should take particular attention to ensure that the move of the laboratory of the new PI does disturb her science as little as possible ensuring a continued productivity. Next, the team can accelerate the implementation of different omics studies in their disease models to grasp pathophysiological alterations at multiple levels and scales. In addition, the establishment and deep analysis of human iPSC-based models in 2D and 3D configurations will nicely complement the existing models available in the team and provide a fundamental system where to confirm the clinical potential of new therapeutics. Given its high reputation, the team is in the position to attract even more European funding and succeed in obtaining ERC support. The team should continue to make efforts in maintaining a high international diversity in the team and continuing the training of PhD students and young researchers.

Team 11: **Control- Interoception - Attention**

Name of the supervisor: Philippe FOSSATI/Liane SCHMIDT

THEMES OF THE TEAM

This team's main theme is the brain basis of higher order beliefs, specifically how they are encoded and updated at the brain level, and how conflicts are managed. The team uses methods such as functional and structural MRI, computational approaches, and responses to pharmacological interventions. Their work focuses on both healthy and clinical populations, the latter including conditions such as depression and autism. Their research sits at the interface between neuroscience, neuroimaging, neuropsychology, neuropsychiatry and psychology.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has addressed the previous recommendation to increase publications in general journals (e.g. Nature Neuroscience, PlosOne, Nature). They have also increased the number of publications that involve more than one team member. They have, as recommended, increased collaboration with other teams, namely team Frontlab to examine prefrontal cortex roles, and team MBB (joint ANR grant).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	8
Senior lecturers and equivalent	
Researchers and equivalent	4
Research support staff	5
Sub-total for permanent research staff	17
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	3
PhD	11
Sub-total non-permanent staff in active employment	14
Total staff	31

EVALUATION

Overall assessment of the team

The team's overall profile is excellent. The team is combining several approaches (neuroimaging, clinical work, pharmacology) to address an ambitious question related to high-level cognition, namely the brain basis of belief updating and conflict management. This is a team with outstanding publications at the international level (e.g. PlosOne, Nature Neuroscience, Neuron), that are highly cited and have a strong impact in the general media. Funding record is excellent, mainly through national (e.g. ANR) calls. Hosting of postdocs and researchers (3 during the period) shows international attractiveness. Public engagements activities are also excellent to outstanding, via national press (e.g. Liberation), online (e.g. websites, podcasts) and school workshops. The team is heavily involved in teaching at postgraduate level across several disciplines (business, psychology, neuroscience, neuropsychiatry, consumer research) and has also developed links with pharmaceuticals (Lilly) and biotech (public-private partnership MAPREG) companies to fund some of its activities.

Strengths and possibilities linked to the context

The production of the unit is outstanding in quality, with over 30 articles published as first or senior author during the period in influential general (e.g. PlosOne, Nature Neuroscience, Nature Communications, Neuron) as well as specialist (e.g. Journal of Neuroscience, Neuroimage, Neuropsychologia) journals in the fields of neuroscience, neuroimaging and psychiatry. Highlights include an impactful JAMA Psychiatry article on the effects of ketamine in individuals with drug-resistant depression (2022, 10 citations; over 3,000 downloads, picked up by 26 news outlets, according to Altmetrics) and the identification of a brain marker for cravings (2023, Nature

Neuroscience, in press, already picked up by 44 news outlets). The team have published 109 articles during the period, and PhD students are included as joint or first authors. Team members are recognised nationally and internationally as demonstrated by their decision roles (e.g. panel members for ANR CE17 and ERC starting grant, doctoral school), committee memberships (e.g. European College of Neuropsychopharmacology) editorial activities (e.g. Frontiers in Decision Neuroscience; Psychology and Economics), and prizes (two members; Halphen Prize from the Académie des Sciences; '30 thinkers to watch in 2022'). They are also active in enabling and educational activities, having supervised eleven PhD students (5 to completion) and delivered teaching in a range of fields (MBA course on Neuroscience for Businesses; Sorbonne masterclass; coordination of Masters 2 in Behavioural and Cognitive neuroscience, Sorbonne; Co-Direction of the Business Foundation Certificate Program, Sorbonne). They have hosted five postdoctoral researcher s during the contract and three international scientists (USA, Italy, Germany). The team has an excellent track record of obtaining funding as PI. During the period they have received one European grant (HorizonEurope, 73k), four national grants (three Agence Nationale de la Recherche and one Ministry of Research, total 306k), regional/local (total 129k) grants, and four projects funded by charities/foundations (total 741k) during the period. In addition, funding was obtained thanks to partnerships with a Phamaceutical (Lilly, 220k) and a Biotech (MAPREG; 2000k) company for their work.
Finally, public engagement outside academia is also impressive, with team work having been disseminated via general media (e.g., Liberation, La Croix, France culture; internationally BBC2), and regular 'Semaine de La Science' activities. Dissemination targets younger audiences as well (via websites, podcasts, visits to military school students, DECLIC events), which is highly relevant given the team's field of research (decision-making, beliefs).

Weaknesses and risks linked to the context

The parallels and links between depression and autism seem to be based on convenience samples and are a risky comparison. ASD is a multifaceted neurodevelopmental disorder with many co-occurring cognitive challenges that will need to be accounted for when assessing higher order processes such as decision-making.

Analysis of the team's trajectory

The team plans to change their name in the next period to 'Belief Decision Neuroscience' team and expand to explore mind-brain-body interactions, with a more diverse range of disease models (ASD, dementia), building on previous discoveries (ketamine and depression, placebo effect, craving).

The team's project is ambitious but builds on their combined strengths in computational, decision, and clinical neuroscience. They will combine established neuroimaging approaches (MRI) with more recent (e.g. machine learning algorithms) methods. The study of clinical populations has the potential for huge societal impact given the costs of depression and obesity.

The team gathers the relevant expertise to deliver the planned projects on both the cognitive neuroscience and translational fronts. Their access to patients makes the plan feasible provided they have the appropriate workforce.
Currently, only limited funding extends beyond 2024 and therefore the team will need to leverage significant external grant income.

RECOMMENDATIONS TO THE TEAM

Given the high standard of publication and successful national funding, team members could apply for larger European or international grants to grow further and deliver their ambitious project. The team should also maintain the variety and high quality of public engagement activities, as their field of research has significant societal relevance. Some pilot work may be required to assess the feasibility of comparing directly autism with mental health/mood and adult-onset conditions.

Team 12: **Brain Development**

Name of the supervisor: Bassem HASSAN

THEMES OF THE TEAM

The team addresses a very challenging question on how genes and cell lineages during brain development result in behaviour during adulthood. This is a fundamental question with broad implications and requiring a plethora of tools and approaches. Above all, the team focuses on cell fate decision from stem cells to neurons and glia. Next, how cells in the brain establish connections to form circuits that, ultimately, determine behaviour. Both lines are addressed in model organisms including fly and mouse.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous assessment of this group did not spot any specific, major point to address. The group was performing very well and still does.

More specifically, the committee recommended hiring permanent staff and keeping broad approaches with balance between focused biological questions and multiple experimental interrogation models.

In accordance with these indications, a hospital-university researcher joined the team (MCU-PH) has joined the team in September 2022, obtained an ANR JCJC and recruited a new postdoc. Also, the cross-species approach has been strengthened.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	
Senior lecturers and equivalent	1
Researchers and equivalent	2
Research support staff	14
Sub-total for permanent research staff	17
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	11
PhD	8
Sub-total non-permanent staff in active employment	19
Total staff	36

EVALUATION

Overall assessment of the team

Overall assessment of the team: exceptional. The team has an exceptional publication record (major contributions in 26 original articles-from ICM inserm bibliography analysis; more than half of the papers in top 5% Journals; two papers i.e. about 9% in top 1% Journals). Attractiveness: excellent (grants comprising international, European, national and local grants reaching above 4 M€), strong appeal on students (7 PhD students, 10 Postdoc), many of which obtained independent positions as PI. The team is internationally recognised for its work (organisation of international events, European Drosophila Neurobiology Conference; involvement in prestigious evaluation panels e.g. ERC, MRC; numerous invitations to prestigious conferences and institutions; 4 awarded prizes).

Strengths and possibilities linked to the context

The team's strengths are evident through their pioneering discoveries in brain development. The involvement in managerial roles within at ICM (Direction Committee, Scientific and Medical Steering Committee, Committee on gender parity) and prestigious international invitations, awards and participation i n evaluation committees (e.g.: ERC consolidator panel, Neuroscience Commission: French National Research Agency) testify the reputation and network of the team. Competitive funding, both from national (ANR) and international agencies (3 EU grants, 1 NIH) as well as from charities (FRM, ARSEP, FRC, France Alzheimer), has provided a substantial resource base. Attractiveness is very high with 7 PhD students, ten Postdoc trained in the 2017–2022 period, including team members from all over Europe, Latin America, China and the Middle East. The team leader is also involved in the gender parity committee at ICM. Team members are engaged in teaching activities, with a member of the team (Dr. El Khattabi) bearing the heaviest workload in this regard. The team shows an outstanding capacity to train PhD students and PostDocs with more than 30 alumni working in Academia, Biotec companies, or as clinicians. The team engaged in significant efforts in knowledge diffusion by participating in public conferences, interviews on media and science popularisation events at the Institute (6 events) and in other context (9).

Weaknesses and risks linked to the context

One additional aspect that appears from the institute webpage is that this group is also acting as institute director. The group should play attention to be embedded within a structure supporting the team leader in both the lab and administration. This is a not always an easy balance. The team has highlighted several additional points in their self-evaluation, even though they clearly had a limited impact on the team's overall achievements so far. There is a notable challenge related to accessing the latest techniques in advanced cell biology, an area of expertise that is currently lacking within the institute. This limitation affects all research groups at ICM. Addressing this deficiency may necessitate a more comprehensive approach within ICM. Up to this point, the primary source of major grant support has been from the Team Leader. Nevertheless, the other two PIs, due to their significant reputation in the field, should also capitalise on their potential to secure international grants and potentially further elevate the quality of their publications.

Analysis of the team's trajectory

The team is engaged in exploring original and ambitious questions related to developmental processes, employing advanced techniques that have yielded outstanding outcomes thus far. Building on their established research areas, the team's forthcoming work will revolve around the following: (i) Investigating the mechanisms that govern neuro- and glio-genesis across various species, with a particular focus on unravelling the precise sequence of developmental events encoded in the genome responsible for generating neuronal and glial diversity. Additionally, the team will delve into examining developmental disruptions that contribute to human diseases or predispose individuals to neurodegenerative conditions. This latter aspect is where Dr. El Khattabi is most likely to synergize her expertise with that of the group. (ii) Pioneering research aimed at establishing connections between circuit development and behaviour, with a special emphasis on understanding the emergence of individuality within circuits and behaviour. To achieve this, the team will use Drosophila as a model. The team has several awarded grants extending up to 2026/7 and three other applications, including an ERC Synergy grant under evaluation. Taken together, staffing and finance appear adequate to support the future research efforts.

RECOMMENDATIONS TO THE TEAM

It is hard to give specific recommendations to such a well-performing lab. The questions addressed are ambitious, approaches sound, techniques state of the art and the results excellent. Having said that, certain aspects of the research approach somehow on an 'inflationary' curve and perhaps leaving space only 'incremental' gains. To better explain, a HUGE field already addresses 'stem cell commitment/neurogenesis' during brain development in all possible flavours and shapes. So much has been produced in recent years that it is hard to imagine 'disruptive' discoveries coming any soon. The broader implications of their work with regard to behaviour gives this groups a very special 'niche' and competitive advantage, which is excellent! Perhaps the group may consider pushing more into this special niche in the future relative to the rather crowded area of 'neurogenesis'.
Considering the reputation of the PIs and in accordance with comments above, it appears that focusing on pursuing substantial, multi-year international funding opportunities could be a high priority, as opposed dispersing/spreading efforts across various smaller applications.

Team 13: Experimental Therapeutics of Parkinson Disease

Name of the supervisor: Etienne HIRSCH/Stéphane HUNOT

THEMES OF THE TEAM

Over the past 6 years, the ETPD team, led by Hunot and Hirsch until 2019, comprised five PIs, ten+ PhD students, postdocs, and three technicians. Contributions include their identification of Xenon gas and GDNF as neuroprotective agents, as well as tetracyclines, especially DOX, for mitigating protein aggregation. Additionally, their research into non-cell-autonomous mechanisms involved in the investigation of the propagation of extracellular alpha-Synuclein in pathological assemblies, its interactions with immune and glial cells, significantly advancing the understanding of PD pathogenesis. Unfortunately, the team will not be renewed in the upcoming term due to the retirement of two PIs and the transition of three others to different teams.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1 – Scientific Production and Activities (Criterion 1): While the recommendation to license patents remains unfulfilled, ongoing discussions with industrial partners and technology transfer offices are in progress to pursue this goal.
2 – Team's Organisation and Life (Criterion 2): Nothing to address
3 – Scientific Strategy and Projects (Criterion 3): The team has headed the recommendation to continue their excellent work and secure additional funding. Since 2019, they've secured nearly 1.4 million euros in funding, with over 510,000 euros secured up to 2024, showcasing their dedication to sustaining and expanding their research efforts despite expiring research grants.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	2
Senior lecturers and equivalent	1
Senior lecturers and equivalent	8
Researchers and equivalent	12
Sub-total for permanent research staff	23
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	4
PhD	11
Sub-total non-permanent staff in active employment	15
Total staff	38

EVALUATION

Overall assessment of the team

Overall this is an excellent team. The team exhibits several notable strengths and areas of potential improvement. They have a commendable publication record, demonstrating a prolific output of high-quality research papers. Their active participation in national and international scientific events, along with their engagement in editorial roles, establishes a solid scientific reputation. The team has also secured substantial competitive funding, fostering a robust resource base for their research endeavours. Additionally, their commitment to training and education is evident, with successful career placements of trainees in both academic and industrial settings. The team will not be renewed, only to mention possible areas of growth would be expanding their research into clinical trials. The team has published around 100 papers (mostly original articles) with a good proportion in top journals including Lancet Neurol, Neurology, J Neuroinflammation. The scientific production is excellent. The team is internationally recognised as shown by the strong collaborative international network with several papers published jointly with international partners from all around the globe and supported by funded projects. The team has been very active with around 100 invited lectures in national and international congresses and meetings (including Gordon conferences, SFN, FENS) and approximately twenty meetings with a role of co-organiser (ISNI, JPND, Era-Net). The team is involved in scientific advisory (SH, MLW), management (EH, JPND) or executive (EH, ERA-NET Neuron; CoEN) boards. The capacity to raise funding has been very good to excellent, with over 3.4 M€ of financial support obtained over the evaluation period from competitive grants and industrial partners.

Strengths and possibilities linked to the context

The team's strengths are manifest in their publication record, which includes 91 peer-reviewed international papers, with a significant proportion in well-renowned journals (Brain, Lancet Neurology…). Major discoveries and contribution to science include the demonstration of the efficacy of Xenon in mitigating low-level excitotoxic insults in Parkinson's disease; of GDNF in preventing dopamine cell loss due to aS aggregation; of doxycycline and related compounds in mitigating aggregation and degeneration in PD; the development of in vitro model showing xCT involvement in microglial-induced neurotoxicity; the investigation of neurological complications from viral infections, supporting environmental links to parkinsonism collaborations with local and international partners worldwide (Brazil, Argentina, USA, Canada, UK, Europe) within common grant funding (i.e. IMI, ANR) have enriched their research landscape. Furthermore, their strong engagement in science dissemination, media appearances, and educational programs (i.e. summer schools, the neurology educational program for medical students and residents at the Antilles regional level as well as the Master program of Speech Therapy at Antilles University) demonstrates their commitment to communicate science to the public and inspire future scientists. Their involvement in research management and evaluation for many governmental agencies and charities (i.e. France Parkinson), management (JPND) or executive (ERA-NET Neuron) boards enhance their reputation and network. Competitive funds, both from national (ANR, PRME) and European agencies (IMI) as well as from charities and foundations (i.e. Fondation de France, France Parkinson, Fondation Recherche Alzheimer), has provided a substantial resource base.

Weaknesses and risks linked to the context

Despite their strengths, there are areas that warrant attention and improvement. While their publication record is commendable, there is potential for further enhancements, particularly in publishing in multidisciplinary journals. Additionally, the translation of their research findings into clinical trials remains an unexplored avenue that could maximise societal impact. The limited research time of one PI due to managerial duties poses a risk to sustained research excellence and should be addressed. Although funding has been satisfactory, continuous efforts to secure competitive funding could further support their research activities.

Analysis of the team's trajectory

NA, Unfortunately, the team won't be renewed next term due to two PIs retiring and three joining other teams

RECOMMENDATIONS TO THE TEAM

Team 14: **Experimental neurosurgery**

Name of the supervisor: Brian LAU/Carine KARACHI

THEMES OF THE TEAM

This team brings together basic scientists and clinicians to investigate the anatomo-functional organisation of the Cortico-Basal Ganglia circuits, with the long-term vision to develop new modulatory interventions by Deep Brain stimulation (DBS), but also with non-invasive approaches, such as video games or the neurofeedback approach in patients with Parkinson's disease. For this purpose, they use a multimodal (tractography and electrophysiology) and translational approach from the non-human primate model to patients with Parkinson's disease undergoing surgery for the implantation of DBS electrodes or under new non-invasive therapeutic approaches. The hope is to provide new information about the structure, circuits, and functions of the basal ganglia in the patients' symptoms.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1) Increase the number of publications with a high IF and the visibility of the PIs. The good level of grants could be improved with applications to international calls. It would be desirable to develop electronic tools and patents. It is mandatory to increase public awareness and interact with socio-economic backgrounds. More PhD students are needed to achieve the objectives of the groups.

Actions taken: As recommended, the team has grown (+8 PhD), the proportion of high-profile journals and the visibility are higher. The collaborations help to obtain significant funding. They also developed industrial partnerships, allowing them to expect the development of new tools and patents. As requested, all PIs are now involved in public awareness activities to interact with socio-economic backgrounds.

2) The team needs to hire permanent and non-permanent positions.

Actions taken: During the evaluation period, they successfully filled non-permanent positions to maintain a high level of innovation and expertise. A young PI has just been hired as an INSERM researcher.

3) The control conditions for the neurofeedback study are not clear. This is a very interesting but challenging project and alternative strategies with contingency plans should be considered.

Actions taken: The five PIs of this team are all involved in the organisation and management of projects, adopting a project's management that requiring strong interactions and providing greater efficiency in carrying out projects.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	1
Senior lecturers and equivalent	1
Researchers and equivalent	3
Research support staff	11
Sub-total for permanent research staff	16
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	6
PhD	15
Sub-total non-permanent staff in active employment	21
Total staff	37

EVALUATION

Overall assessment of the team

The attractiveness of the team projects combined with their ability to mobilise funds and partners are excellent. This has allowed the team to pursue its aims and become an attractive team for young clinicians but also researchers, as demonstrated by the recruitment of an INSERM researcher to develop the translational axis of their research on intrnsic motivation. Their research program is innovative and on the right way to be well carried out thanks to their excellent production and collaborations. To conclude, the overall evaluation of this team is excellent for all research aspects.

Strengths and possibilities linked to the context

Between 2017–2022, the work of this young pathophysiology team has resulted in a significant number of publications (>60 articles) in the field of clinical research (Brain; Mov. Disord.; Ann. Neurol.), of which roughly a third come from work carried out mainly by three PIs of the team. These PIs frequently appear as the last authors of articles by their students published in good journals of their respective specialities (Neurology; Neuroimage; Neuro Oncol). The analysis of the scientific output of this team reflects their highly collaborative character, often involving other teams in Paris, and at the national and European level. The majority of publications from these collaborations include several authors and in the large majority of these publications, their team members do not appear first, or even last author, but more frequently co-authors. This is the case for one of the team leaders, who, from 2017 to 2022, has very rarely appeared as the last author despite having some supervised students and post-docs. We must highlight the production of major articles published in high-profile journals and fallout for the knowledge provided. The paper by Welter et al. in 2017 in Lancet and that by Munuera et al. in 2018 in Nature Neuroscience deserves mention.
The last point that can be emphasised is that only three articles involve non-human primates, although this is a theme that is widely highlighted in the team project. This raises important questions on the viability of this research axis, given the difficulty of macaque supply, since the crisis induced by the Covid-19 pandemic? Despite these reservations, globally, the scientific production of this team can be described as excellent. The scientific appeal and fundraising ability of this team are also excellent. Each of the PIs was able to obtain funding, either at European (HBP; MSCA), international or national level with the ANR or foundations or cooperation with companies. Since the last evaluation, the members of this team have also been able to increase their attractiveness, which has allowed them to increase the number of students and post-docs, as well as their involvement in collaborative projects, requests for expertise by evaluation bodies, or funding. They have also been able to acquire mainly national recognition, but in development at the international level, by the mastered approaches but also by their openness to new therapeutic approaches. Among the various positive points listed above, the ability to raise funds and create collaborations of the members of this team are the strengths of this team. They also know how to combine and synergize clinical and basic research programs. The translational research axis of the patient to studies at the fundamental level on the Non-Human Primate and a return to the patients to verify the transposition of the discoveries remains among the strengths of this team.

Weaknesses and risks linked to the context

Although translational research from the patient to the non-human primate model is a strength of this team, it can become a weakness for the objectives of this team, if they do not have a strategic plan in the face of the current crisis on the supply of these animals. This type of primate investigation has already shown its invaluable contribution in many areas of basic and clinical neuroscience, but it is an approach that takes a long time before it can benefit from it, especially in terms of training young researchers in this approach. Perhaps the last weakness of this team is being engaged in too many collaborative projects at the expense of the time invested in their own projects.

Analysis of the team's trajectory

The team have three main projects and the staff and finances are in line with those:
1) Decipher the role of cortico-subthalamic networks in non-motor aspects of gait.
2) Determine the neural mechanisms of intrinsic motivation.
3) Characterise the medial STN area by its neuronal constituents and its connectivity with the basal ganglia and cortex.

Aim 1. *Decipher the role of cortico-subthalamic networks in non-motor aspects of gait.*
In this first project, the team will seek to understand how in PD, dysfunctional motor and non-motor (executive, motivational, emotional) processes contribute to gait disorders, and how re-establishing dopamine transmission and modulation of the cortico-subthalamic network (by DBS) influences motor and non-motor processes during gait. This project is led by two PIs. For this project, they will collaborate with the BDN Unit (Univ. Oxford), the ISIR

(Sorbonne Univ.), Neurospin and a team of Tours Univ. This project is funded by the ANR, the foundation of France and Medtronic.

Aim 2. *Determine the neural mechanisms of intrinsic motivation.*
In this second project, the aim is to understand the brain networks involved in intrinsically motivated decision-making, with a focus on the role of dopamine and frontal cortices linked to the basal ganglia. They will seek to determine whether intrinsic motivation can accelerate neurofeedback training to restore function of cortico-basal ganglia networks by allowing PD patients to control their own brain rhythms. The project includes a preclinical part in Non-Human Primate to understand whether when and how DA is associated with choice preference. For that, they will perform behavioural and physiological experiments in monkeys. In the second component of this project, they will leverage intrinsic motivation to enhance Neurofeedback training in PD patients. They hypothesise that patients can be trained to control their own pathological neural activity to reduce their symptoms. This project is led by two PIs and requires collaboration with multiple teams; ENS-Paris, IMN & INCIA of Bordeaux, other team in ICM and the Neurosurgery Dep. of Salpêtrière Hospital. This project is funded by two ANR grants and a CIFRE partnership with Healthy Mind.

Aim 3. *Characterise the medial STN area by neuronal constituents and its connectivity with the basal ganglia and cortex.* For this third goal, they associate again investigation on the monkey and human brains to study the role of this subcortical structure, the region of the medial Subthalamic Nucleus (STN) in severe refractory psychiatric conditions, such as obsessive-compulsive disorder and depression, with the goal of proposing new therapeutic approaches in patients with refractory pathological aggressiveness. This project is led by Karachi in collaboration with Neurospin and IBrain, and O. Guillin (psychiatrist, Unité des Malades Difficiles-CHU Rouen). This project is financially supported by the TELOS Foundation and will be sponsored by the CHU Rouen.

RECOMMENDATIONS TO THE TEAM

It is an excellent team with an interesting research program which is based on strong expertise. The main recommendation that we can make to the members of this team, would be to ensure their need of Non-Human Primate and protect their PhD students from a risk of supply difficulties. Secondly, to keep the leadership in the innovative fields of research they built over time, you need to focus more your attention on the projects that you became pioneers. Thirdly, a solution will have to be found so that Brian Lau consolidates its leader position in his research fields and thus really appears as a true project leader, by being last author of the articles resulting from his students' work. Co-last author solutions can be considered in the case of co-direction. Finally, take care about your young recruit who will allow you to carry out your translational research project between NHP and the patients, but also between the fundamental and the clinical field, which will allow you to better understand the patient disorders to better care for them.

Team 15: Frontal functions and pathology

Name of the supervisor: Richard LEVY

THEMES OF THE TEAM

The team's overarching focus is the neurobiological basis of high-level functions (e.g. creativity, cognitive control) supported by the human prefrontal cortex and associated networks. They have a long-term translational objective to improve diagnostic and intervention methods in conditions affecting the prefrontal cortex. The team uses a variety of methodological approaches (computational models, neuroimaging, neuropsychology, brain stimulation), with patients (neurosurgery, neurodegenerative diseases) as well as healthy individuals.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team followed previous recommendations to keep up with high quality outputs and funding. As recommended, they have strengthened links with other teams (via cross team ECOCAPTURE project, and collaboration with team 18). To strengthen their computational approach workforce, they have recruited a new staff member with expertise in the field.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	4
Senior lecturers and equivalent	1
Researchers and equivalent	5
Research support staff	0
Sub-total for permanent research staff	**10**
Non-permanent teacher researchers and researchers	0
Non-permanent research support staff	0
Post-docs	3
PhD	10
Sub-total non-permanent staff in active employment	**13**
Total staff	**86**

EVALUATION

Overall assessment of the team

Altogether, the team demonstrates an excellent to outstanding profile. Production is competitive at the international level with articles in top tier journals (e.g. PNAS, Neurology, Brain) and over 470 articles published during the period (30% as first or last author). Funding success is outstanding (>13,000 k€ during the period, including 2 ERCs, 4 Marie-Sklodowaska-Curie grants and 10 ANR). Interactions with non-academic world are outstanding, both with the industry (16 clinical trials, 2 CIFRE, 17 consortia) and with the wider public (general media, national newspapers and TV, patient groups). The team is highly attractive, having trained twelve postdoctoral years and recruited two PIs, with team members involved in a wide range of editorial (e.g. Cortex) and influential roles (e.g. CNRS steering committees, national guidelines).

Strengths and possibilities linked to the context

The team has published an impressive number of original articles during the period, about 30% as first or senior author in top tier journals in a variety of scientific domains (e.g. PNAS, Neurology, Cortex, several articles in Brain and JNNP). Publications with consortia/large teams are also published in highly regarded international journals (JAMA network open). Importantly, PhD students and postdoctoral researchers are involved, and have been

first author in top tier journals (Neurology, Cortex), demonstrating effective training. Of the 37 reviews published, a high proportion was in top journals (e.g. Lancet Neurol; Nat Rev Neuroscience, Trends in Cognitive Sciences) which increases the team's visibility internationally. The team's funding, having received>13,000 k€ during the period, with competitive and international (totalling about 5,000 k€; eight European, including two ERC consolidator grants of about 2,000 k€), national (e.g. 10 ANR, 4 as PI) local (about 700 k€), and charity funded (5 grants, total about 1,800 k€) projects. Funding was also received from pharmaceutical companies (700 k€). The team has also developed open-source software packages (e.g. BCB Brain Connectivity and Behaviour toolkit to assess brain connectivity anomalies, Cog Toolkit) and databases ECOCAPTURE (partly shared) and SOCRATES (patients with degenerative dementia). The team's attractiveness is outstanding. Staff participated in over 100 national and international conferences (e.g. European Congress of Psychiatry, Conference on frontotemporal Dementia, European Congress of Neurosurgery, Meeting of the British Neuropsychological Society) and organised 25 events during the period (including Society for Neuroscience events, winter school). Four team researchers are also involved in seventeen consortia (e.g. GENFI Genetic Frontotemporal dementia Initiative). Team members sit on several editorial boards (e.g. Cortex, Frontiers) and have won two prizes (CNRS bronze, one early career researcher). One coordinated two European projects. The team hosted twelve postdoctoral researchers and supervised sixteen PhD students and 9 medical theses. Importantly, the team is growing, with three new PIs having joined or shortly joining. Public engagement is also an outstanding strength of this team, with Creativity masterclasses and Art & Science School, one YouTube channel on Imagination (>12.00 subscribers), public debate interventions (Open Brain Bar, Brain week, Pint of Science), TV (e.g. France 5, M6, RMC) and radio (La Méthode Scientifique, Radio France, France Inter, RFI) appearances, and press (e.g., Le Monde, Science et vie). Interaction with clinical settings is strong with many links with pharmaceutical companies, sixteen clinical trials, and involvement in national clinical guidelines (e.g. 2 Haute autorité de la Santé, one European guidelines for primary progressive aphasia).

Weaknesses and risks linked to the context

No weaknesses were identified.

Analysis of the team's trajectory

The team's future project is well aligned with previous successes and therefore appears achievable given the infrastructure in place (e.g. presymptomatic cohort availability, tool development, neuroimaging) and planned collaborations with other ICM teams. The two axes (cognitive neuroscience and translational) are well integrated. The plan to explore the neural basis of creativity further and develop models should increase the team's visibility in this field at the international level even further, and provide a solid base for translational development. The translational axis is also strong and ambitious, with an ecological approach to behavioural phenotyping and plans for innovative therapeutic applications. Several current grants extend beyond 2023 (e.g. two ANR to 2025; one charity grant to 2024) showing feasibility to sustain the project and giving the team time to apply for further funding.

RECOMMENDATIONS TO THE TEAM

The main recommendation is to keep up with the high quality of their activities, scientific outputs, funding, interaction with the wider public, and translational discoveries. Given their excellent profile and ambitious project, there is potential for further European grant funding (e.g. Horizon Europe, EU4Health). Further funding will allow the team to hire support staff for their clinical research activities, for example database curation, patient recruitment, project coordination, and ethical approval applications.

Team 16: **Myelin Plasticity And Regeneration**

Name of the supervisor: Brahim NAIT-OUMESMAR/Violetta ZUJOVIC

THEMES OF THE TEAM

The team has directed efforts towards comprehending the molecular processes involved in oligodendrocyte differentiation and remyelination and pinpointing therapeutic approaches that promote remyelination for human disorders. Research endeavours have revolved around three major themes including 1) the mechanisms of oligodendrocyte differentiation and regeneration, with emphasis on the role of neuronal activity and transcription factors in oligodendrocyte development; 2) the impact of immune cells in remyelination and 3) the cell fate and repair potential of neural stem and progenitor cells. Established methods encompassed a range of experimental models, including in vitro systems, ex vivo studies, and in vivo approaches comprising a non-human primate model of demyelination and remyelination.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the former evaluation, the team activities were recognised as excellent, and the prospective scientific strategy and project as outstanding. Recommendations for the current period were in the three domains of scientific production and activities, the team's organisation and life and scientific strategy and projects.
Recommendations for the present period covered scientific production, team organisation, and strategy. The team confirms that these recommendations were considered, leading to more R&D contracts, patents, structured lab meetings, and collaborative endeavours with one of the teams at the ICM. These collaborations resulted in joint research grants, publications, and the transition of Brahim Nait-Oumesmar, from this team to Stankoff's team.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	
Senior lecturers and equivalent	1
Researchers and equivalent	3
Research support staff	8
Sub-total for permanent research staff	12
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	7
PhD	8
Sub-total non-permanent staff in active employment	15
Total staff	27

EVALUATION

Overall assessment of the team

The overall assessment of this team is excellent. Scientific production is excellent (major contributions in 17 original articles over 38; over half of the papers in top 5% Journals; 2 in top 1%; 4 in top 10% cit. percentile; 4 patents). Attractiveness is excellent (grants up to ~ 3 M€), strong appeal to students (12 PhDs, 7 postdocs, including international fellows) some of which obtained research positions abroad/in France. The team is internationally recognised: organisation of international events (eg Euroglia, ECTRIMS, ESNI); invitations to prestigious conferences (e.g. Gordon Conference on Myelin); Five received prizes.

Strengths and possibilities linked to the context

The Team has made significant scientific contributions in the fields of oligodendrocyte physiopathology and multiple sclerosis (MS). Notably, they discovered links between cognitive deficits in a rodent schizophrenia model and prefrontal cortex hypomyelination. This defect can be rescued by treatments or environmental enrichments (Nat Commun, 2020). They have also unravelled new mechanisms of oligodendrocyte differentiation (Glia, 2018; Brain Comm, 2022; JMC 202) and identified Ephrins' role in limiting Schwann cell entry into the CNS and key actions of blood vessels in Schwann cell migration (Acta Neuropath 2019). Their work on adaptive immune cells in myelin repair using a humanised mouse model has important translational implications for MS (Brain, 2017). They developed a new non-human primate model for demyelination-remyelination studies (PNAS, 2022). The Team established preclinical tools, models and pipelines to identify pro-remyelination drugs and macrophage state modulators. They filed 4 patents (e.g. Patent EP22305962.7: VEGFR-1 inhibitors for promoting myelination; EP21161575.2: Compounds for use in progressive multiple sclerosis). All the PhD and Postdocs participated in at least one major publication as first author. Team members are strongly committed to the promotion of gender equity (Nat Hum Beh, 2019; coordination of the ICM gender equity committee). Team members have other key responsibilities at ICM (data analysis director, data management and histology facilities). The Team has secured about 3M funds including international (e.g., NIH, NMSS, IPMSA), national and local grants, and grants/contracts from companies. Team members have received prizes (5) for studies/activities in the MS field (e.g. Sanofi innovation award). They take part in national and international scientific bodies (e.g. president of the French Glial Cells, IHU work package co-coordinator on MS, NeurATRIS, FCNI, GRD, ECTRIMS, ISNI) and contribute to research evaluation for international MS societies, funding agencies (ERC, MRC) and national institutions (HCERES evaluation committee, ARSEP). The team is actively involved in public engagement (e.g. BAW) and has close interactions with patients' associations (ARSEP, IPMSA) by participating in meeting and fund rising events. Training commitment is testified by attractiveness for undergraduate students (more than 10 trained students) and for international young researchers (from Sweden, Netherlands, Argentina, Spain, Germany), and by responsibilities in the executive committees of the Doctoral School BioSigne (University Paris Saclay) and of the ISN Schools Initiative. Training efforts resulted in affective placement of alumni at foreign universities.

Weaknesses and risks linked to the context

In relation to the former period, no major weaknesses or risks are identified. Nonetheless, this assessment must now account for the forthcoming shift in team composition and the adoption of a fresh investigative approach. These aspects present both opportunities and potential risks. While it's important to note that the new Team leaders have already secured some funds to support the new project, also with joint grants, these will serve as an initial bridge for the upcoming term and there is need to promptly expand the available resources. Also, one specific critical element is the limited productivity of Violetta ZUJOVIC as major author during the last term (1 original article and one submission on biorxiv in 2021), which highlights some of the risks and the need to improve the team leader output.

Analysis of the team's trajectory

In its new composition, the team will have as team leaders Fanny MOCHEL & Violetta ZUJOVIC and the name of Immunity, metabolism and neurodegeneration. The team scientific plan is supported by existing funds (nearly 2 M€ and joint leader grants) and driven by a common hypothesis: manipulating cellular and systemic metabolism can yield effective therapies for acquired and inherited demyelinating diseases. The Team's strategy centres on influencing peripheral immune cells and their metabolism to slow the disease progression in neuroinflammatory and neurometabolic diseases. The scientific plan revolves around three main objectives. In the first one, investigations will examine relapsing remitting and primary progressive MS patients to associate specific transcriptional patterns of immune cells with the remyelination potential assessed in the same patients and in experimental animals grafted with patients' derived cells. Patients will be stratified based on patterns of neuro-inflammation or remyelination thus enabling to select and adapt disease-modifying therapies as well as to dissect and modify MS macrophages predisposition to a pro-inflammatory state. The second aim focuses on Adrenoleukodystrophy (ALD) and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) which are inflammatory demyelinating diseases like MS. The Team aims at validating a diffusion tensor magnetic resonance imaging approach for the detection of early inflammatory lesions in patients in order to direct the patients towards early therapeutic interventions and reduce mortality. This work will be paralleled by monitoring the impact of hematopoietic stem cell grafts in ALD and by a multicentric placebo-controlled phase 3 study with leriglitazone, a drug which has both metabolic and immune targets – in adult patients not eligible for human stem cell transplants. The expectation is to provide prognostic biomarkers able to specifically identify patients at earlier disease stages and direct them towards most appropriate therapies. Parallel efforts will be devoted to determine if the use of leriglitazone can be extended to ALSP and another genetic leukodystrophy by preclinical studies and possibly clinical trials. The team will be jointly involved in multi-omics profiling to decipher the genetic programs responsible for aberrant responses in patients' macrophages to pro-inflammatory or pro-regenerative signals. In the third aim, knowledge acquired on myeloid cells will be used to identify the master genes essential to govern myeloid cell pro-inflammatory or pro-regenerative polarisation with

focus on metabolic leverages driving cells into desired states. New druggable targets (genes and/or metabolites) will also be validated in the patient's tissues and preclinical models.

RECOMMENDATIONS TO THE TEAM

The Team takes an original research angle and has a strong potential to reach therapeutically relevant applications. The team's diverse scientific expertise and the potential for joint grant applications present a strong foundation. However, there are critical points that should be taken into account. The team is newly formed, thus it's crucial to implement strategies to promote collaboration (e.g. joint lab meetings, progress reports, and journal club of all the groups). Funds and workforces to support the above lines of research are secured until 2024. Only one relevant grant extends to 2027 (PHRC). Therefore, the team leaders should promptly seek additional funding to facilitate the project's development. Given the team's evident potential for growth and impact, it's advisable to explore European funding opportunities, which can offer substantial resources to support ambitious research. More in general, it's also recommended to continue building synergies with Stankoff's team due to the proximity and complementary nature of their research interests. Also, considering some challenges in Violetta ZUJOVIC productivity, we advise supportive monitoring by the institutional bodies to make sure that in the new term the team will successfully express all its full potential also thanks to synergies within the new team composition.

Team 17: **Motivation, brain and behaviour**

Name of the supervisor: Mathias PESSIGLIONE/Sébastien BOURET/Jean DAUNIZEAU

THEMES OF THE TEAM

The team's research centres around the mechanisms by which assessment of costs and benefits contribute to behavioural decisions, based around a decision theory framework. Their remit spans both healthy and pathological brains. There are four main methodological approaches: neuroimaging and human neuropsychology, non-human primate neurophysiology and pharmacology, computational modelling and metacognition. These approaches are used to address fundamental scientific questions about how information is integrated to produce behavioural outcomes, subclinical questions about the contribution of internal states to this process, and clinical questions about how distortions to the cost-benefit trade-off might give rise to behavioural disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report made two major recommendations. The first was that recruitment of women as team leaders should be encouraged. The balance between male and female team members has improved, including through the recruitment of one new PI who is female.
The previous committee recommended increasing collaborations with other ICM teams working on cellular and animal models other than primates. The team has successfully implemented this through both internal and external collaborations, both funded by ANR grants and is already producing findings at the pre-publication stage that are available as preprints.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	3
Senior lecturers and equivalent	0
Researchers and equivalent	2
Research support staff	1
Sub-total for permanent research staff	**6**
Non-permanent teacher researchers and researchers	0
Non-permanent research support staff	0
Post-docs	4
PhD	11
Sub-total non-permanent staff in active employment	**15**
Total staff	**21**

EVALUATION

Overall assessment of the team

The team's performance has been excellent to outstanding, demonstrating an impressive capacity for collaborative work that brings multiple perspectives to a central question. The team is internationally well recognised for its empirical and computational approaches to decision-making theory. Scientific output is excellent to outstanding, with a high volume of team-led publications in high-profile journals (e.g. Nat. Neuroscience, Biological Psychiatry), and funding has been raised from large research grants at national (ANR) and international (European) level (total>5500ke).

Strengths and possibilities linked to the context

This team has a well balanced, highly productive and well-considered set of research areas that are highly complementary. In terms of scientific output, the team has an excellent to outstanding publication record, having published 81 papers in the evaluation period (average approx 3.4 per year per full-time equivalent), some of which are significant developments and thus were accepted by prominent generalist (e.g. Nature Neuroscience, Nature Communications, PLoS Biology, Current Biology) and field-specific (e.g. Brain, Biological Psychiatry) journals. Many of these include co-authors from other teams or institutes, evidencing the remarkable nature of their collaborative outlook. To support this (and ongoing) work, during the period, the team secured significant funding (around 5600 k€), including from European (278 k€) and national (6 ANR) competitive calls. The team is highly attractive, having had success in attracting PhD students from all over the world, including the Indian subcontinent, the Middle East, the USA and within Europe. These students are productive (producing on average 2.7 papers from their PhD work), frequently take lead authorship on the lab's publications, and have been successful in securing research jobs following their degree. A particular strength is the recruitment of a new team member whose work will bring novelty in incorporating psychology and metacognition, a clear indicator that the team is continuing to seek out new research areas and opportunities. The PIs regularly give invited seminars in international locations (e.g. Barcelona, Vienna, London). The contribution of the team's activities to society is excellent to outstanding. Team members responded rapidly to the emerging global pandemic in 2020, contributing to the incorporation of psychology into epidemiological modelling. More widely, they act as advisors for charitable groups that address important social aims (e.g. motivating children to attend school) and for commercial work with medical aims [MOU4]. They have also produced an online platform for psychological experiments which have dual value in involving the general public in research and providing a much-needed vehicle for experimental subject recruitment. They also communicate their science to lay audiences via diverse media (e.g. The Conversation article; one book 'Les vacances de Momo Sapiens'; high school workshops).

Weaknesses and risks linked to the context

This is an ambitious and attractive team, but their ability to capitalise upon applications from visiting researchers is limited by space constraints.

Analysis of the team's trajectory

In the new contract period, the team's work will build upon the solid foundation that they have already put in place to investigate the mechanisms of cost-benefit trade-offs as a motivator of behaviour, but they also introduce new perspectives that expand the scope of the work by addressing new challenges. Firstly, they will seek to identify the neural signature of cost-benefit arbitration through an AI-based neural network approach, whereby the networks are trained to reproduce the outcomes of decision-making processes, which may involve several cognitive modules. This approach allows hypothesis-generating regarding likely neuronal architecture, and can also be disrupted (creating 'lesions') to test likely outcomes of changes to the process. The second challenge links with the field of psychology, seeking to establish how psychological factors such as self-confidence feed into decision-making systems. The research will incorporate questions about differences between intrinsic vs extrinsic motivational factors, using surveys of voluntary participants, some of which has already begun. There is clear potential for application of the team's developed crowdsourcing platform here. The final challenge is to extend the work beyond the laboratory, in two senses. Firstly, cohort studies with human participants are planned, capitalising upon smartphone technology to predict outcomes that depend upon longer timescales than can be assessed in the laboratory. Secondly, the team plan to incorporate evolutionary ecology by mapping motivational decision-making processes and neuroanatomy across primate species and relating this to species ecology. This element of the project is risky because it relies upon (1) finding robust cranial anatomy phenotypes that are predictive of neural anatomy (2) incorporating sufficient species to make credible conclusions about adaptations to dietary processes. The reliance on collaborators rather than direct hosting of non-human primate research at the unit's facilities is a further risk to the team's approach.

Planned staffing is likely to be sufficient to support the proposed projects and the new behavioural neurology unit (led by team members) should accelerate translational research.
However, this does not induce any risk for the compared cognition project of the team because this part of the program involves studying living species that can be scanned.

RECOMMENDATIONS TO THE TEAM

Given the team's solid track record in high impact discoveries, the proportion of funding obtained from international and European calls (e.g. ERC, Horizon Europe) could be increased, for example, through international collaborations or consortia.

Team 18: Alzheimer's disease and prion diseases

Name of the supervisor: Marie-Claude POTIER/Stéphane HAIK

THEMES OF THE TEAM

The team's work is focused on the common molecular mechanisms, including protein misfolding and transmissibility, involved in Alzheimer's and prion diseases. The team combines animal, cellular and neuropathological models, basic, translational and therapeutic research. Three themes are developed: Aim1: What are the causing events leading to protein misfolding in sporadic AD and prion diseases? Aim2: The role of strains and their cell tropism in specific patterns of propagation of misfolded proteins. Aim3: Biomarkers and therapeutic research from preclinical models to clinical applications

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous committee recommends:
i) Increasing the quality and level (IF) of publications and the funds from international agencies.
Actions mentioned by the team:
The team has published as principal authors, 36 articles and sixteen reviews with thirteen articles *in high-profile journals. 5*, and obtained 6 international and European grants for a total of 1.5M€
ii) The team needs to set up a clear strategy to manage and coordinate internal interactions between members in order to strengthen the organisation and life in the team. Team members must show in the future that they are really working together as one single team with complementary expertise in order to target and reach efficiently common/shared objectives. The project looks vast, with several objectives that are not necessarily complementary.
Actions mentioned by the team:
Thanks to three common grants between PIs, they developed synergical research on strain mechanisms in AD. They have transferred technologies from the prion field to AD (RT-QuIC for Tau and protein misfolding propagation in C elegans). They are now planning to apply single cell technologies developed in AD field to prion diseases as soon as prion experimentations will be resumed. Two additional funded projects in collaboration with Prof. Jucker and Blennow involve PIs from both the AD and the prion fields. In terms of management and coordination, the team has recruited students working on these projects. They have also organised team meetings and retreat with all PIs/members.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	5
Senior lecturers and equivalent	
Researchers and equivalent	8
Research support staff	22
Sub-total for permanent research staff	35
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	11
PhD	11
Sub-total non-permanent staff in active employment	22
Total staff	57

EVALUATION

Overall assessment of the team

The overall assessment of the team is excellent. The team is well recognised for its work in Alzheimer and prion field and is very attractive as shown by (1) its scientific production which is excellent including publications as principal authors in NEJM, Acta Neuropathol., Lancet Neurol., JAMA Neurol., Brain, J. Exp. Med., Alzheimer's Dement., Nat. Com., Clin. Infectious Dis., euro. Surveill.; (2) their involvement in scientific evaluation committees in CNRS, ANR, MRC and European commission as well as the editorial activities (Cell. Mol. Life Sci; front. In Mol. Neurosci.); (3) the integration of 4 new permanent scientists and a visiting professor (2023–2027). Moreover, the team has attracted talented students and postdocs on a regular basis with among ten postdocs, fourteen PhDs, seventeen master students. The scientific capacity of the team to raise funding is outstanding, and it has obtained international (CJD Foundation), European (Horizon Europe 2022–2037) and national funding (for example 7ANR, 2 NeurATRIS, 3 Grant-InVs) and 21 grants from foundations and charities (ARC, FRC, FRM...) for a total of ~8.4 M€.

Strengths and possibilities linked to the context

The team is nationally and internationally recognised and the team's PIs have key positions in national/international scientific/medical research evaluation/steering committees (European Commission, CNRS, French National Agency for Research, French society of neuroscience, France Alzheimer, Fondation Lejeune, Trisomy 21 Research Society). They participate in several national and international consortia and conferences (French surveillance network of CJD, EUROCJD) and coordinate the French National Center of Reference for prions, European College of Psychopharmacology ECNP networks, European Brain Research Area cluster, and the Centre of Excellence for Neurodegenerative diseases. They organised several national and international conferences on prion disease, Alzheimer's disease and Down syndrome (e.g. Biannual congresses of the T21 research society; ECNP annual congresses) and provide scientific support to national authorities and agencies involved in public health (member of 'Santé Publique France', coordinator of one of the largest blood biocollection of human prion). One of the team leaders is a corresponding Member of the French Academy of Medicine. Scientific production is remarkable and higher than in the previous contract (with 180 original articles, letters and 42 reviews in 2017–2022: 36 articles and sixteen reviews as principal authors with thirteen articles *in high-profile journals.* (e.g. Lancet Neurol., JAMA Neurol., Brain, Alzheimer's Dement., Nature Com.); eight articles and three reviews *in high-profile journals in the field* (Neurology, Acta Neuropathol. Com., eLife) and reviews (Curr. Opin. Neurobiol., Free Radic. Biol. Med. Pharmacol. Ther) and co-auteurs for 31 articles. All members of the team (PIs, PhD students and postdocs) are authors of publications. The team has obtained around ~8.4 M€ for the period 2017-22. The team's ability to raise funding is outstanding from various local, national and international institutions or charities: two European grants (Horizon Europ), 7 ANR, three grants from 'Institut de veille sanitaire' and numerous grants from partnerships with the socio-economic/cultural environment and medical/charities foundations (ARC, FMR, FRM). Industrial partnerships and therapeutic research of the team lead to three patents on prion diseases treatment. The team has attracted four new permanent scientists and a visiting professor for 4 years (2023–2027). The team has trained fourteen PhD students, ten post-docs and seventeen master's students. Four PIs have the academic credentials to supervise PhD students (HDR) but only three HDR will be in the team for the new contract. The team is largely engaged in scientific culture diffusion towards the general public via interviews, articles (Le monde, Libération, Figaro Santé, Arté) and popularisation events ('prion day', Alzheimer's day and the Down syndrome day). Several staff members have administrative responsibilities within the ICM (e.g. Steering Committee, experts for ICM QUANT platform, HISTOMIC platform) Editorial board responsibilities as Associate Editor.

Weaknesses and risks linked to the context

There are no major weaknesses

Analysis of the team's trajectory

The transversality of the team's projects is a strength, enabling it to develop preclinical/clinical bases and approaches (analysis of patient tissues, diagnostic and treatment data).
The team's project has three aims:
Aim 1: What events underlie protein misfolding in sporadic Alzheimer's and prion diseases?
This part of the project encompasses multiple aspects of amyloid pathology in Alzheimer's disease, exploring the roles of APP overexpression, cholesterol and viral infections in Aβ production and its impact on the disease

progression. The hypothesis of a vascular or cerebral source of Aβ will be demonstrated using organoids, which is debatable since not all the vascular system is found inside organoids.
In addition, very interesting and promising studies are considering a multidimensional approach to understanding the causes and mechanisms of CJD, involving genetic, somatic and environmental factors (epidemiological study at national level).
This project is led by the two team leaders and involves 4 other permanent researchers (CR, MCU, MCUPH).
Aim2: The role of strains and their cell tropism in specific patterns of propagation of misfolded proteins.
The group want to better identify TAU strain diversity and identify the mechanisms of inter-neuronal aggregate propagation in C. elegans model and then in several mammals models (in vitro and in vivo). They hypothetize that similar mechanisms occur for prion and TAU and C elegans model used by the team for prion propagation will be used to test this for TAU strain specific tropism.
This project is led by the two team's leader and involved five other permanent researchers.
Aim3: Biomarkers and therapeutic research from preclinical models to clinical applications.
This third aim is translational research and aims to develop innovative approaches for the diagnosis and treatment of both Alzheimer and prion's diseases.
This subgroup's project is highly relevant. This project is led by one Director of Research, a clinician, an engineer and it is important to highlight the arrival of a renowned visiting professor with an international reputation in the field of Alzheimer's disease biomarkers. We could wonder if the critical mass isn't too low in terms of permanent staff within this subgroup. In the coming years, this subgroup will need to be strengthened by permanent recruitment.

RECOMMENDATIONS TO THE TEAM

It is an excellent team where research program is based on strong expertise of the team leaders.
The main recommendation could be to encourage young PIs to increase their autonomy and visibility either concerning the supervision of PhD students and their involvement in higher European/international grants.
Considering the reputation of the team leaders, it appears that focusing on pursuing substantial, European funding as 'porteur' such as ERC could be a high priority.

Team 19: **Cellular mechanisms of sensory processing**

Name of the supervisor: Nelson REBOLA

THEMES OF THE TEAM

The group developed research projects focused on deciphering cellular mechanisms controlling the activity of individual neurons in the central nervous system (CNS), pointing to the variability in the composition and density of NMDA receptors and dendritic computations as the source of heterogeneity in computational properties among cortical neurons. They found: (1) Activity-dependent modulation of NMDAR controls dendritic function in cortical neurons. (2) GluN3A subunits form excitatory glycine receptors in SST-INs in neocortex. (3) There are interneuron-specific dendritic computations in the neocortex. (4) There is a behavioural state-dependent modulation of dendritic inhibition in somatosensory cortex.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The committee recommended building an international reputation by publication of high impact papers and attendance and presentation at specialist conferences, recruiting highly capable scientists preferably with the skills that are currently limiting within the group, and focusing on a few key projects to balance relatively safe and ambitious projects, and to develop contingency plans in the event that some projects do not turn out as planned. The committee also recommend developing and maintaining strong collaborations in the areas where the team has limited technical expertise and considering how NMDAR function and modulation could be relevant in a disease context.

The team has followed the HCERES recommendations. During the evaluation period, they have published two papers *in high-profile journals.* and recruited highly capable scientists with complementary skills, which clearly contributed to the implementation of technical approaches that were not mastered by the group leader. They reached the balance between safe and ambitious projects, with the Zinc project being relatively safe and GluN3 being more ambitious. The group established collaborations, e.g. with Valentina Emiliani (Institut de la Vision) and Graham Ellis Davies (Mount Sinai, NY, USA), published and got a Marie Currie grant together with Alberto Bacci. They started to interact with pharmaceutical partners to explore the possible design on new therapeutical approaches based on GluN3A receptors.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	
Senior lecturers and equivalent	
Researchers and equivalent	1
Research support staff	1
Sub-total for permanent research staff	2
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	3
PhD	1
Sub-total non-permanent staff in active employment	4
Total staff	6

EVALUATION

Overall assessment of the team

This excellent team (created in 2017) published 9 papers, including one in Cell Reports and two papers in Neuron with PI as the first or last authors. The productivity is excellent considering the small group size. Very importantly, the team built up a multidisciplinary lab to study both synaptic/cellular function using electrophysiological and two-photon microscopy, as well as in vivo neuronal network dynamics using multiphoton intravital calcium imaging in awake mice. The team has been able to attract excellent funding, national and international PhD students, postdoctoral fellows and to recruit a permanent researcher (INSERM-Nicolas Chenouard). The team is nationally and internationally recognised and is regularly involved in the organisation of courses and workshops both at the national and international levels.

Strengths and possibilities linked to the context

Identification of GluN1/GluN3A receptor as excitatory glycine receptor is a major finding in the field. These and other studies from the team are of high quality and impact and were published in high-impact journals including one recent paper in Neuron and two in Cell Reports. The team was able to obtain around 2.5 million euros, including a competitive international grant (ERC - Starting grant). During the 2017–2022 period, the team was able to establish two national collaborative grants (one as coordinator and another as collaborator) attesting to the ability to attract national collaborations. They also obtained international funding via the NARSAD Young investigator award. The laboratory is well equipped with three slice electrophysiology rigs, one of which is equipped with a dual scan-head two-photon imaging (and photoactivation) system. Dr. Nelson Rebola is the scientific director of the Electrophysiology Core Facility and is part of the consulting experts' committees for the IGENSeq platform. In general, the team is well integrated with a good visibility in France. It contributed to local and international courses: Applications of Fluorescence Microscopy' (Institut Pasteur, Paris, France) (2017, 2018), 'Paris Neuroscience School', Paris, France. (2017, 2018), Mechanisms of synaptic diversity in the brain. BENEFRI workshop, Bern, 2019, Switzerland., Master Course Novel Technologies applied to Human Neuropathologies, Paris, France (2021, 2022).

Weaknesses and risks linked to the context

During the report period, this team was particularly focused on setting up experimental approaches and to obtain original results to generate publications, hence they did not spend enough time in communication of their findings.
The reputation at the international level needs to be further strengthened in the future.
No products for the social-economical word are being in development, although the group could take a lead by developing drugs for targeting GluN3A receptors and specific neural circuitries.

Analysis of the team's trajectory

The new projects of the team are ambitious but strongly based on preliminary results and require the use of experimental approaches that are already implemented in the team. This limits the risks and increase the overall strength of the present scientific strategy and the chances to get new insights into cognitive mechanisms. These new directions are aiming to relate particular circuits to behavioural functions. The team will establish the role of layer 1 in the encoding of contextual information in V1 and study the behavioural functions of excitatory glycine-gated NMDARs. Moreover, it aims to dissect the role of locus coeruleus inputs in processing of visual information (stability of neuronal assembles) in V1 and decipher dendritic computations of GABAergic interneurons within neural circuits in vivo. These projects are exceptionally well designed, and the experimental details worked out perfectly well. The topics are carefully chosen and represent clear knowledge gaps that the team has ideal resources to address. A very exciting and innovative program. The staffing and finances are in line with the proposed project.

RECOMMENDATIONS TO THE TEAM

The group should organise more international symposia to gain more visibility, increase communications with the general public and establish ties to industrial partners to explore the unique option to target SST positive interneurons through GluNA3 receptors in different neurological conditions.

Team 20: **Structural dynamics of neuronal networks**

Name of the supervisor: Nicolas RENIER

THEMES OF THE TEAM

The group focuses on three major themes: First, the development of methodology for characterising adult axonal structural plasticity without using viral labelling. Second, exploration of postnatal development and plasticity of the vascular network in the brain and its interaction with neuronal activity. They have a pipeline for quantifying the entire cerebral vascular network, including capillaries. Third, the investigation of neuroendocrine processes that influence behaviour, with a particular focus on nesting behaviour in pregnant mice. They identified the Edinger-Westphal nucleus as crucial for this behaviour. They aim to integrate their research directions, collaborating with other institutions, to understand how the brain responds to energy balance cues from the body and how vascular plasticity might impact these processes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

At the time of the last report, the team had only been in place for one year. The recommendation was to maintain a high level of publications in the top journals and maximise funding opportunities to enable the full exploitation of technical developments. The committee recommended having at least one HDR in the team for PhD supervision. In addition, the committee recommended recruiting qualified scientists preferably with the skills that are currently limiting within the team, and to focus on key projects with promising results. The team has achieved a consistent level of publication success, as well as collaborative publications. The PI obtained his HDR for supervising PhD students. The team successfully recruited a post-doc, a student, and two bioinformatics-savvy engineers to aid in the development of advanced 3D imaging analysis techniques. At present, the three initial research directions have advanced to a stage of maturity, ensuring that the team has established stable avenues for their scientific inquiries.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	
Senior lecturers and equivalent	
Researchers and equivalent	3
Research support staff	5
Sub-total for permanent research staff	8
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	4
PhD	4
Sub-total non-permanent staff in active employment	8
Total staff	16

EVALUATION

Overall assessment of the team

Overall, this team is an outstanding, internationally visible team, clearly illustrated by their scientific output, grant acquisition and their ability to attract talented students and Post-docs. The team was established in 2017 and has a size of ~10 members. The team has gained international recognition for their expertise in developing tissue clearing, light sheet imaging, and image analysis tools for mapping the mouse brain and other organs. They have made significant contributions to the fields of whole brain imaging, neurovascular plasticity, and neuroendocrine regulations. The recognition in these fields is evident from their high-class publications in the most visible journals. They have also been active collaborators, with ten collaborative papers published since 2019, including some in high-impact journals. The strengths of the research are the application of advanced imaging technology in the field of 3D brain imaging in neuroscience. The main questions are centred on the cross talk of neuronal and vascular plasticity. The team has advanced from being a technological team to one that addresses important biological questions using these technologies. Another sign of excellence is the procurement of a high amount of third-party funding with approximately 4 million euros including prestigious awards and grants, such as an ERC starting award, two French ANRs, the Paris Emergence(s) competitive award, two UK-based grants, two internal grants, and three regional grants for equipment. This funding has enabled them to hire talented researchers and acquire essential equipment for their projects, including two light sheet microscopes and computing infrastructure.

Strengths and possibilities linked to the context

The strength of the team is its expertise in 3D brain imaging, enabling them to unlock cutting-edge opportunities in brain mapping. Furthermore, they have started to develop research programs to investigate mechanistic questions in behavioural, axonal, and vascular plasticity. By following this strategy, the group has in a relatively short time developed into an internationally leading team in the area of vascular biology and light sheet imaging. The team has published highly visible papers and has many more in the pipeline with contributions from all members of the team (for example: Topilko *et al* Neuron 2022, Kirst *et al* Cell 2020). The team's ability to raise funding is outstanding, including an ERC starting grant. The team is very active in knowledge diffusion, which included the organisation of sixteen workshops in tissue clearance and light sheet imaging. They have set up a website to share the vascular mapping resource and have established additional open access tools for the distribution of their data and knowledge with the scientific community. Overall, the group has demonstrated outstanding capacity in technology development, scientific performance, acquisition of funding, open scientific practices and science dissemination.

Weaknesses and risks linked to the context

Most projects are still in a rather descriptive phase. Therefore, it might be important to move deeper into the biological question for at least some of the projects in the future – for example by using mouse genetics, virus delivery tools for gene editing and optogenetics. In addition, the in-house collaboration could be intensified.

Analysis of the team's trajectory

The team seems to be on a highly successful path, with a remarkable number of innovative projects. The subjects being explored are broad, and some of the projects are extremely complex (e.g. vascular plasticity on behaviours). One important additional path the team is pursuing is to improve the technology of clearance and light sheet imaging further. The team has sufficient grant money to be able to follow these different lines of research among those is an ERC starting grant for the analyses of the vascular aspects and an ANR grant to study neuromodulatory mechanisms and nesting behaviour. The team has a healthy mixture of high gain/risk and low-risk projects. In the future, it is likely that the group need to make some strategic decisions on which key projects they need to focus. Because progress is being made in all areas, there is no reason to make any recommendation to change focus at this point.

RECOMMENDATIONS TO THE TEAM

This is an outstanding team with excellent output of highly visible papers. The success of the team is based on the establishment and development of 3D brain imaging, which they successfully apply to answer basic questions in neuroscience. Because the technology is already very mature, it is likely that biological aspects of the work program will become even more important in the future. Therefore, it will be important to continue to complement their own technology with other methods. Overall, the panel was very impressed by the achievements of the team and therefore recommends that the team continue as outlined in the proposal. One area of improvement could be a better integration into the ICM by initiating more in-house collaboration.

Team 21: **Genetics and development of brain tumours**

Name of the supervisor: Marc SANSON/Emmanuelle HUILLARD

THEMES OF THE TEAM

The team aims at understanding the carcinogenesis of tumours in the adult central nervous system, identify new biomarkers and develop novel treatments. The multidisciplinary team of clinicians and basic scientists covers a wide range of competences ranging from developmental neurobiology to brain tumour genetics. Using these assets, they study several brain tumour entities, focusing on gliomas, meningiomas and lymphomas. Their work is organised along several main tasks: (1) molecular classification of tumour entities, (2) identification of biomarkers, (3) mechanisms underlying tumour initiation and progression, (4) disease model development, (5) target identification, and (6) design of novel treatments.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team found excellent solutions to implement the recommendations of the previous report. To address scientific output, they successfully increased the number of international trainees (3 international MD/PhD students, 5 international PhD students, 2 international postdocs). In 2022, they recruited a permanent researcher with strong expertise in metabolic imaging (Francesca Branzoli, PhD). However, a search for 'Francesca Branzoli' on the ICM webpage yields only two hits, which may suggest that individual researchers should be made more visible on the website. The team was able to secure international grants, including training grants of the EU and grants from American funding agencies. In terms of team organisation, they implemented adequate instruments to structure and steer a team. As to the request to employ more long-term technical staff, they were successful and could also establish long-term positions. This is remarkable given the difficulties of finding appropriately trained candidates. A total of twelve research technicians in a team of 40 is an outstanding ratio.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	5
Senior lecturers and equivalent	3
Researchers and equivalent	4
Research support staff	35
Sub-total for permanent research staff	47
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	7
PhD	22
Sub-total non-permanent staff in active employment	29
Total staff	76

EVALUATION

Overall assessment of the team

The internationally highly visible team made outstanding progress in all evaluation dimensions. Particularly impressive are their landmark publications, overall scientific production, and contributions to research networks. They were exceptionally successful in recruiting national and international funding, and excelled in attracting and educating postdoctoral and doctoral researchers. Their efforts in educating the public are of utmost importance. They developed an excellent link to the pharmaceutical industry, essential for drug development. Overall, this team is outstanding in all regards.

Strengths and possibilities linked to the context

The team has outstanding papers including Peyre/Kalamarides (2021) in the New England Journal of Medicine on genetic mechanisms underlying the development of sporadic cerebral cavernous malformations, Rosenberg/Sanson (2018) in Nature Comm on recurrent mutation of Protein Kinase C alpha in rare gliomas, Hernandes-Verdin/Alentorn (2023) in Annals of Oncology on four molecular subtypes of primary central nervous system lymphoma and Touat/Ligon (2020) in Nature on mechanisms and therapeutic implications of hypermutation in gliomas. These studies delivered outstanding insights into the genetics of gliomas and other entities, new biomarkers, interindividual heterogeneity, and, particularly important, the mechanisms underlying resistance to therapy in gliomas. In addition to these highlights, they published>300 articles on a large range of topics, 85 with team members as first/corresponding/last author, and over 40 review articles. Many of their publications appeared in journals with top 10% field-specific impact. All team members, basic researchers and very prominently clinical researchers contributed to the top publications. Several of these studies resulted in contributions to the WHO 2021 classification of brain tumours, which is of outstanding relevance. Moreover, their translational work bears a strong impact on patient care. All these contributions generated a worldwide recognition of the teams work. The highly multidisciplinary team consisting of a large proportion of physician scientists and a perfect fraction of basic researchers, postdocs, PhD students and technicians has proven to be remarkably productive. Innovative research on brain tumours is particularly dependent on such a team effort. The team established new tumour mouse models which are one of the key assets for translational research. The vast clinical and basic science expertise in the team puts them in an internationally highly competitive position. The application of single cell RNAseq in all its ramifications and the bioinformatics resources the team can tap into are a cornerstone of their success. This is extremely well implemented and will yield many more interesting insights. The currently ongoing establishment of imaging mass spectrometry to obtain spatial distribution of cell types is imperative. The extensive know-how in imaging is another strength of the team. The team was exceptionally successful in recruiting funding (>10 M€ raised over the period from national and international sources). The team has had numerous interactions with industry partners, regarding glioma preclinical research (Sanofi, Transgene, Carthera, Nutrithéragene, Servier, Scipio), characterisation of potential therapeutic targets in human tumour samples (Abbvie, Bristol Myers-Squibb, Novartis), and development of software and pipelines for research and clinical care (Owkin, Olea Medical, SOPHiA Genetics/Radiomics). Team members have given numerous interviews, organised conferences for lay audiences (patient associations, contributors), and contributed to university science festival. They have co-organised or participated in several workshops involving the team's clinicians, researchers, engineers, platforms' representatives, patients and caregivers (Cancéropôle, CURAMUS, rare brain cancer networks). Team members have produced podcasts for a general audience to raise awareness on the biology and management of brain tumours.

Weaknesses and risks linked to the context

Important weaknesses were already noted by the team in their SWOT analysis (scientific production by trainees could be improved, large amount of research themes that may dilute productivity, gender ratio, relatively low number of postdocs trained, more responsibilities and involvement in ICM's committees, limited number of successful patent applications, limited number of scientific publications from academic-industry partnerships). The panel agrees that these points need attention.
The team investigated gliomas, meningiomas and lymphomas. The choice of these entities is well motivated and explained by the team, yet more emphasis could be placed on taking advantage of synergies arising from this particular combination. This could be done on the level of technique, concepts, and clinical strategies, each of which have a vast potential of transfers between the different entities.

Analysis of the team's trajectory

Dividing the previous team into two new teams appears to be the response of the team to the realisation that more focus is required. The two new teams perfectly continue the research program and can build on a fantastic base of previous published and unpublished results. Studying the neurovascular interface, the meninges and the meningeal lymphatic system in the context of brain tumours is an excellent choice. In particular, including Jean-Leon Thomas in the team, a pioneer in describing the meningeal lymphatic system promises significant synergies. The second team, studying cancer evolution, mechanisms of resistance to chemotherapy, development of therapeutic strategies to overcome resistance, and interactions between brain tumours and immune system is highly promising. Here, the mechanisms of therapy resistance and new therapies to overcome this need special attention.

New Team 1 (Huillard/Peyre) – text placed here because there was no distinct location provided by Sarali:
Themes of the team
The team studies the neurovascular interface, the meninges and the meningeal lymphatic system and wants to understand the structure and function of these systems in the context of vascular malformations and brain tumours.
Overall assessment
The team leaders are internationally visible and were prominently involved in the landmark 2021 paper showing PIK3CA mutations as the most frequent mutations in sporadic cerebral cavernous malformations and

perivascular fibroblasts rather than endothelial being causal. Their publication record is excellent, and the research proposed is of remarkable quality and highly promising. They combine clinical expertise in the most ideal way with basic research, predicting a highly successful outcome of their proposed research agenda. Together, the team has an outstanding potential.

Strengths and possibilities linked to the context

Aim 1.1 'imaging and functional study of meningeal lymphatic vessels in dural sinus malformations and meningioma progression' is outstanding and essential to study. Aim 2 'molecular characterisation and modelling of dural and brain vascular malformations' is also very well conceived. Aim 3 'Explore the links between brain tumours and vascular malformations' is exceptional. The multidisciplinary team brings in ideal expertise and uses unique mouse models and human imaging techniques of the neurovascular interfaces. This line of research represents a new and timely research direction at the ICM.

The team has outstanding papers, including the New England Journal of Medicine (2021), on genetic mechanisms underlying the development of sporadic cerebral cavernous malformations in Nat. Communications (2018), on recurrent mutation of Protein Kinase C alpha in rare gliomas, in Annals of Oncology (2023), on four molecular subtypes of primary central nervous system lymphoma.

The specific combination of clinical and basic research expertise makes the team highly attractive for junior researchers and in particular physician scientists.

Weaknesses and risks linked to the context

The proposed aims are challenging. From the information given in the self-assessment form the group seems to be rather small – is the workforce in terms of research technicians and PhD/Postdocs sufficient to reach the aims?

Three out of the six-team members have clinical duties further limiting their time for research – how is this in general managed?

Is organoid work already fully established?

Trajectory

As the team has just started, this is too early to analyse. However, judging by the track record of the team leaders and their research proposal, the endeavour is well on track.

Recommendation

Further focus and prioritise the work plan.

RECOMMENDATIONS TO THE TEAM

As already stated in the trajectory analysis, the team is very well positioned in almost all aspects. The points discussed under weaknesses need attention. A reduction in research topics into more focused areas will be an important and ongoing process. The division in two teams is already a great start. The apparently low paper output of the trainees needs a systematic analysis. It might help to have several thesis committee meetings a year for the under-performers, but there might also be shortcomings in supervision.

Further thoughts could be given to strategies for optimising the use and exchange with the basic research laboratories and their technical skills and conceptual know-how. Here, cancer neuroscience could figure more prominently.

Regarding the very challenging task of sharing clinical duties with research time, the team could attempt to develop optimal solutions with the institutions involved. Having protected research time that allows full focusing on the work itself and co-workers is of utmost importance. This may require more personnel in the hospital and clearly defined non-negotiable time periods for research.

New Team: **Brain tumour heterogeneity, immunity and therapy**

Name of the supervisor: Touat – Bielle

THEMES OF THE TEAM

The new team 2 aims at studying three main themes: (1) Tumour heterogeneity and patient outcome. This involves diverse cell populations in the microenvironment of the tumour and their adaptive heterogeneity. This will be related to patient outcome and therapy resistance. (2) Identifying mechanisms mediating resistance to treatment of brain tumours. Based on their seminal work published in 2020, they will attempt to find new treatment strategies targeting DNA repair deficiency. (3) Understand the crosstalk between tumour cells and immune microenvironment and identify key immunosuppressive nodes that might be targeted to enable immune therapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

N.A.,

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

EVALUATION

Overall assessment of the team

Both internationally visible team leaders were prominently involved in the landmark 2020 paper showing that hypermutation could generate adaptive resistance mechanisms in recurrent gliomas. Their publication records are outstanding and the research proposed is of exceptional quality. They combine clinical expertise in the most ideal way with basic research, predicting a highly successful outcome of their proposed research agenda. This combination makes the team exceptionally attractive for junior researchers. Together, the team has an outstanding potential.

Strengths and possibilities linked to the context

The team published a landmark paper in Nature on mechanisms and therapeutic implications of hypermutation in gliomas (Touat/…/Bielle/Ligon (2020)). In addition, both team leaders published a large number of papers, many of which appeared in journals of the top 10% field-specific impact. Together, this gives them an excellent international visibility. The team commands several unique resources:1/Coordination of national cancer networks (POLA, LOC) with unique expertise and cohorts including prospective and randomised trials datasets and biobanks (POLCA, BLOCAGE, PRECIS, EpiBrainRad), 2/Large clinically-annotated CNS tumour biobank, including paired primary/recurrent tumours collected before and after treatment, 3/Excellent recruitment of new patients for academic and industry trials, 4/Technology platforms, translational and clinical research, neuropathology research, genetically engineered mouse models, preclinical development, 5/Local collaborations with immunology (CIMI) and mathematics including artificial intelligence. The multidisciplinary team consists of a large proportion of physician scientists and basic researchers, postdocs, PhD students and technicians. Innovative research on brain tumours is particularly dependent on such a team effort. Heterogeneity and resistance are two of the key challenges in neuro-oncology. The team is ideally suited to address these questions. Their excellent link to national cancer networks, clinical work and patient materials in combination with the exemplary research infrastructure at ICM puts them into a highly privileged and internationally leading position. The ongoing developments in single cell omics, multiplex spatially-resolved imaging, novel bioinformatics tools, small animal MRI, and several other tools provide an ideal research environment to boost progress. Their aim to develop novel immune-competent models that replicate the course of the human disease is of key importance. In terms of preclinical models, their aim of including iPS-derived cell cultures and organoids is centre stage.

Weaknesses and risks linked to the context

A major weakness concerns the broad range of topics and tumour entities that intersects with a broad array of methods, together forming a rather complex matrix. While all three major aims are extremely well justified, the total work burden of pursuing all the aims in all dimensions is very ambitious even considering a funding period of five years and the large size of the team.

While the development of new preclinical models is of utmost importance, it is also highly time consuming. While the team is experienced in generating mouse models, their experience in iPS and organoid work appears to be less developed and needs particular attention.
Ideas on tumour immunotherapy need to be more developed. However, collaborations with immunologists at SIRIC provide an excellent basis to drive this forward.
Limited time and complicated schedules of physician scientists, a problem mentioned by the team as well. This is a very difficult problem and solutions are in place, but the team should nevertheless attempt to negotiate better conditions with the participating institutions.

Analysis of the team's trajectory

As the team has just started, this is too early to analyse. However, judging by the track record of the team leaders and their research proposal, the endeavour is well on track. The team can build on a large workforce, outstanding technical environment, exceptional clinical infrastructure and patient cohorts, and excellent grant support.

RECOMMENDATIONS TO THE TEAM

Further focus and prioritise the work plan. This concerns the scientific questions, approaches and number of disease entities. As emphasised by the team, the international competition is very strong and concentrating workforce on certain aspects rather than getting too broad will optimise success. Involve a senior scientist as a mentor. Overall, this is an ambitious and exceptionally promising project that is highly likely to yield new key discoveries in neurooncology.

Team 22: **Repair in Multiple Sclerosis: from biology to clinical translation**

Name of the supervisor: Bruno STANKOFF/Catherine LUBETZKI

THEMES OF THE TEAM

The goal of the team is to dissect the key mechanisms underlying myelin formation and regeneration and to exploit this knowledge to improve monitoring and treatment of multiple sclerosis (MS). The team exploits a combination of fundamental science, translational imaging and clinical research. Basic science research focuses on glia-neuron crosstalk at the node of Ranvier and its role in myelin plasticity and repair and on the discovery of promyelinating compounds. Translational imaging research aims at developing new imaging tools to stratify MS patients based on their remyelination potential, detect immune cells activation and presymptomatic brain alterations. Clinical research translates fundamental knowledge to MS patients.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Given the outstanding performance of the team, no specific recommendations were given in the previous report

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	2
Senior lecturers and equivalent	2
Researchers and equivalent	6
Research support staff	9
Sub-total for permanent research staff	19
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	6
PhD	11
Sub-total non-permanent staff in active employment	17
Total staff	36

EVALUATION

Overall assessment of the team

The team is internationally well recognised for its work, as documented by the organisation of several international congresses (7), responsibility in key International Committees and Societies (19), several invitations to International conferences (>80) and many scientific awards (15). Scientific production is outstanding, documented by many articles published in the best journals in the discipline. The scientific appeal and capacity to raise funding of the team are also outstanding. The team received international (3) and national fundings, and grants from industries raising about 8 M€. The team attractiveness for talented and promising early career scientists from France and abroad is excellent. The team trained sixteen PhDs and three post-docs, including eight international fellows. The overall assessment of the team is outstanding.

Strengths and possibilities linked to the context

By coupling MRI to powerful imaging tools to monitor remyelination, inflammation and neuronal damage the team showed that MS patients could be stratified according to mechanisms underlying tissue damage (Bodini, Nature Rev Neurol 2021). Furthermore, the team revealed that persisting innate immune cell activation and remyelination failure predominate in the periventricular lesions (Bodini, J Nuc Med. 2020; Poirion Neurology 2021; Tonietto, Brain 2023) and that choroid plexus alterations occur at pre-symptomatic disease stage (Ricigliano, Radiology 2021; Neurol Neuroimmun 2022). These imaging studies improve disease course prediction and have

an exceptional impact on mechanisms underlying remyelination failure, bringing us closer to the development of new therapeutic. The basic science focus of the team is on discovery of new promyelinating drugs and on microglia-neuron crosstalk at nodes of Ranvier, a preferential microglia-axon contact site, which influences microglial phenotype and myelin repair. Fundamental research articles and reviews are published in very high impact Journals (Ronzano Nat Comm 2021 top 2% J top 5% cit; Maas Nat Comm 2020; Lubetzki Nature Rev Neurol 2020; Lubetzki Lancet Neurol). Team members are leading authors in 36% of publications. All PhDs and post-docs belonging to the team are first authors in at least one publication, highlighting the excellent quality of the research training within the team. The team's ability to raise funding is outstanding, with 8 M€ of funds. Team members are in the Executive Committee (vice-president) of the largest clinico-scientific meeting on MS (ECTRIMS) and in other key steering committees. The team has also institutional responsibility, showing attention to the life of the Unit. Members of the team are internationally recognised as key opinion leaders in the field of MS, myelin imaging and remyelination. They are editors of leading neurology journals (e.g. *BRAIN*), organisers of several meetings on MS and myelinating cells (ACTRIMS-ECTRIMS 2020, Euroglia 2023, GRC-myelin 2022, ARSEP meeting, etc) and were speakers at numerous international conferences (>80). Young team members received fifteen prizes for best oral communications or scientific achievements (e.g. R Moltalcini award, Eur Charcot Awards). The team has activated appealing teaching programs (Univ diploma on myelin diseases; ECTRIMS teaching courses) and attracts international fellows (8 from Italy, Brazil, UK, Greece). The team has established strong links with patient associations (ARSEP, FISM) and actively contributes to their scientific and fundraising activities. The team is very active in knowledge diffusion to general audience (e.g.: TV, Radio broadcasts, lay audience press) and participates in educational events for general public (e.g.: the Brain Week).

Weaknesses and risks linked to the context

No specific weaknesses are observed

Analysis of the team's trajectory

B. Stankoff will lead a new multidisciplinary team (11 permanent and 2 emeritus researchers) with basic science competence and translational approaches aiming to prevent MS progression by stimulating myelin repair and neuroprotection through devices or pro-myelinating molecules. Research projects will be supervised by 4 PI with complementary expertise in the fields of neuroglial interactions (A Desmazieres), neuropharmacology of myelin (B Nait Oumesmar), translational imaging (B Bodini) and clinical research (C Louapre).
The team proposes three collaborative projects: 1) Interplay between neuronal physiology and myelin dynamics: from concepts to cure, 2) Targeting the neuroinflammatory component to promote repair in MS and 3) Brain interfaces as key actors on MS lesion pathophysiology. The hypothesis behind the project 1 is that the node of Ranvier acts as a neuroglial communication site where not only microglia but also astrocytes and OPCs sense neuronal activity and adapt their state to neuron function. Using cutting-edge methodologies (e.g. live label-free imaging) and a variety of preclinical screening in various species, they will assess metabolic and transcriptional changes in neuron and glia during de- and re-myelination and investigate how such changes correlate with repair. Parallel investigations will be performed in MS patients using myelin-specific MRI techniques in combination with a novel PET synaptic tracer. Breakthroughs are expected by combining myelin and synapses imaging. Repair will be quantified in different functional systems (e.g. in spinal cord or the visual system) and the most promising remyelinating approaches will be tested in clinical trials.
In project 2 the team proposes a translational approach to dissect how the inflammatory environment negatively impacts remyelination. The mechanisms of action of previously identified drugs that counteract factors inhibiting myelin deposition (e.g. H3/VEGF receptor antagonists) will be investigated in humanised preclinical assays (iPSC-derived OPCs, brain organoids, chimeric mouse model). Progress of the most promising promyelinating approaches towards clinical trials will be supported by improved imaging and neurophysiological platforms, whose enhancement will also significantly facilitate the assessment of their therapeutic potential.
In objective3 by means of recently published imaging tools (e.g. real time vessel wall MRI, diffusion in perivascular space) the team will systematically explore the fluid trafficking between the CNS and periphery, whose abnormalities can play a role in MS pathophysiology, with the ultimate goal of identifying novel biomarkers for disease prediction and monitoring from the earliest stages. The projects will have an exceptional impact on our understanding of the mechanisms underlying remyelination failure, and will be fundamental in the delineation of a myelin-repair therapy.
The team has already secured funds to support the proposed projects.

RECOMMENDATIONS TO THE TEAM

In the Swot analysis, the team has pinpointed various weaknesses and potential threats. Nonetheless, there are no precise recommendations that emerge from our assessment. Building on one of the observations made in the Swot analysis, the team is encouraged to capitalise on various forms of global funds, including those from the EU. This realm of funding remains relatively unexplored by the group, despite the fact that the PIs are fully qualified for that.

Team 23: Normal and abnormal motor control: movement disorders and experimental therapeutics

Name of the supervisor: Marie VIDAILHET/Stéphane LEHERICY

THEMES OF THE TEAM

The team is engaged in translational and clinical research on the pathophysiology of motor control and the development of experimental therapeutics for movement disorders. Their research topics are on three main themes: (1) To investigate network function and dysfunction in movement and behavioural disorders, (2) To build a dynamic progression model of PD that will be used for predictive and precision medicine, (3) To develop innovative therapeutic approaches in movement disorders using focused ultrasound, non-invasive stimulation, and drugs targeting metabolic dysfunctions.
For the next contract, this team will evolve to three independent teams as follows:

- Team FLAMAND ROZE & POUGET – 'From Movement to Cognition: insights from motor disorders'
- Team ARNULF & OUDIETTE – 'DreamTeam: sleep, dreams, and cognition'
- Team SLIWA – 'Neurophysiology of social cognition'
- A fourth team will also originate around Fanny Mouchel in combination with Violetta Zujovic from another team: team Fanny Mochel & Violetta Zujovic (Immunity Metabolism and Neurodegeneration).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report encouraged the team members to publish in even higher impact journals.
Accordingly, the team has increase of its scientific productivity and publications impact factors, with over 150 articles in journals in renown journals of their field including (e.g. Brain, Neurology, Lancet Neurol, Annals Neurol, JAMA Neurol, Nature Medicine, eLife, Nat Comm, Nat. Hum Behav, Nat. Communication, Plos Biology, Curr Biol; Sci. Adv).
Previous report: The team should be more active in collaborating with the ICM neuroinformatics group.
Accordingly, concrete collaborations and PhD student exchanges have been realised with the team of Stanley Durrleman and Olivier Colliot. (Projet Charlotte Rosso and Fabrizio De Vico Fallani, Project Iceberg Stephane Lehéricy and Stanley Durrleman). Signal processing and interactions with physicists have also been initiated and led to one patent on EEG signal detection (Patent: US 10,939,838).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	9
Senior lecturers and equivalent	3
Researchers and equivalent	7
Research support staff	21
Sub-total for permanent research staff	40
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	16
PhD	25
Sub-total non-permanent staff in active employment	41
Total staff	81

EVALUATION

Overall assessment of the team

The team is internationally well recognised for its work in translational and clinical research on the pathophysiology of motor control and the development of experimental therapeutics for movement disorders as revealed by first, its scientific production which is remarkable including publications in journals such as Brain, Neurology, Lancet Neurol, Annals Neurol, JAMA Neurol, Nature Medicine; second, its scientific appeal and capacity to raise funding which is exceptional including for example 7 ANR and two ERC grants these last five years; third, its remarkable capacity to attract talented and promising early career scientists from France and abroad with among sixteen PhDs, eight Post-docs, and twenty Master students eleven obtained contracts/permanent jobs, without forgetting its capacity to allow younger PIs to develop their own teams for the next contract.

Strengths and possibilities linked to the context

The team is internationally well recognised for its work with more than 500 papers published these last five years including some key contributions with clinical impacts - Thus the Scientific production is remarkable -(e.g. Brain, Neurology, Lancet Neurol, Annals Neurol, JAMA Neurol, Nature Medicine, Sleep, Sleep Med., Movement Disorders, Journal of Neurophysiology, Brain Stimulation), but also high-impact generalist journals (eLife, Nat Comm, Nat. Hum Behav, Nat. Communication, Plos Biology, Curr Biol, Sci Adv). Several PIs are internationally recognised and invited to give lectures in international meetings. In agreement with its scientific productivity, the scientific appeal and capacity of this team to raise funding are exceptional. For example, the team has obtained numerous grants over the last 5/6 years such as: ANR CADETS ANR Momic, ANR JCJC DreamGate, ANR-JCJC Neurosocio, ANR-PRC SocialNeuroNet, ANR-JCJC SleepTight ANR JCJC PSP-tau, as well as International: ERC Stg, ERC Cog. In parallel, the team was attractive for talented and promising early career scientists from France and abroad, for example among sixteen PhDs, eight Post-docs, and twenty Master students trained during this time period, eleven obtained contracts/permanent jobs (engineer, full-time researchers, full-time medical doctor, research assistants), created or joined start-ups (patents), or entered the medical curriculum (competitive interview for medical school/Sorbonne Université). The team is large fourteen PI and 21 permanent tec
hnical staff) with scientific objectives focused on the pathophysiology of motor control and the development of experimental therapeutics for movement disorders. The team's main contribution to knowledge is to establish relationships between network dysfunctions in movement and behaviour disorders with perturbations of sleep and dreams as biomarkers of the early stages of these diseases, providing the corresponding physio-pathological explanations thanks to the use of a large set of technology to investigate the brain functioning.

Weaknesses and risks linked to the context

There are no major weaknesses during the last five years with the main objectives successfully addressed. The fact that this team is going to evolve to three independent teams could be considered as a risk for the future.

Analysis of the team's trajectory

Indeed, as mentioned above, for the next contract, this team will evolve to three independent teams as follows:
Team FLAMAND ROZE & POUGET – 'From Movement to Cognition: insights from motor disorders'
Team ARNULF & OUDIETTE – 'DreamTeam: sleep, dreams, and cognition.'
Team SLIWA – 'Neurophysiology of social cognition'
The three future teams, emerging from the current team (FLAMAND-ROZE & POUJET, OUDIETTE &ARNULF and SLIWA) have already solid track records and funding from competitive grants (ANRs, ERCs) and innovative projects.
For the feasibility of the projects, see the following teams.
See the trajectories of the teams 27, 28 and 29.

RECOMMENDATIONS TO THE TEAM

NA see teams 27, 28 and 29 for recommendations to the teams.

Team 27 (new team): From movement to cognition: insight from motor disorders

Name of the supervisor: FLAMAND-ROZE/POUGET

THEMES OF THE TEAM

This team aims to investigate various aspects of motor and cognitive control, particularly inter and intra subject variability in developmental and acquired disorders and, when available, in genetically related animal models. They are planning to decipher these variabilities to offer new perspectives for understanding the standard functions and pathological dysfunctions related to motor control. To implement this program, they will investigate the brain network interplay using two complementary approaches: translational multi-models (healthy/pathological, preclinical/human models) and stimulation-recording paradigms. The team will take advantage of peculiar pathological neurodevelopmental models to understand various aspects of motor and behavioural control, including their interactions. They will also study the neurovascular coupling and decoupling in detail using fUSi (Focused UltraSound imaging) and TUS (transcranial focus ultrasound stimulation) of cortical and subcortical structures and networks. Altogether, the team hopes that these approaches will allow to better understand the intra and inter-subject variability during high-level motor control tasks. The final objective is to provide translational research to have implications for patient care and a possible 'experimental therapeutic' perspective.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

see team 26

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

EVALUATION

Overall assessment of the team

The overall assessment of the team is outstanding. The team is internationally well recognised for its work with the two PIs world leaders in their field of research. The Scientific production is outstanding with important recent publications made by the two PIs, e.g. Lancet Neurol., Annals of Int. Med., J. Clin. Invest., eLife, Nat. Comm., Plos Biol., as last or co-last authors. Its scientific appeal and capacity to raise funding are remarkable, with three ANRs ongoing as PI and partner of an ERC grant. The team's ability to attract talented and promising early career scientists from France and abroad is excellent with PhDs, Post-docs and Master students who have now obtained contracts/permanent jobs.

Strengths and possibilities linked to the context

The strategy of this team relies on the coherence and complementarity expertise and the long-standing collaborative experience of the team members, in continuity with the research made by the group Vidailhet – Lehericy. The team capitalise on the well-phenotyped patient groups and the extraordinary recruitment of rare diseases that they can use as a powerful research paradigm (national reference centre for many rare neurological diseases, including Tourette's syndrome, dystonia, and mirror movement disorders). One of the strengths of this group is based on its strong collaborations with physics group for new technical developments (focused ultrasound, ultrasound imaging, physic for medicine) and animal model labs (Ecole Normale Sup., Paris ; Institut Fer à Moulin, Paris ; Institute of Cognitive Science, Lyon) Computational neuroscience (Ecole Normale Sup. Department of Cognitive science). The team has international recognition in its field. Its contribution is remarkable. The team aims to better understand motor and cognitive control in a translational and clinical approach, paying particular attention to inter-subject variability. Some technological developments have been successfully transferred to patient care (e.g. neuromodulation using focused ultrasound, and improved imaging exploration of movement disorders). Almost all permanent members of the team, including the clinicians, participate in the publication effort of the team. Funding (national, international) is remarkable with more than twenty grants (50% as coordinator, 50% as partner) for a total of around 5000 K€ and more over the evaluation period.
As a whole, the team (11 PIs between 2017–2022) published over 400 papers in scientific or medical journals; One hundred and seven articles were published in renown journals of their field (Brain, Lancet Neurol., Annals of

Int. Med., J. Clin. Invest., eLife, Nat. Comm., Plos Biol). Team members have been invited for a number of oral presentations at international and national conferences or seminars. During the last term, 4 members of the team obtained permanent research positions (3 researchers - CR, 1 research director - DR.) and four clinical researchers (2 full professors - PU-PH, and 2 Associate Professors - MCU-PH). Among sixteen PhDs, eight Post-docs, and twenty Master students, eleven obtained contracts/permanent jobs (engineer, full-time researchers, full-time medical doctor, research assistant), created or joined start-ups (patents), or entered the medical curriculum (competitive interview for medical school/Sorbonne Université). Most M2 students have pursued a neuroscience course (PhD). Special attention was given to gender issues, diversity of initial training, and inclusion.

Weaknesses and risks linked to the context

Three junior researchers will leave the team in 2024 (D. Oudiette and T. Andrillon, and J. Sliwa), and new permanent researchers are not yet recruited. However, the team has candidates ready to apply for INSERM/CNRS positions. Computational modelling approaches and neuro-informatics collaboration are the team's relative weaknesses. Therefore, they are now starting collaborations with the ICM neuro-informatics group (S Durrleman) and the Aramis team (O. Colliot), and they wish to promote an internal postdoc to a permanent position (V. Vasudevan). One possible threat could be Competition with European and North American groups on ultrasound imaging (Oxford and Caltech), but the team has several areas of specific expertise.

Analysis of the team's trajectory

The team aims to investigate, for the new contract, in continuity with the current one, the various aspects of motor and cognitive control, particularly inter and intra subject variability in developmental and acquired disorders and, when available, in genetically related animal models. To implement this program, they will investigate brain network interplay using two complementary approaches: translational multi-models (healthy/pathological, preclinical/human models) and stimulation-recording paradigms. They will take advantage of peculiar pathological neurodevelopmental models to understand various aspects of motor and behavioural control, including their interactions. They are also planning to study the neurovascular coupling and decoupling in detail using fUSi (Focused UltraSound imaging) and TUS (transcranial focus ultrasound stimulation) of cortical and subcortical structures and networks.

Three themes will be developed:
Theme 1. Investigating the source of variability in motor processes: better understanding the variability of evolution between and within individuals from development (genetically disrupted corticospinal development) to motor recovery (post-stroke corticospinal lesions) (PI: Caroline Dubacq, Charlotte Rosso, and Emmanuel Flamand-Roze).

Theme 2. Study the different interactions between brain networks to perform a movement optimally, to compensate or generate a dysfunction. (PI: Yulia Worbe, Cécile Gallea, and Marie Vidailhet).

Theme 3. Exploration of the neuro-metabolism variability in motor (dys) function (PI: Nadya Pyatigorskaya, Stéphane Lehericy, and Pierre Pouget).
Interestingly, the diseases of interest such as Parkinson Diseases or congenital mirror movement disorders will be completed by a part of the program which will be focused on the motor deficits occurring following a stroke.

These projects are moderately risked. The staff and finances are in line with the proposed project.

RECOMMENDATIONS TO THE TEAM

The next contract period will be critical for this team. It is recommended that the two new PI keep focus on the main topics for which they are internationally recognised, without forgetting to develop a research program in which their collaboration will provide added value. One challenge will also be to keep a strong relationship – partnership between the preclinical work and the clinic which has been a force of this team in the past.
Nevertheless, the feasibility of proposed programs is high enough with appropriate resources available.

Team 28 (new team): Sleep, dreams, and cognition

Name of the supervisor: Arnulf – Oudiette

THEMES OF THE TEAM

The Dream Team sprouts from the Mov'it team, which investigates mechanisms of movement disorders, notably during sleep. Isabelle Arnulf and Smaranda Leu-Semenescu led sleep research within the Mov'it team, making resounding discoveries on REM sleep behaviour disorder (RBD: prodromal Parkinson's disease), and narcolepsy, a rare disease characterised by excessive daytime sleepiness. The team aims to investigate mechanisms of movement disorders, notably during sleep and dreams with a special focus on cognition. The goals are: 1) discovering why we sleep and dream; 2) understanding the mechanisms of neurological sleep disorder.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

see team 26

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

EVALUATION

Overall assessment of the team

The overall assessment of the team is remarkable. In the past five years, the team has published in top clinical journals and generalist journals. The team has been successful in obtaining numerous competitive academic research grants, at the international, European levels. The team is internationally well recognised for its work. In the past five years, the team has published over 100 articles, including publications in top clinical journals (e.g. Brain, Neurology, Lancet Neurol, Annals Neurol, JAMA Neurol, Nature Medicine), reference journals in their field (Sleep, Sleep Med.), but also high-impact generalist journals (eLife, Nat. Comm, Nat. Hum Behav, Curr Biol, Sci Adv). Four studies have been listed by the Lancet Neurology in the top ten most important advances in Sleep Research in 2021 and 2022. This production highlights the nice complementary between the team PIs. The team includes a strong clinical team (1 PUPH, 1 MCU, 3 PH, 3 PhD students) and a growing basic research team (2 CRCN, 1 IE, 1 postdoc, 4 PhD students). Importantly, this production reflects the integration and coherence within the team with a high number of publications that include the PI leading different research angles in the team as well as different team members (PIs, PhD students, postdoc/research assistants). The team has also trained 4 new PhD and MD students with a doctoral thesis, who typically published in high-impact articles as first authors. They have been successful in obtaining numerous competitive academic research grants, at the international (e.g. Sleep Research Society; National Health and Medical Research Council, Australia), European (ERA-NET cofund, MSCA Doctoral Network), and national level (3 ANR, Fonds Unique interministériel). Furthermore, one PI has been selected for the audition of the prestigious ERC consolidator grant (section SH4, final results in 2023). Their discoveries have been largely featured in the national and international media (e.g. Forbes, The Economist, Scientific American, The Conversation, Le Monde, Le Temps, etc.), demonstrating their originality and potential impact beyond academia. A large part of their production is the fruit of an extended international network, with collaborative efforts between multiple centres, nationally or internationally, both for clinical trials and basic research on the cognitive functions of sleep. In recent years, PIs have created a new course (UE) on the topic of 'research in sleep and dreams' for medical school students. One PI teaches neurology and sleep medicine at various levels from first to third medical school cycles. Another PI is a member of the pedagogic committee of the Cogmaster, the leading cognitive science program in France.

Strengths and possibilities linked to the context

The team has a strong expertise in sleep and dreams, with a unique access to rare sleep disorders (e.g. narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome) and large cohorts of patients with parasomnia (e.g. RBD, sleepwalkers).
Combined with a large visibility in the media, this allows this team to attract excellent students and secure collaborations with national and international researchers. Their position on trending topics in sleep research

(e.g. lucid dreaming, local sleep, creativity) gives to this team a critical momentum. The team aims at strengthening its attractiveness by recruiting new trainees to complement the team creativity and complementarity. The team has a large visibility in the media and is particularly active in communicating science to the general public. The team (PIs) also extensively contribute to create norms for diagnosing/treating rare sleep disorders, and propose recommendations for social actors (e.g. forensics). The team is recognised for its unique profile at the intersection of different cognitive fields and at the borderland between clinical and basic research. It is also important to note that a young leader in sleep and consciousness research has joined the team in 2021 and started a permanent CRCN position in 2022.
The overall activity of this team is remarkable.

Weaknesses and risks linked to the context

There are some challenges and risks for this team: Space issues limit the size and attractiveness of the team. Not enough involvement within the ICM. Not enough postdocs and international students. The team comprises a majority of early-career researchers (2 CRCN, 1 MCU, 2 PH in 2023), who are emerging leaders in their field. The young clinicians have less international visibility than the team leader and need to gain it before IA retires circa 2030. To the opinion of the HCERES experts, these weaknesses should be considered as minors.

Analysis of the team's trajectory

The team aims to investigate mechanisms of movement disorders, notably during sleep and dreams with a special focus on cognition. The goals are: 1) discovering why we sleep and dream; 2) understanding the mechanisms of neurological sleep disorder. Interestingly, the research on dreams and sleep functions has traditionally been stalled by two main difficulties: namely the lack of (i) access and (ii) experimental control over mental and cognitive processes happening during sleep. In their past work, this group was able to overcome these limitations by studying people whose unique sleep peculiarities open a window into the sleeping mind: i) lucid dreamers, who are conscious of dreaming in REM sleep and can signal it to the experimenters using muscular codes; ii) sleepwalkers and patients with REM sleep behaviour disorder (RBD) whose overt behaviours allow us to objectively visualise ongoing cognitive processes during NREM and REM sleep, respectively (Arnulf et al., Sleep 2017) In addition, the team showed that these patients exhibited facial expressions during sleep (J Sleep Res 2019; J Sleep Res 2021), which could potentially inform about the function of dreams in emotion regulation. In particular, they found a temporal association between rapid eye movements and facial emotions in REM sleep (Sci Rep 2022). In parallel, the team discovered that local slow waves in awake (healthy) participants could predict behavioural (e.g. sluggishness, impulsivity) and subjective experiences (e.g. mind-wandering, mind-blanking) in a region-specific manner (Nat. Comm 2021), providing a new framework to understand the functional outcomes of cognitive fatigue. Their research involves basic and clinical research.
The research project for the next contract is to study sleep disturbances as a core symptom of numerous health issues such as aging, depression, Parkinson's disease or Alzheimer's disease. To address this question, they are planning to explore the cognitive functions of sleep and dreams in different situations using multiple approaches such as combined EEG/fMRI. They have already obtained several grants to support these studies (4 ANR and 2 ERC grants). One of the finalities of their work is to identify sleep biomarkers to predict neurodegenerative disorders.
The feasibility of the proposed programs is high, considering the quality of the team and PIs. All the resources, human and finances are adequate with the proposed programs.

RECOMMENDATIONS TO THE TEAM

This group proposes an ambitious project that builds upon the respective expertise of the team members to chip away at the mystery of why we sleep and dream. Their approach is rather unique at the international level in close collaboration between clinicians and scientists. The team should maintain his leadership by keeping its strong relationship between basic researchers and clinicians in the future, which was a force of the team Vidailhet & Lehericy in the past.

Team 29 (new team): **Neurophysiology of social cognition**

Name of the supervisor: Sliwa

THEMES OF THE TEAM

This team proposes a research program entitled 'Neurophysiology of social cognition'. The main question is how does the brains of social beings give meaning to their society? In this new team, they will study how society is encoded by neurons in the brain studying mainly non-human primates. The methodologies used are cognitive sciences, electrophysiology and in vivo brain imaging.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

see team 26

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

EVALUATION

Overall assessment of the team

The overall assessment of the team is outstanding. The research plan of this team includes very innovative and ambitious components which have never been investigated yet with a combined use of fMRI and non-human primates, a research program granted by an ERC and proposed based on previous important publications of the PI. The team is internationally well recognised for its work. The scientific production is outstanding, Science 2017 and key review papers in this field of research more recently. Its scientific appeal and capacity to raise funding are remarkable, with an ERC program just starting. Attracting talented and promising early career scientists from France and abroad cannot be evaluated for this young team.

Strengths and possibilities linked to the context

The PI obtained important funding including one ERC StG *NEURO-SOCIETY and one* ANR JCJC *NEUROSOCIO, plus* IBRO Return Home Fellowship and ANR PRC *SocialNeuroNet.* The PI is an expert in this field of research with an outstanding network of collaborations. She has published few but important papers and review articles (Annu Rev Neurosci., Science).

Weaknesses and risks linked to the context

The possible weaknesses of this team – research program is due to the originality of this later (also a strength) which should be conducted in a colony monkeys.

Analysis of the team's trajectory

The team proposes a research program entitled 'Neurophysiology of social cognition'. The main question is how does the brains of social beings give meaning to their society? In this new team, they will study how society is encoded by neurons in the brain. Briefly, the concept of the proposed research program is as follows: 'we immediately understand who is friend or foe, which children belong to whom, and what hierarchy governs the relationships of others'. The brain must be able to possess mechanisms that extract social knowledge about the structure of our society from sensory information about individuals'. Thus the team aims to identify how the social network is encoded by the monkey brain and how these neural representations are formed from the perception of individuals. They are planning to study these questions using a multi-scale approach combining state-of-the-art techniques. An exploratory approach at the whole brain level, using functional magnetic resonance imaging (fMRI) in monkeys and humans, should enable them to chart the brain territories involved in representing social-network topology and individuals' social categories.
More specifically, the following aims are to be addressed:

- Aim 1 is to discover neural circuits and mechanisms for representing social-network topology

By analogy to how place cells in the hippocampus represent space, they will investigate whether 'social-network place cells' represent individuals organised according to their social network position.

- Aim 2 is to discover neural mechanisms for transforming social perceptions into concepts about individuals

They will investigate the interplay between neural circuits for social perception, located in secondary sensory cortices, and neural circuits for cognition, located in associative cortices.
The team's research plan includes three innovative components: 1. The transfer of social networks studies from sociology and psychology, into the field of neurobiology; 2. Unique opportunity to scan semi-free ranging animals with rich social knowledge; 3. Investigation of how this skill is generated at a multisensory level, including through social touch and olfaction, which have never been mapped yet with fMRI in monkeys, and which knowledge in humans is also limited.

RECOMMENDATIONS TO THE TEAM

The committee would recommend considering 'sub-questions' to the main objectives of the proposed research program, which could be carried out more easily, taking into account Rhesus monkey worldwide shortage and the difficulty to conduct in 3 years PhD for students which will be involved in this program.
To the opinion of experts to the feasibility of this program is at high risk. However, the PI is an expert in this field of research. The funding is appropriate.

Team 24: Sensory Spinal Signalling

Name of the supervisor: Claire WYART

THEMES OF THE TEAM

One axis of the work of this team is to investigate the molecular, cellular and network mechanisms underlying the signalling pathways originating from the cerebrospinal fluid and bridging the nervous system to other systems/organs. The second axis will dissect the molecular organisation and functions of motor circuits and neurosecretory epithelia in the brainstem, an overlooked area of the vertebrate brain.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1. Maintain or increase the level of productivity. If and when the zebrafish findings are validated in mice and humans, then there will be more opportunities to engage non-academic activities.

Actions taken: The level of productivity of the team has increased steadily. As requested, the team performed investigations in rodents by establishing collaboration with M. Lehtinen, Harvard Medical School supported by the HFSP coordinated by Wyart. Similarly, translational research for identifying genes mutated in idiopathic scoliosis patients is currently led by L.
Marie-Hardy, C. Wyart, H. Pascal-Mousselard.

2. Fully integrate the research programmes of the three principal PIs (Wyart, Bardet & Moussellard).

The composition of the team has changed since the previous evaluation with Dr. Bardet who moved to Sorbonne-University and Cantaut-Belarif obtained a CNRS researcher position in the team the same year. The research proposals of the 4 PIs became highly collaborative now.

3. The main focus must be on validating the zebrafish findings in mammals, but there should also be a 'plan B' should this not materialise.

Actions taken: the HFSP project coordinated by Wyart enabled extension of the body of work in mice by teaming up with Prof. Lehtinen. To build a preventive plan B, Dr. Wyart elaborated a completely novel project on motor control focused on the brainstem (ERC Consolidator CoG for Wyart 2022–2026 supporting 2 postdocs, 1 grad student).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	1
Senior lecturers and equivalent	1
Researchers and equivalent	3
Research support staff	8
Sub-total for permanent research staff	13
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	
Post-docs	12
PhD	7
Sub-total non-permanent staff in active employment	19
Total staff	32

EVALUATION

Overall assessment of the team

The team is internationally well recognised for its work with original publications in leading journals.
The team discovered an axial sensory system in the spinal cord that contributes to sensing spinal curvature, and adjust locomotion, posture and morphogenesis. This system is composed of interoceptive neurons contacting the cerebrospinal fluid (CSF), referred to as 'CSF-cNs', which are coupled to an acellular polymer bathing in the CSF and called the Reissner fiber (Reissner, 1860). Between 2017-22, the work of this team led to twenty original publications in generalists and specialised journals, both in basic science and clinics. Thus, the scientific production is outstanding to remarkable. Its scientific appeal and capacity to raise funding are exceptional. Both team leaders successfully obtained competitive grants to secure their research projects with the European ERC as well as ANR grants. The team has attracted and trained number of M.Sc., PhD students and postdocs who successfully evolved in medical, academic and non-academic fields including Cantaut-Belarif who was awarded in 2020 a CNRS permanent researcher position.
To address the physiopathology of this CSF-cNS, the team used optogenetic, physiological and imaging approaches to highlight the roles and connectivity of CSF-cNs within the spinal cord and in the brainstem in the control of the modulation of speed and posture during active locomotion.
The overall assessment of the team is outstanding to outstanding to remarkable.

Strengths and possibilities linked to the context

Creativity, Productivity, Effectiveness: fundamental approaches are amenable fast in zebrafish and can be inspired by human genetics in order to establish the role of genes involved in disease (Adolescent Idiopathic Scoliosis) & zebrafish models of spine deformities can help screen molecules.
The feasibility of the program proposed is high and the funding is appropriate for the proposed research program.
Between 2017-22, the work of this team led to twenty original publications in generalists and specialised journals, both in basic science (5 eLife, 3 Current Biology, 2 Nature Communications, 1 Cell Report, 4 Scientific Reports, 1 Glia, 1 Plos Comput. Biol., 1 Plos Biol, 1 Neuron, 1 Mol Neurodeg) and clinics (42 publications).
Both team leaders successfully obtained competitive grants to secure their research projects: Wyart with the European ERC-CoG (2022–2026), and in France, the Fondation pour la Recherche Médicale (FRM, 2020–2023), and the Fondation Bettencourt-Schueller (FBS, 2020–2024) as well as three ANR grants as partner (2022–2026); Cantaut-Belarif was awarded a French Young Researcher grant from the ANR as a coordinator (2022–2025).
The team has attracted and trained more than 29 M.Sc., seventeen PhD students and twelve postdocs who successfully evolved in medical, academic and non-academic fields including Cantaut-Belarif who was awarded in 2020 a CNRS permanent researcher position and her first independent ANR grant.
Wyart directs multiple schools and currently coordinates the European Training Network ZENITH enrolling fifteen grad students in Europe (https://zenith-etn.com, 2019–2024).

Weaknesses and risks linked to the context

Weaknesses: Translation to humans will require building models in mammals over the five years to come – this step needs additional staff.
Attracting talented and promising early career scientists from France and abroad is difficult to evaluate for this new team.

Analysis of the team's trajectory

The team project has four aims:

Aim 1. Decipher sensorimotor integration in brainstem and spinal cord *in vivo*.
The team is planning to explore the molecular properties, functional organisation and impacts of exteroceptive and interoceptive sensory systems on motor functions and morphogenesis. They will investigate mechano- and chemo-sensory ciliated sensory cells and how they modulate motor circuits in brainstem and spinal cord for forward locomotion and steering (project supported by the ERC Consolidator project of Wyart for 2022–2026).

Aim 2. Investigate how neuromodulation impacts motor control and morphogenesis including relationships with the noradrenergic, serotoninergic and dopaminergic signalling pathways.

Aim 3. Probe how the CSF sensory & secretory niche operates recently, they discovered that during infection in the central nervous system, cerebrospinal fluid contacting neurons detect metabolites of pathogenic bacteria invading the cerebrospinal fluid, and release neuropeptides and cytokines to enhance

innate immunity (Prendergast *et al., Current Biology 2023*). Thus, they are planning to investigate inter-organ communication between the nervous system and the notochord involved in the adjustment of body shape (YCB).

Aim 4. Investigate CSF-mediated signalling throughout the body from fish to mammals.

The cavities of the nervous system provide a long-range communication pathway throughout life to adjust morphogenesis of the body. The work in zebrafish revealed an interplay between the Reissner fiber, cerebrospinal fluid-contacting neurons and the floor plate in order for the developing axis to be aligned. Here, the team is planning to identify whether cerebrospinal fluid contacting neurons and whether the SCO can be found in human samples including the identification of mutations in families with Idiopathic Scoliosis.

The project is reasonably risked. The staffing and finances are in line with the proposed project.

RECOMMENDATIONS TO THE TEAM

This is an excellent team with a well-focused research program established using innovative research methodology, under an international leadership of the PI in this innovative research topic. It would be important for the future to implement their research by using other species than zebra fish, including rodents. Validation of CSF-neurons and their functions in non-human primates (ICM collaborations) would be an issue.

The feasibility of the program proposed is high and the funding is appropriate to the proposed research program.

Team 25: **Gene Therapy**

Name of the supervisor: Nathalie CARTIER

THEMES OF THE TEAM

The main goal of the team is to advance gene therapy strategies to develop new disease-modifying therapies for neurological incurable disorders, including both neurodegenerative disorders and infantile leukodystrophies. The team's work is finalised to explore new therapeutic targets as well as practical applications to improve preclinical efficacy and tolerability in rodents and non-human primates.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendation of the previous report solicited to tighten the collaboration with clinicians on the target diseases to accelerate the clinical exploitation of the team's finding both in terms of access to the patient's registry, high-quality clinical information, neuropathological examinations, and patients' material. On this line, the team has successfully established new collaborations with clinical experts on two main target diseases (Drs. Salachas and Bruneteau for ALS and Dr. Deiva for mucopolyssacharidosis). However, no more specifics are provided about the general frame of these collaborations and their specific synergic initiatives.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Staff categories	Workforce
Professors and equivalent	1
Senior lecturers and equivalent	
Researchers and equivalent	2
Research support staff	6
Sub-total for permanent research staff	9
Non-permanent teacher researchers and researchers	
Non-permanent research support staff	1
Post-docs	2
PhD	5
Sub-total non-permanent staff in active employment	8
Total staff	17

EVALUATION

Overall assessment of the team

The team is highly recognised at International level for gene therapy applications in neurological diseases. This is a key topic for the ICM mission to translate preclinical work in clinical opportunities. Prof. Carter has received important accolades recognising her pioneering work on driving gene therapy clinical trials. In the reporting period, the publication track record is excellent considering the relative small size of the team with two articles of high-impact (Sailor et al., 2022; Aigrot et al., 2022) and a number of publications in specialistic journals. The group is very active in research valorisation with 6 patents, three of which are already licensed to industrial partners in the present contract. They have been very successful in obtaining competitive grants funding and sponsored research contracts by the industrial sector. The Team size is relatively small for the many activities carried out altogether with few post-doc researchers (2–3) and a lack of a sufficient international environment.

Strengths and possibilities linked to the context

The team has performed pioneering work in gene therapy and has a strong international visibility. The development of new gene therapy strategies and their validation in small and large animals is a fundamental aspect of the ICM mission. Additionally, ICM offers a very supporting environment for this kind of translational research thanks to the strong clinical facilities and medical infrastructure. Moreover, ICM provides the best conditions to valorise this research for developing alliance with the private sector and develop academic start-ups.

Weaknesses and risks linked to the context

During the reporting period, the Team has finalised preclinical work by validating new therapeutic targets and gene therapy applications. However, new clinical trials have not yet been finalised by the Team under the direct ICM supervision. Additional efforts should be implemented to facilitate the clinical translation of these gene therapy applications, leveraging on the strategic clinical infrastructure developed by ICM. Ideally, ICM would act as the first proponent of stage 1/2 clinical trials originated by its internal research before negotiating with companies the subsequent clinical implementation of the new gene therapy product.
For the time being, Prof. Cartier has now moved to the private sector and will develop the clinical translation of her work in the company.

Analysis of the team's trajectory

The loss of this Team for the next contract without the acquisition of other groups with similar expertise and interest poses the high risk to ICM to lose its leading position on this strategic scientific field. It is recommended that ICM activate appropriate policies and initiative to fill this gap with new recruitment that will ensure to maintain a leadership position in the clinical translation of gene therapy applications for neurological diseases.

RECOMMENDATIONS TO THE TEAM

The team has not been confirmed for the next mandate.

CONDUCT OF THE INTERVIEWS

Dates

Start: 11 octobre 2023 à 8 h 30

End : 13 octobre 2023 à 18 h

Interview conducted : on-site

INTERVIEW SCHEDULE

October 10th 2023

	Arrival of the committee and evening dinner (only committee members and Hcéres Scientific advisor)
7 p.m.	Dinner in town for the committee

October 11th 2023

7:30 a.m.	Pick up at the hotel for the transfer at ICM
8 a.m.-8:30	Welcome coffee
8:30 a.m.-8:50 a.m.	Closed session with the committee (room 1,005)

Whole committee (room 01–02)

9 a.m.-9:10 a.m.	Presentation of the committee
9:10 a.m.-10:10	Presentation of the unit by the present director Alexis BRICE (ex-post) and the future director: Stephanie DEBETTE (project/trajectory). Plenary session (40′ presentation + 20 ′ discussion with the committee)
10:10-10:30	Coffee break

Sub-committee #1 (room 04)

10:30-11:05	Presentation of scientific program of the team # BACCI: Title: Cellular physiology of cortical microcircuits. (20′ presentation + 15 ′ questions)
11:05-11:40	Presentation of scientific program of Team # REBOLA: Title: Cellular mechanisms of sensory processing. (20′ presentation + 15 ′ questions)
11:40-12:15	Presentation of scientific program of the team # NAIT-OUMESMAR/ZUJOVIC – future team # MOCHEL/ZUJOVIC: Title: Myelin plasticity and regeneration. (20′ presentation + 15 ′ questions)

Sub-committee #2 (room 01–02)

10:30-11:05	Presentation of scientific program of the team # DAUNIZEAU/PESSIGLIONE/BOURET – future team # DAUNIZEAU/PESSIGLIONE: Title: Motivation, Brain & Behaviour. (20′ presentation + 15 ′ questions)
11:05-11:40	Presentation of scientific program of the team # FOSSATI/SCHMIDT: Title: Control-Interoception-attention. (20′ presentation + 15 ′ questions)
11:40-12:15	Presentation of scientific program of the team # BOILLEE: Title: ALS causes and mechanisms of motor neuron degeneration. (20′ presentation + 15 ′ questions)
12:15-12:50	Debriefing of the whole committee (room 1,005)
12:50-2 p.m.	Lunch (open to all PIs)

Sub-committee #1 (room 04)

2 p.m.-2:35 p.m.	Presentation of scientific program of the team # DURR/STEVANIN – future team # DURR/HUMBERT: Title: Basic to translational neurogenetics (20′ presentation + 15 ′ questions)
2:35 p.m.-3:10 p.m.	Presentation of scientific program of the team # DE JUAN SANZ: Title: Molecular physiology of presynaptic function. (20′ presentation + 15 ′ questions)
3:10 p.m.-3:45 p.m.	Private meeting of the sub-committee# 1 (report preparation)

Sub-committee #2 (room 01–02)

2 p.m.-2:35 p.m.	Presentation of scientific program of the team # LEVY – future team # LEVY/VOLLE. Title: Frontal functions and pathology. (20′ presentation + 15 ′ questions)
2:35 p.m.-3:10 p.m.	Presentation of scientific program of the team # COHEN/BARTOLOMEO/NACCACHE – future team # BARTOLOMEO/NACCACHE/SITT: Title: Physiological investigation of clinically normal and impaired cognition. (20′ presentation + 15 ′ questions)
3:10 p.m.-3:45 p.m.	Presentation of scientific program of the team # CORTI/CORVOL: Title: Molecular pathophysiology of Parkinson's disease. (20′ presentation + 15 ′ questions)
3:45 p.m.-4 p.m.	Coffee break
4 p.m. – 4:20 p.m.	Presentation of scientific program of the team # BURGUIÈRE: Title: Neurophysiology of Repetitive Behaviours. (10′ presentation – ex-post – + 10 ′ questions)
2 p.m.-4 p.m.	Visit of the ICM platforms by Mr. Orestis FAKLARIS, the Hcéres representative of supporting personnel
4:20 p.m.-7 p.m.	Private meeting of the whole committee room 1,005
7 p.m.	Transfer from ICM to your hotel
8 p.m.	Dinner in town for the committee

October 12th 2023

7:45 a.m.	Pick up at the hotel for the transfer at ICM
8:30 a.m.-9:00	Welcome coffee

Sub-committee #1 (room 04)

9:00-9:35	Presentation of scientific program of the team # CHARPIER/CHAVEZ/NAVARRO – future team # NAVARRO/PONCER: Title: Dynamics of networks and cellular excitability. (20′ presentation + 15 ′ questions)
9:35 a.m.-10:10	Presentation of scientific program of the team # HASSAN: Title: Brain development. (20 ′ presentation + 15 ′ questions)

Sub-committee# 2 (room 01–02)

9:00-9:35	Presentation of scientific program of the team # RENIER: Title: Laboratory of structural plasticity. (20′ presentation + 15 ′ questions)
9:35-10:10	

Presentation of scientific program of the team # WYART: Title: Sensory spinal signalling. (20′ presentation + 15 ′ questions)

10:10-10:30 Coffee break

Sub-committee # 1 (room 04)

10:30-10:50 Presentation of scientific program of the team # HUILLARD/SANSON: Title: Genetics and development of brain tumours. (10′ presentation – ex-post – + 10 ′ questions)

10:50-11:10 Presentation of scientific program of the team # HUILLARD/PEYRE: Title: Neuro-vascular interfaces in Brain Tumours and Vascular Malformations. (10′ presentation – Project/Trajectory – + 10 ′ questions)

11:10-11:30 Presentation of scientific program of the team # TOUAT-BIELLE: Title: Brain tumour heterogeneity, immunity and therapy. (10′ presentation – Project/Trajectory – + 10 ′ questions)

Sub-committee #2 (room 01–02)

10:30-11:05 Presentation of scientific program of the team e # HAIK/POTIER: Title: Alzheimer's disease and prion diseases. (20′ presentation + 15 ′ questions)

11:05-11:40 Presentation of scientific program of the team # LAU/KARACHI: Title: Experimental neurosurgery. (20′ presentation + 15 ′ questions)

11:40-12:50 Private meeting of the whole committee room 1,005

12:50-2 p.m. Lunch

Sub-committee #1 (room 04)

2 p.m. – 2:35 p.m. Presentation of scientific program of the team # BAULAC/LEGUERN – future team # BAULAC: Title: Genetics and physiopathology of epilepsies. (20′ presentation + 15 ′ questions

2:35 p.m.-3:10 p.m. Presentation of scientific program of the team # STANKOFF/LUBETZKI – future team # STANKOFF: Title: Repair in multiple sclerosis: from biology to clinical translation. (20′ presentation + 15 ′ questions)

Sub-committee #2 (room 01–02)

2 p.m.-2:20 p.m. Presentation of scientific program of the team # VIDAILHET/LEHERICY: Title: Normal and abnormal motor control: movement disorders and experimental therapeutics. (10′ presentation – ex-post – + 10 ′ questions)

2:20 p.m.-2:40 p.m. Presentation of scientific program of the team # FLAMAND-ROZE/POUGET: Title: From movement to cognition: insight from motor disorders. (10′ presentation (10′ presentation – Project/Trajectory – + 10 ′ questions)

2:40 p.m.-3 p.m. Presentation of scientific program of the team # ARNUF/OUDIETTE: Title: Sleep, dreams, and cognition. (10′ presentation – Project/Trajectory – + 10 ′ questions)

3 p.m.-3:20 p.m. Presentation of scientific program of the team # SLIWA: Title: Neurophysiology of social cognition. (10′ presentation (Project/Trajectory + 10 ′ questions)

3:20 p.m.-3:40 p.m. Coffee break

2 p.m.-4 p.m.	Visit of the ICM platforms by Mr. Orestis FAKLARIS, the Hcéres representative of supporting personnel
3:40 p.m.-7 p.m.	Private meeting of the whole committee (report preparation)
7 p.m.	Transfer from ICM to the hotel
8 p.m.	Dinner in town for the committee

October 13th 2023

7:30 a.m.	Pick up at the hotel for the transfer at ICM
8 a.m.-8:30	Welcome coffee

Sub-committee #2 (room 01–02)

8:30 a.m.-9:05 a.m.	Presentation of scientific program of the team # COLLIOT/DURRLEMAN: Title: Algorithms, models and methods for images and signals of the human brain. (20′ presentation + 15 ′ questions)
9:05 a.m.-9:25 a.m.	Presentation of scientific program of the team # DE VICO FALLANI: Title: Systems neuroengineering to model interface brain networks. (10′ presentation – Project/Trajectory – + 10 ′ questions)
9:25 a.m.-9:40 a.m.	Coffee break

Whole committee (room 01–02)

9:40 a.m.-10:10	Meeting with engineers, technicians and administrative personnel in French
10:10-10:40	Meeting with students and post-docs
10:40-11:10	Meeting with scientists, no team leader or lab directors
11:10-11:40	Meeting with team leaders
11:40-12:00	Coffee break

Whole committee (room 04)

12:00-12:30	Meeting with the present and the future directors of the centre
12:30-1 p.m.	Discussion with the representative of the funding bodies
1 p.m.-2 p.m.	Lunch
2 p.m.-4 p.m.	Private meeting of the whole committee (report preparation, closed-door) room 04
4 p.m.	End of the visit

PARTICULAR POINT TO BE MENTIONED

GENERAL OBSERVATIONS OF THE SUPERVISORS

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle et démarche participative
Sorbonne Université

à

Monsieur Eric Saint-Aman
Directeur du Département d'évaluation de la recherche
HCERES – Haut conseil de l'évaluation de la recherche et de l'enseignement supérieur
2 rue Albert Einstein
75013 Paris

Paris, le 21 février 2024

Objet : Rapport d'évaluation ICM - Institut du cerveau et de la moelle épinière

Cher Collègue,

Sorbonne Université vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « ICM ».

Sorbonne Université n'a aucune observation de portée générale à formuler sur le rapport d'évaluation transmis.

Je vous prie d'agréer, Cher Collègue, l'expression de mes cordiales salutations

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle
et démarche participative

École Pratique
des Hautes Études | PSL

Le Président

Cabinet de la Présidence
Tél : +33 (0)1 53 63 61 86
Presidence.ephe@ephe.psl.eu
Site : www.ephe.fr

À Paris, le 2 février 2024

Réf. : MH / JB / AC / 2024 - 025

Objet : Observations à portée générale - DER-PUR250024398 - ICM - Institut du cerveau et de la moelle épinière

L'EPHE remercie le comité de visite du HCERES pour le rapport sur cette unité et n'a pas de remarque particulière à formuler.

Michel HOCHMANN
Président de l'École Pratique des Hautes Études

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