Research evaluation

# EVALUATION REPORT OF THE UNIT

Maladies neurodéveloppementales et neurovasculaires – NeuroDiderot

## UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité,
Institut national de la santé et de la recherche médicale, Inserm
Commissariat à l'énergie atomique et aux énergies alternatives, CEA

**EVALUATION CAMPAIGN 2023-2024**
GROUP D

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High Council for evaluation of research and hignter education

In the name of the expert committee[1] :

Vania Broccoli, Chairman of the committee

For the Hcéres[2] :

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the French Research Code, evaluation reports drawn up by expert committees are signed by the chairmen of these committees and countersigned by the Chairman of Hcéres.

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, Milan, Italie |
| **Experts:** | Ms Valérie Castellani, Université de Lyon (Inserm CSS4 representative)<br>Mr Julien Cau, CNRS - Centre national de la recherche scientifique, Montpellier (PAR representative)<br>Mr Bogdan Draganski, Centre hospitalier universitaire Vaudois, Lausanne, Suisse<br>Ms Frédérique Liegeois, University College London, Royaume-Uni<br>Mr David Loane, Trinity College Dublin, Ireland<br>Mr Tsvetan Serchov, CNRS - Centre national de la recherche scientifique, Strasbourg |

## HCÉRES REPRESENTATIVE

Mr Giovanni Stevanin, Inserm – Institut national de la Santé et de la recherche médicale, Bordeaux

## REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Ms Christine Guillard, Faculté de Santé, Université ParisCité
Mr Matthieu Resche-Rigon, Faculté de Santé, Université ParisCité
Mr Philippe Ruszniewski, UFR de Médecine, Université ParisCité
Ms Sabine Sarnaki, UFR de Médecine, Université ParisCité
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Mr Etienne Hirsch, ITMO, Inserm
Ms Sophie D'Ambrosio, CEA
Ms Claire De Marguerye, Délégation Inserm Paris IDF Centre Nord

# CHARACTERISATION OF THE UNIT

- Name: Maladies neurodéveloppementales et neurovasculaires
- Acronym: NeuroDiderot
- Label and number: UMR1141
- Composition of the executive team: Pierre Gressens

## SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE5 Neurosciences et troubles du système nerveux

## THEMES OF THE UNIT

The research unit Maladies neurodéveloppementales et neurovasculaires (NeuroDiderot) is aiming to establish an integrated environment between basic and translational research mainly focused on neurodevelopmental and neurovascular diseases. NeuroDiderot is a centre where INSERM and University researchers are integrated with clinicians of the AP-HP Hospitals Robert Debré and Lariboisière to create a cross-disciplinary and multiscale research environment. The main research topics of NeuroDiderot revolve around neurodevelopmental biology, neurogenetics, neuroimaging, neuroimmunology and neurovascular interaction with the ultimate goal to decipher pathological mechanisms that can unlock new opportunities for better clinical diagnosis and curative treatments. Team 1 (NeuroKines) is interested to better understand how alterations of immunity, inflammation and mitochondrial metabolism contribute to the genesis and progression of neurological lesions during brain development. Through mechanistic studies in preclinical models, human samples and patient cohorts, the team seeks to identify new predictive diagnostic biomarkers and therapeutic targets. Team 2 (NeuroDev) is dissecting the genetic defects of inherited microcephaly forms, leukodystrophies, mitochondrial diseases and neuroendocrine diseases. Using a combination of cellular and animal models, the team explores the pathophysiological mechanisms triggered by disease mutations and their impact on the pathological outcome. Team 3 (NeoPhen) investigates the physiological role of sleep during the neurodevelopment, as well as the pathophysiological mechanisms of sleeping and breathing in mouse models of pediatric diseases and at the clinical level in patients with ventilatory and sleep disorders. Moreover, the team explores the interplay between sleep alterations and pathological neurodevelopment or mood disorders. Team 4 (GenMedStroke) aims to improve the molecular diagnosis of hereditary cerebrovascular disorders by identifying the causative genes and better understanding their pathophysiology by combining studies in patients and mouse models. Moreover, the team exploits neuroimaging, phenotypic assessments and preclinical models to develop biomarkers for disease stratification and therapeutic strategies to delay or slow down the disease progression. Team 5 (InDev) is focused on advancing MRI/EEG imaging in infants and adolescents to identify association and causalities between early anatomical alterations and neurodevelopmental diseases or prematurity. Moreover, anatomical changes are correlated with late clinical states, cognitive performance, neuroplasticity, language and epilepsy prognosis.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The first Inserm-University Unit at the Hospital Robert Debré was created in 1995 as a single team and progressively expanded in number of personnel and teams reaching the current size of five teams with about 160 people (including 18 full-time researchers, 33 researchers with teaching or clinical duties and 56 permanent technical staff). Since its creation, NeurodiDerot has been directed by the same director who has maintained his functions throughout the 2009, 2014 and 2019 reporting periods. NeuroDiderot is located at the AP-HP Hospital Robert Debré and occupies a total of 2000 m2 into the Bingen building. However, the Unit will double this space when the new building which will host the Child Brain Institute will become operative. Part of the clinicians are also located in the neurological departments of the Robert Debré and Lariboisière hospitals as well as at NeuroSpin at Saclay, part of a world-class academic research campus.

## RESEARCH ENVIRONMENT OF THE UNIT

The primary location of the NeuroDiderot unit is situated in an environment highly conducive to advanced clinical research (Hôpital Robert Debré).
The unit's teams are actively participating to FHU federations. Specifically, they take on leading roles in FHU federations such as I2-D2 (focused on the Early Identification of Individual Trajectories in Neurodevelopmental Disorders with teams 1, 2, 3, and 5) and NeuroVasc (for team 4), while assuming a more secondary role in FHU Apollo (specifically for team 3).
The involvement of the unit's personnel in notable scientific entities, such as the Groupement de Recherche (GDR) and Groupement d'Intérêt Scienctifique (GIS) Autisme, strengthens the unit's and its teams' capacity to establish collaborative initiatives, facilitating the progress of their research.
Teams also have the opportunity to leverage the benefits of the local DIM C-Brains program (Ile-de-France

region), which includes support for scientific networks, a PhD program, and specific financing for scientific equipment and scientific events.
Through the Université Paris Cité, the unit gains advantages from the supplementary grants provided by the University under the IDEX Scheme (PIA 1).
Finally, the unit holds a role in Neuratris, one of the national research infrastructure (RI) in biology and health. This strategic involvement proves advantageous for the unit, providing avenues to surmount scientific and technical challenges inherent to its translational research. It also facilitates the exploration and development of inventive translational research methodologies.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 26 |
| Maîtres de conférences et assimilés | 7 |
| Directeurs de recherche et assimilés | 8 |
| Chargés de recherche et assimilés | 10 |
| Personnels d'appui à la recherche | 56 |
| **Sous-total personnels permanents en activité** | **107** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 16 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 7 |
| Doctorants | 32 |
| **Sous-total personnels non permanents en activité** | **56** |
| **Total personnels** | **163** |

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

| Nom de l'employeur | EC | C | PAR |
|---|---|---|---|
| AUTRES | 32 | 8 | 16 |
| INSERM | 0 | 8 | 30 |
| UNIVERSITÉ PARIS-CITÉ | 1 | 0 | 7 |
| CEA | 0 | 2 | 1 |
| **Total personnels** | **33** | **18** | **54** |

# GLOBAL ASSESSMENT

The mission of NeuroDiderot is to gain a better mechanistic understanding of neurodevelopment and the clinical manifestations and underlying pathological mechanisms of neurodevelopmental diseases, in order to develop novel translational approaches for better diagnosis, prognosis and cure of the patients. This ambitious objective requires a strong partnership between basic and clinical research, high integration between multi-scale approaches from the bench to the bedside and vice versa. This is a rather unique and strategic topic in the French scientific landscape with strong clinical significance. NeuroDiderot is renowned for its studies on preterm/perinatal brain lesions with pioneering experimental models, and clinical research in neuroimaging, epilepsy, neurovascular and neurogenetic diseases as well as sleep disorders. Among the unit's major discoveries are the demonstration that mitochondria function at a temperature of 50 °C, the neuroprotective role of neuroglobin, the impact of sleep quality on physiological and pathological neurodevelopment, and the identification of 6 genetic causes of leukoencephalopathy and intracranial fetal hemorrhage.
The unit is organised in five research teams supported by three technical platforms (open to external users) and 4 facilities (mostly for internal needs). The Unit is embedded in the Robert Debré hospital campus and affiliated to the University Paris Cité, Inserm and CEA, creating a rich and multidisciplinary ecosystem to foster research innovation, clinical development and knowledge dissemination.

**In the reporting period, the overall scientific output of Neurodiderot was found very good to excellent by the expert committee.** The unit generated a **good scientific production** in quantitative terms (730 original articles, 27% as leading authors), but the number of original research articles in high-profile international journals remained definitively low as leading authors (n=9 in Nature Comm, Cell Rep, Curr Biol, Lancet journals and PlosBiol) and fair in collaboration (n=30). Neurodiderot has a strong technical support and high number of dedicated full-term personnel (56 Research supporting personnel and 51 permanent researcher positions). This exceptional workforce provides a huge support to the technical platforms/facilities and to the scientific projects developed within the teams. However, over the past years the unit expanded its research interests in many different directions and diseases to the point to excessively fragment its critical mass. This likely reflects the outcome of the scientific production more oriented to descriptive and clinical studies (67% of the production) rather than to transformative research on disease mechanisms and technological development (33%). As such, the unit needs to reinforce its basic and preclinical research components with the recruitment of external accomplished scientists. This opportunity will be given within the framework of the future Child Brain Institute where the unit will converge gaining new infrastructure, resources and space. On this perspective, Neurodiderot should consider reinforcing preclinical research on those clinical disciplines and pathologies that constitute the backbone of its mandate and where the possibility of groundbreaking findings is the highest. This initiative will promote a better match between fundamental and clinical research in order to consolidate more coherent and integrated research axes covering all the space from basic to translational research up to clinical studies. Similarly, Neurodiderot has suffered from the lack of recruiting talented young scientists outside the unit and the low number of postdoctoral research fellows (n=7). Increasing the attractiveness of the unit to recruit more accomplished and expert scientists should be considered a priority for the unit in the next period. However, a major downside of the unit which threats its overall position in the field is the poor state of the building and its infrastructure where the unit is hosted. The building and its premises require urgent renovation to properly host the personnel and research instrumentation in a decent and rewarding environment. The unit was able to finance its research in a consistent way with>20M€ collected through competitive calls at the national (ANR, PHRC, coordinating them in 1/3) or international (H2020, Eranet Neuron, NIH, 50% as coordinators) levels. Finally, the unit actively participated in science diffusion through didactic publications or interviews (~100 in various journals or in TV media), interaction with patient associations and its portfolio of pharmaceutical or startup partners (Servier, UCB, etc). The unit also submitted fourteen patents, 4 of which being licensed and one at the origin of the creation of a startup.

# DETAILED EVALUATION OF THE UNIT

## A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

In the previous report of the HCÉRES, the recommendations on scientific production and activities were related to:

1) increasing high-profile publications;
2) training more students;
3) organising more symposia and meetings.

The first objective has not been reached during the present contract period. The unit has an extensive scientific production which, however, lacks sufficient studies in high-quality journals (only 10 out of 730 publications) with a transformative impact. Additional strategies are urgently needed to assure a timely and effective increase of the scientific quality and the number of mechanistic studies for the next contract. The unit has shown factual progress on the other two remaining aspects raised in the previous report with the recruitment of a substantial higher number of doctorate students and increasing involvement in the organisation of national and international scientific meetings.

Next, regarding the unit's organisation and life, the previous report recommended to:

4) reinforce the interactions and sharing of expertise and resource;
5) improve the relative balance between the teams in terms of size and impact;
6) stimulate the scientific animation also involving external collaborative centres (NeuroSpin, Necker);
7) attract more young scientists and full-time researcher (CR) positions;
8) to increase the flexibility of the technical platforms and their quality control standards.

The unit remains with very uneven teams in terms of size, impact and resources, leaving unresolved critical aspects on the points raised in the previous report. In addition, the unit has not been yet successful in attracting good candidates for new CR positions. This aspect requires additional and urgent efforts by the directorship to assure the timely recruitment of new young talents. Nonetheless the unit succeeded to obtain a tenured position for the engineer responsible of the Robert Debré imaging platform and four permanent zootechnicians for the animal house.

Finally, recommendations on scientific strategy and projects were focused on:

1) reinforcing the synergies between the different teams with a clear plan defining the scientific priorities;
2) evaluating the focus of the current projects that spread in a wide variety of diseases and conditions.

Neither of the aspects seem to have been fully addressed by the unit with a dedicated and clear implementation plan.

# B – EVALUATION AREAS

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

### Assessment on the scientific objectives of the unit

The quality of the scientific objectives of the unit was evaluated as very good by the scientific committee. NeuroDiderot focuses on translational research in neurodevelopmental disorders and diseases of small brain vessels which is of strategic relevance in France for both diagnosis and also therapeutic development since part of a national presidential plan. The general significance of the objectives is evident as exemplified by research on topics of obvious importance such as the mechanisms underlying developmental and neurovascular disorders with the ultimate goal to unlock new opportunities for better clinical diagnosis and curative treatments. NeuroDiderot is well positioned to perform a competitive scientific programme on these thematic lines. **The committee found the scientific position of the unit in line with its mission, but emphasised the heterogeneity of the topics treated by the unit, sometimes also falling outside the neurodevelopment and the neurovascular fields**.

### Assessment on the unit's resources

**The resources were found excellent.** NeuroDiderot operates at the interface between basic research and its transfer to the clinic, and brings together Inserm, APHP, Université Paris Cité, CNRS, and CEA researchers with expertise neurodevelopment, neurovascular disorders, epilepsy, neurogenetics, neuroimaging, pharmacology, and bioinformatics with academic clinicians from several departments of Robert Debré and Lariboisiere Hospitals. Several researchers and clinicians of the unit are internationally reputed experts in their fields as demonstrated by the publication record, distinctions (10 prices, such as Fondation de France/Jean Valade) and invitations to conferences. In addition, the ability to obtain funding (144 contracts for a total amount of>20M€) is remarkable, often following responses to competitive calls for tender at national level (31 ANR including 10 as carrier, 4 PHRC as carrier), at the level of private foundations (3 FDF, 2 AFM, 1 FRM as carrier) and at international level (Erare as partner, 2 Euranet Neuron as carrier, 1 FP7 as partner and one H2020 as carrier, 1 NIH as partner).

### Assessment on the functioning of the unit

NeuroDiderot decision-making process is centred on its director. A management board that gathers the team leaders meets three to four times per year. Few other responsibilities are distributed to the unit laboratory council which consist of representative of researchers (PIs), engineers/technicians and doctoral/postdoctoral students. Decisions are taken with a consensus, if not by majority vote. Safety measures, gender equity and data protections were considered well managed. **Overall, this functioning was then thought as excellent even if some researchers and support staff felt uncomfortable with the work conditions.**

### *1/ The unit has set itself relevant scientific objectives.*

#### Strengths and possibilities linked to the context

The general relevance of the scientific objectives of the unit are evident since, neurodevelopmental and neurovascular disorders and stroke are part of a major plan launched by the French President and a health care priority of the Ministry of Health and of the Ministry of Research.
Reducing the burden (by facilitating early diagnosis and finding new therapies) of these disorders will reduce their economic impact, which is a major goal of the unit research.
NeuroDiderot strategy is to combine preclinical, translational, and clinical research to get a better understanding of the cellular and molecular mechanisms involved, to design new therapeutic strategies, and

to test them in human patients. The unit possesses the required multiple competences to perform the experiments and clinical trials, analyse, disseminate and valorise data.

It is located at Robert Debre hospital specialised for neurodevelopmental disorders and at very short distance from Lariboisere hospital which is the reference centre for neurovascular disorders.

### Weaknesses and risks linked to the context

Considering the context described context the unit has the unique opportunity to further develop even more ambitious scientific projects. This might be facilitated for example by the significant reduction of the number of investigated pathological conditions focusing on a precise selection with higher relevance and hot scientific potential.

## *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

NeuroDiderot is supported by excellent financial resources and scientific infrastructure and equipment. Over the 2017–2022 period the institute has obtained total budget>20M€, from a total of 144 grants from competitive calls including in France, 31 ANR (10 as coordinator) and 4 PHRC as coordinator, and at the international level, they obtained two Eranet Neuron and one H2020 as coordinator, one E-Rare and one NIH grant, as partners. Moreover, the unit runs three recognised core facilities: 1) Platform for in vivo phenotyping (NemoClinics); 2) Neuroinflammation platform and 3) Human brain organoid platform (HumBO).

### Weaknesses and risks linked to the context

With regard to foreseeable problems for the future, the animal facility is described to be close to full capacity only considering the current animal breeding, housing and experimentations. Doubling the capacity is anticipated after the construction of the new IHU building which, however, will be in some years from now. Given the changing context of animal experimentation, the unit would benefit from revising this objective and also try to be fully up to date with the current French and EU regulations for animal breeding and care.
The NemoClinics platform will benefit from further advertising, so that its potential and technical services are fully utilised by the scientific community and companies.
Most importantly, there is a pressing need for the refurbishment of the lab and office space in order to improve the attractiveness of the unit.

## *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

An occupational health and safety group composed of three unit members is organised in order to maximise the security and to perform regular training sessions about the risks at work for the unit. Moreover, an equality and professional parity group has been set up at Inserm, with two IR acting as local contacts.
The NeuroDiderot is one of the founders of CATIBioMed and thus has access to a remote protected backup servers with high capacity.
The gender balance is excellent with more than 60% of female staff (permanent staff: 62% females vs 38% males and Post-Docs/PhDs: 66% females vs 34% females) and most teams are led or co-led by women. In addition, the unit has recruited eleven new permanent members (7 supporting staff and 4 PIs/researchers/clinicians) but the majority of the PIs are experienced/senior researchers with long years of research experience in the middle and/or end of their scientific careers.

### Weaknesses and risks linked to the context

Considering the physical conditions of the unit premises, the unit employs suitable, though likely suboptimal (such as having meals in 'corridor' areas in the middle of rodent smelling), hygiene and safety measures. The unit lacks a centralised data security policy, leading each team to develop its own procedures. The CATIBioMed is now being charged to teams who are abandoning this storage system because it is so expensive. This is a real problem for data storage in the unit. Additionally, without a dedicated IT specialist, there is a lack of assurance regarding the security of workstations and data.

Regarding human resources management, while there is overall adherence to procedures established by supervisory authorities, certain aspects, particularly in ITA/BIATSS job descriptions, may not be consistently implemented. Of note, ten permanent members have left the unit (4 emeritus DR, 2 PUPH and 4 supporting staff) during the current period, fully compensated, however, by eleven new members.

The allocation of the support staff within the unit is uneven, leading to tensions among the personnel. Several support staff members say that they feel uncomfortable within the unit, according to anonymous questionnaires and confidential discussions. The reasons for this discomfort vary from the quality of life in an old building to difficulties with specific interpersonal interactions, including insufficient support or discussions with their supervisor. The existing policy contributes to an evident fragmentation between the teams which is perceived as 'important' and distressing, negatively impacting the overall cohesion of the unit. Additionally, this approach hinders the unit's ability to effectively support promising projects by allocating support staff were needed.

## EVALUATION AREA 2: ATTRACTIVENESS

### Assessment on the attractiveness of the unit

The Unit is a world leader in neurodevelopmental disorders and neurovascular diseases and has a very good attractiveness as a scientific research centre. It has a visible scientific production in terms of papers (>730 articles), leadership in terms of conference participation and organisation, national outreach and engagement on neurodevelopment disorders, which is a research priority in France. The very good attractiveness of the unit is demonstrated by number of excellent Prizes awarded to Faculty (10), the amount of funding secured at international agencies such as NIH or H2020, and some truly excellent core equipment and technologies. However, the research labs and general facilities for all staff in the unit are poor, and the buildings require urgent renovation to properly host the personnel and research instrumentation in a decent and rewarding environment. The poor building quality is a significant issue for the unit and is evident by the lack of recruitment of young talent scientists from outside the unit despite a fair number of postdoctoral research fellows (n=16) in the recent phase. The buildings issue needs to be addressed immediately because it is threatening the overall attractiveness of NeuroDiderot at the national and international level.

*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

The scientific structure includes several platforms and core facilities. The unit has been successful in financing high-level equipment/infrastructure needed for its research, including animal core facilities, and various imaging and molecular biology devices. The unit has quite unique platforms for in vivo phenotyping of developing rodents, neuroinflammation and human brain organoid platforms that are open to external users. Funding from international agencies such as H2020 and Eranet-neuron, as coordinator, or FP7 and NIH as partner has ensured visibility of the unit.

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

While the unit already has a limited number of international students and researchers, conditions of the unit's premises pose a significant obstacle to recruiting staff, ranging from PhD students to prospective team leaders. Waiting until the end of the next mandate to solve this problem risks undermining the unit's scientific momentum, which could be hard to recover from. The unit has recently made three platforms accessible to the public. This initiative should be continued to enhance their visibility and integration into the national ecosystem. Their organisation also has to evolve to achieve this (establishment of steering committees, clarification of access conditions, and allocation of dedicated staff). Despite being strong assets for the unit due to various reasons, it appears that the unit is not leveraging these three platforms to enhance its partnership with the private sector and attract new group leaders.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

### Assessment on the scientific production of the unit

Over the 2017–2022 period, NeuroDiderot generated around 730 original articles and 211 other publications including reviews, editorials and book chapters. Nearly 27% of these are signed in a leading position (first, last, corresponding authors). The overall scientific production is preponderant in the areas of clinical research (67%) and the remaining in fundamental studies (33%). Original research studies are published in internationally reputed journals, but few in top-notch generalist journals (2 in Brain, 2 in Nat. Comm., 1 in Sci. Transl. Med., 1 in Cell Rep., 2 in Ann. Neurol.). Around 12% of publications involved at least two teams in the unit and the relative output is coherent with the size of the teams and their number of tenure scientists and engineers. **Given these factual outputs the overall production of the unit was estimated as very good to excellent in the reporting period.**

*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

The most relevant scientific production of NeuroDiderot is clustered on the scientific domains this unit is involved in, in particular, perinatal brain damage, pediatric neuroimaging, epilepsy, neurovascular diseases and sleep disorders. The unit has a longstanding interest in perinatal brain lesions and their impact on brain health along neurodevelopment and adulthood. Original animal models of these pathologies were devised by this unit in the past that have provided a competitive asset to explore disease aspects and mechanisms underlying these complications and their outcome. The unit has a strong clinical component interested in epilepsy, sleep disorders, leukodystrophies, microcephaly and neurovascular diseases that contribute to give high visibility to the unit in these specific clinical domains.

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

In quantitative terms, the scientific production of the unit is strongly unbalanced in favour of the clinical research 67%). This outcome reflects the uneven size between clinical and basic research with a lack of sufficient personnel fully dedicated and expert on fundamental and mechanistic studies.
Despite the scientific production being consistent, the number of publications in high-visible journals is low as already noted during the evaluation of the previous mandate (see recommendations to the Unit). This outcome reflects the major focus on descriptive studies and some objective hurdles to keep the pace with methodological innovations and multilevel data integration. It is notable some important lack of integration between fundamental and clinical research. In fact, some of the major topics in the clinical area, such as epilepsy and autism-spectrum disorders, are not equally represented in fundamental studies. Conversely, basic research on infective diseases, stroke and mood disorders in adulthood is less strategic in this unit. Finally, the number of shared papers between the teams is not high (12%), suggesting that scientific integration and shared interests is not yet consolidated. Many papers have been published in open access journals, although much less of them are posted on HAL or other public archives.

## EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

**Contribution to Society during the period was very good to excellent**. Scientist at NeuroDiderot has been active in science communication with the general public through diverse outreach activities (interviews, newspapers, etc.; ~100 events). This is in part facilitated by the obvious societal relevance of some of the core research topics related to neurodevelopmental disorders. The unit has also been active in facilitating the diffusion of the knowledge the institute has accumulated to clinicians, as well as establishing some collaborations with private partners such as Mithra, Curadev, Servier, et UCB. The unit also submitted fourteen patents, 4 under licensing and one at the origin of a startup.

*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

The unit has established some collaborative contracts with private partners such as Mithra, Curadev, Servier and UCB, which also include three contracts for shared (CIFRE/industry) PhDs (1 with ResMed and 2 with IRBA Biomedical Res Inst of the army). Moreover, a total number of fourteen patents have been filed and a company is being created based on one of these patents. Several members of the unit participate on a regular basis to events for dissemination of generated knowledge to the general public as well as associations of patients and their parents (AFM-Téléthon, RET syndrome Europe Parent Organization). Several examples include topics of infectious disease, like AIDS and COVID-19, sleep disorders, light and mood and genetics of neuromuscular disorders. Some members have already performed in that area, including at the National Academy of Medicine during sessions dedicated to school children and adolescents. All teams have published in the general media (Le Monde, etc.) and taken part in national TV programmes (BFMTV, etc.) for a total number or>90 contributions.

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

These strategies need to be strengthened in the future, with most PIs rather than a subset taking part in most public engagement activities. Encouraging postdocs and PhD students to interact with the wider public could also increase the visibility of NeuroDiderot.

# ANALYSIS OF THE UNIT'S TRAJECTORY

The unit was relatively isolated geographically in the past. However, its trajectory has to be considered in light of the coming creation of the Child Brain Institute IHU InovAND, financed by the French government in addition to founding secured by the Director of the NeuroDiderot unit. This provides a wonderful opportunity for the teams to develop their projects within a highly supportive framework, benefiting from novel infrastructures, and access to technological platforms and resources, which should translate into a gain in international visibility. It will also provide means to attract novel teams and enrich the current unit with novel colleagues and expertise.
In the mean time for the new contract, the unit keeps a dual goal to develop both basic and translational research activities. These objectives comply with the recommendations of Inserm. The vision of the unit remains to address multiple disease contexts rather than making a focus on some, with ultimate translational goals. A continuum of three major objectives has been defined, which will address at multi-scale levels from molecular to humans:

i. the physiopathology of neurodevelopmental disorders to generate basic knowledge
ii. the design of novel therapeutic approaches from this basic knowledge using state-of-the-art screening approaches,
iii. and the transfer of these innovations to patients through an ambitious plan of clinical trials. The unit implemented a human brain organoid technical platform that complements the current models and will be likely instrumental to an improved understanding of the mechanisms of action underlying the diseases of interest as well as personalised medicine studies.

Some changes have been made in the organisation and composition of the teams, with team 1 being split into two teams and team 4 no longer being part of the Institute. The restructuring of team 1 appears to be appropriate, given the size it has been reached over the past contract and the wide range of issues being studied by its different groups.
The unit globally progressed in the scientific production, with also some publications in visible journals, keeping the goal to further improve this trajectory. This should help the NeuroDiderot teams to strengthen their international recognition and also increase their attractiveness. A clear strategy for strategic recruitment of promising young scientists should facilitate reaching this goal and promote the successful turnover of the scientific personnel. Strengthening the collaborations with the national and international community working on brain development would also be of high benefit for the teams. Narrowing the topics to focus more on selected pathologies should be considered as well as a strategic choice to enrich the basic science studies while keeping the translational research at its highest level. This would also enhance the synergy between teams and reinforce the identity and spirit of the unit.
Communication to the large public, missions of outreach built on the longstanding close contacts established with patient associations is at the core of the valorisation activity of the unit. In this sense efforts toward patenting and contracts with the industry are rather underestimated. In terms of internal initiatives, efforts to integrate environment impact of the research, for instance through green lab actions are relatively modest. Social life for students and post-doc appears not particularly supported.

# RECOMMENDATIONS TO THE UNIT

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

During the site visit, the committee felt a good general spirit and atmosphere between the research personnel of the unit. However, different feedback was also received from some technical and researcher personnel that felt far less well integrated and gratified. Given these very opposite reactions, a specific psychical risk survey may be organised inside the unit with the supervising bodies and the human resources delegates.
During the reporting period, NeuroDiderot had scarce success to attract young talents with competitive external funding (e.g. ATIP-Avenir awardees) or ensure the promotions of internal candidates to tenure positions (CR1 researchers, …). The advent of the new Child Brain Institute with the associated new building offers an unprecedented opportunity to arrange a structured recruitment with very competitive conditions. The committee recommends organising an international search for recruiting external research personnel to favour the integration of new talents, expertise and collaborations and promote a rich, international and multidisciplinary research community. NeuroDiderot should prioritise the recruitment of teams performing preclinical research in the fields, making its reputation on the clinical side (epilepsy and autism-spectrum disorders) to better match its preclinical and translational research and, ultimately, to further improve its international visibility in these specific fields. The recruitment of the external team leaders can be finalised with the direct involvement of the scientific advisory board to assure maximal transparency and efficacy.
The committee recommends that the unit finds a solution to establish a reliable service for IT and infrastructure/building management. It also recommends that the unit implements a unique strategy with common operative guidelines for backing up data generated by its teams on internal platforms and remote backups.

## Recommendations regarding the Evaluation Area 2: Attractiveness

A major weakness of this unit is represented by the current conditions where it operates. In fact, the committee inspected its working space, realising that the current state of the building, its premises and furniture are in serious decline. The building is very old and poorly maintained creating unpleasant conditions for the daily work of the personnel (rodent-smelly odours in the corridors even in zones where some personal eats, waste liquids in common spaces, lack of recreative rooms…). It is surprising that the directorship and the stakeholders have not yet taken action to renovate the building. The conditions are so serious that might create multiple safety issues in the near future. As such, the committee urges responsible and swift decisions on this delicate matter.

The committee recommends that NeuroDiderot scientists are more proactive in applying to European grants, including ERC grants, Doctoral Networks and Marie Skłodowska-Curie postdoctoral fellowships, in order to attract high-potential research fellows from abroad who might be potential candidates to INSERM/University tenure positions.

## Recommendations regarding Evaluation Area 3: Scientific Production

The committee recommends that NeuroDiderot increase the output of its fundamental research in terms of both scientific quality and quantity. The unit should aim to raise the impact of its original research by publishing more studies in highly visible journals. This goal requires synergic actions in multiple directions as, for instance, strengthening approaches of data integration and validation of omics studies, facilitating the integration of clinical and basic research on molecular pathophysiological processes and setting functional biological readouts with high informative value. The unit has progressively expanded its interest in too many different diseases with the downside to excessively dilute and fragment its efforts for a better comprehension of their molecular mechanisms. Thus, an additional effort should be undertaken to concentrate the work on pathologies where the potential and the probability of transformative findings are the highest and corresponding more to the mission of the unit. It is also recommended to increase the percentage of publications deposited in open archives (the report says only 'a small number of papers have been put in HAL.') in order to achieve a coverage as complete as possible.

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

Some senior scientists of NeuroDiderot are active in science dissemination to the general public by interviews to newspapers, presence in social media and public debates. Some of them are members of scientific boards of patient's associations and participate regularly to their meetings. These initiatives need to be strengthened in

the future, with most PIs rather than a subset taking part in public engagement activities. Encouraging postdocs and PhD students to interact with the wider public could also increase the visibility of NeuroDiderot. Moreover, it is missing a proactive and structured plan of the unit on this aspect. For instance, the committee recommends the organisation of series of events dedicated to the general public on neurodevelopmental disorders and related topics with shared presentations between clinicians and researchers. The unit is invited to enhance its interaction with the private sector to generate more synergies and financial resources by establishing contracts of research, service activities and other forms of partnership. For this goal, it is of primary relevance to increase the high-quality standards and related official certifications of the technical platforms in order to become more attractive to private companies.

# TEAM-BY-TEAM OR THEME ASSESSMENT

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|---|---|
| **Team 1:** | Team 1 – 'NeuroKines', Glial homeostasis, neuroinflammation, and neuroprotection |
| Name of the supervisor: | Pierre Gressens & Pascal Dournaud (next contract: Pierre Gressens & Juliette Van Steenwinckel) |

## THEMES OF THE TEAM

NeuroKines (Team 1) is made up of 6 groups, whose overarching goal is to investigate the cellular mechanisms and role of immunity and metabolism in brain injury caused by intrinsic and extrinsic factors during critical neurodevelopmental periods. There is a significant emphasis on injury-induced changes in glial homeostasis (particularly the role of microglia), blood brain barrier dysfunction, metabolic dysfunction and mitochondriopathies, with a specific focus on developing neuroprotective strategies for the injured pediatric brain. Where possible, the NeuroKines groups incorporate clinical studies that inform the preclinical model development, support diagnostic/prognostic biomarker development and inform novel treatment strategies, so there is a strong bidirectional translational research emphasis in the unit.

# CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Prior recommendation to improve the profile of publications in higher impact journals has been partially adopted. In this cycle the NeuroKines team published research articles in renowned journals, including Glia, Brain, Annals of Neurology, Brain Behaviour & Immunity, Cell Death & Disease, and eLife. For the next phase, the team should aim for publication of research findings in top-tier scientific and medical journals (Cell, Science, Nature suite of journals).

In the last cycle questions arose about how well the zebrafish platform has grown into the unit's research activities and how it contributes to new clinically relevant models of neurodevelopmental brain injury. Some work of the team has been effectively produced using zebrafish.

There was a request to integrate the mitochondrial studies into NeuroKines projects, and this has been fully implemented. Immunometabolism and mitochondrial mechanisms are now incorporated into many projects in the NeuroKines portfolio, and this novel area of research will be a central focus of new Team 2 (3I Brain) and its future activities.

# WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 5 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 4 |
| Chargés de recherche et assimilés | 5 |
| Personnels d'appui à la recherche | 19 |
| **Sous-total personnels permanents en activité** | **34** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 5 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 1 |
| Doctorants | 8 |
| **Sous-total personnels non permanents en activité** | **14** |
| **Total personnels** | **48** |

# EVALUATION

## Overall assessment of the team

Team 1 overall assessment profile is excellent. Their particular strengths lie in their ability to attract major funding, lead international projects/collaborations, and the visibility of the team in the neurodevelopment brain injury field. Among their main achievements can be cited the development of a multidimensional integrated platform to study neuroinflammation, the measure of the functioning temperature of mitochondria, the identification of oxytocin receptor agonists to alleviate epileptic seizures in zebrafish models, and the characterisation of novel 3DNA nanoparticles to target microglia. There is a need to focus the preclinical research on more mechanistic studies and avoid descriptive analyses. In addition, there is a need to elevate these clinical relevant projects to the next level using advanced approaches that will lead to publication in top scientific journals.

## Strengths and possibilities linked to the context

The programmed reorganisation of the NeuroKines team with the independence of the 3I Brain team in the coming cycle (new team 2,) is fully justified given the large size of Team 1 and the need to better focus more on its key and principal scientific questions. The NeuroKines team has a strong focus on neuroinflammation and particularly the role of microglial subsets/phenotypes in encephalopathy of prematurity (EoP) using competitive experimental systems including mouse models and advanced human brain organoids and hiPSC-derived microglia. These advanced approaches are novel and important for translational research in neurodevelopmental disorders, giving to the team a relevant international visibility. Combination of basic research and translational biomarker identification in EoP is a strong asset for transformative research in the field. The NeuroKines team has been very productive with 224 original articles in the 2017–2022 period, including 94 as leading authors in speciality journals with good reputation such as Annals of Neurology, Glia, PlosBiol or BBRC, as well as 99 reviews or book chapters, representing an excellent production. During this period the team also secured an excellent to outstanding amount of 4.03 million euros funding through national (ANR as coordinators), European and international (Horizon Europe, ERA-Net Neuron as coordinators) calls. Given the 163 invited lectures and seven prizes obtained (Christian Nezelof-Imagine Award, Fondation de France » Medical Award), the recognition is evident as shown also by the organisation of 36 meetings at the national (Journée scientifique et citoyenne sur les troubles du spectre autistique, Epilepsy day at Robert-Debré, Ligue Française contre l'épilepsie) or international (France-Lebanon meeting on autism, EURONEURO, Fetal and Neonatal Neurology, Global Symposium on Ketogenic Therapies for Neurological Disorders) levels. Interaction with society was excellent since team members submitted three patents (2 under licensing) and co-created a startup.

## Weaknesses and risks linked to the context

Some of the studies on early brain insults on long-term outcomes have remained descriptive lacking mechanistic interrogation. Mechanistic studies at the level of hypothalamic dysfunction and circuit disruptions, neuroimmune/metabolic signalling between the periphery and brain, and proof of concept pharmacological/genetic interventions were not fully exploited that would have increased the potential impact of these studies. The discontinuation of the zebrafish facility will stop abruptly interesting studies focused on new models of neurodevelopmental disorders and mechanistic studies on infantile epilepsy and microglia ontogenesis. The link between neurodevelopmental injury and obesity is a significant clinical issue, but the animal models used to investigate underlying pathophysiological mechanisms and identify potential treatment strategies were not optimal.

## Analysis of the team's trajectory

The team's trajectory and research aim for the next period is focused on neuroinflammatory pathways and the role of microglia in EoP and fetal alcohol syndrome in order to develop novel treatment strategies (microglial targeting nanoparticles and MSC therapies). Although zebrafish is a very informative model for neurodevelopment disorders, the facility and zebrafish group will move to another unit for the next mandate which is unfortunate. This will abruptly halt interesting studies focused on new models of neurodevelopmental disorders and mechanistic studies of infantile epilepsy and microglial ontogeny. As such, the team will maintain its focus on rodent models and translational research. Advanced technologies will be used in preclinical studies, and the inclusion of human iPSC models of microglia and brain organoids is innovative and important for clinical translation. There are strong partnerships and collaborations described with other teams such as Team 2 and

Team 3. The microglial focused neurotherapeutic strategies are in the pipeline and have been described by the group in quality research articles in international journals (Brain, Ann. Neurol.). The flow cytometry biomarker approach to assess systemic inflammation and ROS in clinical populations holds some promise, but changes might be small and overweighted by the high genetic heterogeneity of these diseases. Additional translational approaches that bridge bench to bedside should be prioritised. The use of non-invasive neuroimaging to assess functional connectivity of neuronal activity during neurodevelopment is novel and has huge translational potential. There are good opportunities to develop this approach further using the preclinical models (e.g. in microglial depletion models) to examine how microglia contribute to neuronal network dysfunction and neurodevelopmental trajectories in EoP. The team has secured 3.3 Million Euros to support research projects, and there are applications under consideration at ANR, Horizon Europe and National charities to increase resources for Team 1 research projects providing solid bases for the future studies.

The complex role of microglia in sex-dependent circuit remodelling during development and its impact on neurobehavior should be more clearly defined and investigated. Sex differences in microglia function in neurodevelopment and following CNS insult should be carefully considered and experimental design needs to take into account neuroanatomical and circuit-level changes that occur during critical neurodevelopmental periods. Key questions include, are sex hormones going to be manipulated or will more advanced models be used to examine sex chromosome contributions (e.g. Four Core Genotypes and XY* models)? Mechanistic studies should be prioritised over purely descriptive studies on sex differences in microglial function in EoP. There are opportunities to incorporate spatial transcriptomics or imaging mass cytometry approaches to provide critical temporal and spatial insight into neuroimmune function and altered developmental trajectories due to EoP. In addition, peripheral immune cell infiltration dynamics following EoP and T cell-microglia interactions may provide novel neurotherapeutic targets for EoP and other neurodevelopmental disorders. For brain immuno-metabolic studies, non-invasive studies should be considered to ensure the metabolic phenotype in microglia is not altered due to tissue processing and/or cell isolation artefacts (Seahorse is not reliable ex vivo). FLIM and other non-invasive approaches may be helpful in this regard. Finally, meningeal immunity is not being considered despite this new frontier of neuroimmunology playing a major role in brain function, CNS injury and age-related neurodegenerative disease. Additional projects in this space should be considered.

## RECOMMENDATIONS TO THE TEAM

The team should strategically focus on mechanistic studies and leverage advanced techniques available to them to identify pathophysiological mechanisms and novel therapeutic targets.

The team should strive for the next level in publications in the coming cycle (Nature, Cell, Science journals). This will help with recruitment of talented postdocs and PhD students to the unit to maintain scientific progress in NeuroKines.

In order to have the authority to manage CR and DR researchers, the co-leader of the team (engineer) must pass the competition to become a researcher.

There are opportunities to incorporate spatial transcriptomics or imaging mass cytometry approaches to provide critical temporal and spatial insight into neuroimmune function and altered developmental trajectories due to EoP. Peripheral immune cell infiltration dynamics following EoP and T cell-microglia interactions should be investigated in detail, and may provide novel neurotherapeutic options for EoP and other neurodevelopmental disorders. For brain immunometabolic studies, non-invasive studies should be considered to ensure the metabolic phenotype in microglia is not altered due to tissue processing and/or cell isolation artefacts (Seahorse is not reliable ex vivo). FLIM and other non-invasive approaches may be helpful in this regard. Meningeal immunity is not being considered despite this new frontier of neuroimmunology playing a major role in brain function, CNS injury and age-related neurodegenerative disease. Additional projects in this space should be considered. The G2 project on early brain insults on long-term outcomes are descriptive and lack mechanistic interrogation. Others have demonstrated how neonatal/pediatric insults alter neurobehavior in adulthood and have implicated chronic neuroinflammatory responses. More mechanistic studies at the level of hypothalamic dysfunction and circuit disruptions, neuroimmune/metabolic signalling between the periphery and brain, and proof of concept pharmacological/genetic interventions are needed to increase the potential impact of this work package. The link between neurodevelopmental injury and obesity is a significant clinical issue, so the animal models should be harnessed to investigate underlying pathophysiological mechanisms and identify potential treatment strategies. The project described in G4 on neurodevelopmental epilepsy is highly significant and clinically relevant. However, there is a disconnection in mechanistic focus (i.e. NMDA receptors) between these studies with other major projects in NeuroKines that focus on neuroimmune and metabolic pathways in EoP, so greater alignment is needed.

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| **New Team 2:** | New Team 2 – '3I Brain' – Brain-immune system interactions in physiology, infection or inflammation |
| Name of the supervisor: | Mireille Laforge & Guislaine Carcelain |

## THEMES OF THE TEAM

Within the large field of neurodevelopmental disorders, the team focuses on the metabolism of cells composing the innate and adaptive immune system and its modifications in the context of maternal and neonate viral infection. The team develops projects with strong connection to the clinic with the objectives to gain scientific knowledge, to develop diagnostic/prognosis tools such as biomarkers for patients as well as novel treatments to normalise immune cell activity.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Not applicable since newly created team from previous Team 1.

## WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 1/1/2025

| **Catégories de personnel** | **Effectifs** |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 3 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 3 |
| Personnels d'appui à la recherche | 2 |
| **Sous-total personnels permanents en activité** | **10** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 1 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 7 |
| Doctorants | 0 |
| **Sous-total personnels non permanents en activité** | **9** |
| **Total personnels** | **19** |

## EVALUATION

### Overall assessment of the team

Not applicable since novel team

### Strengths and possibilities linked to the context

Not applicable

### Weaknesses and risks linked to the context

Not applicable

### Analysis of the team's trajectory

This is a newly created team that emerged from internal reorganisation of team 1The scientific plan holds promises, although very ambitious. Strength relies on excellent expertise and dynamism of the team leaders and already significant assembled workforces that will include eleven senior researchers (3 researchers, 5 with clinical

and teaching duties and 1 clinician) and two technical staff with permanent positions). The team will have to build international visibility in the field of neurodevelopmental disorders given its recent involvement on these topics and, therefore, the need to become a player in international consortia in the field.

The projects are based on a solid scientific background, which makes the proposed hypotheses very relevant. The central postulate is that metabolic and immune dysfunctions occurring early in life (prenatal/neonatal) could affect both innate and adaptive immune cell components, thereby not only affecting brain development and maturation, but also leading to persistent effects throughout life. This is an original approach to study the interplay between brain and immune cells. The quality of the project proposed to be developed is excellent. The team applies its dual expertise in immunology and infectiology to characterise immune cells and their metabolic properties in different contexts of pediatric brain alterations, ranging from neurodevelopmental disorders such as autistic syndrome, premature birth, and maternal viral infection to hyposerotonemia. Using multiple approaches, the proposed studies nicely combine analyses of immune cells from samples of well-established patient cohorts and from animal models. For many parts, the feasibility of the project is high.
The projects related to the context of childhood diseases are well integrated into the themes developed by the Institute, and the PI plans to work closely with several teams. The projects of the team will benefit from this environment and the close connection to the clinical department of the hosting hospital.
The team attractiveness is already very good to excellent, the PIs have assembled a solid workforce with several permanent scientists (n=3) and physicists (n=6) and a significant number of technical support staff (n=3 including 2 with permanent positions) and students (7 students and postdocs to start the project).
The team leaders have been active in their search for funding. They have already received>4 million euros for the first two years including from the ANRS and PHRC at the national academic level, from pharmaceuticals (Astremiha, Janseen) and from foundations (FRM, FRC), and more applications are underway at the national and European levels.

Although the general objectives are clear, the pathogenic contexts behind the studies are quite broad and may seem disconnected for some. There may have a risk of diluting efforts and delaying completion of the projects.
The team may also consider going beyond the characterisation of metabolic and immune cell changes in the different contexts of their study by strengthening the investigation of mechanisms of action in the preclinical models they suggested.
The outcome of the translational WP3 dedicated to therapeutic strategies to restore immune functions seems very ambitious and highly challenging.

## RECOMMENDATIONS TO THE TEAM

The committee recommends that the team focuses on a smaller number of pathological contexts to deepen understanding of how they affect brain maturation. A move toward investigating mechanisms of action would greatly increase the visibility of the team and the impact of its work. The committee recommends that the team works at establishing itself as leader in the field of immune cell metabolism and neurodevelopmental disorders, for example through participation of team members in international meetings. Up to now, the team leader has recognition in immunometabolism in the context of adult infectious diseases. To consolidate the team, it will also be important to keep as a goal the production of outstanding publications supporting the translational efforts and to attract more postdocs.

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| **Team 2 (Future Team 4):** | Team 2 – 'NeuroDev', Cellular dysfunctions in neurodevelopmental disorders (future Team 4) |
| Name of the supervisor: | Odile Boespflug-Tanguy & Nicolas de Roux (next contract: Vincent El Ghouzzi & Nicolas de Roux) |

## THEMES OF THE TEAM

Team 2's main objective is to characterise the genetic, cellular and molecular bases of neurodevelopmental (NDD) and neuroendocrine (NED) disorders such as microcephaly, leukodystrophies and mitochondrial dysfunction. The long-term translational aim is to develop novel therapeutic avenues to improve outcomes in children with these conditions. They have a cross-disciplinary angle combining experimental, computational and clinical approaches, with in vivo as well as in silico models to characterise pathophysiological mechanisms. They use both mice models of genetic alterations, and human-based models using patient-derived induced pluripotent stem cells (iPSC).

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Previous recommendations included adopting a high-risk approach for high impact findings, and increasing interactions with the non-academic world (charities, patient groups, policy, general public) as well as industry.
The team addressed innovation by launching the HumBO facility and a clinical trial platform. They have developed collaborations with pharmaceutical companies, including for clinical trials and drug screening: 7 patents have been filled and on scientists of the team has co-funded Akttyva Therapeutics (https://akttyva.com/ USA) in the field of therapeutic development assisted by AI. They have also developed links with 'patients associations' dedicated to rare disorders (AFM-Téléthon, Enfance-Microcéphalie, Connaître les Syndromes Cérébelleux), and published in general-impact recognised journals (Brain, Cell Report). They have also developed links with hospitals and other teams from the unit, and developed several translational projects with potential therapeutic avenues.
Another recommendation concerning increasing training was addressed by the training of ten PhD students and eight postdocs. This is encouraging but modest over five years considering the team size (15 staff members with HDR diploma).

## WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 13 |
| Maîtres de conférences et assimilés | 2 |
| Directeurs de recherche et assimilés | 2 |
| Chargés de recherche et assimilés | 2 |
| Personnels d'appui à la recherche | 8 |
| **Sous-total personnels permanents en activité** | **27** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 6 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 4 |
| Doctorants | 8 |
| **Sous-total personnels non permanents en activité** | **18** |
| **Total personnels** | **45** |

# EVALUATION

## Overall assessment of the team

The team's profile is overall very good to excellent, with particular strengths in their ability to attract funding, a large collaboration networks (24 teams, 50% at the international level), increased links with industry with 7 patent submissions, and some highly cited articles in neuroscience, genetics and clinical journals such as Am J Human Genetics, Cell Reports and Nature communications. The main scientific achievements of the team included the development of a novel facility dedicated to IPSC and organoids, the identification of Neuroglobin as a gene therapy for neurodegeneration and the identification of genes causing leukodystrophies.

## Strengths and possibilities linked to the context

The profile, resources and organisation of the team are excellent. The team benefits from 8 support staff for nineteen permanent staff members, which is an impressive ratio. They also have a state-of-the-art human brain organoid core facility (HumBO created in 2019) specialising in the development of forebrain organoids. Scientific objectives are well defined and address a gap in the field of rare genetic diseases, with state-of-the-art in-vivo and in-silico approaches.
The team's attractiveness is overall excellent, with good international and national visibility (5 prizes such as Best junior paper at CSBM 2022 and Interface-Inserm). Team members are invited to present at international and national conferences (15 during the period, and 7 meetings organised), and sit on relevant committees (e.g. WHO,). They also sit on editorial board of international journals for the field (e.g. Frontiers in neuroscience, Frontiers in drug discovery, Cells, Neuroendocrinology) and grant committees (ANR, telethon scientific council). For their work on microcephaly, the team collaborates internationally (USA, Japan, Switzerland). Team members coordinate national, European and international networks on leukodystrophies (e.g. Leukofrance, LeukoMaroc) demonstrating wide impact and leadership. The team also contributes to national initiatives dedicated to identifying the genetic causes of these conditions (Plan France Médecine Génomique PFMG, 2025). They hosted two international scientists and recruited two new researchers (one junior professor) during the period, with two additional staff members joining in the next period.
The grant income during the period 2017–2022 was about 5M€ from 36 grants (27 as leader or co-leaders), mainly from charities and foundations (around 1000 k€) and national (1,800 k€, including 5 ANR grants) as well as PIA-related (1245k€) initiatives. The international income was proportionately lower (577 k€ European, 110 k€ international); the team is part of European networks (Euro-Micro, principal investigator; MEPICephaly as co-investigators) and one FP7 project (co-investigator, RD-Connect).
The team's scientific production during the contract was excellent. They published 135 articles (91 as first/senior author), eighteen reviews, and three book chapters over five years. The quality was high, with articles in highly regarded international peer reviewed journals of wide readership (e.g. review in Neuron; invited commentary in Nat Comm; original articles in Brain; Cell Reports; Lancet Neurol; Am J Hum Gen; Sc Report) and more specialised journals (e.g. Eur J endocrinology; J Clin Endocrinol Metab; Neurology). Importantly, several were highly cited (e.g. 3 with>45 citations from 2018 and 2019) demonstrating high impact. PhD students (16 trained) and postdocs (9 hired) published as 1st authors in highly regarded international journals, showing a strong junior training culture in the team.
During the period, the team's contribution to society was very good to excellent. Team members have many partnerships with relevant charities (e.g., AFM-Téléthon, Enfance-Microcéphalie, Connaître les Syndromes Cérébelleux). They wrote several articles in national general press during the period (Sante magazine, Le Figaro, Journal des Femmes ; Epsiloon). Seven patents were filed, including 6 in partnership with a private company (e.g. Attykva therapeutics, USA) that is an emerging startup from the team. Of note, the team is involved in scientific and medical training (>600 hours/year).

## Weaknesses and risks linked to the context

Only one competitive funding from European or international funding bodies as principal investigator was obtained during the period evaluated (PHC Napata), and one as participant (Eranet). The publication rate corresponded to one original article per permanent staff per year, but it should be acknowledged that many PIs are not full-time researchers (4 versus 15 clinicians researchers). Most income and interaction with the wider public is carried out by a subset of the team members, mainly clinicians. The scientific topics are varied, ranging from microcephaly to puberty to mitochondria disorders.

## Analysis of the team's trajectory

Team 2 will become Team 4 and continue its scientific themes with additional staff members (1 DR and 2 CR, but lacking a very famous researcher at the international level moving to another institute) and technicians (2

IR and 1IE). They will study the role of autophagy in network development and maturation, determine the mode of action of neuroglobin in neuroprotection, develop an integrative work to identify novel targets from drug repurposing using in silico and omics approaches, and link early and late stages defects on cortical development to inherited microcephalies. The panel welcomed the addition of electrophysiology and AI expertise in the team to allow a better understanding of disease mechanisms and accelerate translation to the clinic. The four groups in this team have already secured funding for the next few years (>3M€ from ANR, FMR, AFM, ANSES, Horizon MSCA Doctoral training network, etc.), with an impressive portfolio of collaborations (Strasbourg, Limoges, Saclay but also Helsinki, Leuven, Rostock, Australia, USA) demonstrating feasibility.

## RECOMMENDATIONS TO THE TEAM

Given its existing international links, the team could apply to competitive international funding (e.g. European such as Horizon or ERC) to increase its grant income and develop the careers of external postdocs recruited. In the field of rare conditions, international collaboration is critical (including beyond Europe) so a more focused approach to grant application could be fruitful, targeting fewer conditions but with more in-depth multiscale projects. Although there has been progress in most areas at the team level, every team member should aim to be involved in income generation, PhD supervision, editorial roles, public engagement, and high impact publications during the next period, to reduce the imbalance between team members. This could be done through a more strategic approach and by providing support/training/mentorship for those who have less experience. It would be beneficial for junior scientists (PhDs and postdocs) to be given opportunities to interact with the wider society and associations, including via social media, YouTube videos, blogs, workshops, lay publications/newsletters, etc. as science communication is becoming more important to the training of scientists.

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| **Team 3:** | Team 3 – 'NeoPhen', New tools for physiological data processing in early neurodevelopmental disorders (Next contract: Team 3 – 'SleepCmd' – Sleep: control of breathing, mood and development) |
| Name of the supervisor: | Christophe Delclaux & Boris Matrot (next contract: Marie-Pia d'Ortho & Boris Matrot) |

## THEMES OF THE TEAM

The team conducts a combination of preclinical, translational and clinical research and investigates the physiology of sleep and its impact on neurodevelopment and the pathophysiological mechanisms of ventilatory and sleep disorders as well as the impact of sleep mood in mouse models and in patients (children and adults). The main research axes are:

1) Central control of breathing;
2) Mechanisms of sleep apnea;
3) Sleep and neurodevelopment;
4) Sleep and mood;
5) Development of new tools for preclinical and clinical research on above topics.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has considered and addressed the recommendations of the previous report very well.
Firstly, as suggested, the team has published several original articles in highly regarded journals in the field, including Am J Resp Crit Care Med., Eur Resp J (two), J Travel Med., Biol Psychiatry, Lancet Psychiatry, Mol Psychiatry etc. as first and/or last authors. Moreover, following the recommendations of the visiting committee, the team has developed new collaborations with the industry, including ATMOSR company for testing drugs in animal models of CCHS, as well as with Withings company resulting in a CIFRE PhD recruitment. Secondly, in an effort to tighten the links between clinical and preclinical research, the team has started a new translational project in depression and light therapy – from mouse models to physiological, neuroimaging, digital, and clinical markers. In addition, with the help of an expert in Central Congenital Hypoventilation Syndrome (CCHS) genetics, a project on gene therapy for CCHS has been developed. However, the team should further try to compensate with additional recruitments the misbalance of higher proportion of clinicians compared to full-time preclinical researchers.
Finally, the team also wisely considered and maintained the variety of different projects, as previously recommended, which has led to successful publication record of 160 original publications, 79 as first or/and last author.

## WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 4 |
| Maîtres de conférences et assimilés | 2 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 4 |
| **Sous-total personnels permanents en activité** | **11** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 0 |
| Doctorants | 5 |
| **Sous-total personnels non permanents en activité** | **8** |
| **Total personnels** | **19** |

# EVALUATION

## Overall assessment of the team

The overall assessment of the team is excellent to outstanding. It has an outstanding publication record of 210 original articles, including highly reputed original journals such as Am J Resp Crit Care Med., Eur Resp J, J Travel Med. The team has recruited one INSERM, one PUPH and two MCUPH during the reporting period and successfully included their research topics. NeoPhen has received 2.4 M€ from various funding sources. The team members are involved in the organisation and presenting in several international meetings, TV and radio interviews.

## Strengths and possibilities linked to the context

One of the major scientific achievements of the team is related to the ventilatory control and pathophysiology of sleep apnea areas using genetic mice models and the development of an original method to characterise apnea in neonatal mice. In parallel, team members also produced an original method to study ventilatory control loops of regulation in the human and characterise sleep apnea pathophysiology in children. Another field of expertise of the team is the multidisciplinary evaluation of digital connected medical devices and solutions led to collaborations with private industries and creation of Digital Medical Hub start up.
The team has attracted and retained talented researchers: the new research axis developed by the inclusion of a newly recruited team member on the links between sleep biomarkers and mood disorders and chronotherapeutics is very successful leading to more than 75 publications, while another researcher recently arrived from another unit brings scientific expertise in physiology of sleep and its effects on neurodevelopment, a topic fitting perfectly well in this unit. In addition, two junior researchers in the team obtained permanent positions at Université Paris Cité (MCU-PH) and two postdocs (France) & fourteen PhD students (including 2 CIFRE PhD, 9 from abroad such as Brazil, China or Netherlands) have been recruited by the team.
The team members, in particular two, have been very active on the international scene and co-organise national and international meetings (Congrès du Sommeil de la SFRMS, International Pediatric Sleep Association, European Sleep Research Society, European Psychiatric Association). At the national level, one investigator is co-director of the GDR CNRS sleep research group, while another is the Scientific Director of the Digital Medical Hub.
NeoPhen team responded to calls for basic, translational and applied research, and received funding (2.4 M€) from local funding, French patient associations and foundations, ANR and several other national investment programs and international foundations.
Several members were interviewed on French TV and radio, and one team member was consulted by the UK Parliament as an expert in the field of light therapy.

## Weaknesses and risks linked to the context

The team has only one Inserm researcher (one recently hired junior researcher acquired by mobility) and one DR Inserm emeritus. As such, the team experiences a strong imbalance between clinical and preclinical researchers. The current lack of European and international grants reduces the attractiveness of the team and the chances to recruitment more valuable postdocs.

One of the team leaders (an engineer) does not have a PhD and therefore an HDR diploma, which may reduce the team's ability to attract good students and postdocs.

## Analysis of the team's trajectory

This team will change its name to SleepCmd: Sleep, Control of breathing, Mood and Development thus building on the previous expertise/strengths on respiratory recordings and phenotypic evaluation, and in addition focus in the future on the successfully integrated research axes of the newly recruited members (sleep and mood and neurodevelopment). The main aims of the future team are, first, pathophysiology and consequences of sleep-related disorders; secondly, innovative methods for sleep-disorder exploration; thirdly, candidate biomarkers and treatments for sleep-related disorders, and finally impact of sleep on neurodevelopment (Sleep2develop project). Moreover, due to the future retirement of one of the team co-leaders, he will be replaced. Development of animal models integrating sleep, breathing disorders and mood could facilitate the further exploitation of the technological platform and strengthen links with clinical work inside and outside the team. The project on effects of light on mood (though on an exciting hot topic and bringing huge amount of funds) has the risk to shift the research focus of the team/unit away from the neurodevelopment and child disorders

focus, toward adult patients. Of note, members of team 3 are involved in 2 European grants, obtained since 2023 (EIT Health).

## RECOMMENDATIONS TO THE TEAM

The team should implement a strategy to attract promising young scientists to compensate for the imbalance between clinical and preclinical researchers (INSERM, CNRS). An effort should be made to hire more postdocs, including from abroad (2 from France hired during the last contract), even though funding from French agencies such as ANR does not allow funding postdoc salaries on the long-term, thus limiting the attractiveness of postdoc positions in France. The team has benefited in successfully incorporating and further developing the research projects of the new recruited members (*e.g.* sleep and mood, and sleep effect on neurodevelopment). However, the development of animal models integrating sleep, breathing disorders and mood might facilitate the usage of the unique technological platform (NemoClinic). They should also initiate collaborations with foreign laboratories and try to apply to international collaborative calls (ITNs, ERANET, bilateral ANR etc.). This would generate new opportunities to recruit postdocs and foreign basic science researchers. However, should this project continue its emergence, its belonging to a neurodevelopmental team may be revised.
Finally, PhD and HDR diploma must be obtained by all PIs in this team (particularly team leaders) in order to attract more students and ensure appropriate/optimal supervision inside the team.

| | |
|---|---|
| **Team 4:** | Team 4 – 'GenMedStroke', Genomic and personalised medicine in inherited neurovascular disorders |
| Name of the supervisor: | Elisabeth Tournier-Lasserve & Hugues Chabriat |

## THEMES OF THE TEAM

The themes of GenMedStroke are focused on the improvement of the etiological diagnosis of hereditary cerebrovascular disorders (CeVD) across the lifespan through causative gene identification. Through the combination of novel and established statistical analysis methods, the team studies the disease genetic architecture in CeVD patients and rodent models. In particular, this is combined with in-depth clinical phenotyping in CADASIL patients with NOTCH3 p.R1231C mutation.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendation to increase the team's visibility by organising scientific symposia was addressed by hosting three international symposia in 2021 and 2022, additionally to the maintained high level of participation in international grants (EJPRD as coordinator) and networks (Aviesan, ANR and Leducq transatlantic networks, as coordinator of partner for the latest). The recommendation to develop (digital) tools that would help clinicians' diagnostic accuracy was responded with the collaboration on several European guidelines (for cerebral small vessel disease and Moya-Moya syndrome) and authoring a book chapter on cerebral vascular malformations for the ITHACA ERN handbook. The recommendation to continue the close collaboration with a departing team member was followed with co-leadership on the RHU-TRTcSVD project and core partnership in the ANR project CADANOTCH. The recommendation to recruit an early career researcher with expertise in the pathophysiology experiments and animal models was only partially addressed by strengthening existing and new collaborations with experts in the domains of interest. The recommendation to reinforce the technical support for research on the Robert-Debré imaging platform was not followed yet.

## WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 3 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 8 |
| **Sous-total personnels permanents en activité** | **13** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 1 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 0 |
| Doctorants | 3 |
| **Sous-total personnels non permanents en activité** | **4** |
| **Total personnels** | **17** |

# EVALUATION

## Overall assessment of the team

The overall assessment of the team is excellent. The team is highly visible notably through its scientific leadership in a domain with high clinical/societal relevance, participation in international networks and invitations to research conferences. The PIs are board members of national and international bodies of research, funding and clinical excellence, two of the team's researchers are the 'laureats' of the 2019 Brain prize. The resources and attractiveness are estimated as excellent to outstanding, with ca. 4 Mio € research funding obtained during the evaluation period including RHU, ANR and NIH competitive grants and recruitment of 4 PhD candidates and three postdoctoral fellows. The scientific output is excellent – the main scientific results are published in specialised top 10–25% neuroscientific journals (116 original articles including 38 as leading team). The links with the society are excellent as evidenced by collaboration in several national and international guidelines, coordination of clinical trials in a rare disorder (CADASIL) and active participation in patients' associations. Major scientific output of the team includes the validation of biomarkers and tools for clinical evaluation (longitudinal variation of white mater changes at MRI of CADASIL patients, correlations between patient questionnaires and clinical scales), development of novel statistical method for disease genetic architecture study, and development of a mouse model of Moyomoya disease.

### Strengths and possibilities linked to the context

The team's topic on genomic and personalised medicine in inherited cerebrovascular disorders has a wide network of collaborations, which is its main asset. The team coordinates the CERVCO, the National Reference Genetic centre for rare hereditary Neurovascular disorders (www.cervco.fr), and of the FHU-NeuroVasc. The combination of expertise in clinical phenotyping, high-throughput genomic technologies and sophisticated statistical analysis brought by the three constituting groups ensures the coherence of research output with great potential for innovation in clinics. This is supported by unique genetic and phenotypic data in patients with CeVDs acquired over more than twenty years resulting in findings published in highly renowned neurological journals – Neurology, Brain, Annals of Neurology. Two of the PIs are at key administrative positions that allow maintaining the intertwining with the National Centre for rare neurovascular disorders CERVCO, the department of genetics NRGN at the St. Louis hospital and the Translational Neurovascular Centre at the Lariboisiere hospital. The strong involvement in coordinating prestigious national initiatives such as the FHU NeuroVasc is giving the team and the unit a high level of visibility. The strong direct interest in clinical evaluation and diagnosis but also in medical teaching also has to be noted.
Overall, these collaborations confirm the team's expertise and recognition in the field CeVD. The team's plan to pursue deciphering the genetic architecture of Moya-Moya disease and cerebral small vessel disease in humans and understanding the role of nitric oxide signalling in Moya-Moya angiopathy is highly commendable. Similarly, the achievements in the CADASIL domain – in both biomarkers research and coordinating randomised clinical trials have brought not only significant funding by the American Alzheimer's Association and the ANR CILCAD, but also underline the quality of research by the team members. Finally, these goals could not have been reached if there were no developments of new statistical approaches, which was the case in the GenMedStroke team.

### Weaknesses and risks linked to the context

The committee did not note significant weaknesses related to the research made on this team and encourages the team members to pursue their efficient balanced efforts on research, interaction with society and attractiveness/visibility.

### Analysis of the team's trajectory

Not Applicable since the team GenMedStroke will not be part of NeuroDiderot for the next funding/evaluation phase.

# RECOMMENDATIONS TO THE TEAM

The committee had no recommendations to provide to this team. For reasons that were not communicated to the evaluation panel, the team GenMedStroke will not be part of NeuroDiderot for the next funding/evaluation phase. The team has been successful in setting up the bench-to-bedside translational strategy on inherited cerebrovascular diseases. The team's trajectory goes upwards, but it seems logical that it does not fit into the future plans of the unit, dedicated to neurodevelopment and its disorders.

| | |
|---|---|
| **Team 5:** | Team 5 – 'InDEV', Imaging neurodevelopmental phenotypes |
| Name of the supervisor: | Lucie Hertz-Pannier & Jessica Dubois (next contract: Jessica Dubois & David Germanaud) |

## THEMES OF THE TEAM

Team 5 InDEVs focus follows the Unit's main line of research on neurodevelopmental disorders affecting cognition, language and sensorimotor function. The overarching topic is the characterisation of the anatomical and functional variability of brain development and its relationship with emerging brain functions. There is a special interest in longitudinal studies of the effects of prenatal alcohol exposure, prematurity, perinatal lesions and epilepsy on individuals' brain and behaviour. The methods used by the team are neuroimaging (mainly magnetic resonance imaging – MRI) and neurophysiology (high-density EEG) with a significant activity in methods development.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendation to attract early career researchers and visiting scientist was followed up with the recruitment of five senior postdocs mostly with competitive funding (foundation Bettencourt Schueller, mobility from Clermont-Ferrand University, ANR, Fondation de France) with contracts surpassing a short stay and allowing for full integration. There was no information about visiting scholars. The remark about the heterogeneity of team members in terms of scientific interests, background and skills that poses a potential threat of dispersion was addressed by giving examples about collaboration projects between NeuroSpin and Robert-Debré Hospital, which only partially covers the raised issue. The recommendation to install regular meetings was followed suit by installing bimonthly PI meetings, monthly team meetings and twice a month methods/journal club meetings under the supervision of an engineer. The evaluators' impression of dispersion over research topics was rebutted with arguments about a common topic centred on perinatal injury vs non-deterministic neurodevelopmental risk factors, common testing and analytical strategy going beyond the scope of a single PI. The recommendation to enforce the Robert-Debré Hospital neuroimaging activities by dedicated engineer time was not followed suit. The team has even defined an additional unmet need of a research assistant for implementation of research imaging protocols at the Robert-Debré Hospital.

## WORKFORCE OF THE TEAM: IN PHYSICAL PERSONS AT 31/12/2022

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 1 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 2 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 3 |
| **Sous-total personnels permanents en activité** | **8** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 2 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 2 |
| Doctorants | 9 |
| **Sous-total personnels non permanents en activité** | **13** |
| **Total personnels** | **21** |

# EVALUATION

## Overall assessment of the team

The overall performance assessment of the team is excellent to outstanding. It has established itself in the niche of paediatric imaging neuroscience with a strong expertise in behavioural assessment, MRI- and EEG-based analysis. The PIs are nationally and internationally established researchers with a substantial number of invited talks (n=118), organisation of research conferences (n=17), awarding of three prizes to PIs, and participation in research steering bodies. The team's research focuses on topics with public health relevance, such as prematurity and fetal alcohol spectrum disorder. The scientific objectives and novelty are evaluated as very good to excellent. The scientific output is very good to excellent (179 original articles with the majority published in the top 25% journals in the field, 36 as leader team). The resources and attractiveness are estimated as excellent to outstanding, with ca. 2 Mio € research funding obtained through 22 grants during the evaluation period. The links with the society are very good to excellent as evidenced by involvement in scientific education, participation in patient's associations and supervisory bodies of authority. This evaluation is also supported by proactive participation in scientific communication events for the general public. Thanks to all these resources, the team identified early markers of pre- and perinatal insults using MRI, developed machine-learning tools to predict prematurity outcome and neuroanatomical features to support the diagnosis of fetal alcohol consequences.

## Strengths and possibilities linked to the context

The team's main asset is the longstanding track record in paediatric imaging neuroscience. The methods implementation and development have achieved a level of sophistication where the researchers can address a large scope of neurobiological questions regarding the normal and pathological brain development including the concomitant functional/behavioural correlates.
There are promising possibilities thanks to the access to patients with pre-, peri- and postnatal brain injuries and unique cutting-edge equipment at NeuroSpin, funded projects and the collaboration with the teams dedicated to data acquisition at ultra-high field 7T machine (NSF/NIH/ANR HIPLAY7 and the ANR MOSAR projects), signal processing (CEA BAOBAB) and at low-field MRI (ANR VLMRI project). There is a new focus on functional ultrasound via the ANR CONEXUS project that carries a great innovation potential for non-invasive investigation of the brain. This extraordinary equipment portfolio motivates the ambitious study of in vivo MRI and post-mortem conventional histology correspondence. Any advances in this field carry an extremely high potential for innovation including benefits for both science, clinical decision-making and therapy.
Beyond this, the topics of memory (ANR HippoXia project), language and sensorimotor function in the context of prematurity, pre-, peri- and postnatal brain injuries, complemented by studies on dysgyria (multiple collaborations across France) and fetal alcohol spectrum disorders give sufficient space for translational activities with great clinical relevance.

## Weaknesses and risks linked to the context

The InDEV team's assets are at the same time a potential threat and risk; the plethora of projects with heavy reliance on equipment, data and expertise outside of NeuroDiderot is a point that requires the team's attention. Already the team's restructuring represents a challenge – how to integrate the new members from teams 1 and 2 and how to ensure the team's management with the new co-leader. Finally, the geographical dispersion remains a challenge that cannot be simply overcome with videoconferencing and the collaboration on several projects.

## Analysis of the team's trajectory

The next evaluation period is accompanied by a generational transition with two senior members leaving the team and a mid-career researcher seconding the management of the team. There are two additional researchers – a neonatology and a neuroanatomy specialist who will join the InDEV team. The InDEV team has been highly successful along all dimensions of the evaluation with an excellent overall score. There is a major restructuring at the PI level in the upcoming period, which represents not only a generational transition, but also a further enlargement in terms of scope and expertise.
InDEV is expanding – due to excellent resources it was able to recruit: nine PhD candidates and two postdocs (7 ANR grants, 2 national grants - IReSP, GIS Autisme et TND, one PIA index, 8 grants from private foundations and 6 institutional PhD grants - University, CEA). The large international collaborations (Netherlands, UK, Switzerland, Canada) and participation to clinical networks (FASD, inovAND) also has to be noted.

The evaluation period was marked by consolidation of the team's position as one of the national and international top units for paediatric imaging neuroscience. The next phase is the expansion, which has the potential for unprecedented success, however, with all the caveats related to dispersion of resources and limited research focus.
The organisation of future projects along four axes:(1) innovative imaging strategies; (2) biomarkers of developmental brain injuries; (3) investigation of developmental trajectories of brain functions, and (4) brain plasticity and therapeutic strategies) makes perfect sense, but the listed projects are far too many for such a small team.
Given that these are collaborative projects, it would be necessary to delineate the team's contribution and ensure that these are feasible and coherent with the overall research vision.
The imaging activities at the Robert Debré hospital are not well-defined and give the impression of a burden rather than an asset because of direct access to patients. If the team's strategy is also the translation in real-world clinic, the ramping up of these activities seems mandatory.

## RECOMMENDATIONS TO THE TEAM

Sharpening the focus of the team's research vision should be a priority. Although already funded, the scope of projects is beyond feasible.
There is additionally a need to enforce the translation between data acquired using high-end (NeuroSpin) and real world (Robert Debré hospital) equipment. The team could focus on establishing and validating quantitative MRI protocols that are MRI vendor independent.
Team leaders are advised to develop a viable strategy for swift publications of methods manuscripts in the specialised journals, and to target high-impact journals for the findings with transformative potential.
Given their high profile in a niche field, the team members should aim to obtain competitive high-profile European funding (ERC, Marie Curie, etc.).
The broad scope of projects organised along the four axes requires a viable strategy for know-how transfer to early-career researchers involved in the projects. One option is to create a system of rotation between the NeuroSpin and Robert Debré hospital early-career researchers to ensure the necessary skill acquisition focused on the collaborative projects. Another suggestion is to intensify the 'methods meetings' with a supervision of a specialist in the field of a particular topic, rather than to have always the same engineer (as currently proceeded).

# CONDUCT OF THE INTERVIEWS

## Date

Start: 05 février 2024 à 8 h 30

End : 05 février 2024 à 18 h 30

Interview conducted: on-site

## INTERVIEW SCHEDULE

Research Lab Visit program
Neurodevelopment and Neurovascular Disorders (NeuroDiderot)
Date of the visit: February 5th2024 (on site)
Present Lab director: Pierre Gressens

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HCÉRES Scientific advisor: Mr. Giovanni Stevanin

Research committee:
Mr. Vania Broccoli (Italy), Expert Panel HCÉRES (President)
Ms. Valérie Castellani (Lyon), CSS4 representative, Expert
Mr. Julien Cau (Montpellier), PAR representative, Expert
Mr. Bogdan Draganski (Lausanne), Expert Panel HCERES
Ms. Frédérique Liegeois (London), Expert Panel HCERES
Mr. David Loane (Dublin), Expert
Mr. Tsvetan Serchov (Strasbourg & Freiburg), Expert

Observers:
Mr. Etienne Hirsch, INSERM
Mr. Philippe Ruszniewski, UFR de Médecine, UPC
Ms. Sophie D'Ambrosio, CEA

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*February 5th*

| | |
|---|---|
| 8:30-8:50 | Welcome coffee (closed-door): Visiting committee with the HCÉRES advisor<br>Hôpital Robert Debré, 48 Blvd Serurier, 75019 Paris<br>Inserm meeting room, Bingen building, +6 |
| 8:50-9:00 | Presentation of the evaluation process to the unit by the HCÉRES advisor<br>Vilmer amphitheatre, main building, ground level |
| 9:00-9:45 | Presentation of the unit scientific outputs and strategy by the lab director<br>(25′ presentation + 20'discussion) |
| *9:45-10:15* | *Coffee break* |
| 10:15-11:45 | Presentation of the scientific program and research results by group leaders |

(20′ presentation + 20'discussion)
Team 1 – 'NeuroKines', Glial homeostasis, neuroinflammation, and neuroprotection
(Team leaders: Pierre Gressens & Pascal Dournaud)
*Future Team 1 – 'Neurokines' (Pierre Gressens & Juliette Van Steenwinckel)*
*Future Team 2 – '3I Brain' – Brain-immune system interactions in physiology, infection or inflammation (Mireille Laforge & Guislaine Carcelain)*

(15′ presentation + 15'discussion)
Team 2 – 'NeuroDev', Cellular dysfunctions in neurodevelopmental disorders
(Team leaders: Odile Boespflug-Tanguy & Nicolas de Roux)
*Future Team 4 – 'Neurodev',*
*Neurodevelopmental and neuroendocrinal disorders: molecular mechanisms and therapeutic strategies (Vincent El Ghouzzi & Nicolas de Roux)*

(10′ presentation + 10'discussion)
Team 4 – 'GenMedStroke', Genomic and personalised medicine in inherited neurovascular disorders (Team leaders: Elisabeth Tournier-Lasserve & Hugues Chabriat)

11:45-12:45 Quick visit of the unit

12:45 p.m.-1:30 p.m. Lunch and debriefing (closed-door with the committee and HCÉRES advisor)

1:30 p.m.-2:30 p.m. Presentation of the scientific programs and research results by group leaders

(15′ presentation + 15'discussion)
Team 3 – 'NeoPhen', New tools for physiological data processing in early neurodevelopmental disorders (Team leaders: Christophe Delclaux & Boris Matrot)
*Futur Team 3 – 'SleepCmd' – Sleep: control of breathing, mood and development (Christophe Delclaux & Boris Matrot)*

Team 5 – 'InDEV', Imaging neurodevelopmental phenotypes (Team leaders: Lucie Hertz-Pannier & Jessica Dubois)
*Futur Team 5 – 'INDEV' (Jessica Dubois & David Germanaud)*

Meetings with the various categories of staff
Vilmer amphitheatre, main building, ground level

2:30 p.m.-3 p.m. Discussion with engineers, technicians and administrative personnel (in French)
3 p.m.-3:30 p.m. Discussion with PhD students and postdocs

*3:30 p.m.-4 p.m.* *Coffee break* and debriefing (closed-door with the committee and HCÉRES advisor)

4 p.m.-4:30 p.m. Discussion with scientists (without team leaders)
4:30 p.m.-5 p.m. Discussion with future/new team leaders
5 p.m.-5:30 p.m. Discussion with the director/co-director (closed-door)
5:30 p.m.-6 p.m. Discussion with the representative of the managing bodies (closed-door) & local representatives
6 p.m.-7:30 p.m. Private meeting of the visiting committee (closed-door)
Salle André Muller, main building, +1
7:30 p.m. End of the visit

## PARTICULAR POINT TO BE MENTIONED

Confidential discussions and responses to questionnaires have shown that some technicians/engineers, but also researchers, are suffering from a lack of attention from their supervisors and a malaise impacting their scientific activities, with insufficient support from human resources. Relevant human resources have been informed.
In addition, it seems that a significant number of technicians/engineers do not have an annual interview with their manager to assess their annual activity and define their missions. This may be detrimental for their promotions and career development and relevant information will have to be transmitted by the PIs to all researchers.
Of note, no representative of the CNU 47-04 or 54.01 committees were able to join the panel of experts, unfortunately.

## GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

**Paris, le 17 mai 2024**

HCERES
2 rue Albert Einstein
75013 Paris

**Objet :** Rapport d'évaluation de l'unité **DER-PUR250024191** – **NeuroDiderot** – Maladies neurodéveloppementales et neurovasculaires

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **NeuroDiderot** – M**aladies neurodéveloppementales et neurovasculaires**.

Ce rapport a été lu avec attention par la direction de l'unité, de la part de laquelle vous trouverez les courriers joints, par le vice-doyen Recherche et le doyen de la Faculté de Santé d'UPCité, par la vice-présidente Recherche d'UPCité, et par moi-même. L'ensemble des acteurs d'UPCité remercie le comité pour son travail d'évaluation.

Le doyen de la Faculté de Santé et moi-même souhaitons souligner que l'unité de recherche NeuroDiderot est une UMR labellisée par l'université Paris Cité, l'INSERM et le CEA qui est adossée à l'hôpital Robert Debré. En son sein, est pratiquée une recherche translationnelle, qui va du fondamental à la clinique, sur les maladies neurodéveloppementales et neurovasculaires, avec pour objectif de déchiffrer leurs mécanismes physiopathologiques afin d'ouvrir la voie vers un meilleur diagnostic clinique et de nouveaux traitements curatifs. Pour le prochain quinquennat, cette unité restructure ses équipes, en total accord avec les tutelles, en vue de son intégration au sein de l'IHU InovAND nouvellement créé, ce qui représente une réelle opportunité scientifique.

Je vous vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

**Présidence**

**Référence**
Pr/DGDRIVE/2023

**Affaire suivie par**
Christine Debydeal - DGDRIVE

**Adresse**
85 boulevard St-Germain
75006 - Paris

www.u-paris.fr

Paris, le 02/05/24

To whom it may concern

**General observations on the HCERES evaluation report of the NeuroDiderot unit (UMR1141 - Neurodevelopmental and neurovascular disorders)**

**Unit - NeuroDiderot**

"In the reporting period, the overall scientific output of NeuroDiderot was found very good to excellent by the expert committee. The unit generated a good scientific production in quantitative terms (730 original articles, 27% as leading authors), but the number of original research articles in high-profile international journals remained definitively low".

We respectfully disagree with the last underlined statement. Neurodevelopmental disorders, although being somewhat fashionable for the media (at least for ASD), do not attract much attention from high-profile international journals in comparison with common neurodegenerative pathologies.

A few days before the visit, along with a 6-page list of questions, the Committee requested the numbers of original papers published in the Top 1% and Top 10% during the evaluated period. Not being experts in bibliometrics and given the short notice, we could only provide the numbers of "Highly cited papers" and "Hot papers" generated by the Web of Science. However, these numbers do not translate into numbers of papers published in the Top 1% and Top 10%. In the meantime, we have compiled the true numbers of original papers published in the Top 1% and Top 10%:

- **Unit - NeuroDiderot: 28 in Top 1%; 166 in Top 10% (27% of the original papers)**
- Team 1 - NeuroKines: 12 in Top 1%; 51 in Top 10%
- Team 2 - NeuroDev: 9 in Top 1%; 54 in Top 10%
- Team 3 - NeoPhen: 4 in Top 1%; 37 in Top 10%
- Team 4 - GenMedStroke: 2 in Top 1%; 14 in Top 10%
- Team 5 - InDEV: 1 in Top 1%; 20 in Top 10%

"The allocation of the support staff within the unit is uneven, leading to tensions among the personnel. More than a third of support staff say that they feel uncomfortable within the unit. The existing policy contributes to an evident fragmentation between the teams which is perceived as 'important' and distressing, negatively impacting the overall cohesion of the unit. Additionally, this approach hinders the unit's ability to effectively support promising projects by allocating support staff where needed".

Allocation of support staff is globally proportional to the size of the Teams as well as their history. In addition, as a general policy, the Unit validates the wishes of the support staff that desire to move from one Group to another Group / Team, adding some dynamics to the distribution of support staff within Teams. We had three internal moves of supporting staff over the last 2-3 years, demonstrating the plasticity of the Unit.

This issue that "more than a third of support staff" would be uncomfortable has not been brought up nor discussed at any time of the visit, including during the closed meeting with the support staff. What are the scientific bases (including methodologies coming from social sciences in this context) that have been used to reach such a striking proportion? Are the procedures validated and, if yes, on which basis? Writing such a proportion in a report to be published online by the HCERES requires in our view a high-standard scientific approach. Otherwise, we ran the risk of discrediting a research unit without any sound basis, which would be totally against the first principle of an objective, unbiased, and high-quality evaluation. Therefore, we strongly disagree with this statement. In addition, this statement in the report is rather quite in contradiction with what is written on page 8 of the same report ("Overall, this functioning was then thought as ***excellent*** even if ***some*** researchers and support staff felt uncomfortable with the work conditions").

In our view there is no fragmentation at all as most support staff participate to the projects of more than one Group and more than one Team. This is absolutely true for support staff involved in biochemistry, molecular biology, histology, cell imaging, cytometry, cell sorting, immune cell phenotyping, metabolism, brain organoids, developing mouse phenotyping, or bioinformatics. Involving support staff in a project involving other Groups / Teams / external collaborators is always based on an agreement of the support staff to engage in that new project.

Mobilizing support staff (with their formal agreement) from different groups in a given promising project has been often the case as reflected by publications. Recent examples include doi: 10.1016/j.nbd.2023.106315, doi: 10.1007/s00702-022-02556-8; doi: 10.1002/glia.24190; doi: 10.1002/ana.26263; doi: 10.1038/s41598-021-00311-9 doi: 10.1038/s41419-021-03446-9; doi: 10.1016/j.celrep.2020.03.070; doi: 10.1093/brain/awz319; doi: 10.1016/j.bbi.2018.09.017; doi: 10.1038/s41467-017-00422-w.

"The unit has not been yet successful in attracting good candidates for new CR positions. This aspect requires additional and urgent efforts by the directorship to assure the timely recruitment of new young talents".

Even if the applications were not successful, the unit has supported several brilliant post-doctoral candidates for the position of Inserm CRCN, whose profiles are perfectly in line with

the teams' research themes:
Cindy BOKOBZA: application in 2023 and 2024, CSS Neurosciences, Team 1 NeuroKines; Dollyane MURET: application in 2023 and 2024, CSS Neurosciences, Team 5 inDEV; Parvaneh ADIBPOUR: application in 2024, CSS Technologies for Health, Team 5 inDEV.

"Encouraging postdocs and PhD students to interact with the wider public could also increase the visibility of NeuroDiderot".

This is an oversight on our part in the report, since the focus was on the participation of permanent researchers. However, doctoral and post-doctoral students also regularly take part in events for the general public (Brain Week, Fête de la Science, etc.).

**Team 1 - NeuroKines**

"The team should strategically focus on mechanistic studies and leverage advanced techniques available to them to identify pathophysiological mechanisms and novel therapeutic targets".

We do agree that mechanistic studies are key. However, this has been the case for many years as demonstrated by several key papers published by members of Team 1: doi: 10.1038/s41467-017-00422-w ; doi: 10.1073/pnas.1802620115 ; doi: 10.1073/pnas.1802620115 ; doi: 10.1093/brain/awz319 ; doi: 10.1038/s41419-021-03446-9; doi: 10.1002/ana.26263. Further building on these strengths, in the next period we used large-scale transcriptomic analyses of microglia to identify several major molecular systems involved in inflammation-induced microglial reactivity. Targeting these pathways has enabled us not only to drastically regulate the reactivity of microglia in our model of the encephalopathy of prematurity, but also to better understand the impact of microglia on brain lesions induced by neonatal inflammation (i.e. white matter lesions). We have now taken advantage of the development of these approaches to generate several sets of data in our EoP model: Single cell RNA sequencing of microglia and astrocytes, single nuclei RNA sequencing of hippocampi (with also depletion/repopulation of microglia using PLX approach), spatial transcriptomic and proteome analysis of microglia (with PLX approach in both males and females) to understand more precisely the transcriptomic (and proteomic for microglia) modifications that affect glial cell populations and subpopulations but also neurons. We are confident that we will be able to identify the major molecular networks that drive such changes and test new neuroprotective strategies that will regulate these systems. As an example, the analysis of microglia subpopulations in our model using the single-cells transcriptomic approach allowed identified the complement C5a receptor as one of the potentially central receptors in the regulation of reactivity. We are currently testing this hypothesis by modulating it in our model. Furthermore, the PLX project, which aims to renew microglia and understand its impact on the long-term effects of neonatal inflammation, will allow us to better understand the mechanisms involving microglia in the persistent cognitive deficits observed in this model.

## Team 2 – 3I Brain

"Although the general objectives are clear, the pathogenic contexts behind the studies are quite broad and may seem disconnected for some. There may have a risk of diluting efforts and delaying completion of the projects".

The experts' comment on the divergence of projects and the risk of dilution of the team's strengths is pertinent and important! However, it should be pointed out that some of the projects led by the co-leader of the team, those related to AIDS and the long COVID project, are projects of opportunity and are currently being finalized. These projects will provide the techniques, protocols and know-how to develop the team's projects, which will focus on brain development and, more specifically, autistic spectrum syndrome. Based on the wealth of expertise and strength of the members of this new team, several contexts have been proposed, such as infection, serotonin and maternal immune activation. Although the factors are diverse, the aims are consistent, as are the results.

"The team may also consider going beyond the characterisation of metabolic and immune cell changes in the different contexts of their study by strengthening the investigation of mechanisms of action".

The research program presented by team 2 clearly emphasises the translational aspect between clinical research with studies in patient cohorts and basic research in different preclinical animal models. Through this preclinical research, the team will be able to understand the mechanisms and pathways involved in immunometabolic dysregulation in the brain and different immune organs. Understanding these mechanisms in animal models and their modulation will allow us to propose the best therapeutic strategy to be tested later in human and reported in the therapeutic axis of our research program.

## Team 3 - NeoPhen

"The team has only one Inserm researcher (one recently hired junior researcher acquired by mobility) and one DR Inserm emeritus. As such, the team experiences a strong imbalance between clinical and preclinical researchers. The current lack of European and international grants reduces the attractiveness of the team and the chances to recruitment more valuable postdocs.
One of the team leaders (an engineer) does not have a PhD and therefore an HDR diploma, which may reduce the team's ability to attract good students and postdocs. ".

We do not agree that there is a strong imbalance between clinical and preclinical researchers within our team. Team 3's research project is translational, with several members of the team having published and leading projects both in preclinical and clinical fields For instance, in a recent publication (https://www.atsjournals.org/doi/10.1164/rccm.202104-0887OC), preclinical results were first authored by a PhD student co-supervised by two clinicians from our team.
Moreover, Team 3 is engaged in numerous international projects. During the reporting period, seven PhD students were co-supervised as part of international collaborations with China, Brazil, and Israel. Additionally, members of Team 3 are currently involved in two European grants (EIT Health and Horizon Europe 2023).

Furthermore, seven out of twelve permanent researchers in Team 3 hold an HDR diploma. The team is led by a pair of experienced researchers with complementary backgrounds: one is a Medical Doctor with a PhD, and the other is an engineer graduated from one of the top engineering schools in France.

**Team 4 - GenMedStroke**

"Recommandations to the team: For reasons that were not communicated to the evaluation panel, the team GeneMedStroke will not be part ... for the next funding evaluation phase".

The main reason for which the GeneMedStroke team will not be part of the next funding evaluation phase is the very strong orientation of the Unit towards neurodevelopment in the future plan. This was discussed with the evaluation panel during the general discussion after all teams presentations and it appeared logical to the jury.

**Team 5 - InDEV**

“The InDEV team’s assets are at the same time a potential threat and risk; the plethora of projects with heavy reliance on equipment, data and expertise outside of NeuroDiderot is a point that requires the team’s attention”.

One of the strengths of the team inDEV since its creation in NeuroDiderot is that part of the expertise required to carry out neuroimaging projects is co-developed at NeuroSpin (Saclay), where the team is fully integrated under a co-labelling by CEA alongside Inserm and UPCité. The related equipment, data and expertise at NeuroSpin which fall “inside” the perimeter of InDEV’s activity cannot be considered as “outside” reliance. Other national and European collaborations are very profitable complements to the team’s activity.

“Already the team’s restructuring represents a challenge – how to integrate the new members from teams 1 and 2 and how to ensure the team’s management with the new co-leader”.

The inDEV team is already working with the two new members from teams 1 and 2, on projects that have been funded for several months (V. Biran: ANR PremaLocom project, ENSEMBLE project - Fondation Paralysie Cérébrale; H. Adle-Biassette: ANR pHCP project), so integration couldn't be easier. The same applies to the new management of the team, as J. Dubois and D. Germanaud have been working and publishing together for more than ten years on both sites (NeuroSpin and Robert-Debré).

“Finally, the geographical dispersion remains a challenge that cannot be simply overcome with videoconferencing and the collaboration on several projects”.

The researchers and students of inDEV team leading projects on Robert-Debré cohorts (e.g. on prematurity and prenatal exposure to alcohol) are regularly at the hospital to allow close interactions with the clinical teams and carry out the follow-up work. The Robert-Debré IT infrastructure and office space do not yet allow data analysis to be carried out there, thus this

is done primarily at NeuroSpin. The creation of the Institut Robert-Debré du Cerveau de l'Enfant, in partnership with the CEA, will modify the current scheme, with new possibilities of ramping up imaging activities in Robert-Debré Hospital (new research MRI scanner, lab space, organization of common databases, etc.).

"The organisation of future projects along four axes… makes perfect sense, but the listed projects are far too many for such a small team. Given that these are collaborative projects It would be necessary to delineate the team's contribution and ensure that these are feasible and coherent with the overall research vision".

The team tried to argue against the criticism of thematic dispersion in the "self assessment" document evaluated by the HCERES (P47: paragraph starting with "During the last 5 years, several projects have been developed, the variety of which could be giving a false sense of dispersion…"). The extent to which inDEV team members are involved in the projects varies from one project to another: leadership in most, collaboration in some. Beyond the research topics specific to each researcher, we wanted to show the coherence of the team's themes, with related scientific and clinical questions, and similar methodological approaches. Actually, sampling a few major neurodevelopmental risk factors and a few functional domains happens to be precious to approach the specificities and commonalities of the mechanisms at play, beyond the possibilities of methodological mutualization. The team aims to retain this relative diversity of themes within the niche acknowledged by the HCERES committee because it is one of the few in France and Europe to be able to carry out such projects on the characterization of the anatomical and functional variability of brain development based on its unique position between Robert-Debré hospital and NeuroSpin. The team's goal is to expand by welcoming new researchers to strengthen our ability to deepen the investigations within our main theme of phenotyping perinatal brain injuries. This is in line with the creation of the Institut Robert-Debré du Cerveau de l'Enfant in partnership between Inserm, UPCité, CEA, APHP and Institut Pasteur.

"The imaging activities at the Robert-Debré hospital are not well-defined and give the impression of a burden rather than an asset because of direct access to patients. If the team's strategy is also the translation in real world clinic, the ramping up of these activities seems mandatory".

Several major projects have been carried out in recent years in inDEV team based on neuroimaging datasets from Robert-Debré hospital, notably on prenatal alcohol exposure and prematurity (evidenced by several publications since 2023 or in progress). Nevertheless, this has indeed required significant effort, as there are several bottlenecks in the current organization for carrying out neuroimaging projects at Robert-Debré. Although access to patients and platforms has been facilitated, there remains a major need in research support staff for Robert-Debré platform (research engineer and research assistant): this remains critical to expand the clinical research projects not only for inDEV team but also for other clinical research teams. Nevertheless, the prospect of the Institut Robert-Debré du Cerveau de l'Enfant is promising to dramatically change the situation in the coming years. And this should promote the translation of research into real world clinic.

**“**Sharpening the focus of the team’s research vision should be a priority. Although already funded, the scope of projects is beyond feasible”.

Given our responses to the previous points, we tend to disagree with this recommendation and are optimistic that the projects will be completed in the next term. Nevertheless, we agree that it would not be reasonable to expand the scope of our research projects in the future, converging toward a good balance between wishful level of diversity in models and methods and sufficient concentration of strengths.

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