Research evaluation

# EVALUATION REPORT OF THE UNIT

## GSC - Gènes, synapses et cognition

# UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Institut Pasteur Paris

Centre national de la recherche scientifique - CNRS

**EVALUATION CAMPAIGN 2023-2024**

GROUP D

Report published on October, 17 2024

High Council for evaluation of research and highter education

In the name of the expert committee :

Simon Thorpe, Chairman of the committee

For the Hcéres :

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 Simon Thorpe, Université Toulouse 3 - Paul Sabatier - UPS, Toulouse |
| **Experts:** | Mr Pascal Fossat, UBx - Université de Bordeaux, Bordeaux<br>Mr Philippe Frachet, Université Grenoble Alpes - UGA, Grenoble (representative of CNU)<br>Ms Suzanne Lesage, Inserm - Institut national de la santé et de la recherche médicale, Paris<br>Ms Susanna Pietropaolo, CNRS - Centre national de la recherche scientifique, Bordeaux<br>Mr David Robbe, Inserm - Institut national de la santé et de la recherche médicale, Marseille<br>Mr Philippe Rondard, Inserm - Institut national de la santé et de la recherche médicale, Montpellier |

## HCÉRES REPRESENTATIVE

Mr Giovanni Stevanin

## REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Bernard Poulain, CNRS
Mr Patrick Trieu-Cuot, Institut Pasteur

# CHARACTERISATION OF THE UNIT

- Name: Gene, Synapse and Cognition
- Acronym: GSC
- Label and number: UMR3571
- Composition of the executive team: Pierre Marie Lledo

## SCIENTIFIC PANELS OF THE UNIT

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

## THEMES OF THE UNIT

The Gene, Synapse and Cognition (GCS) unit regroups multiple teams that study brain mechanisms underlying various phenomena. In particular, the unit studies the molecular and cellular mechanisms underlying synaptic plasticity and attempts to provide links to learning, memory and social communication at the behavioural level. The approach is distinctly multilevel and aims to capture the dynamics of neural circuits and interactions between brain areas.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The GSC research unit was created in January 2004 as the UMR3571. The unit is located on the first and second floors of the Fernbach building on the Institut Pasteur campus of Paris and is the main component of the Neuroscience Department of the Pasteur Institute. This implementation at the same location facilitates interaction and synergy between the teams. The institutional stakeholders of the GSC unit are the CNRS and the Institut Pasteur. During the reporting period, the unit included six research teams and three technological core facilities accessible to the whole Pasteur campus. Each team is labelled 'research unit' by the Institut Pasteur. The Neuroscience department also includes three additional teams headed by young researchers not affiliated with the CNRS institution. The GSC unit perfectly aligns with the Institut Pasteur's primary mission, contributing to the research effort on infectious diseases that target the brain.

## RESEARCH ENVIRONMENT OF THE UNIT

The GSC unit is well integrated within the Institut Pasteur, where it is a major actor of the Department of Neuroscience and where two PIs of the unit have successively been heading the Strategic Neuroscience Research Axis. This duality brings mutual scientific and technological benefits, such as from the GSC unit to the Institut Pasteur, its unique expertise in Neurosciences and brain diseases and its own technological facilities such as membrane protein biochemistry, high-resolution microscopy and behavioural experiments. Conversely, the unit takes advantage of the Institut Pasteur's environment and well-established infrastructure: the numerous core facilities available at the campus, the technology transfer office of the Institut Pasteur, necessary for collaborations with industries or start-ups (Avatar Medical Spinoff), collaboration agreements with several Universities (Université Paris-Cité, Sorbonne Université or Paris Saclay), inclusion in the local IDEX since 2022, and access to university doctoral contracts (ED3C doctoral school from Sorbonne Université). The GSC unit also benefits from multiple fundamental research, clinical/industrial collaborations at the in-situ, regional, national and international levels. At the level of the Institut Pasteur, they include the Labex INCEPTION led by one of the PIs of the unit and diverse collaborations with other Pasteur Institutes (Hearing Institute, Institut Pasteur of Lille). At the level of the region Ile-de-France they include Dim c-Brain, IVM, INRIA, and collaborations with several hospitals in Paris (Robert Debré, Saint-Anne). National-level collaborations involve multiple PIA programs (labex BIOPSY, Fondamental, PEPR PROPSY, FHU, NOR-SUD, etc) and at the international level, they include the INEXT instruct program, RIIP, NIH, Autism Speaks etc. At the unit level, most teams are involved in clinical studies that include the diagnosis and treatment of autism, mood disorders, addiction, and infections. One team leader (team #2) has developed industrial partnerships for the development of allosteric modulators of channel receptors, and two PIs (team #4 and team #6) have created the AVATAR MEDICAL spinoff and the start-up NeuroBiomics Biosciences.

## UNIT WORKFORCE: 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 | 6 |
| Chargés de recherche et assimilés | 14 |
| Personnels d'appui à la recherche | 29 |
| **Sous-total personnels permanents en activité** | **55** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 4 |
| Personnels d'appui non permanents | 4 |
| Post-doctorants | 25 |
| Doctorants | 26 |
| **Sous-total personnels non permanents en activité** | **59** |
| **Total personnels** | **114** |

## 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 |
|---|---|---|---|
| INST Pasteur Paris | 0 | 12 | 21 |
| AutreS | 6 | 8 | 8 |
| **Total personnels** | **6** | **20** | **29** |

# GLOBAL ASSESSMENT

The Genes, Synapses and Cognition Unit is a research centre attached to the Institut Pasteur and the CNRS. During the evaluation period, it was composed of six teams, although one of them was recently disbanded following the decision of the PI to accept a position at the University of Colorado. **The individual teams are all excellent or even outstanding**, with team leaders who all have high international visibility and have each made some major contributions over the past five years. One can cite the characterisation of the effects of genetic variants in autism and addiction (Nature Genetics 2022, Progr Neurobiol 2021), the development of novel classes of allosteric modulators targeting nicotinic receptor subtypes (Cell Mol Life Scie 2022), the establishment of links between food consumption and microbiota (Science 2022), and the creation of DIVA, a software platform allowing any volumetric data to be visualised and analysed in Virtual reality with the creation of a spinoff (Avatar Medical). The panel noted that there are nevertheless some problems at the level of the unit itself. First, the unit does not include all the relevant on-site teams from the Neuroscience department. All the GSC teams also belong to the Institut Pasteur's Department of Neuroscience, but an additional three teams could logically be part of the same entity. The lack of coherence of the ensemble is also evident from the fact that many of the publications listed by the lab do not use Genes, Synapses and Cognition in the affiliation. While there is some evidence of collaboration between the teams, the number of joint publications within the institute remains small (around 3%). Overall, the panel considered that the unit contains many excellent teams and that the institute has superb facilities, a large number of skilled support staff, and has been **very successful in obtaining funding** (>4M€ per year) from a wide range of sources (180 grants), both national (e.i.: 30 ANR with 20 as coordinator) and international (ERC, NIH, H2020, IMI …70% as project leaders) or from foundations (e.i.: Robert de Spoelberch Foundation…).

Together, this makes the laboratory an **excellent to outstanding unit and a very attractive working environment**. That said, the panel considers that it should be possible to further improve the institute's standing in future years by further promoting the future Integrative Neuroscience unit as a key player in Neuroscience research in the Parisian research environment.

# DETAILED EVALUATION OF THE UNIT

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

The previous Hcéres evaluation concerned the Department of Neuroscience at the Institut Pasteur, which has a larger perimeter than the GSC Unit. Mainly, it was asked to 1) reinforce the follow-up of doctoral student training, 2) increase communication between PI and permanent staff, 3) improve the gender balance, 4) facilitate the scientific activities of Team 5, 5) increase the use of shared platforms, 6) ensure recruitment of technical staff, 7) enhance interactions between groups, 8) think about collective answers to internal calls at Pasteur, 9) define policies for recruitment of new teams and 10) identify the research areas that need to be reinforced.
Each response has been tailored to its respective recommendation, indicating a serious consideration of feedback and dedication to enhancing the unit's organisation and research endeavours.
Key actions include:

1. Initiatives to foster cohesion among PhD students, despite decentralised programs (due to the involvement of multiple doctoral schools), through unit-wide programs, workshops, and faculty advisors.
2. For the management of Unit PIs and Staff: Each team within the GSC Unit operates independently, but there are structures in place (GSC office made up of group PIs, laboratory council and personnel committee) to address HR issues. One remaining question concerns the management of personnel profiles (e.g. IP, Inserm, CNRS, universities…) to support their career development according to their affiliations.
3. Efforts to address the gender imbalance in PI recruitment (gender taken into account during the last call for new teams in 2023), demonstrating a commitment to inclusivity and diversity.
4. On the productivity of G5 group, positive outcomes are noted with increased productivity and affiliations (INRIA labelization), demonstrating an effective response to previous recommendations.
5. Discussions (one or twice a year) and investments in shared equipment and facilities to enhance collaboration and resource utilisation.
6. Two engineers have been recruited for specialised roles in equipment maintenance and behavioural analysis.
7. Promotion of interactions across research groups through regular scientific presentations and strategic collaboration initiatives.
8. Launching thematic research axes based on campus-wide topics, resulting in high-impact publications (Nature journals, Neuron, etc.).
9. Strategic management of growth, with a focus on replacing departing teams and collaborating externally to navigate space constraints and maintain departmental size.
10. The definition of Human neuroscience as the priority for novel recruitments of teams in 2023.

# B – EVALUATION AREAS

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

### Assessment on the scientific objectives of the unit

Globally, the GSC unit has a strong basic and translational approach with a diverse portfolio of research programs and strong clinical links as it hosts several neurologists, psychiatrists and psychologists. It offers a collaborative environment with multidisciplinary and multiscale approaches gathering several disciplines including molecular, genetic, cellular, behavioural and clinical levels. **Overall, the scientific program and objectives are excellent to outstanding**, promoting strong integration between fundamental and translational research, with exceptional capabilities to attract competitive funding.

### Assessment on the unit's resources

As of 31/12/2022, the GSC unit regroups 114 staff members, including 26 tenured researchers (associates and directors), professors and university hospital researchers and lecturers, and 29 permanent administrative and technical staff. **The ratio between researchers and technical staff is excellent** in comparison to other research units in France and allow the maintenance of the unit's know-how and expertise. During the last contract, nineteen researchers held an HDR, showing the capacity of the unit to train numerous PhD students. A total of 55 PhD students were trained during the evaluated contract period with 31 theses defended and 55 post-doctoral fellows were hired with some of them performing second post-docs. All early career researchers (PhDs and post-doctoral fellows) published at least one article in a peer-reviewed journal during their internship, confirming the functional organisation of the structure for education and training. In terms of financial resources, in addition to recurring institutional support from the Institut Pasteur private entity and the public stakeholder, CNRS that represents 17% of the budget, the remaining funding resources (an average of €4.2 million per year during the 2017–2022 period) were obtained from international (NIH, HFSP, Brain Initiative), European (ERC, HBP, IMI), national (ANRs, PIA, diverse donations and grants from patient associations or foundations, such as Bettencourt, COGNACQ JAY, Fondamental, FRM, INCa, Inserm…), regional or local (AAP Idex, I-Site…) sources, as well as resources from industrial collaborations (Servier, Sanofi, Roche…). **Overall, the unit's resources are outstanding** with 88% of projects obtained as coordinators (i.e. AIMS-2-TRIAL, IMI, HFSP, R2D2 Horizon, numerous ANRs…). Several PIs won prizes and distinctions such as the Prix de la Fondation Roger de Spoelberch and the silver medal of CNRS.

### Assessment on the functioning of the unit

The GSC unit follows perfectly the rules and regulations of the principal tutorship, the Institut Pasteur, regarding the human resource management, safety, environment, ethical protocols, animal experimentation, as well as data and scientific protection, storage and sharing. Together, they cover all the key aspects of the life of the institute. The committee noted, however, feedback indicating a certain lack of communication between the direction and Neuroscience department and insufficient consultation of non-team leaders with respect to decision-making. Gender equity in team direction is also an unsolved concern.

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

#### Strengths and possibilities linked to the context

The GSC unit actively promotes multidisciplinary research across multiple scales on the development, structure and function of the brain in humans and animal models to elucidate physiological and pathological mechanisms. To reach this goal, the unit develops multiple levels of organisation, ranging from molecules and cells to circuits, systems and behaviours. The unit comprises six teams, one of which (team #3) is currently leaving. The research is organised into five scientific domains (Human genetics, Scientific organisation and functioning, Neuronal circuits and behaviour, The brain-body connection, From research to biomedicine. This facilitates internal communication and the swift identification and management of operative and organisational needs.

This richness in scientific projects, approaches and models of the unit provides an outstanding environment for pursuing cutting-edge research and technical developments while encouraging transversal collaborations that fits perfectly into the environment of the Institut Pasteur. Notably, complementary research in humans and animals and cellular models, as well as mathematical models, facilitates the integration between fundamental and translational research, allowing the development of new tools and strategies for innovative treatments and diagnosis of patients. A major strength of the GSC unit is the scientific and physical integration between fundamental and applied research with complementary preclinical and clinical projects where scientists and clinicians can actively cooperate, creating a vibrant cross-fertilising environment. In addition, the unit has developed several collaborations with industrial partners (BASF, Sanofi, Roche, Servier, Cortecnec), issued five patents in the field of neurodegenerative, psychiatric and infectious diseases, created two spinoff start-ups (Avatar Medical and NeuroBiomics Biosciences) and has organised yearly a round-table under the auspices of the week of the Brain.
Among their main achievements, researchers of the unit have developed several cutting-edge research platforms, including a culture room for human induced pluripotent stem cells (hiPSCs), electrophysiological systems for high-resolution and deep-brain imaging in vivo, and a behavioural phenotyping platform.

### Weaknesses and risks linked to the context

Relatively few clinical trials have started based on medical products or therapeutic strategies made in the GSC unit.

## *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

One major strength of the GSC unit is its inclusion in the Neuroscience department at the Pasteur campus, which is dedicated to the study of all aspects of biology with a particular focus on infectious diseases, thus giving access to its powerful technological and animal facilities, as well as common resources for administration, financial management and computing. Conversely, the GSC unit has developed specific platforms run by two CNRS research engineers. They allow the production of viral vectors and human induced pluripotent stem cells (hIPSCs), and include a shared imaging facility with three 2-photon and one 3-photon microscope, a high-density Neuropixels electrophysiology recording setup, and a shared fluorescence nanoscopy microscope as well as allowing studies of animal behaviour. GSC is a multidisciplinary unit of 114 members, divided into 6 teams, gathering psychiatrists, neuroscientists, geneticists, biologists and physicists. It comprises 55 permanent and 59 under-contract staff members, including 26 PhD students (55 trained during the last contract, 31 with thesis defended) and 25 post-doctoral fellows (25 at the end of the contract for the next term). The unit includes 33 engineers/technical staff for 22 tenure clinicians, researchers, professors and associate professors, which is an exceptional ratio for supporting research activity. In terms of financial resources, the GSC unit has been successful in competitive and prestigious funding by local, national (e.g. 32 ANR projects, 20 as PIs, 8 PIA– INCEPTION, REVIVE, PRAIRIE …–, PEPR and IHU), European (ERC, H2020, IMI …70% as project leaders) and international bodies (NIH, HSFP, Robert de Spoelberch Foundation…) as well as from foundations (FRM, COGNACQ JAY, FONDAMENTAL…). In the present contract, the unit obtained more than 180 grants, receiving an average of 4.2 M€ in grants per year. Some students also received prestigious prizes such as Marie-Curie individual grants, Bourse L'Oréal, EMBO, the UNAFAM prize…

### Weaknesses and risks linked to the context

Since the departure of team #3, the unit should recruit/attract new and excellent teams with young researchers to keep its size and the space dedicated to the department. The committee regrets the lack of ANRs Jeunes Chercheurs. There are notable differences between teams in their ability to obtain research funding (for example from 1.5 to 8M€ during the period).

## *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

The functioning of the GSC unit complies with the regulations on human resource management, safety, environment, ethical protocols concerning medical projects and animal experiments, data as well as scientific

heritage protection. Several members of the GSC unit are active representatives in committees for Health and Safety, Ethics in research and recruitment and in the Ethics committee for experimentation with animals for approval of protocols at the Institut Pasteur. In accordance with principles enacted by the Institut Pasteur, which obtained the 'HR Excellence in Research' (HRS4R) label, the unit has a clear and open policy regarding recruitment, employment and working conditions. Since 2022, a gender equity plan has been launched aimed at improving work-life and gender balance and dealing with sexist and sexual violence. This organisation ensures full compliance with rules and directives defined by the stakeholders but also stimulates additional actions to implement innovative management choices (e.g. water monitoring, carbon footprint through COE commitment, waste and noise management). Since 2021, the Institut Pasteur has been deploying a mandatory laboratory notebook tool offering LIMS (Laboratory Information Management System) functionalities, ensuring the continuity and sustainability of research work within the GSC unit and the Institut Pasteur. It has also adopted a new policy concerning the sharing of research data and software codes (FAIR). The GSC unit complies with the protection of scientific assets and computer systems through secured storage at the Institut Pasteur via a specific department dedicated to cybersecurity. The unit has set up a Data Management Plan (DMP) with an open science approach. In terms of health safety, the Institut Pasteur has implemented a business continuity plan to cope with emergencies such as those provoked during the recent Covid19 crisis.

### Weaknesses and risks linked to the context

Although the global gender balance at the GSC unit is at equilibrium, there is a recurrent concern regarding the fact that all the team leaders are males. There is no formal process to support the career development of early career researchers (PhD students and postdocs), providing, for example, grant writing guidance or feedback on fellowship applications (e.g. via internal review panels or mentorship schemes). There is no forum where representatives of each staff category can raise issues or suggest changes. During meetings with each staff category, the committee noted the lack of an official laboratory council with elected representatives from the different staff categories. Also, the research staff complained about their limited participation in decision-making, difficulties in information flow, and a certain lack of transparency. The technical and administrative staff also complained about the lack of communication on the part of the PIs, especially during the choice of candidate team leaders and their future in the event of the departure of their respective PIs.

## EVALUATION AREA 2: ATTRACTIVENESS

### Assessment on the attractiveness of the unit

**The attractiveness of the unit is overall excellent to outstanding.** The GSC Unit provides an attractive environment largely based on the quality of its research scientists. This is supported by the high number of prestigious distinctions awarded to the team leaders (e.g. silver CNRS medal). The Unit also benefits from state-of-the-art equipment (e.g. multi-photon imaging facility) to support its ambitious research programs. It is also attractive (with more than 6 new PhD/postdocs each year from more than eleven countries due to its participation to international expert panels and EU funded projects) and the quality of its staff hosting policy.

*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

During the contract period, the team leaders have received many scientific prizes (n=14). Some of them are highly competitive, such as the Prix de la Fondation Roger de Spoelberch, CNRS Silver medal, election to Academia Europaea, and one postdoc received the Bourse France L'Oréal-UNESCO pour les 'Femmes et la Science'. Team leaders also participate actively in expert panels for organisations that include Pasteur Institute, MRC Laboratory of Molecular Biology Univ. of Cambridge, Aviesan ITMO Neurosciences and the Hcéres.

The unit has developed strong European networks. Team #1 has actively contributed to the European guidelines for the Pheland McDermid syndrome and to a European database of patients. The team is a partner in the two largest European projects on autism research, AIMS-2-TRIALS and CANDY. In addition, the team leader recently coordinated a third European project, R2D2 Mental Health (2022). This new European-funded project of €11 million will gather 22 institutions in Europe, Israel, and Australia, and it aims to identify both risk and resilience factors for neurodevelopmental disorders. In addition, one PI received an ERC Advanced Grant, and a team was one of the three recipients of the 2022 European Innovation Council's accelerator funding call for the development of visualisation techniques to help in cardiac surgery.

During the evaluation period, lab members organised more than ten international meetings (e.g. Conference Jacques Monod). The unit has been highly attractive for external scientists. The unit hosted visits from two invited professors from Univ. of Göteborg and Univ. of Roma-Sapienza, as well as three clinicians. The unit also trained 55 PhD students, including 6 PhD students with Master diplomas from foreign universities (UK, 2xFinland, Croatia, Chine, Argentina); 64 Postdocs and 109 Masters students (among them 11 are from abroad, 4xGermany, 3xUK, 1 Denmark, 1 Spain, 1 Hungary, 1 USA). Almost all PhD students published a first author article with a means of 1.6 articles per PhD student.

The unit is heavily involved in European grants, with one as coordinator (R2D2 MentalHealth, 2022). The unit has tight interactions with clinical centres in France that include the Saint Anne and Robert Debré Hospitals and across Europe (through large international collaborative consortia) as well as with patient associations (particularly during the national Autism Day yearly). The unit strongly promotes open science, with most publications in Open Access and all in open archives (HAL-Pasteur).

The committee was extremely impressed by the remarkable success rate in obtaining external funding (20.8 M€ obtained from external calls). The sources include international (NIH, HFSP, Brain Initiative), European (ERC, HBP, IMI), national (32 ANRs, 8 PIA, diverse donations and grants from patient associations or foundations, such as Bettencourt, Cognacq Jay, Fondamental, FRM, INCa, Inserm), as well as regional or local (AAP Idex, I-Site) sources. They also obtained resources from industrial collaborations (Servier, Sanofi, Roche) with> 80% of projects obtained as coordinators.

The committee considers that the unit is particularly attractive because of the high quality of its research platforms, which include state-of-the-art imaging facilities, cutting-edge behavioural assays (touch-screen-based assays) as well as the EEG platform installed in the pediatric psychiatric department of the Robert Debré Hospital. Several software packages have been developed (TRamWAy, Genuage, Live Mouse Tracker (LMT)), some of which are used worldwide. This supports its role as a leader in studying the neural basis of behaviour.
The unit was heavily involved in the international EMBO/Institut Pasteur course Integrative Structural Biology with the participation of leading global experts in the various disciplines of biophysics.
Most members of the unit are internationally recognised, as indicated by the large number of invitations to conferences (n=10/researcher/year on average) and their contribution to the organisation of scientific meetings (e.g. the 9th international symposium on photochromism ISOP 2019 at Institute Pasteur, and the 2019 Jacques Monod conference, 'Ligand-gated ion channels: from atomic structure to synaptic transmission', in Roscoff, France).

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

The heterogeneity of the Unit is a strength and, at the same time, a potential weakness because of the difficulties related to the coexistence of different theoretical and technological approaches. A balance in the involvement of senior and junior members of the Unit in the different research projects is a major objective that should be regularly considered.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

### Assessment on the scientific production of the unit

The list of publications provided by the unit includes a total of 277 articles (2017–2022). Around 58% of the publications included a lab member as first or last author. These include many prestigious journals such as Science, Science Translational Medicine, Nature Medicine (3), Nature Communications (7), Nature Biomedical Engineering and Neuron (1). Given that the lab has 26 researchers and 29 support staff, this corresponds to around one publication/year/permanent position which is certainly **excellent**, but not particularly outstanding given the superb resources of the Institut Pasteur.

*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 unit has used the HAL archive to make its publications visible. Indeed, given the variability in the use of affiliation addresses, the HAL archive is one of the few ways of obtaining a complete listing of the lab's output. Roughly 87% of the production is open access, a value that is substantially better than the average for the CNRS and the Institut Pasteur.

The unit's strategy for authorship of articles appears to be very good, and technical support staff are regularly invited to sign publications when appropriate.

The GSC unit also has clearly defined rules regarding research integrity.

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

Analysis of the unit's production is complicated by the lack of standardisation concerning the affiliations used for publications. For example, articles frequently use the name of the team, rather than the name of the lab for the affiliation. This strategy corresponds to what the Institut Pasteur calls a 'unit,' which differs from the list of units evaluated by the Hcéres. This makes it virtually impossible to find the lab's output using open-source bibliographic tools like OpenAlex.org or commercial tools such as Scopus.

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

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

The GSC unit is heavily involved in the transfer of knowledge to society. Several patents were filed during the previous contract (n=5) and collaborations are underway with major healthcare players (SERVIER, ROCHE, etc.). The unit participates in knowledge dissemination via its contacts with patient associations (e.g. for autism spectrum disorders), book writing for the lay public, Master courses and partnerships with associations. The unit director is also a regular columnist for the French 'Les Echos' magazine. Numerous press releases are also published. Students of the unit created a blog for science popularisation. **The committee found this involvement of the unit excellent.**

*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 numerous interactions with the socio-economic world constitute a major strength of the unit, together with its willingness to file patents. The development of several partnerships with patient associations (Autism families) and hospitals, especially Necker and Robert Debré, provides strong societal links. The interactions with the general public are developed through press activities (e.g. regular contribution of the unit director as columnist in 'les Echos') and several operations of science popularisation (e.g. 'les nouveaux neurones d'un cerveau adulte participent à l'apprentissage sensoriel ; un facteur sanguin impliqué dans la depression').

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

Points of weakness for the unit include the lack of interactions with secondary schools, which are necessary to push new generations toward science. The number of patents could be increased given the unit's remarkable levels of technological development. Risks may be related to the research for mechanisms of intractable disease and potential difficulties in converging the results of pre-clinical and clinical studies.

# ANALYSIS OF THE UNIT'S TRAJECTORY

The trajectory of the unit is not yet clear. The decision of one team leader to take up a position at the University of Colorado required a change in strategy because at one point this team leader was being proposed as the future director of the laboratory. When the Self-Assessment Document was submitted (June 2023), the suggestion was that the future director would be the previous co-director, with an earlier unit director as his deputy. At the time of the visit, the situation was not clarified, particularly for the co-director.

The Self-Assessment Document also noted that the Department of Neuroscience at the Institut Pasteur had launched a campaign to recruit two new team leaders. The call resulted in 50 applications and, following auditions in early 2023, 9 were shortlisted. Subsequently, the Institut Pasteur's Scientific Council approved three of the candidates. However, the recruitment was blocked at the level of the Institute's direction. All three candidates have now taken up positions elsewhere. As a result, if a new team leader is to be appointed, the entire process will have to be relaunched, making it very unlikely that a new team could be installed for the start of the new five-year period. This is very unfortunate.

One point that requires clarification is the fact that the Department of Neuroscience already includes three other teams that could potentially be included in the future 'Integrative Neuroscience Unit'. It appears that the only real objection to these three teams joining the five teams that already belong to the UMR 3571 is that they currently do not have any CNRS personnel. However, it appears that this restriction should not be an issue. The panel members are well aware of CNRS labs that have teams with no CNRS employees, so this should not be a reason to block the integration of the three existing teams into the future unit.

# RECOMMENDATIONS TO THE UNIT

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

The panel considers it important to regroup with the other teams of the Department of Neuroscience at the Institut Pasteur. While the panel was not been able to evaluate these three other teams, it seems likely that they would fit well with the five existing teams.

The unit should continue to press the Direction of the Institut Pasteur to allow the creation of the two additional teams for which suitable candidates had already been found.

The panel encourages the unit to develop its links with INRIA, which could help reinforce the highly original research program developed by the current team 6.

While the possibility of seeking an additional affiliation with Inserm may seem attractive to recruit additional researchers and support staff, the panel feels that this could complicate the situation. Affiliation to Inserm would require evaluation and validation by Inserm of all the teams in the unit, and this could be problematic in a situation where there is already considerable confusion caused by the existence of Units within the Institut Pasteur that do not correspond to Units evaluated by the Hcéres.

The panel considers it vital to work to improve women's career prospects within the lab because male scientists' current domination of the direction of both the unit and the teams is a major problem. This could be helped by giving more autonomy to female members within research teams and giving them a more significant role in direction or co-directions.

Finally, improving the decision-making at the unit and neuroscience department level may require more consultations of non-team leaders.

## Recommendations regarding the Evaluation Area 2: Attractiveness

The unit should improve its attractiveness by providing a more encouraging and clearer path for developing a solid post-doctoral career. Several post-doctoral fellows from several European and non-EU countries have joined the unit. It is crucial that they are encouraged to continue working in the Unit, developing their careers as independent scientists with the possibility of tenure, so that they may develop their own research projects in the future.

## Recommendations regarding Evaluation Area 3: Scientific Production

It is vital that the unit has a consistent policy concerning the affiliations used for publications. The current system where the Institut Pasteur has many 'units' not clearly identified in the open-source Research Organisation Registry (ror.org) is very problematic. Currently, the ror.org listing has eighteen child organisations listed for the Institut Pasteur (https://ror.org/0495fxg12), none of which correspond to either the Department of Neuroscience or the UMR 3571.

While the lab's list of publications is globally impressive, and some of the PIs are very productive and have excellent visibility, the volume of publications is not high for a lab with such a large number of permanent researchers and support staff. With 55 permanent staff members, the overall production level corresponds to roughly one publication per year, and this does not take into account the fact that the lab has also benefited from a similar number of non-permanent researchers in the form of PhD students and postdocs. The panel, therefore, recommends that all the research staff make an effort to increase their productivity and not rely so much on the small number of visible PIs.

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

A larger involvement of researchers rather than team leaders in the interactions with lay public would be an important improvement for some teams. It could make the relationships with patient associations and educational institutions more dynamic.

# TEAM-BY-TEAM ASSESSMENT

**Team 1:** Human genetics and cognitive function

Name of the supervisor: Mr Thomas Bourgeron

## THEMES OF THE TEAM

Overall, the team aims to advance the understanding of the genetics, pathology and treatment of autism and other neurodevelopmental disorders by bridging the gap between basic and clinical practice. The team has played a historical role in identifying the genetic basis of autism, highlighting the genetic heterogeneity of this complex neurodevelopmental pathology, and trying to identify common biological mechanisms that could constitute relevant therapeutic targets. The team combines methods for whole genome analyses and brain imaging in autistic patients with genetic mouse models and their characterisation using sophisticated behavioural tools. The team is also interested in evaluating the complex interactions between genetic and environmental factors, both at the preclinical and clinical levels.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

One concern emerging from the previous report focused on PhD mentoring. This issue has been tackled by ensuring the participation in two publications as first author of the PhD student present in the team and the involvement in the thesis direction of two researchers.

The request to improve the control of an autism database and develop more interactions between different experimental approaches has been fulfilled by hiring two new staff members with research engineer positions. One is a former post-doc newly recruited since April 2023 with expertise in brain anatomy and behaviour. The second one was trained by team 1 and has been in charge of diverse databases of the Institut Pasteur, including those related to autism spectrum disorders.

Lastly, the query about the dynamics of the 'resilience' research theme has been answered by launching a specific European project coordinated by the PI (R2D2 Mental Health) and by implementing novel animal models showing intermediate phenotypes and carrying genetic mutations closer to patients.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 0 |
| Chargés de recherche et assimilés | 2 |
| Personnels d'appui à la recherche | 11 |
| **Sous-total personnels permanents en activité** | **16** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 0 |
| Personnels d'appui non permanents | 3 |
| Post-doctorants | 1 |
| Doctorants | 2 |
| **Sous-total personnels non permanents en activité** | **6** |
| **Total personnels** | **22** |

# EVALUATION

## Overall assessment of the team

**The overall assessment of the team is excellent to outstanding**. In particular, its scientific production is outstanding (110 articles in high standard and more specialised journals) and the level of national (ANR, foundations) and international funding (>8M€ during the evaluated period) is truly remarkable. The multidisciplinary nature of the team is evident at all levels, as is the use of cutting-edge methodologies. The team is part of the largest European funded projects on autism and interacts with hospitals and patient associations while at the same time developing innovative tools for preclinical models (e.g. Live Mouse Tracker). Key achievements of Team 1 are the development of clinical and genetic databases as well as a website related to autism and neurodevelopmental disorders, including quality control, preprocessing and analyses of the data. They have also set up an EEG platform in the child psychiatry department of the Robert Debré hospital and developed new paradigms and tools to explore social communication in mouse models of autism.

## Strengths and possibilities linked to the context

The team is nationally and internationally recognised for identifying the first mutated genes associated with autism and its research on genetic and environmental modulators of the autistic phenotype. The team covers various topics, from genetics studies in human cohorts to cellular and mouse models. The team's research is based on large clinical databases that provide important phenotypic information based on biological and clinical markers, which are critical for accurate phenotyping of autism and neurodevelopmental disorders. The team has increased its number of permanent staff members (16 on 31/12/2022 versus 12 on 30/06/2017) by multiplying technical staff by three, but it also lost three tenured researchers. The team hosts multidisciplinary staff such as psychiatrists, neuroscientists, and geneticists with complementary expertise and benefits from the tight interactions with clinical centres in France and Europe, as well as patient associations. The application of multiple levels of analysis (genotypic, clinical and brain imaging data) to the complexity of autism is a major strength of the team, allowing the combination of cellular, mouse models, whole genome sequencing and clinical data as well as brain imaging. The team uses databases and develops analysis tools available as open-access software packages (e.g. Live Mouse Tracker, an open-source machine learning tools to investigate social interaction in a group of mice). The team's scientists and clinicians have actively contributed to the European guidelines for the Pheland McDermid syndrome and to a European database of these patients. The team has also built an EEG platform at Robert Debré Hospital to collect data on neurodevelopmental disorders through the child psychiatric department. Success in obtaining national and international funding is excellent (Connie Maeva Foundation, IMI2 AIMS-2-TRIAL, ANR and an impressive number of grants from patient associations and foundations; 99% as coordinator). The team is a partner in the two largest European projects on autism research, AIMS-2-TRIALS and CANDY. In addition, the team leader recently coordinated a third European project, R2D2 Mental Health.

Over the past contract, the team's production was particularly abundant (110 publications representing 38% of the unit's output). Overall, the publications are outstanding, with a high proportion in high-profile peer-reviewed journals, e.g. Nature Medicine, and Nature Genetics. Additionally, eight out of nine recent PhD graduates have contributed to at least one publication as co-authors. The team attractiveness is excellent to outstanding: it has attracted foreign researchers (2 invited scientists) and recruited eleven PhD, five postdocs and nineteen trainees. Contributions to society are also excellent to outstanding: the team organised specific days at the Institut Pasteur for the families concerned by autism. In addition, the team leader has written a book dedicated to lay audiences, and is a member of the French Academy of Sciences, the Institut Universitaire de France, the European Molecular Biology Organisation, the Academia Europaea and the National Ethical Committee.

## Weaknesses and risks linked to the context

Beside the obtention of important European funds, the team seems to have difficulty obtaining national funds and PhD fellowships. The limited number of PhD students (9 PhDs defended during the last contract) and post-doc fellows is indeed surprising, taking into consideration the huge datasets handled through the research projects of the team at multiple levels and the amount of funding. However, the lack of space and PIs with habilitation to direct research (2 remaining at the end of the contract from 5 initially) may limit the recruitment of new young researchers, PhD students and post-doctoral fellows. During the last contract, the team had a very impressive number of funded projects (>50). However, it is notable that more than 92% were obtained by the team leader. In addition, although the team has a leadership position in the genetics of autism, a major neurodevelopmental disorder with a high impact on health and education, interactions with industrial companies remain limited, and no patent licensing was obtained during this contract. Interactions with the

general public could be more developed (i.e. Forums des métiers, Forums des masters, associations de patients…).

### Analysis of the team's trajectory

The team's trajectory has been successfully developed across the years, starting from the identification of the genetic basis of autism to the development of innovative models based on multilevel data to predict the clinical trajectories of children with autism. These predictive models will be of crucial relevance: 1) to identify different forms of autism and neurodevelopmental disorders with similar or distinctive origins; 2) to stratify patients and design targeted clinical/educational trials for autistic patients; 3) to provide precision medicine and educative care for people concerned by autism and related disorders. The objectives of the team during the next mandate will be twofold. The first topic is the identification of risks and resilience factors in autism and neurodevelopmental disorders. By comparing genetic data from 13,000 patients with autism and 200,000 individuals from the general population, the team has shown that 4% of patients carried strong genetic factors. At the same time, 1% of the general population also carried them with lower cognitive performance combined with lower socio-economic status (Rolland et al., 2023), highlighting the importance of such genetic and environmental factors. The launch of the recent European-funded project, R2D2-MH, coordinated by the team leader, supports this objective. The second topic is fostering the innovation for new diagnostic and interventions for autism and neurodevelopmental disorders in Europe. Thanks to three European-funded projects, the team has set up tools to collect standardised multidimensional data relative to autistic patients. The team will build the InovANd Institute of Robert Debré to provide each child with the best diagnosis coupled with personalised care and education. Since 2022, the team leader has started the coordination of R2D2-Mental Health, a new European-funded project of €11 million gathering 22 institutions in Europe, Israel and Australia, which aims to identify both risk and resilience factors for neurodevelopmental disorders that will secure a part of their financial resources for the strategy of the next term, at least until 2027.

## RECOMMENDATIONS TO THE TEAM

Increasing the number of PhD students would be highly beneficial to the team, as well as promoting the participation of the junior team members in the diffusion of the team's autism research to the general public. The latter mission seems accomplished mainly through the activities of the team leader, through book publications and interactions with schools and families. Interactions between pre-clinical and clinical researchers should be promoted via regular joint initiatives and meetings. Recruiting a junior researcher with habilitation to conduct research is also important to secure the capacity to perform high-quality research and hire students.

**Team 2:** Channel-receptors

Name of the supervisor: Mr Pierre-Jean Corringer

## THEMES OF THE TEAM

Team 2 studies the mechanisms underlying membrane neurotransmitter receptors, emphasising pentameric channel receptors and G protein-coupled receptors (GPCRs). The team is composed of two separate subgroups, with one working on GPCRs and downstream interacting proteins (Usher complex and PDZ) in the auditory system, and the other one working on pentameric receptor channels and the regulation of their activation by the local environment, including allosteric modulators. The two themes reinforce each other as they use similar approaches and methodologies.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report mentioned the need to increase outreach activities. Team 2 has made a solid effort to participate in popularising science via the publication of videos and podcasts. It has also strengthened connections with private companies (BASF, CortecNet), welcomed young scientists and high school pupils, and increased participation with patient associations (deaf patient association).

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 0 |
| Maîtres de conférences et assimilés | 0 |
| Directeurs de recherche et assimilés | 2 |
| Chargés de recherche et assimilés | 3 |
| Personnels d'appui à la recherche | 4 |
| **Sous-total personnels permanents en activité** | **9** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 1 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 5 |
| Doctorants | 7 |
| **Sous-total personnels non permanents en activité** | **13** |
| **Total personnels** | **22** |

## EVALUATION

### Overall assessment of the team

**Team 2 is an excellent to outstanding research team** with research focused on molecular neuroscience, studying activity and control of post-synaptic receptors. It is subdivided in two subgroups that share common approaches but different scientific interests. They use state-of-the art techniques with dedicated high level. devices (cryo-electron microscopy, nuclear magnetic resonance and voltage-clamp fluorometry). The team published 38 articles during the evaluation period, with 21 of them as leading author. Given that the team has five full-time researchers and four full-time support staff, this is a satisfactory level of production. The publications include several in high impact journals that include Nature, Nature Communications, Science Advances and Plos Biology, as well as more specialised journals. The work of the team has important economic consequences as illustrated by the filing of a patent and its relationships with industrial partners such as SANOFI and BASF.

### Strengths and possibilities linked to the context

Among their main achievements, the researchers of team 2 have isolated bacterial pentameric channel receptors, determined mechanisms of desensitisation of GABA-A receptors, and developed a new model of

conformational changes of GlyR. They also pursue their study of the nicotinic acetylcholine receptors mechanisms of conformational changes and mode of actions of nanobodies and developed new cutting-edge techniques (Cryo-EM). They also studied protein-protein interactions in cochlea in the Usher type 2 syndrome and they enlighten a mechanism of interaction between the membrane protein usherin and two proteins containing PDZ domains. The team has a high level of international recognition, as illustrated by the team leader's numerous invitations to international meetings. He was awarded the CNRS Silver medal (2018) and an ERC Advanced Grant (2018). The publication record is globally excellent, with 38 articles, some in high-profile journals such as Nature, Nature Communications, Science Advances and Plos Biology. In particular, the team's remarkable contribution in the pentameric ligand gating ion channels field includes 6 articles and one review (Annu Rev Biochem) published in highly visible journals as last or co-last authors. The team has used a combination of state-of-the-art biophysical approaches, including molecular simulation, to study the molecular basis of these channels and the mode of action of ligands using allosteric modulators (small ligands and camelid antibody fragments called nanobodies). The team's ability to raise funding is excellent, with 2.8 M€ raised over the evaluation period (2017–2022) from international (ERC advanced), national (3 ANR as leader and 3 as partner), private partnerships (BASF) and charities (Fondation pour l'Audition). The team has an outstanding capacity to train PhD students (n=9). All of them published at least one article signed as first author. Many postdocs (n=7) were also trained. The team's staff are strongly involved in teaching (Pasteur teaching course) and disseminating knowledge, including to the general public (association of deaf patients).

### Weaknesses and risks linked to the context

The team leader is expected to assume a director's role in the future Unit. This situation raises questions regarding the management of his own projects on channel receptors. The organisation of the human resources, particularly the assignment of specific principal investigators (PIs) to manage these projects, is unclear. Two other risks concern the existence of separate subgroups with different aims and projects and the renewal of funding after the end of the ERC grant (2024).

### Analysis of the team's trajectory

The team's projects are well focused and highly relevant regarding scientific objectives. The techniques to be used are highly innovative (cryo-electron tomography). The development of nanobodies is very interesting and offers many possibilities. These projects are realistic and feasible since team 2 is a robust research group with high scientific standards, recognised researchers in the field (one holding the silver medal of the CNRS) and because new PIs joined the group during the last period. However, securing funding for the next contract will be critical, although several ongoing European and national grants (ANR) will hopefully guarantee funding.

## RECOMMENDATIONS TO THE TEAM

The main recommendation is to reinforce links between the two subgroups to avoid the risk of separation in the short-term period. This can be achieved by defining joint projects, and improved team management with regular meetings and workshops.

**Team 3:** Synapse and circuit dynamics

Name of the supervisor: Mr David DiGregorio

## THEMES OF THE TEAM

Team 3 is dedicated to research on elucidating the role of nanoscale organisation of synapses in the control of neural circuit activity and associated behaviours. Researchers of the team use ex vivo cerebellum preparations to study microcircuits and use state-of-the-art techniques such as STED, 2-Photons, and calcium imaging techniques coupled with mathematical models. They planned to go one step beyond by developing in vivo experiments to study all levels from nanoscale synaptic physiology to behaviour.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report mentioned lack of funding as a weakness, but team three obtained 4 ANR grants and one FRM subvention during the reporting period, which secured the team's research.

The report also encouraged increasing the amount of editorial work, but this was not possible given that the PI accepted a heavy charge related to the direction of the Institut Pasteur's Neuroscience Department during the current evaluation period.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 0 |
| Maîtres de conférences et assimilés | 0 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 1 |
| **Sous-total personnels permanents en activité** | **3** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 0 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 6 |
| Doctorants | 2 |
| **Sous-total personnels non permanents en activité** | **8** |
| **Total personnels** | **11** |

## EVALUATION

### Overall assessment of the team

Team 3 had an ambitious project to associate nanoscale mechanisms of presynaptic activity to behaviour. In the period of evaluation, they studied these presynaptic mechanisms underlying neural circuit integration in well-known microcircuits of the cerebellum. Some of the results were published in high impact journals that include Neuron and Nature Communications. Additionally, the team has developed tools to study synaptic activity and neural circuit activity, using new sensors and computational models. These technological tools have also been published in high quality journals that include Nature Methods and the Journal of Neuroscience. They make a point of using open science journals and make the methods available to the community using open source models. Given that the team includes two permanent researchers, the overall production of ten articles is reasonable but not outstanding. Overall, **this is, however, an excellent team.**

### Strengths and possibilities linked to the context

For a small team composed of just two researchers with permanent positions, the team nevertheless benefited from the availability of several postdocs (n=11) and PhD students (n=4). They successfully developed cutting-edge devices using 2-photon microscopy and high-resolution microscopy, including the first acousto-optical microscope in France that allows ultra high-speed two-photon imaging in 3D.
The team was well funded, obtaining around 1.5 M€ of funding during the evaluation period, including five grants supported by ANR (two as coordinator).

### Weaknesses and risks linked to the context

The team's small size, absence of any new permanent staff, reliance on external funding, and limited technical support are all clear weaknesses. However, the decision of the team leader to take up a position at the University of Colorado recently means that such considerations are no longer pertinent.

### Analysis of the team's trajectory

Not applicable since the team leader has moved to the USA and was not interviewed

## RECOMMENDATIONS TO THE TEAM

Given that the team is not part of the unit's future project and was not interviewed, the panel has no recommendations.

**Team 4:** Perception and Memory

Name of the supervisor: Mr Pierre-Marie Lledo

## THEMES OF THE TEAM

Team 4 is dedicated to understanding how brain circuits control behavioural responses. More precisely, team 4 uses cutting-edge techniques of neural circuit dissection to understand the function of brain circuits using a multi-scale approach, that emphasises interactions with other parts of the body and their potential dysfunction in disease. It is an ambitious and wide project divided into five topics: neuronal replacement, neuro-inflammation, emotions and sensory representation, olfaction and emotion disorders, and brain-gut interactions.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report noted the large number of research topics covered, with a risk of dispersion. The current project brings together all these themes under a very general umbrella, going from neuronal replacement to the brain-gut axis through psychiatric disorders. Overall, the team's objectives remain very general, and the panel could not identify a set of specific working hypotheses or axes that guide the team's direction. In that sense, the situation has not evolved. However, the scientific productivity of the team remains outstanding, suggesting that this lack of clear focus might be a successful strategy rather than a weakness.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 2 |
| Maîtres de conférences et assimilés | 1 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 5 |
| Personnels d'appui à la recherche | 2 |
| **Sous-total personnels permanents en activité** | **11** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 3 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 6 |
| Doctorants | 4 |
| **Sous-total personnels non permanents en activité** | **13** |
| **Total personnels** | **24** |

## EVALUATION

### Overall assessment of the team

Globally, **the panel considered that the team is excellent to outstanding**. The level of scientific production is remarkable, with a total of 42 original and review articles, most of them in top-ranking journals that include Nature Medicine, Science Translational Medicine, Science, Cell, etc. Team members were leading authors for virtually all of them. Given that the team comprises 9 permanent researchers, this implies around one publication per year each, which is very good taking into account high reputation of some of these journals. The level of funding is excellent with several long-term funding initiatives, but even during the course of the evaluation period the team has obtained around 1.6 M€ of funding.
The team works on many different topics to understand how brain circuits control behaviour in health and disease. The team is dynamic with 24 people including 6 post docs (13 hired during the contract) and 4 PhD (11 trained during the last contract). The team also benefits from two permanent technical staff.
Team 4 is committed in collective tasks for the institute and has a strong track record of communication toward society and economic world.

## Strengths and possibilities linked to the context

By studying the relationship between the body and the brain, the team has demonstrated the importance of the intestinal microbiota in triggering depression (Nat Comm 2020; Cell Report 2020). They have also shown the importance of nerve connections along the gut-brain axis and, in particular, the key role of the vagus nerve (JCI Insight 2022; Mol Psy 2023). Finally, they have also shown the key role of blood circulation in the gut-brain axis by showing that food consumption is under the control of bacterial compounds that act from the gut directly to the brain (Science 2022). The level of publication during the evaluation period is outstanding both in terms of productivity and in terms of quality. The researchers of the team have collectively contributed to more than 40 peer-reviewed articles which, in most cases, were signed by a team member as lead/senior author. Many of these articles were published in prestigious journals such as Science, Cell, Neuron, Nature Communication, Cell Reports. Similarly, the ability of the team to raise funding is outstanding. The team obtained grants from a variety of international and national agencies (NSF, HFSP, H2020, ANR, Several Life Insurance Foundations, France Parkinson, FRM to name a few), and academic consortium (e.g. Labex), for a total of 12.5 Million Euros.

The team has a critical mass that is impressive with a total of 24 members, with fifteen out of them holding permanent positions (7 Scientists, 5 Clinicians,1 Engineer and 2 Technicians). This can allow the team to work with stability and take risks. The team has a strong and diverse outreach activity that includes publishing popular books in French, writing articles in the general press, and participation in round-tables and radio shows.

## Weaknesses and risks linked to the context

A significant weakness of the team is that despite its outstanding scientific production, it was hard for the panel to distinguish clear scientific directions or working hypotheses, either when looking at the written document or during the interviews. It was also very difficult for the panel to understand the team's organisation. During the online presentation, the name of six researchers was associated with six general directions, many overlapping, making it challenging for the panel to evaluate the synergy between those researchers and the number of PhD students/postdoc they supervised. It appears that the team leader is leading all those projects. Because the PI will retire at some point during the next evaluation, it would have been helpful to evaluate the degree of independence of the other researchers to help envision clearly the future directions and leadership of the team.

In addition, there was no concrete evidence for clear collaborations with the other teams of the institute. All these weaknesses are mitigated by the outstanding production of the team and its ability to obtain funding, which suggests that the lack of clarity in the team's organisation may allow for an agile workforce redeployment according to scientific opportunities.

## Analysis of the team's trajectory

Team 4 is a very strong team with eleven permanent staff members, an impressive track record and an outstanding level of funding. Although there is no mention of the recent recruitment of new PIs, the team is large enough to succeed in reaching the research aims. There are only four contracts covering the start of the next contract, which means that the team will need to secure funding rapidly.

# RECOMMENDATIONS TO THE TEAM

Taking into account the heavy administrative duty of the team leader, the panel recommends spreading the responsibility for each research topic to other PIs of the group.

**Team 5:** Integrative neurobiology of cholinergic systems

Name of the supervisor: Mr Uwe Maskos

## THEMES OF THE TEAM

The team focuses on unravelling the role of nicotinic acetylcholine receptors (nAChRs) in neuropsychiatric disorders, particularly drug addiction, schizophrenia, and Alzheimer's disease. They also investigate peripheral system pathologies, including autoimmune psychosis, chronic obstructive pulmonary disease (COPD), and lung cancer. They use animal and cell models, brain imaging, and translational approaches to understand mechanistic contributions and test hypotheses in patient cohorts. Their methodologies include in vivo brain imaging, cognitive modelling, human induced pluripotent stem cells (hiPSCs), and collaborative studies with clinical teams.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended, at the level of the unit, developing inter-group collaborations. The team contributed to such collaborations by participating in two main projects: a rational drug-design approach with team 3, capitalising on the structural biology expertise of team 3, and a collaboration with team 2 on a project involving establishing two-photon imaging of the prefrontal cortex. This aims to investigate the role of human mutations in nicotinic receptors on excitatory-inhibitory microcircuits. These collaborative efforts highlight the interdisciplinary approach of the GSC Unit and its commitment to advancing research. In addition, as recommended, the team successfully recruited a new permanent researcher and a technician.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 0 |
| Maîtres de conférences et assimilés | 0 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 2 |
| Personnels d'appui à la recherche | 5 |
| **Sous-total personnels permanents en activité** | **8** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 0 |
| Personnels d'appui non permanents | 1 |
| Post-doctorants | 5 |
| Doctorants | 6 |
| **Sous-total personnels non permanents en activité** | **12** |
| **Total personnels** | **20** |

## EVALUATION

### Overall assessment of the team

This **excellent to outstanding team** focuses on unravelling the role of nicotinic acetylcholine receptors (nAChRs) in neuropsychiatric disorders through animal and cellular models, employing cutting-edge technologies for brain activity assessment. Their substantial funding exceeding 5M€ from ANRs, ERANET, INCa, and FRM supports their research, facilitating the translation of preclinical insights into potential treatments. With 41 peer-reviewed publications, including 29 in prestigious journals, and a significant portion in leading positions, including three invited reviews, alongside international postdoc recruitment, their excellence and attractiveness in the field are evident.

## Strengths and possibilities linked to the context

The team possesses outstanding expertise in the field of neurobiology, particularly in the study of nAChRs and their role in neuropsychiatric disorders. In particular, the team published papers on the role of non-neuronal nicotinic receptors linked to COPD (Nature Comms 2021) and peripheral inflammation (Transl Psych 2024), as well as the influence of the microbiome (NPP 2023). Highly productive in scientific publications, the team has produced 41 publications in peer-reviewed journals, with 29 appearing in renowned journals, including three invited reviews, with more than a third in leading positions. Notable highlights include publications in high-impact journals such as Nature Medicine, Neurobiology of Aging, and Current Biology. Scientific production is logically distributed within the team. Additionally, they have received 9 invitations to keynote presentations at conferences such as Embo and Eranet. They aim to comprehend the mechanisms of central and peripheral pathologies using animal and cellular models and develop cutting-edge technologies for assessing brain activity. For example, they have implemented two-photon *in vivo* calcium microscopy for brain imaging in rodents. This technology allows for precise and high-resolution imaging of neuronal activity in live animals, providing insights into brain function and dynamics at the cellular level. They also conduct hiPSC work *in vivo* to unravel the genetic and cellular mechanisms of psychiatric disorders. Their research extends to translating preclinical findings into potential treatments. New projects have been initiated in connection with the Institut Pasteur's priorities on 'Microbes and Brain' and their links to autoimmune disorders. They engage in interdisciplinary collaboration with national and international preclinical and clinical teams, spanning France, Canada, and Ukraine. The team demonstrates excellent attractiveness with students and postdocs recruited from eleven countries, including Italy, Spain, Portugal, the United Kingdom, Brazil, Iran, Croatia, Hungary, Greece, Germany, and Poland. They contribute significantly to the societal impact of their research activity with two US and European patents filed. The team has obtained extensive funding from ANRs (4) and ERANET (1) as coordinator, but also from INCa, and in addition was labelled as an 'FRM Equipe'. Additionally, they participate in the recently funded IHU 'reConnect' supported by the Institut de l'Audition, which is also a unit within the Institut Pasteur.

## Weaknesses and risks linked to the context

More than half the team's staff are on temporary contracts, overseen by a sole research director who also assumes the role of team leader and directing the Pasteur Institut's Department of Neuroscience. This configuration prompts several considerations for the future, particularly regarding the management of numerous projects. There is a need for clarity in organising human resources, specifically in assigning designated principal investigators (PIs) to oversee all ongoing projects, with delegation of responsibility to other researchers within the team. Such a restructuring will not only enhance the development of these researchers' careers but also ensure the sustainability of the team's endeavours. While there is significant engagement in societal communication and participation in Institut Pasteur's internal training programs (predominantly overseen by the team leader), the level of involvement in university teaching appears to be limited.

## Analysis of the team's trajectory

Team 5's project aims to advance the understanding of various aspects related to neurobiology and associated diseases, building upon solid foundations and several excellent publications. The project encompasses various focal points, ranging from advancing the understanding and treatment of neurodegenerative diseases such as Alzheimer's, to exploring associated autoimmune diseases, with particular attention to the potential role of the microbiota. Additionally, the team will continue to advance cutting-edge technologies to enhance their experimental methodologies. These objectives align well with the unit's themes and other projects at the Pasteur Institute, fostering numerous collaborations. The team comprises a significant staff size, with a majority on non-permanent contracts. Funding sources are as yet insufficient for the beginning of the next contract.

# RECOMMENDATIONS TO THE TEAM

The panel's recommendations are as follows:
First, stabilise temporary staff within the team to ensure long-term stability and expertise. Efforts should also focus on attracting academic staff (i.e. 'maîtres de conférences' or professors).

Second, clearly and formally identify responsibilities within the team, with a Principal Investigator assigned to each project. This should support the career advancement of permanent staff by providing professional development opportunities and gender balance improvement, thus ensuring the long-term sustainability of the team.

Additionally, it is advisable to limit the number of projects undertaken by the team based on the resources available in the coming years. This will effectively manage the workload and ensure adequate attention and resources for each project.

**Team 6:** Decision and Bayesian computation

Name of the supervisor: Mr Jean-Baptiste Masson

## THEMES OF THE TEAM

The Decision and Bayesian Computation team aims to understand information processing in biological systems, using Drosophila as the primary experimental model. The team has been developing several software packages to help understand the computational substrates underlying information processing and developed applications in a wide range of areas.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The self-evaluation report simply states that the team followed the recommendations of the previous Hcéres panel concerning overextension concerning scientific topics and methodologies. In this respect, they completed two research axes related to biomolecular dynamics in cellular organelles and the development of Virtual Reality data analysis and visualisation. They have now focused their research on embodied neuroAI using Drosophila larva as the model system.

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

| Catégories de personnel | Effectifs |
|---|---|
| Professeurs et assimilés | 0 |
| Maîtres de conférences et assimilés | 0 |
| Directeurs de recherche et assimilés | 1 |
| Chargés de recherche et assimilés | 1 |
| Personnels d'appui à la recherche | 5 |
| **Sous-total personnels permanents en activité** | **7** |
| Enseignants-chercheurs et chercheurs non permanents et assimilés | 0 |
| Personnels d'appui non permanents | 0 |
| Post-doctorants | 2 |
| Doctorants | 5 |
| **Sous-total personnels non permanents en activité** | **7** |
| **Total personnels** | **14** |

## EVALUATION

### Overall assessment of the team

The panel considers that **this is an excellent to outstanding team**. It is a highly original research group that combines a number of innovative approaches with the aim of understanding the physical principles underlying biological information processing. Specifically, they are trying to develop a fully embodied neuroAI model of the Drosophila larva that can elucidate the underlying computational constraints.
During the evaluation period, the team produced 23 publications, 4 of which were published in collaboration with other teams within the lab. The journals are of variable quality, but include PLoS Computational Biology, Journal of Molecular Biology, Frontiers in Bioinformatics, Scientific Reports, and Bioinformatics. There are other journals that are surprising for a Neuroscience department (SIAM Review, Physical Review) and reflect the unusual background of the two PIs.
In particular the team has developed Genuage, a software package for visualising multidimensional point cloud data using virtual reality, published in Nature Methods in 2020. The team has also been directly involved in the creation of Avatar Medical which has employed up to 9 scientists and engineers.

## Strengths and possibilities linked to the context

During the period from 2017–2022, the team obtained 562 k€ of funding, including five ANR-funded projects as coordinator. The team's two permanent researchers have both been selected to Prairie Research Chairs for the Paris Region AI Research Institute.

The team has also been involved in creating a spinoff – AVATAR Medical – which was one of the three recipients of the 2022 European Innovation Council's accelerator funding call. It is developing visualisation techniques to help in cardiac surgery.

The team published 23 papers during the period, with publications in reviews that include Scientific Reports, PLoS Computational Biology, PLoS Genetics, Cell Reports, and J Physics. Many of the team's publications involve collaborations with other labs. Indeed, it is clear that the team's expertise is much in demand. The team is well connected internationally, with active partnerships with the Janelia Research Campus and the Allen Institute in the USA.

## Weaknesses and risks linked to the context

The team openly admits that it is not particularly active in sharing its knowledge with the general public, with the exception of occasional events to promote their software packages.

There was also a lack of international funding (1 fellowship only).

## Analysis of the team's trajectory

The future of the team will concentrate on four primary areas. The first concerns the development of mathematical models and algorithms and the development of software packages, and it is hoped that this will be done in collaboration with INRIA. There is even the possibility of the team being attached to INRIA, which would be a very unusual development because there are only a few teams with INRIA labelling outside the main INRIA campuses.

The other themes concern Embodied NeuroAI, the study of neurodegenerative and neuro-inflammatory diseases using Drosophila larvae as an experimental model, and the development of novel statistical methods.

These are ambitious projects, but the team is well placed to take advantage of its network of contacts and ensure the feasibility of the projects. The team has an ANR contract overlapping the current and next contract periods to ensure a smooth translation.

# RECOMMENDATIONS TO THE TEAM

The panel was impressed by the breadth of approaches developed by this small team, composed of just two permanent research staff. While the individual research projects are certainly interesting, the thematic coherence of the team is difficult to perceive, and there is a fear that the choice of topics is opportunistic rather than motivated by a clear vision in neurosciences.

One solution would be to recruit additional staff members who could each be assigned more specific research topics. This may be possible in the context of an affiliation with INRIA.

However, without such additional manpower, the panel considers that it may be better to restrict the number of topics to ensure more thematic coherence and to make efforts to obtain funding at the international level.

# CONDUCT OF THE INTERVIEWS

## Date

**Start:** 15 mars 2024 à 8 h 30

**End:** 15 mars 2024 à 18 h

**Interview conducted: online**

## INTERVIEW SCHEDULE

8:30-9:00 Welcome coffee (closed-door): Visiting committee with the Hcéres advisor

9:00-9:10 Presentation of the evaluation process to the unit by the Hcéres advisor

9:10-9:55 Presentation of the unit scientific outputs and strategy by the lab director

(25′ presentation + 20'discussion)

9:55-10:15 Coffee break

10:15-11:45 Presentation of the scientific program and research results by group leaders

(15′ presentation + 15'discussion)

Team #6: Decision and Bayesian computation (Jean-Baptiste Masson)

Team #1: Human genetics and cognitive function (Thomas Bourgeron)

Team #2: Channel-receptors (Pierre-jean Corringer)

11:45 a.m.-1 p.m. Lunch

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

(15′ presentation + 15'discussion)

Team #4: Perception and Memory (Pierre-Marie Lledo)

Team #5: Integrative neurobiology of cholinergic systems (Uwe Maskos)

2 p.m.-3:15 p.m. Debriefing (closed-door with the committee and Hcéres advisor)

3:15 p.m.-3:30 p.m. Coffee break

**Meetings with the various categories of staff**

3:30 p.m.-4 p.m. Discussion with engineers, technicians and administrative personnel (in French)

4 p.m.-4:30 p.m. Discussion with PhD students and post-docs

4:30 p.m.-5 p.m. Discussion with scientists (without team leaders)

5 p.m.-5:30 p.m. Discussion with present team leaders (without present/future lab directors)

5:30 p.m.-6 p.m. Discussion with the representative of the managing bodies (closed-door)

6 p.m.-6:30 p.m. Discussion with the directors (past and future) (closed-door)

6:30 p.m.-7 p.m. Private meeting of the visiting committee (closed-door)

7 p.m. End of the interview

## PARTICULAR POINT TO BE MENTIONED

There was no interview of team 3. The team leader has accepted a position in the USA and never replied to our invitation.

# GENERAL OBSERVATIONS OF THE SUPERVISORS

The institution responsible for submitting the application, which is also responsible for coordinating the response for all the research unit's supervisory authorities, has not submitted any general comments.

The Hcéres' evaluation reports are available online:
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