Evaluation of Research

EVALUATION REPORT ON THE UNIT

IGF - Institut de Génomique Fonctionnelle

UNDER THE SUPERVISION OF INSTITUTIONS AND RESEARCH BODIES:

Université de Montpellier

Centre national de la recherche scientifique - CNRS

Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2025-2026
GROUP A

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High Council for the evaluation of research and higher education

On behalf of the committee of experts:

Christophe Mulle, Chairperson of the committee

For Hcéres:

Coralie Chevallier, Présidente du Hcéres

In accordance with articles R. 114-15 and R. 114-10 8° of the Research Code, evaluation reports drawn up by the committees of experts are signed by the chairpersons of these committees and countersigned by the president of Hcéres.

To facilitate the reading of the document, the terms used in this report to designate functions, occupations or responsibilities (expert, researcher, teacher researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are generic and gender neutral.

This report is the outcome of an evaluation by a committee of experts the composition of which is specified below. The assessments it contains are an expression of the independent and collegial deliberation of the committee. The data within it are the certified accurate data extracted from the application forms submitted by the supervising bodies on behalf of the unit.

This version of the report is public under Article R. 114-23 of the Research Code. Sections of the report considered confidential, and responses to points of attention from supervisors are not included in it.

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UNIT CHARACTERISATION

- Name: Institut de Génomique Fonctionnelle
- Acronym: IGF
- Label and number: UMR 5203, U1191
- Number of teams: 23
- Composition of the executive team: Mr Philippe Marin (Unit director), Ms Nathalie Guérineau (deputy director), Mr Thierry Durroux (deputy director) and Ms Audrey Fisseau (general secretary)

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The main objective of the IGF is to decipher the mechanisms underlying cell communications at the molecular, cellular and physiological levels and their alterations in pathologies, in order to identify novel therapeutic targets for innovative treatments. There is a strong historical focus on GPCRs (G-protein coupled receptors) from structure to function and ion channels, on cell signalling or cell-cell communication mechanisms. The IGF is currently structured in two scientific departments which illustrate the fields covered by the research teams: a "Neuroscience" department (with 14 teams), and a "Physiology and Cancer" department (with 9 teams) involved in cardiology, endocrinology and cancer biology.

A general scientific objective of the IGF is to provide new basic information, and develop innovative tools and approaches in cell communications within these areas, as well as to translate these findings in the development of novel therapies. Studies are conducted to elucidate the basic mechanisms involved in physiological processes and how these can be affected in various pathologies, including neurological and psychiatric diseases, heart dysfunction, neuroendocrine disorders, diabetes and cancer. The basic biomedical research topics of the teams are based on multi-disciplinary approaches and on multiple levels of complexity, spanning from molecular and structural studies of signalling molecules at the atomic scale, to investigations of molecular networks at the cell, organ, and whole animal level. Four main topics are covered: 1) GPCR structure, signaling and function; 2) cell biology and physiology of voltage-gated ion channels and ligand-gated channels; 3) cellular signalling networks and their physiological and behavioural impact; 4) development of new therapeutic approaches by translation to clinical studies of basic biomedical research findings. The scientific projects are made possible by the close proximity of technological facilities, providing the teams with state-of-the-art technologies in genomics, proteomics, in vivo imaging and medium throughput analysis of signaling events. The teams mainly perform animal experimentation using mouse, zebrafish and Drosophila. In addition, many of the teams implement or develop innovative approaches to study cell communication in human samples and cells (e.g. functional explorations on human sensory neurons and spinal cord).

The IGF has established strong collaborations with clinical teams of Montpellier University Hospital, favouring translational research. In parallel to the basic research projects, some IGF teams are led by clinicians with a clear biomedical focus (psychiatric diseases, brain tumours, diabetes).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Institute of Functional Genomics (IGF) was created in 2005. It originates from the CNRS and Inserm Center of Pharmacology and Endocrinology (CCIPE) which became affiliated with both the University of Montpellier and to the Inserm upon its creation. In the last two decades, the IGF has grown to become a major biomedical research institution in France and Europe, building on, and expanding from, the initial scientific themes centered on cell signalling processes and the development of innovative pharmacological tools.

The IGF is located within the Arnaud de Villeneuve (AdV) CNRS Campus located in the North of Montpellier. The current IGF is then composed of two interconnected buildings, one of which opened in 2010, covering a total of 6,560 m2. This provided space to research groups (including new groups) and a few start-up companies, and to further expand and develop the technological facilities that are now part of the service unit Biocampus.

The close proximity of the IGF with the University hospitals, the new Faculty of Medicine and the other major sites dedicated to health and biological research in Montpellier, is a major asset of the unit, considering that it favours scientific interactions with other major biology and clinical research laboratories in Montpellier. Within the AdV Campus, the IGF is directly connected with the Institute of Human Genetics (IGH) and in close proximity to the Center for Structural Biochemistry (CBS).

In addition, the site hosts the Inserm regional administration, and Genopolys, a service unit building dedicated to communication and training, offering a conference amphitheater, meeting rooms and laboratories for training sessions directed toward the lay public, the industry or clinicians.

UNIT RESEARCH ENVIRONMENT

The IGF is major research unit of the University of Montpellier, with both the CNRS and Inserm as supervising bodies. As such, the IGF hosts a large number of teachers-researchers (33 professors and associate professors), as well as staff scientists and technical support from the CNRS (42 staff scientists) and Inserm (22 staff scientists), and technical support on either permanent positions or short-term contracts from the CNRS and Inserm (115 ITAs).

The IGF researchers are involved in numerous training programs of the University (at the bachelor, master and PhD level) and actively participate in the governance of the University's Biology and Health Pole. The University of Montpellier is labeled as an i-SITE (Initiatives – Science - Innovation - Territoires – Economie), in frame of the Future Investments Programme (PIA). This allows the IGF to have access to funding for emerging, and collaborative interdisciplinary research projects which reached more than 1.1 M€ across 15 research grants over the reporting period. Through the i-SITE funding, the Biology and Health Pole of the University has launched long thematic programs (PTLs), which can directly benefit the IGF teams (development of new complex cellular models, and analysis at high spatial and temporal resolution), with a strong involvement from IGF researchers.

The IGF host technological platforms of the service unit Biocampus, three of which are part of National Infrastructures in Biology and Health: the genomic MGX platform (France Genomics infrastructure), the life imaging IPAM platform (France Bio Imaging infrastructure) and the proteomics platform (ProFi infrastructure).

The IGF has established and long-standing collaborations with clinical teams of Montpellier University Hospital, facilitated by its close vicinity to the hospitals and the new Faculty of Medicine of Montpellier, and by the presence of hospital practitioners in the majority of the IGF teams (24 PUPH, MCUPH, PHU or PH). The translational research topics covered by major collaborations includes stroke, chronic pain, spinal cord injury, multiple sclerosis, and cancer.

IGF teams are also involved in national collaborative programs with IGF researchers being part of the management bodies, including i- GPCRnet International Research Network, GDR "Microglia and Neuroinflammation" – now a "Thematic Network" of the CNRS, APPICOM thematic network.

UNIT WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	24
Maitres de conférences et assimilés	9
Directeurs de recherche et assimilés	28
Chargés de recherche et assimilés	40
Personnels d'appui à la recherche	63
Praticien hospitalier	7
Sous-total personnels permanents en activité	**171**
Enseignants-chercheurs et chercheurs non permanents et assimilés	33
Personnels non permanents d'appui à la recherche	57
Post-doctorants	5
Doctorants	73
Sous-total personnels non permanents en activité	**168**
Total personnels	**339**

BREAKDOWN OF THE UNIT'S PERMANENT STAFF BY EMPLOYER: IN PHYSICAL PEOPLE AS OF 31/12/2024. NON-SUPERVISING EMPLOYERS ARE GROUPED ON THE HEADING "OTHERS".

Nom de l'employeur	EC	C	PAR
U Montpellier	26	0	4
CNRS	0	42	36
Inserm	0	26	21
Autres	7	0	2
Total général	**33**	**68**	**63**

GLOBAL ASSESSMENT

The IGF stands as a highly recognized biomedical research center with a long-standing and excellent national and international visibility. The scientific policy is very clear with scientific themes centered on cell signalling processes and the development of innovative pharmacological tools. The IGF is a multidisciplinary research institute combining expertise in neuroscience, endocrinology, cardiology and cancer biology. This disciplinarity diversity fosters strong scientific and technological interactions across the unit; the predominance of neuroscience related topics in most teams is considered by all team leaders as an asset. The IGF teams, which range overall from excellent to outstanding, perform exciting science with innovative cutting-edge technologies. The excellence of the research at the IGF is supported by a very efficient infrastructure, a modern building and several high-quality platforms and facilities. Overall, the IGF is a vibrant and healthy research environment with a fluid organization, excellent platform services and coordination. Its strategic location within the biomedical and University campus allows for strong collaborations with clinicians, in addition to multiple productive collaborations between the teams. All the teams have been very successful in raising competitive funds for their research. The productivity has increased very significantly over the previous mandate, keeping a very high standard with a considerable number of high-profile research articles. A substantial number of these articles stem from internal and international collaborations. The IGF published around 1250 articles during the reporting period, including publications with authors in positions of responsibility in prestigious generalist journals such as Science Advances, Nature Communications, PNAS, Current Biology, eLife, and high-ranked journals in the fields of neuroscience, neuropsychiatric disorders or inflammation such as Nature Neuroscience, Brain, Molecular Psychiatry, Immunity, Journal of Neuroinflammation. The IGF is very well integrated in the socioeconomic world with successful interactions with industries, and a strong implication in sharing knowledge with the general public and patients' organizations. The scientific trajectory for the next mandate is exciting, based on a strong impetus on innovative strategies and on emergence of new methodologies. The IGF presents a well-structured plan aimed at strengthening the position of the Institute as a major biomedical center exploring biological mechanisms at multiple levels, from basic to translational research.

DETAILS OF THE EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations of the previous Hcéres evaluation report have been taken into account, along the different points listed below.

The IGF has kept "a high level of scientific output and to focus on projects based on core expertise and methodologies". There is a considerable augmentation of the productivity, when compared to the previous term (1,252 *vs*. 728 papers in the previous term), with 10% considered to be in "highly visible" journals.

"Involvement of PIs in Master programs to attract PhD students". Several IGF scientists have taken on responsibilities in Master's courses of the University of Montpellier. There is a clear increase in the number of PhD students trained as compared to the previous term (144 *vs*. 84). The IGF remains an attractive research center for students of the CBS2 doctoral school. Actions may be still be considered to increase the international visibility of PhD training opportunities at the IGF. In addition, it may be worthwhile to improve the overall level of supervision provided by to PhD students by researchers (holding or not an HDR), taking into account the fact that the number of fellowships provided by the CBS2 doctoral school is limited, but other fund sources exist.

The "number of co-authored publications across IGF teams" is very satisfactory (circa 30%). Collaborative grant funding has been improved. The IGF has been efficient in promoting the use of electronic lab books.

The "transfer of power from the Executive group to the PI Council" has been very smooth.

The management team has taken appropriate actions to "improve dissemination of information internally".

Ensuring "technical support to each team" is still not ideal due to budgetary cuts, but the IGF has created a very interesting core facility (R&D service) to support many of the teams' technical needs.

The numbers of women team leaders will increase during the next mandate (from 5 women out of 30 currently to 9 women out of 29 team leaders at the beginning of the next mandate). Further measures should be progressively taken to improve this ratio.

The IGF has strongly improved the quality of support provided to the teams.

With regards to a "strategy for translational project development", the IGF has kept strong relationships with the university hospital and can take advantage of a significant number of hospital practitioners in the teams. The IGF acknowledges that efforts must be pursued in that direction, and further exploit the opportunities given by the proximity with clinicians.

The recruitment of two new teams, as well as the proposed internal reorganization of teams within the IGF, fit well with the main focus on mechanisms of cell communication investigated at multiple scales.

Regarding the "user demands for a non- SPF facility", the IGF has created a novel conventional animal facility (EXPE 3), including 8 novel rooms dedicated to animal experimentation, at the beginning of 2021.

Overall, the institute has addressed most of the recommendations in an effective manner, demonstrating a clear commitment to improving its scientific environment, internal organization, and long-term strategic vision.

B - EVALUATION AREAS

EVALUATION AREA 1: THE UNIT'S SCIENTIFIC OBJECTIVES, ORGANIZATION AND RESOURCES

Assessment of the unit's scientific objectives, organization and resources

The IGF 's scientific objectives, organization, and resources are excellent to outstanding, with a long-standing and excellent national and international visibility, with clear general objectives. This is supported by excellent infrastructure, a modern building, located in a strategic environment within the biomedical and University campus. The IGF strongly invests in Biocampus platforms, which creates outstanding conditions for developing the scientific objectives. The IGF practices in terms of organization, health and safety, data protection and human resources appear fully satisfactory.

1/ The unit has set itself relevant scientific objectives and is organized accordingly.

2/ The unit has resources adapted to its scientific objectives, profile of activities and research environment and mobilizes them.

3/ The unit has premises, equipment and technical skills adapted to its scientific policy and research objects.

4/ The unit's practices comply with the rules and guidelines set by its supervisory bodies in terms of human resources management, safety, environment and data protection as well as scientific assets.

Context-related strengths and opportunities for the four references above

1) The IGF has set clear objectives as a biomedical research center with a long-standing and excellent national and international visibility. All the IGF research teams study cell communications, at multiple scales of analysis, in physiological and pathological conditions, with the aim to identify novel therapeutic targets for innovative treatments. A clear strength and originality of the IGF lies in its multidisciplinarity, as team projects integrate topics related to neuroscience, endocrinology, cardiology or cancer biology, with a predominance of neuroscience.

2) The financial resources appear outstanding, especially with a considerable increase in grants raised by the teams of the IGF since the beginning of the current mandate. There is a large variety of financial sources from national to international public bodies, as well as from foundations and through industrial contracts. 3) The IGF has outstanding technical resources in the specific teams, and as a consequence of a long-term involvement in developing common technical platforms which are part of the service unit Biocampus, and operated by skilled technical support employees. As examples of new achievements during the current mandate, it is worth highlighting the creation of a conventional animal facility, of a core facility (R&D service) to support teams' technical needs, and a histology platform. Overall, there is a strong investment of the IGF in Biocampus platforms, which creates outstanding conditions for developing the scientific objectives. 4) The IGF management team complies with the rules and guidelines of its supervisory bodies. It makes commendable efforts in the management of human resources through a well-defined process of career advancement. The IGF has taken interesting steps toward a sustainable development policy, exemplified by its actions to support bicycle use, an effort that should be further continued. Health and safety measures are implemented in a fully satisfactory manner. There is an overall satisfying gender balance, except at the level of scientists and team leaders, for which a significant improvement is planned during the next mandate.

Context-related weaknesses and risks for the four references above

1) The rationale for a current general organization in two departments (Neuroscience and Physiology) does not appear extremely clear (discussions on this point during the site interviews) and may create artificial borders. In fact, this division will not be pursued in the next mandate. 2) Budgetary restrictions at the national level have led to a sizeable loss of common support from the supporting institutions, as well as at the local level (for the building projects). This may hamper some of the actions targeting collaborative projects for instance. With regards to the high international visibility of the IGF, and the world-leading position of its teams, the success in obtaining large grants like ERC grants could be improved (1 ERC grant currently, and one Impulscience). 3) The IGF faces an important risk of flooding on the AdV Campus threatening conventional animal facilities and areas dedicated to animal experimentation. In order to eliminate this risk, the construction of a new building is planned, although the financial plans do not appear secured yet. 4) As in many research units in biology, the gender balance is not satisfactory at the level of team leadership, albeit this will significantly improve during the next mandate.

5) Although the management team is perceived as doing a great job by the community, additional efforts may be implemented to improve the communication process – in particular by making the team leader reports accessible to all IGF members.

EVALUATION AREA 2: THE UNIT'S SCIENTIFIC RESULTS, IMPACT AND ATTRACTIVENESS

Assessment of the unit's scientific results, impact and attractiveness

The IGF 's scientific results, impact and attractiveness are excellent to outstanding. The institute is highly recognized for its scientific achievement in the field of cell-cell communication at multiple biological scales. This is exemplified by the excellent level and quality of the publications, with a marked rise in the number of publications compared to the previous mandate. IGF researchers are highly visible at the national and international levels, showing strong participation in international collaborative networks. Two new teams have been recruited following a competitive evaluation process during the reporting period.

1/ The unit is recognized for its scientific achievements that meet quality criteria.

2/ The research activities of the unit result in quality scientific production.

3/ The unit participates in the coordination and management of its community.

4/ The unit's scientific production respects the principles of scientific integrity, ethics and open science. It complies with the guidelines applicable in this field.

Context-related strengths and opportunities for the four references above

The scientific production reflecting the multi-scale research performed at the IGF, from molecular to physiological and translational studies, is excellent to outstanding. It is very noteworthy that there has been a very significant rise in the number of publications over the previous mandate (1,242 original articles vs. 728

publications), with 42% of articles signed in positions of responsibility. The list of "main" publications provided at the IGF website highlight a very significant number of high-level publications in large-audience journals, such as Science Advances (8), Nature Communications (33), Cell Reports (9), eLife (15), Current Biology (3). A large proportion of papers published in high-level journals correspond to studies of GPCRs and ion channels (from structure to function), which remain as a highly visible strength of the IGF worldwide. Nonetheless, the unit has also been very productive in the fields of endocrinology, inflammation, molecular and integrated neuroscience, cardiovascular diseases and cancer.

Internal collaborations between several teams are highlighted by a high number of co-authored publications (around 30%), possibly as a consequence of the IGF policy to support collaborative grant funding. An impressive number (two thirds) of IGF publications involved a collaboration with at least one foreign lab. Notably, these have led to articles in Science, Nature and Cell.

The IGF shows a strong commitment to support open science. The IGF has made considerable efforts to implement the electronic lab notebook eLabFTW. 4) The IGF teams are regularly invited to talk at major international meetings, indicating excellent international visibility. The scientific achievements of IGF team members have been recognized by prestigious prizes and distinctions, and numerous professional promotions.

One of the major assets of the IGF is the outstanding quality of platforms and facilities with the AdV Campus.

The IGF shows a constant high ability to recruit permanent researchers through competitive selection at the CNRS (5 CRCN), Inserm (2 CRCN), or Universities (2, including a CNRS CPJ and an assistant professor). 7) IGF researchers regularly take part in the organization of scientific events, including at least eight major meetings such NeuroFrance 2025 meeting organized in Montpellier, for which the IGF teams were instrumental for its success. They participate in the scientific bodies of numerous foundations (e.g. presidency of the scientific council of the FRC, FFRE, SFD, French Society of Proteomics), evaluation committees and learned societies, mainly at the National level. 8) IGF researchers coordinate major collaborative research grants, and in general the IGF researchers have been very efficient in obtaining research grants with a steep increase from 2021 (158) to 2024 (219). 9) The IGF hosts on average 30% of foreign PhD students. PhD students in their large majority have an excellent appreciation of the IGF as a training and scientific environment.

Context-related weaknesses and risks for the four references above

The level and quality of publications of some of the teams could be improved.

Given the excellent quality of scientific achievement at the IGF, one may expect to have a higher amount of major EU grants (one ERC, one Impulscience, and one EIC has been obtained during the current mandate).

The number of PhD students relative to researchers and teacher-researchers in some teams could be improved.

EVALUATION AREA 3: INCLUSION OF RESEARCH ACTIVITIES IN SOCIETY

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

The IGF has excellent to outstanding interactions with the socioeconomic world, and the IGF researchers have made considerable efforts in sharing knowledge with the general public and with patient associations such as ARSEP or Ligue contre le Cancer. The IGF has strong economic interactions, hosting two start-ups (ApoRepair, NBX Biosciences), incubating a new project (Theralan), contributing to other companies (Sim&Cure, Stent'Up), and establishing partnerships with pharmaceutical industries.

1/ The unit stands out for the quality of its interactions with the cultural, and socioeconomic world.

2/ The unit develops products and services for the cultural, socioeconomic world.

3/ The unit shares its knowledge with the general public and participates in social debates.

Context-related strengths and opportunities for the three references above

The IGF has longstanding and excellent interactions with the industry, a clear strength of the institute promoting and enabling the development of innovative technologies. This is exemplified by the operation of a cooperative laboratory (Eidos) with the company Revity, by numerous (14) contracts of IGF researchers with private companies, by 5 PhD Cifre fellowships, with the participation of several researchers in the Scientific Advisory Board of Biotechs/Pharma (13 companies).

The IGF is involved in promoting the creation and development of start-up companies (ApoRepair, NBX Biosciences, and Theralan which are currently hosted in the institute, Sim&Cure, Stent'Up). Ten patents have been filed. Beside the main strengths of the IGF in basic biomedical research, there is a clear engagement to promote translational and clinical studies in the institute, which is made possible by the involvement of a considerable number of clinicians within the staff, with some of the team mains projects directly focused on translational and clinical topics.

The IGF is actively engaged in sharing knowledge, through outreach events with the general public (e.g. participation in the apprentis-chercheurs program, 3 books written by Joël Bockaert for a lay audience, involvement in the Declics meetings for secondary high school students) and through strong interactions with patient associations or foundations (e.g. participation in the young researcher days organized by the ARC foundation, to the "Journée Parlons Recherche" organized by France Parkinson foundation, to the "100 chercheurs dans les écoles" event organized by the AFM-Telethon).

Context-related weaknesses and risks for the three references above

No clear weakness is noted. As a minor point, the number of patents filed during this period has decreased which may not be significant. There may also be a risk for the breadth of translational projects since a clinical team is leaving IGF.

ANALYSIS OF THE UNIT'S TRAJECTORY

Following the long-term scientific history of the unit, the scientific trajectory for the next mandate is exciting, based on a strong impetus on innovative strategies and on emergence of new methodologies. The IGF presents a well-structured plan aimed at strengthening the position of the Institute as a world-class biomedical research center exploring the complexity of biological mechanisms at multiple levels, from basic to translational research.

The document presents a list of principles and strategies to reinforce the scientific output and visibility. It will be interesting to evaluate the role of the new scientific committee. Actions will be taken to improve success to obtain the most competitive grants, such as starting or consolidator European grants. The separation into two departments will be terminated, as it may create artificial borders. The actions proposed to consolidate the emergence and the use of new technologies are excellent, e.g. a better organization to use of AI and computational biology.

The gender balance at the level of leaders of the new teams will significantly increase and should further improve with the future recruitment of new teams. A considerable number of competitive research grants have already been obtained by most of the teams, covering the resources for at least the first years of the next mandate.

RECOMMENDATIONS TO THE UNIT

RECOMMENDATIONS REGARDING THE EVALUATION AREA 1: SCIENTIFIC OBJECTIVES, ORGANIZATION AND RESOURCES OF THE UNIT

The committee encourages the IGF to pursue the very clear scientific objectives in cell-cell communications at multiple levels of organization.

Even though there is a predominance of neuroscience, given the variety of disciplines represented (cardiology, cancer, endocrinology, gut), it would be interesting to promote scientific projects linking the brain to the body, currently a very timely scientific topic. This may be one of the criteria for the recruitment of new teams.

The committee also suggests to capitalize on the great possibilities offered by the use of human tissues/cells for basic science related questions.

The committee encourages the IGF board to communicate on a clear policy for space attribution in relation to team growth, and to the recruitment of new teams.

RECOMMENDATIONS REGARDING THE EVALUATION AREA 2: THE UNIT'S SCIENTIFIC RESULTS, IMPACT AND ATTRACTIVENESS

The committee encourages the IGF as a whole to continue providing very high-quality science, building on the strengths of the teams, and possibly also increasing the impact of publications at the expense of the number.

Even though the IGF is highly recognized world-wide, it may be interesting to increase the attractiveness for PhD students from abroad, by structured actions and targeted communication, possibly in partnership with other centers of Montpellier, notably the INM and MND with which it may also be interesting to better structure common activities. Applications to European doctoral networks – the low success rate of which is well acknowledged – could be more decisively targeted and supported, given the strengths of the IGF, such as numerous European collaborations, as well as a major involvement of some the teams in translational research and innovation.

The committee recommends that the IGF continues to develop a strategy for translational projects, and to improve the integration of translational teams in IGF, as this is an explicit general scientific objective.

RECOMMENDATIONS REGARDING EVALUATION AREA 3: INCLUSION OF RESEARCH ACTIVITIES IN SOCIETY

The committee encourages the IGF researchers to continue their strong participation in socioeconomic activities and possibly increase the number of patents filed.

TEAM-BY-TEAM ANALYSIS

Team 1: Environment, Biomarkers, Neuropsychiatry

Name of the supervisors: Ms Sylvaine Artero et Mr Philippe Courtet

THEMES OF THE TEAM

The overarching interest of the team is on biomarkers, treatments and factors associated with the incidence of neuropsychiatric diseases. The team essentially exploits their robust clinical research competences to undertake epidemiological studies involving biochemical, imaging or psychological evaluations to unveil candidate biomarkers and factors associated with the incidence of neuropsychiatric diseases.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The previous report forwarded 2 main recommendations: i) to increase the focus of the research efforts and ii) to bolster collaborative efforts with other IGF groups.

The research trajectory of the group in the last 5 years does not seem to have effectively addressed both recommendations.

The scientific output still seems rather diverse, ranging from depression/suicide, dementia and motor dysfunction, as exemplified in the selected 5 major contributions. This allowed the group to provide several meritous contributions in different fields of brain diseases but seems to fail to position the group as a major recognized player in any particular niche of research.

The recommendation to increase collaborative efforts within IGF also seems to have been attempted, with relatively limited success, with 2 examples of collaborative efforts listed by the group. The co-habitation of this clinical and epidemiological teams with different groups at IGF with a main molecular focus in animal models would have been a golden opportunity to align clinical with pre-clinical expertise to bolster translational efforts, either confirming information from animal studies in humans or detailing clinical information in animal models.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	6
Praticien hospitalier	2
Sous-total personnels permanents en activité	**15**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	0
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**19**

EVALUATION OF THE TEAM

Overall assessment of the team

The scientific output of the team is classified as excellent with numerous publications in different topics, from precipitating factors to biomarkers, related to different neuropsychiatric diseases, from suicide ideation to bipolar disease. The scope of activities seems somewhat diverse, and the impact of the publication may have been more robust with increasing collaborative efforts, mainly within the institute. The team supported a strong training activity in spite of correct but relatively limited attraction of funds.

Context-related strengths and opportunities

The team has achieved a remarkable quantitative output of scientific publications. Thus, contributions were provided in different areas, with particular emphasis (based on a subjective analysis) of suicide and mood-related pathologies, unveiling new life-style factors related to precipitation of symptoms, identifying risk factors and proposing new biomarkers, as well as developing new tools for diagnosis/follow-up.

The integration of expertise in epidemiology and in clinical research provides the team with remarkable potential to undertake relevant and competitive research, especially in an environment of more fundamental research. The robustness of the clinical and epidemiological expertise is reflected by the extensive scientific output of the team and by the regular participation of several (5) of the team members in international symposia focused on different topics. The reported number of research papers is truly impressive (620 articles in the evaluated period), but few were published in leading journals. The quality of the clinical expertise and of the epidemiological analysis is truly impressive, to such an extent that one would expect more collaborations to emerge within the ecosystem of the Institute as well as the participation of the team in a larger number of collaborative studies word-wide. This variety of interests may be a valuable asset to engage in different collaborative efforts focusing on different angles of approach of different neuropsychiatric diseases, both within their institute and with external collaborators. The different interests of the team have also contributed to the attraction of funds through several grants (5 grants, such as from France Alzheimer, ANR, PHRC or King Baudouin Foundation) with different focuses, ensuring the sustainability of the team's research efforts. It is also worth mentioning the attractiveness of the team to recruit different trainees and the remarkable extent of their training efforts with an average of 2 PhD students and 1 post-doc per research staff (7 post-docs, 14 PhDs, and 25 Master students). The ability to hire such a number of graduation students is a faithful indicator of the attractiveness of the team resulting from the variety and overall quality of its scientific scope and production. Another positive aspect to be remarked is the outreach efforts engaged by the team members, both in terms of communication to the press, organization of scientific symposia & meetings and the participation in the development of new food products and exploitation of biomarkers in partnership with start-ups. The communication with society was also cherished by the group through media (radio, journals, magazines) as well as digital media.

Context-related weaknesses and risks

Although the team has a remarkable volume of scientific production, the impact of their scientific efforts does not seem to be as high. This might result from the scattering of the scientific focus, with relevant contributions made in several different neuropsychiatric conditions tackled from different angles. This variety of scientific questions and angles of approach could be an advantage if it was easy and immediate to understand their inter-relation; however, there is rather an impression of scattering of activities, with a difficulty in recognizing the team as a world leader with an outstanding and continuous contribution in any defined area. A greater integration of collaborative efforts with several teams at IGF would have been an asset and its limited extent leaves the impression of a missed opportunity.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will not be reconducted in the next mandate. The clinicians of the team have chosen to establish a research unit fully dedicated to psychiatry within the Montpellier University.

RECOMMENDATIONS TO THE TEAM

The decision of the team to leave IGF may somewhat hamper the possibility of exploiting clinical and epidemiological know how within the institute. It is hoped that IGF ecosystem will be able to maintain tight links with the team to take advantage of the valuable expertise of the team. The team should continue, but also strengthen, the recognized clinical competences of most of its members. In particular, it would be desirable for the team members to concentrate their activities to better define the team's focus and position the team as a leader in a specific area of neuropsychiatry.

Team 2: Calcium channel dynamics and nociception

Name of the supervisor: Mr Emmanuel Bourinet

THEMES OF THE TEAM

The team explores the impact of voltage gated calcium channels in the pathophysiology of chronic pain with a main focus on Cav3.2 and 3.3 in peripheral neurons and the circuitry of the spinal cord. The team has investigated furthermore the sense of touch in a broader sense. In a translational effort, findings from preclinical animal models are validated and expanded to human tissue using ex vivo molecular and functional measurements in sensory neurons and human spinal cord taken from organ donors. In a second line of research, autoimmune disorders of peripheral neurons causing demyelination are investigated. Again, a strong emphasize is on the translation to clinical studies by analyzing factors in the blood of patients.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team has attracted more students (5) and post-docs (1), as recommended from the previous report

The collaborations within the IGF have been strong in the reporting period resulting in 42% collaborative publications with a total of 8 other IGF teams.

The team has successfully implemented the suggestion to focus on the human tissue project with a number of important publications and grant acquisition.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The team has shown an outstanding scientific performance. Even though the team is quite small it has developed important novel techniques and tools to study peripheral and spinal cord physiology in health and disease. This allowed to publish a number of seminal papers in the evaluation period. The team has an excellent national and international visibility.

Context-related strengths and opportunities

The team is well established and at the forefront of Cav channel research in the periphery and in the spinal cord. The team has developed sophisticated transgenic mouse models and recording techniques to target specific subtypes of mechanosensitive and nociceptive peripheral afferents. During the evaluation period, the team has published an impressive number of papers of high quality in this subject area. Electrophysiological recordings of mechanogated currents in sensory neurons lead to the discovery of TACAN, a novel non adapting mechano gated channel involved in sensing mechanical pain. Outstanding is the team's contribution to the first comprehensive atlas of human spinal cord cell subtypes using single-nucleus RNA sequencing, a tour de force, which is now the main reference in the field. Based on this study further investigations on human spinal cord and DRG have been conducted and are ongoing. Furthermore, the discovery of the contribution of low threshold c-fibers to social interactions on the behavioral level is remarkable. The team has a successful collaboration with the university hospital to perform *ex vivo* molecular and functional investigations of human sensory neurons and human spinal cord. This technique is quite unique and is an important step for the translation of preclinical findings in chronic pain patients. Advanced RNA sequencing techniques and electrophysiology techniques are used on these samples and have resulted in a number of highly relevant discoveries in neurodegenerative disease and pain contributing to the excellence initiatives the IGF is involved in, for one of which E. Bourinet has been member and then president. The team is also part of the label "Ion Channel Science and Therapeutics", which is an important endeavor. A further research area of the team is the investigation of the role of adhesion molecules in the organization of the nodes of Ranvier and their implications in the pathophysiology of demyelinating peripheral neuropathies. They were able to show that autoantibodies targeting the node of Ranvier are present in chronic inflammatory demyelinating polyneuropathy, a rare neuromuscular disease. The team mentored and significantly contributed to the scientific independence of one of their team members (A. Francois, who was able to secure significant funding and be appointed group leader at the IGF to start his own projects). Strong collaborative interactions of the team within the IGF are present. The funding was very secure and stable for the past years. The team, including all team members and also with strong collaboration within the IGF, has published innovative research in high-ranking journals. Particularly, the work on social touch, published in Science Advances, the involvement of TCANs in mechanical pain published in Cell and the characterisation of the composition of the human spinal cord published in Neuron are noteworthy. The team has educated a good number of PhD students (4 finished, 3 about to finish) and one team member was so successful (Amaury Francois) that he won the CNRS bronze medal and he was appointed as team leader to establish his own research at the IGF.

Context-related weaknesses and risks

External funding is secure at the moment, but are running out in 2026. Two new grants are starting and running until 2030, which gives some stability. New grants are submitted and envisioned and should hopefully be granted.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team is well established. It has a clear view on the future projects. The translational aspect of validation and new discoveries in human tissue and patients is very exciting and will have high impact. The main expertise on Cavs will certainly be continued successfully. Here the T-type channels signalosomes are an interesting extension that could have important implications in modulating Cav function more indirectly. The investigation of autoantibodies in demyelinating peripheral neuropathies is also very promising for new discoveries and it can have a direct impact on clinical practice and patient well-being. There are a lot of interesting projects going on that can hopefully be funded to have enough support for scientific staff. The team is successfully collaborating with groups within IGF and outside. The change in the team structure might bring new impulses, but also means a loss of knowledge. The departure of Jérôme Devaux results in the end of the autoantibody project, while the arrival of reseacher will be highly beneficial for the DRG/spinal cord analysis of human donors as she is the expert in this.

RECOMMENDATIONS TO THE TEAM

The performance of the team is outstanding. All projects should be continued. Particularly the human DRG/spinal cord project is truly unique and will yield high gain.

The team will require more technical assistance, ideally from the CNRS or the university, or possibly through a salary in their future grant applications.

Team 3: Neural circuits and value coding

Name of the supervisor: Mr Amaury François

THEMES OF THE TEAM

The team's research focus is on the mechanisms of the perception of social and affective touch. Here the team follows the idea that the activation of low threshold mechanoreceptive C-fibres in the skin are the origin of a dedicated neuronal circuit that conveys touch-seeking behaviors and promotes social interactions. The team is studying this pathway in health and in pathological conditions, like autism spectrum disorder and pain.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team was only established in 2023 and had not been evaluated by the previous committee.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Praticien hospitalier	0
Sous-total personnels permanents en activité	**2**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	**3**
Total personnels	**5**

EVALUATION OF THE TEAM

Overall assessment of the team

This young research team has a relatively unique research question within France and Europe that was marked by an outstanding publication in 2022 in Science Advances. The investigation of specific types of peripheral touch sensors that convey information about the pleasantness of social touch has a lot of potential. While the circuitry for the discriminative sensory perception of touch is well known, much less is known about the networks underlying the emotional and motivational value to tactile stimulation. Here the team has a clear distinction for further, highly important research. Firstly, the physiological mechanism and properties of the sensory neurons and cortical processes will be further investigated and then be related to pathological conditions.

Context-related strengths and opportunities

The team has a strong focus on peripheral mechanisms of perception, particularly of social touch and pain. This research focus is quite unique and allows for the investigation of novel research questions in this context with little competition. Expanding the research to distinct pathologies related to social touch is very promising and also including itch as another sensory modality can be very successful. The physiological mechanisms of itch are still understudied and will allow the team to contribute with important fundamental work to this topic. Another strength of the team is the systems approach to sensory perception, which includes peripheral afferents, but also cortical processing that generates behavior. Often groups focus only on the periphery or only on cortex, which has led to a dichotomy in understanding sensory processing. The approach used by this team is very refreshing. The team has a broad technical expertise that is state-of-the-art and is contributing to the development/improvement of techniques (e.g. machine learning algorithms for behavioral analysis). Collaboration with Emmanuel Bourinet's team very successful contributes to the development of new experimental approaches (skin preparation containing c-fibers, automatic behavior analysis) and highly relevant insight into the mechanisms of c-fibers in social touch. The recent collaborations outside the IGF and Montpellier show great potential and suggest a very good standing of the team that makes their research and expertise (on c-fiber physiology and social interactions) attractive for collaborations. Recent publications in Nature and Cell Reports Medicine are particularly noteworthy. The productivity within the team is now growing resulting in a constant research output of high quality and relevance. Very good funding with an "Impulscience" grant from the Schueller-Bettencourt Foundation shows the ability of the team to secure major competitive funding. Further funding was also acquired. Total about more than 3Mio. The key publication of the team in Science Advances was awarded a CNRS Bronze Medal. It can indeed be considered as a breakthrough in the field of touch research. The team has a very good international visibility with invitations to international conferences and talks. Engaged in organizing symposia and in public outreach.

Context-related weaknesses and risks

No clear weaknesses are obvious at the moment.

Funding is secure for the next three years. Efforts should be made soon to acquire further funding, perhaps on European level (ERC). The quality and topicality of the research subject would allow this.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team was selected in an internationally competitive call from the IGF for young PIs in 2023 and was ranked 1st. From here the team developed an excellent standing in peripheral somatosensation, which resulted in a number of high-profile collaborative and own publications. Taking mechanoreception as the starting point and investigating it in different pathologies has a very strong potential for successful future research. The team has demonstrated that with extending the research to pain and autism spectrum disorders. In the future the team will be led by Antoine Besnard and Amaury François. The two team leaders have different expertise and interests, but as a commonality "motivated behaviors" can be seen.

RECOMMENDATIONS TO THE TEAM

Given that the anticipated promotion of Antoine Besnard did not occur, his mentoring should be carefully considered.

Given the strong previous track record of the team leader in pain research, this topic should even be strengthened.

The collaborations within the IGF could be strengthened further. Collaboration with Emmanuel Bourinet very successful and should be continued.

Attempt to apply for ERC.

Team 4: Stress hormones and plasticty

Name of the supervisor: Mr Freddy Jeanneteau

THEMES OF THE TEAM

The main team objectives are to understand how neuromodulator signalling organizes context-dependent adaptations of behaviour to environmental factors and/or internal states. Previous work has investigated integrated signalling by multiple neuromodulators on a single receptor, or on a single neuron, changing the activity of a neuronal circuit and altering behaviour. Current research in the team aims to understand how these complex signalling mechanisms can impact human cognitive activity and psychopathology. The team plans to develop these themes in the future to decipher neural correlates of stress state transitions, using mouse models they have available.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

It was recommended that the team increase the number of PhD students (through Cifre contracts or co-supervision). It was also recommended that they reduce the number of axes in accordance with the small size of the team.

The team has responded to these recommendations by increasing the number of collaborative networks, which should allow completion of the current projects and increase efficiency in the primary theme of resilience to stress. The future project is more focused on interactions between metabolism and psychiatric disorders.

The team has supported candidates applying to assistant professor positions, and should continue to do so.

The team also plans recruitments of a post-doc and a technician thanks to the team's funding. They should nonetheless continue to try to recruit PhD students to advance the team's projects and to provide training in this interesting field.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent. They have excellent publication success, a sustained funding level, and good visibility within their field. The small number of permanent members in the team, and the lack of technical staff, are threats to stable progress of the science. However they successfully recruit post-docs and visiting scientists, which should allow their research to advance.

Context-related strengths and opportunities

This team has had excellent publication productivity in recent years (21 publications on the main themes of the team). Among the highest profile publications are a PNAS publication in 2019, on neurotrophic priming of glucocorticoid receptors in synaptic bases of memory; a Biological Psychiatry paper in 2024 on the role of oxytocin and vasopression in a model of Prader-Willi syndrome; and a Cell Reports Medicine publication on therapeutic effects of neuropeptides in a model of autism. In addition, the team has published review articles, on PTSD and the role of glucocorticoids on memory, for example. At least 8 publications during this period have resulted from collaborations with other teams in the IGF. The team has had continuous funding during the evaluation period, including a FRM équipe grant that ended in 2021, and an ANR (partner) that will continue into 2026. In addition, the team leader coordinates an ERA-Net project that will continue to 2027. Until last year the team hosted 2 long-term post-docs, as well as an assistant professor currently posted to another university. A new PhD student joins the team in 2025, in cotutelle with Harvard University. The team has hosted multiple visiting scientists (4 visiting professors, 1 foreign PhD student), indicating their visibility within the field. One of the visiting scientists was recruited as an assistant professor to the team (currently seconded to another university). The involvement of the team leader in Masters teaching (10 h/year, Neurosciences M2) should allow the team to interact with more students. The team is now poised, with the necessary tools, to approach neuromodulators' roles in stress resistance. The team is well-respected and has been able to rely on collaborations to move their research project forward. The team also has the opportunity to continue collaborations within the IGF, including publishing with personnel from the shared institute platforms.

Context-related weaknesses and risks

The only clear weakness of the team is its very small size. The team publishes efficiently, thanks largely to a large network of national and international collaborations, but in-house staff remains an essential component of a research program. Ideally, the team would recruit more permanent staff, and they should continue to support candidates for CNRS, Inserm, and university recruitment campaigns. In the meantime, the team should maintain and reinforce its collaborations within the IGF (their co-publications with other teams in the unit are notable), as well as maintaining its national and international collaborations. Apart from its collaborations, the team could increase its communications with the general public, particularly because their research themes will definitely be of considerable general interest. Finally, without a current assistant professor in the team, contact with undergraduate and Masters students are limited. The team members should consider increasing their teaching activities to attract students.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team's future research will focus on neuromodulators in stress resistance and anhedonia. They will aim to define « metabotypes » which may predict responses to stress and/or resistance to treatments for psychiatric disorders. Social defeat and subsequent tests of social preference will be used to observe coping strategies and correlate these strategies with biomarkers analysed by a collaborator in the United States. The team will then determine whether altering the metabolic balance with different energy sources or meal timings can alter the behavior of animals faced with social defeat. The team also projects using 5HT2AR agonists with antidepressant properties to identify the activated neuronal networks; this project will be undertaken with two collaborators in France. Thanks to their considerable network of international and national collaborations, the team will combine omics, animal behavior, and psychedelic treatments to examine the neural bases of these different responses.

They are well-positioned to undertake significant research on these questions, The team has developed biosensors, imaging methods, genetically-modified mouse models, and connectivity approaches they can use to access neuronal populations involved in these processes. The long-term goal is the identification of novel therapeutic targets for enhancing resilience to depression. The funding obtained by the team is appropriate to support their scientific goals It is important to underscore that this team regularly collaborates with other IGF teams and technical platforms, as well as with other local institutes. With these collaborative interactions

reinforcing their productivity, they should be able to maintain their current level of quality publication. The lack of permanent staff in the team, and the limited number of short-term staff, remains a threat to the project's feasibility.

RECOMMENDATIONS TO THE TEAM

The team has excellent collaborations established within the research unit, and they surely will maintain these interactions.

Recruiting PhD students and/or post-docs to increase the workforce will be an important priority, particularly as prior trainees have been successful.

The team has a very good reputation on the national and European level, and they are poised to continue their success.

As stated above, an effort to recruit permanent staff should continue, in addition to the collaborative network that will underpin the planned research for the next years.

Team 5: Molecular and structural mechanisms of neuromodulation

Name of the supervisor: Mr Guillaume Lebon/Cyril Goudet

THEMES OF THE TEAM

The team investigates the molecular and structural bass of G-protein coupled receptors (GCPRs) with a focus on the metabotropic glutamate receptor 5 (mGluR5) and Adenosine 2A receptor. The structural analysis of these receptors with electron microscopy and x-ray crystallography is used to understand the mode of action of allosteric modulators, which affect the endogenous neuromodulatory effect of these receptors. This insight is used to develop novel allosteric modulators and photoactivatable modulators that can render the receptors light sensitive. These tools and substances are then applied to models of neurological disorders and particularly to chronic pain, Alzheimer's disease and Autism-Spectrum Disorders to prove their therapeutic potential.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations from the previous report were accomplished very well. Namely, the productivity should have been maintained and actually productivity was increased as compared to the previous report. An IE was hired for 2 years and the search for a new IE is ongoing. In addition, 5 postdocs were hired and 4 PhD candidates trained. The management and the co-chairing of the team as well as research topics and relation to other IGF teams were asked to be made clearer. This request was fully accomplished and well laid out. The division of labour amongst the team leaders is clear and the structure of the team with three pillars is well justified and makes sense.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The team is ranked as excellent to outstanding. It has a very important research focus on the mechanisms of allosteric modulation of GPCRs to derive novel treatment strategies for neurological disorders, particularly chronic pain, Alzheimer's and Autism Spectrum Disorders. The team spans a huge repertoire of techniques from structural biology using X-ray and single particle cryo-EM, over generating novel compounds to testing them in vivo. The development of light-activatable modulators of GPCRs is quite novel and unique and has great potential for future basic research and therapeutic applications.

Context-related strengths and opportunities

The team is working on a very interesting and important research topic, namely understanding the structure and function of G-protein coupled receptors (GPCRs), which represent the most abundant neuronal receptor family that is essential and can modify all cellular function. The team investigates these receptors from the molecular level (using x-ray crystallography) with and without bound ligands, over developing new allosteric modulators to their function in vivo. Here, the focus is on important disease models, like chronic pain, Alzheimer's, schizophrenia and Autism spectrum disorders. The development of novel modulators of GPCRs has very strong translational potential. Furthermore, the photoswitchable ligands, which were developed and also structurally analysed by the team, are potentially great tools for basic preclinical animal research to understand the function of these receptors in greater details. The team has proven this for example in outstanding recent publications modulating sensory pain thresholds and comorbid symptoms of chronic pain using their diverse set of photoswitchable tools in pain associated areas (mainly amygdala), but also other disease models. These tools allow for spatio-temporal control of GPCRs. A patent is pending for photoswitchable mGluR negative allosteric modulator. Developing allosteric modulators for GCPRs based on rationally designing them from the acquired structural data is a great approach that holds great potential and could be expanded to other classes of GPCRs. The team, particularly Guillaume Lebon is at the forefront of EM development in Montpellier. He is leading the cryoEMontpellier Block Allocation Group, has implemented single particle cryoEM in the team and acquired funding with the Centre de Biologie Structurale for a new Glacios EM machine. This microscope will significantly strengthen the research of the team and collaborations within Montpellier. The team has also addressed the diverse signalling pathways being engaged by agonist binding in conjunction with positive allosteric modulators. Here the focus was on mGluR5, which is a potential target for novel treatment strategies. They analyzed the conformational changes upon binding of different ligands. This work will help to develop new ligands with selective pharmacology, which could increase safety for novel drugs. The team has a strong and unique knowledge in designing the photoswitchable ligands with an established pipeline, which will allow for the discovery and prove of function of novel molecules in the future. The team has strong collaborations within the IGF, in Montpellier and internationally for all their research projects and techniques, which will allow to continue the research on the highest international level and to multiply the output of the team. Altogether, the team has a unique set of techniques at hand that fosters the development of highly relevant new molecules for research and with therapeutical potential. These new drugs are analysed from the molecular to the in vivo level, which will give a comprehensive view about structure-function relationships. The team was also strong in educating students, PhDs and postdocs with a good number in recent years. The funding is secure to some extend for the next years to continue the work, with more grants submitted.

Context-related weaknesses and risks

There are little weaknesses to be recognized. Soley, the small size of the team with (in addition to the 2 team leaders) 2 technicians, 1 post-docs and 2 PhD students might be too small to achieve all the goals in the future. The recruitment of a new postdoc and a research assistant together with the transition of Arnaud Monteil with a PhD student will increase the team size. The inclusion of A. Monteil might also pose a risk, but the project seems to match the expertise. The recruitment of new students seems difficult, yet it is essential. Lack of enough lab space might impair the conduction of all planned research projects.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team has proven an ambitious and multi-approach pipeline from structure to function for the understanding of GPCRs and the development of novel compounds modulating their signalling. This successful approach will be continued. The team structure is based on three pillars: 1. Structural basis of GPCR signalling, 2. Therapeutic innovation and photopharmacology, 3. Pathophysiological function and CNS disease. The team is currently

lead and will be led by Guillaum Lebon and Cyril Goudet. Both co-lead pillar 2 and Guillaum is mainly responsible for pillar 1, while Cyril leads pillar 3. Yet, there is strong interaction of the pillars, all influencing each other. New questions, based on the previous work have been developed and are the natural and necessary extension of the current knowledge generated by this team. Specifically, the structural mechanism of GPCR signalling at synapses and in single cells by deciphering the functional units/interations will be investigated in health and disease. Furthermore, the photopharmacological tools will be further developed towards therapeutical applications in chronic pain and Alzheimer's. This will yield exciting and important results for translation.

Arnaud Monteil (researcher) will join the team with Alexandra Typou (PhD student) from team 6 (ion channels) that will be discontinued. They will add a new aspect to the current research by adding their expertise on ion channels to investigate the interaction of GCPRs with sodium channels. This merging of expertise makes a lot of sense and is a good extension of the current theme of the team on downstream GPCR signalling pathways and how certain GPCR modulators could selectively engage a specific pathway.

RECOMMENDATIONS TO THE TEAM

The focus so far was on the mGluR5 and A2A GPCRs, may be this focus is too narrow and could be expanded in the future to further GPCRs? Otherwise, the research is of highest quality and importance and should be continued at this level. Collaborations within the IGF, particularly with the newly established teams should be continued and could be expanded.

The successful inclusion of Arnaud Monteil should be monitored closely.

Team 6: Ion channels in neuronal excitability and diseases

Name of the supervisor: Mr Philippe Lory

THEMES OF THE TEAM

This team has expertise in the structure and function of voltage-gated calcium and sodium channels, as well as sodium leak channels. They have described the physiological rules of these channels in diverse functions from hormone secretion to muscle excitability. They have recently focused on channelopathies linked to dysfunction of Cav3.1, NALCN and Nav1.4 channels and the electrophysiological characterization of missense variants of these channels. They have identified gain of function variants in Cav 3.1 channels associated with pathology, and they have investigated the structure as well as the function of Cav 3 channels more globally. In parallel, they have detailed the role of sodium leak channels in numerous cell types and functions, as well as in neurodevelopmental diseases.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations in the previous report were the following:

- "The team should continue performing ambitious research"

The team has indeed continued investigating the pathophysiological roles of ion channels in collaboration with clinicians and structural biologists.

- "The team should grow in size by increasing the number of PhD students or hiring post-docs. Beside securing funding for the coming years, the team should make sure that the two new team members are well integrated to create synergy."

The team has trained/is training five PhD students, which is more than during the previous period. The two new team members, Drs Guérineau and Nicole have both published during this evaluation period. One of them has obtained funding. However, Dr Guerineau has not trained any PhD student during this period and Dr Nicole has only trained one in co-direction.

Since the team is closing, changing the size of the team is not relevant anymore. However, the team should support the transition of Dr Guerineau and Nicole, as well as the permanent IE, to new teams (Dr Arnaud Monteil will move to the team of Lebon/Goudet).

- "The team should keep focusing on Cav3 and NALCN channels": this is what they did.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The team work is excellent, with major impacts on the molecular bases of diseases linked to Cav3, NALCN and Nav1.4 dysfunction. The team has excellent productivity (> 30 publications). It has strong fundraising capacity, visibility, and recognition, reflected in the obtained grants (Era-NET, ANR, FRM), invited talks and academic responsibilities. The capacity of the team is reinforced by strong national and international collaborations.

Context-related strengths and opportunities

This team has a long-standing expertise in ion channel structure-function and pathophysiology. Over the last years they have focused on characterizing the impact of ion channel disease mutations on ion channel functions to understand their link with neurodevelopmental and muscular diseases. For this, they have established collaborations with clinicians, who identify gene mutations in patients. They have furthermore collaborations with Cryo-EM specialists to understand the binding of ion channel modulators with therapeutic potential. The team is particularly interested in three channel families: Cav3, NALCN and Nav1.4, which all regulate cellular excitability. Their achievements include: (1) Identification and electrophysiological characterization of Cav3.1 pathogenic variants involved in a severe neurodevelopmental disease called "Childhood Cerebellar Ataxia" and evaluation of the therapeutic potential of Cav3.1 channel blockers; (2) Investigation of the binding mode of new Cav3 antagonists with therapeutic potential; (3) Investigation of the role of NALCN channels in the excitability of endocrine cells and of the link between NALCN variants and neurodevelopmental disease; and (4) identification and electrophysiological characterization of pathogenic variants of Nav1.4 in patients suffering from muscle weakness condition. All this work has led to > 30 publications by all the team members in good journals like *Genet. Med, J. Physiol. or Cell Res*. The two PhD students who defended over the evaluation period have both published their work. The team has sufficient funding to carry on through the end of 2027. Permanent team members hold many teaching and institutional responsibilities, showing strong dynamism.

Context-related weaknesses and risks

The team leaders have serious responsibilities in directing the unit as well as participating in teaching and other management, which might eventually impact their commitment to research (although it does not seem to be the case currently).

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will not be reconducted so there is no future trajectory for this team. All remaining team members will move into new teams within IGF.

RECOMMENDATIONS TO THE TEAM

Since the team will not be reconducted, there are no recommendations.

Team 7 Cerebrovascular and Glia Research

Name of the supervisor: Mr Nicola Marchi

THEMES OF THE TEAM

The team investigates the cellular, molecular, and clinical mechanisms underlying neurovascular diseases, with a focus on cerebrovascular pathologies and neuroinflammatory processes. The team integrates fundamental neuroscience with clinical neurology and imaging, combining expertise from medical doctors and basic researchers. Its main axes concern (1) the mechanisms, biomarkers, and therapeutic targets in stroke and vascular pathologies, (2) cerebrovascular and neuroinflammatory mechanisms contributing to epilepsy and seizure networks, and (3) collaborative studies on the impact of environmental contaminants and anti-seizure drugs on neuro-glial-vascular function.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team has addressed all the recommendations of the previous evaluation. Importantly, it has strengthened the integration between clinical and fundamental components, notably by consolidating the research linking patient-derived biological samples with mechanistic studies in animal models. Collaborative interactions between clinicians and researchers have been reinforced, resulting in a more coherent research strategy. A key recommendation was to strengthen the common ground between the two main PIs. In response, N. Marchi and E. Audinat have aligned their research around shared themes on cerebrovascular and neuroinflammatory mechanisms in epilepsy, leading to joint ANR-funded projects running until 2028. The team has significantly improved its fundraising by securing multiple ANR and institutional grants. The recommendation to develop more mechanistic approaches in addition to descriptive studies has been improved through the implementation of high-resolution proteomic and transcriptomic analyses. The project also reflects a strong integration at IGF through the third collaborative axis with the Jopling team.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Praticien hospitalier	1
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels non permanents d'appui à la recherche	1
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**3**
Total personnels	**11**

EVALUATION OF THE TEAM

Overall assessment of the team

The team is excellent to outstanding, with a strong translational profile bridging clinical neurology, vascular biology, and neuroinflammation. The scientific output is excellent with about 35 publications on basic research and more than 200 publications on clinical research. Fundraising capacity, visibility, and recognition have increased, reflected in numerous invited talks, reviewing roles and obtained grants (ANR, ANSES, IRESP). The synergy between clinicians and fundamental researchers positions the team ideally to tackle the key questions of their project.

Context-related strengths and opportunities

This is a multidisciplinary team comprising medical specialists and researchers as permanent staff. Its combination of clinicians and laboratory scientists allows unique access to human samples, including intracranial clots and blood from stroke and epilepsy patients. Scientific output is of excellent quality, with a large number of publications in journals specialized in neurology (NEJM, Radiology, Clinical Neurology and Neurosurgery, American Journal of Neuroradiology) and neuroscience (Cell Reports, Glia, Epilepsia). During the reporting period, the team published more than 200 articles, among which many are signed in senior position. Their key achievements include: 1) In the context of ischemic stroke, the team used mechanical thrombectomy to access intracranial thrombi and blood, revealing proteomic and inflammatory biomarkers linked to the clinical evolution of patients (*NEJM 2024*; *J Neurointerv Surg 2024*). 2) In epilepsy, the team developed innovative MRI approaches to identify epileptogenic zones and correlated imaging with neuro-glio-vascular pathology. It demonstrated that seizures alone trigger amyloid and tau pathology, revealing a mechanistic link between epilepsy and neurodegeneration (*Trends Mol Med 2024*; *Epilepsia 2022*). In addition, ongoing projects explore microglial and T cell modulation of seizure propagation and neuroprotection. 3) It uncovered the role of Piezo1 mechanoreceptors in neuroinflammatory networks (*Neurobiol Dis 2023*). 4) A new research line investigates how low-level environmental contaminants alter brain barriers and neurodevelopment (*Environ Pollut 2024*). This work combines zebrafish and rodent models to reveal sex- and dose-dependent neuroinflammatory effects. Overall, the team integrates clinical, molecular, and systems-level approaches to uncover mechanisms of brain vulnerability and repair. It has demonstrated excellent attractiveness, obtaining several competitive grants (4 ANRs, ANSES, IRESP). The research axes are complementary: Axis 1 on stroke biomarkers and vascular mechanisms; Axis 2 on neuroinflammatory mechanisms in seizures and epilepsy; and Axis 3 on environmental neurotoxicology. The integration of advanced methodologies (multi-omics, flow-based vascular models, spatial transcriptomics, EEG analyses) and the connection with patient-derived material enhance its translational impact. Supervision of 6 doctoral (3 foreigners) and 4 postdoctoral researchers (1 foreigner) is active. Collaborations within IGF and with hospital departments offer excellent potential for future development. The team leaders are implicated in the editorial boards of Glia and Epilepsia. One team leader was the president of the scientific council of the Foundation for Research on Epilepsy for 9 years; he has also founded and managed the GRD "Microglia and Neuroinflammation". As a team involved in clinical research, it has also a strong relationship with patients.

Context-related weaknesses and risks

Several projects rely on access to patient samples and clinical data, which may face logistic difficulties. Increasing visibility and the ability to publish in prestigious journals will depend on the ability to synthesize findings from multiple ongoing basic and clinical projects into coherent publications.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team demonstrates a clear and ambitious trajectory, building on strong clinical–scientific synergies. Axis 1 evolves from descriptive clot proteomics to functional biomarker validation and identification of molecular targets, reinforcing its translational dimension. Axis 2 broadens into neuroimmune regulation in epilepsy, addressing aging and genetic epilepsies with mechanistic animal models and innovative imaging and molecular approaches. Axis 3, developed jointly with IGF partners, reflects openness to environmental and public health aspects, integrating toxicology and developmental neuroscience. The projects are well-funded, technologically advanced, and includes high-risk/high-gain components such as machine learning analyses, spatial transcriptomics, and 3D-printed vascular models. These elements demonstrate strong capacity for innovation and risk-taking, consistent with international trends in translational neurovascular research.

RECOMMENDATIONS TO THE TEAM

Consolidate and prioritize research axes to maintain scientific focus and ensure timely, high-impact publications.

Articulate internal coordination between clinical and basic components to optimize research continuity and common publication strategy.

The team could make efforts to improve their interactions with the non-academic world (industry, outreach activities).

Team 8: Neuroproteomics and signaling of brain disorders

Name of the supervisor: Mr Philippe Marin

THEMES OF THE TEAM

The team investigates the molecular and cellular mechanisms underlying brain disorders using integrated neuroproteomics and signalling approaches. Research themes include the characterisation of GPCR interactomes and phosphoproteomes. They focus on serotonin, glutamate and chemokine receptors, and their roles in neurodevelopment, cognition, and psychiatric disorders. They also explore therapeutic strategies for Alzheimer's disease and multiple sclerosis, combining proteomic, cellular, and translational approaches to identify new biomarkers and disease-modifying targets.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

This large team has maintained output with 161 publications over the reporting period.

Philippe Marin's appointment as Unit Director has been well-managed, and productivity has been maintained through the leadership of several independent PIs. The succession of the new team leaders is underway to ensure continuity.

The recommended diversification strategy led to new researcher recruitment and the emergence of independent teams. This reflects the team's dynamic structure, capacity for renewal, and strategic vision. The team has retained scientific continuity and expanded its research scope, while maintaining a strong collaborative and interdisciplinary environment.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Praticien hospitalier	0
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels non permanents d'appui à la recherche	3
Post-doctorants	1
Doctorants	10
Sous-total personnels non permanents en activité	**14**
Total personnels	**25**

EVALUATION OF THE TEAM

Overall assessment of the team

The team has an excellent to outstanding international profile of leadership in neuroproteomics and GPCR signalling. Its interdisciplinary strategy, combining molecular, cellular, and translational approaches, has contributed to the understanding of brain disorders. A significant strength has been the generation of independent groups. Sustaining technical support and attracting postdoctoral talent remain key challenges for the next mandate.

Context-related strengths and opportunities

The team's work on GPCR interactomes and phosphoproteomes has advanced understanding of receptor signalling dynamics, neuroplasticity, and their implications for psychiatric and neurodegenerative diseases. The complementary expertise of its principal investigators provides an integrated research environment capable of addressing complex questions from molecular mechanisms to translational applications. The team has made significant scientific progress, including the identification of dynamic GPCR interactomes and phosphorylation networks that regulate key neurodevelopmental, cognitive, and neuropsychiatric processes. The integration of advanced proteomic platforms, including single-cell proteomics, and access to cutting-edge imaging technologies for monitoring neurotransmitter release, provide powerful tools to sustain high-level research. They have identified novel therapeutic targets and molecular pathways in serotonin and glutamate receptor signalling. Their data suggest new perspectives for disease-modifying strategies in schizophrenia, depression, and cognitive dysfunctions. Their technological resources and collaborative networks are key strengths. Moreover, their large-scale proteomic and biomarker studies for MS identified CD138 as a diagnostic marker, exemplifying the team's clinical relevance. Several PIs have established or are in the process of creating their own teams, both within the IGF and in other institutions, evidencing the strength of the mentoring structure. The team has also recruited new researchers and set up collaborations in complementary fields, including neuroepidemiology, electrophysiology, and neurodegenerative disease mechanisms. Finally, the team benefits from strong integration within the institutional and academic landscape of Montpellier and from thematic programs and funding opportunities at national and European levels. Its ability to secure competitive funding, combined with its strong publication record, collaborative network, and translational orientation, provides a solid foundation for continued excellence and innovation in the next mandate.

Context-related weaknesses and risks

Notwithstanding their productivity and international recognition, the team faces challenges. They highlight that a lack of stable technical support may increase the administrative and experimental burden on researchers and potentially limit the capacity to fully exploit the technological platforms. This structural vulnerability is particularly critical given the team's extensive reliance on complex proteomic workflows, large-scale data analysis, and advanced imaging, all of which require continuous technical expertise and maintenance. Although the team has successfully attracted PhD students and young investigators, international postdoc recruitment remains limited. Efforts to secure targeted funding for postdoctoral positions and to strengthen international visibility through joint projects and networks could help mitigate this risk.

Maintaining cohesion and coordination across several semi-independent subgroups requires regular strategic alignment with the overall research vision. As several PIs are developing independent teams or relocating to other institutions, there is a significant risk of fragmentation if replacements are not recruited or if funding is not sustained.

Also, while commendable, the diversification of research themes complicates resource prioritisation, funding and personnel allocation. Again, strategic focus and coordination will be essential to maintain coherence and ensure that all research lines remain feasible and synergistic.

Finally, several team members have teaching and administrative duties that limit research time. Ensuring a balanced distribution of teaching and research responsibilities and securing technical and administrative reinforcement will be crucial to sustain productivity.

ANALYSIS OF THE TEAM'S TRAJECTORY

Building on a solid foundation, the team has expanded to integrate complementary domains, including synaptic signalling, neurodevelopment, and translational neuropharmacology.

Their work in GPCR interactomics and phosphoproteomics provides new insights into the contributions of receptor signalling networks to neurodevelopmental, cognitive, and neuropsychiatric disorders. This translational work has, and will continue to, reveal novel therapeutic targets and disease-modifying strategies based on receptor pathway modulation. Thus, the team's research continues to link proteomic discovery with clinical utility. Combining mechanistic and translational approaches provides a coherent trajectory from molecular understanding to therapeutic innovation.

The fact that several PIs have established or are in the process of forming independent teams, both within and outside the IGF is very positive and bodes well for the future. Similarly, the integration of new researchers with complementary expertise in neurodegeneration, electrophysiology, and epidemiology ensures continuity while broadening the team's scientific reach. This process of renewal, combined with a high degree of autonomy among PIs, positions the group for sustained productivity and innovation.

The team enjoys strong institutional support with access to advanced technological infrastructures that facilitate the development of next-generation studies in single-cell proteomics, synaptic function, and circuit-level signalling. These resources, along with the unit's growing R&D support and new thematic programs at the University of Montpellier, provide exciting potential for future growth.

Proposals to build on existing strengths while strategically addressing identified challenges are realistic and ambitious. They highlight the need for stable technical support, postdoctoral recruitment, and balanced resource allocation.

Overall, the team is very well positioned to maintain its upward trajectory and make significant contributions at both national and international levels.

RECOMMENDATIONS TO THE TEAM

The committee strongly encourages the team to maintain its dynamic and integrative research strategy, which successfully bridges molecular mechanisms with translational neuroscience.

The team requests increased technical support to ensure the continuity of expertise in proteomics, imaging, and in vivo experimentation. While this would be helpful, the committee feels that the recruitment of international postdoctoral fellows should also be prioritised to promote innovation and enhance global visibility. The team should continue fostering the autonomy and mentoring of emerging investigators while preserving coherence and synergy among subgroups, ensuring that diversification remains a strength rather than a source of fragmentation.

Strategic planning for resource allocation and coordination will be important to balance the growth of new projects with the sustainability of ongoing lines of research.

As evidenced by their achievements, maintaining and deepening strong integration with clinical collaborators and translational initiatives will further enhance the societal and therapeutic impact of the team's discoveries in brain disorders.

Team 9: Neuronal circuit of social and affective touch

Name of the supervisor: Mr Emmanuel Perisse

THEMES OF THE TEAM

The team studies how the brain assigns value to sensory stimuli during learning and how this information guides value-based decisions. The goal is to identify the neural code underlying value representation and to understand how appetitive and aversive systems interact to encode absolute and relative value. Using the fruit fly *Drosophila melanogaster* as a model, the team combines advanced genetics, in vivo two-photon calcium imaging, molecular approaches, and behavioural assays to dissect the circuit mechanisms supporting value-based choices.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team has not been evaluated by the previous committee

The team has not been evaluated by the previous committee

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Praticien hospitalier	0
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**2**
Total personnels	**5**

EVALUATION OF THE TEAM

Overall assessment of the team

Over the past five years, the team has delivered excellent to outstanding research on neural mechanisms of value computation and stress-dependent modulation of aversive learning in Drosophila. They uncovered how relative aversive value is computed in the mushroom body, revealing distinct "better than" versus "worse than" learning, published in *Current Biology*, and inspiring cross-species work with S. Trouche. Their output includes primary studies and integrative reviews.

Context-related strengths and opportunities

By mutual agreement, the teams of E. Perisse and S. Trouche have merged into a unified memory circuits team. This evolution is fully aligned with Inserm criteria (critical mass of permanent staff) and opens clear opportunities. By combining complementary expertise and resources, the merged team is now well positioned to address shared questions across species, bridging fly and mouse approaches to generate original insights into memory and valuation circuits. The team leader has also maintained the ability to secure funding, providing a solid basis to support the integration and sustain momentum. During the evaluated period, the most notable scientific advances include the demonstration that dopaminergic and aversive systems interact within the fly mushroom body to compute relative aversive value during associative learning, with identified circuit mechanisms enabling "better-than/worse-than" value comparisons and more efficient value-based decisions. The team also made substantial progress on how prior noxious experience reshapes subsequent nociceptive processing, uncovering stress-induced analgesia mechanisms and showing that CO_2-related stress signals can rapidly and dose-dependently reduce nociceptive avoidance, with evidence pointing to a key role of the respiratory/tracheal system. In the evaluated period, the team has included 2 PhD students and 1 postdoctoral fellow. One of the PhD student will finish in 2026 and the other in 2027. The team leader participated in several conferences and was involved in the organization of meetings. He gave a talk during the Brain awareness week and since 2023 he is the coordinator of the school events.

Context-related weaknesses and risks

The merge of the Trouche and Perisse teams will require particular attention to ensure that both team leaders can continue to develop their scientific independence and fully establish themselves as experts in their respective fields.

Within Aim 1, the proposed interlink between the fly and mouse approaches is not yet fully articulated, and the level of integration remains to be clarified. The team will progressively need to define how to co-manage shared research questions and personnel involved in cross-species projects. While this may represent an organisational challenge, it also offers a valuable opportunity for the leaders to build a genuinely synergistic programme. It seems that the research topic between the two groups will need to fit and the aim of Dr Perisse on investigating the sensory perception of nociceptive stimuli is lost in the new trajectory.

By contrast, the integration within the second project appears more mature. In Aim 2, the interaction between Projects 3 and 4 would benefit from the development of a more explicit integrative framework to strengthen coherence across the proposed lines of research.

ANALYSIS OF THE TEAM'S TRAJECTORY

The trajectory of the newly formed team originates from the recent merger of the Perisse and Trouche groups, a strategic decision aligned with Inserm requirements for a critical mass of permanent staff. This merger represents both a structural challenge and a scientific opportunity. It brings together complementary expertise in memory circuits across species, from fly to rodent, enabling an ambitious cross-species and multi-level research strategy. Integrating behavioural, genetic, and circuit-level approaches in flies with sophisticated in vivo manipulations in mice offers the potential for original insights into the computation of memory and valuation. At the same time, the success of the merger will depend on the ability of both leaders to maintain their scientific independence while establishing a unified, coherent medium-term strategy that is operationally functional.

The proposed projects reflect this dual dynamic. Several axes—particularly within the second project—already show strong integration, with clear cross-species complementarities and high potential for synergy. However, Project 1, and in particular the articulation between fly and mouse approaches, remains insufficiently developed at this stage. The rationale for cross-species hypothesis transfer is solid, but the operational integration and co-management of shared scientific questions, tools, and personnel require further refinement. Likewise, the interaction between Projects 3 and 4 in Aim 2 would benefit from a more explicit integrative framework to ensure conceptual and methodological coherence.

The recruitment strategy is coherent, ambitious, and central to the team's future trajectory. The intention to support candidates for tenured CNRS/Inserm or lecturer positions each year demonstrates a proactive approach, and the variety of labels is used appropriately to limit internal competition. The plan to recruit a computational researcher is particularly relevant, as such a profile could provide a unifying modelling framework linking fly and mouse approaches and strengthening the valuation theme. The team has demonstrated its ability to attract strong candidates—several reaching interview stages at CNRS or University level—underlining its visibility, even though none have yet secured positions. The strategy for recruiting postdocs, research assistants,

and PhD students is realistic and supported by robust funding, including the capacity to guarantee fourth-year PhD salaries when required.

The team leader has obtained funding as coordinator that will allow to continue his research ambitions for the next years.

RECOMMENDATIONS TO THE TEAM

Looking ahead, it will be important for the team to regularly reflect on how the ongoing integration progresses, ensuring that the complementary expertise of the two leaders continues to enrich the scientific agenda.

The plan to recruit a computational researcher is particularly promising, as it could ultimately provide a unifying framework for the cross-species investigations. To guide this evolution while preserving flexibility, the team would benefit from articulating a few medium-term objectives without imposing rapid restructuring.

At the organisational level, the committee encourages the establishment of a clear and realistic long-term strategy for sustaining research in both mice and flies.

Formalising the co-leadership structure—especially with respect to scientific direction, resource allocation, and strategic decision-making—will be essential to maintain efficiency and avoid unnecessary complexity.

Finally, the committee strongly recommends that the institute ensures the appropriate technical support and space allocation required to match the team's ambition and excellence, particularly regarding specialised facilities for in vivo mouse work.

Team 10: Physiopathology of neuronal plasticity

Name of the supervisor: Ms Julie Perroy

THEMES OF THE TEAM

The team is interested in a broad range of research areas that loosely centre around neurotransmitter receptor protein:protein interactions and crosstalk between different receptor types. They use the umbrella term 'receptosome' to encompass the components involved in receptor signalling and aim to gain insights into neuronal function and dysfunction by developing new tools and gathering data at multiple levels, from modelling to the molecular to the whole-animal.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

For the most part, the team has addressed the recommendations of the previous report. They have become more multidisciplinary by expanding from 3 to 8 permanent members, adding competencies in molecular biology, pharmacology, network physiology, and in vivo imaging.

The team's productivity has risen markedly since the last assessment, with publications in impactful *journals*. These outputs indicate successful interdisciplinary collaboration within IGF and with national and international partners.

They have a very ambitious scientific program that bridges molecular, cellular, and systems-level neuroscience, particularly in relation to the mechanisms and pathophysiological implications of synaptic and neuronal plasticity. They propose to correlate the molecular dynamics of glutamate receptor complexes (receptosomes) to neural network activity and behaviour. This multiscale approach aims to link protein-protein interactions, synaptic plasticity, and cognitive function.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Praticien hospitalier	0
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels non permanents d'appui à la recherche	2
Post-doctorants	0
Doctorants	7
Sous-total personnels non permanents en activité	**11**
Total personnels	**21**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be excellent to outstanding and set to improve still further with the addition of new PIs with complementary expertise. They have decent levels of national funding and evidence of effective leadership, productive collaborations, and consistent publications.

Context-related strengths and opportunities

The team, soon to be renamed "Physiopathology of Neuronal Plasticity", has experienced a period of sustained consolidation and expansion. New permanent members have added complementary expertise across various disciplines and techniques. The team's composition enables an integrated programme that bridges molecular, cellular, network, and behavioural levels of investigation. The team aims to connect synaptic receptor dynamics and signalling with neural network activity and behavioural plasticity. This is a highly competitive and ambitious goal to address questions at the leading edge of neuroscience. An advantage of this broad objective is that it involves all team members as co-investigators, while still allowing principal investigators to oversee different subprojects, fostering cohesion and creativity. Work on glutamate receptor interactions, especially mGlu5, and signal integration has been productive. Though not unique, their concept of the "receptosome" and its role in synaptic and behavioural plasticity has generated valuable new data. Research linking dynamic receptor complexes to neurodevelopmental and neuropsychiatric disorders demonstrates an elegant integration of molecular mechanisms with translational relevance. Additionally, the development of BRET-based tools and other advanced biosensors for in vivo imaging reinforces the team's technological leadership and may lead to the creation of widely applicable methodologies. The team's current grant income and collaborations with new partners (optical imaging) and strong links with theorists and clinicians, provide resources and expertise to research from molecules to patients, thereby increasing translational impact. They demonstrate commitment to training and outreach, with initiatives such as the creation of a dual medicine–science programme, supervision of PhD students, and active engagement in teaching and mentoring, all reflecting a strong dedication to education and knowledge dissemination. Interdisciplinary collaborations with industrial partners (Promega, PerkinElmer, Resolve Stroke) and the launch of clinical applications in neurointensive care indicate potential for bridging fundamental and applied research.

Overall, the team's metrics suggest dynamism, cohesion, and adaptability. The development of advanced tools, and the integration of theory, experimentation, and translational approaches are notable strengths. These assets, combined with a collaborative network of national (e.g. E. Hosy, IINS, Bordeaux), provide valuable opportunities for scientific leadership and discoveries.

Context-related weaknesses and risks

The team provides evidence of progress and productivity, but going forward, there are notable challenges and potential risks.

(1) The most obvious concern relates to the ambitious scale of the overall project. This multidimensional approach, though conceptually attractive, is 'high risk' and requires sustained coordination, careful management of resources, and efficient communication among the diverse specialists within the team.

(2) The number of subprojects and collaborations will require substantial administrative and organisational inputs from team leaders, potentially diverting time from scientific supervision and strategic planning. Ensuring effective coordination across subprojects and maintaining a coherent collective direction will be essential to ensure the team's cohesion and scientific focus. The current expansion phase, with multiple new members, students, and technical developments, also creates pressure on supervision and mentoring capacity. The number of permanent scientists has increased, but continued recruitment of grant-supported PhD students and postdocs could challenge supervision resources, especially in experimental areas requiring advanced technical expertise (optical imaging, biosensor engineering, in vivo electrophysiology). Workload distribution will be required to ensure training quality and project integration across the team.

(3) Another potential weakness is the inherent technical and conceptual complexity of the team's approach. The combination of molecular imaging, behavioural modelling, and in vivo monitoring of signalling pathways is methodologically demanding and depends on maintaining cutting-edge technological platforms and engineering support. Delays or failures in tool optimisation can slow or prevent progress. The reliance on sophisticated equipment also implies a dependency on stable technical personnel and financial resources for

maintenance and upgrades. Furthermore, the integration of theoretical and experimental approaches, while conceptually enriching, requires sustained and continuous effort to ensure that modelling remains tightly linked to empirical data and not pursued as an isolated line of research.

At the strategic level, while the team's funding is currently strong, the sustainability of long-term support is partially dependent on external grants. Changes in national research policy, funding priorities and research structuring would affect research continuity and challenge flexibility.

Finally, while the team's scientific output and visibility have improved significantly over the review period, the challenge will be to sustain this momentum and ensure future high-impact discoveries and publications. Addressing these potential risks through effective leadership, streamlined management, and continued support from institutional partners will be crucial to securing the team's long-term success and international standing.

ANALYSIS OF THE TEAM'S TRAJECTORY

The overall aim of the team is '*linking the synaptic molecular dynamics and signalling pathways of neuronal plasticity with the changes in neural network activity underlying behavioural learning.*' This statement encompasses a broad, complex and highly ambitious series of goals.

Given the team's track record and composition, it is likely they will make new findings in areas within this overall aim that will contribute to the field, for example, their focus on the dynamics of protein:protein interactions on glutamate receptor trafficking and signalling pathways. It should be noted, however, that even for individual glutamate receptors, their component subunits and auxiliary proteins, this represents a daunting ambition in an internationally active and highly competitive area of research.

The proposed research ranges from modelling through molecular and protein analyses and network activity to in vivo work. A briefly described prototypic study is the analysis of mGlu5 and its cognate proteins. This receptor complex mediates multiple signalling pathways at individual synapses and between synapses in the same and in different neurons. Citing examples of biosensors to monitor calcium- and cAMP-mediated downstream changes in ERK or CREB the team propose to determine how this complexity leads to adaptation of network activity and ultimately animal behaviour. This alone is a hugely ambitious goal, even considering the mentioned collaborators.

The projects on NMDA receptor variants and autism spectrum disorders and on SARS-CoV-2 effects on synaptic stability are well-funded, but it is not explained how these studies fit into the team's overall research vision.

Team members have distinct and complementary areas of expertise. They will continue to be productive and generate interesting new data, but they will need to interact closely and collectively to provide an output greater than the sum of their individual research groups.

RECOMMENDATIONS TO THE TEAM

The team should continue to capitalise on its strong scientific momentum and focus on further developing the coherence and integration of its multidisciplinary research program.

The strategic coordination among molecular, cellular, network, and behavioural approaches to ensure efficient translation of findings will be a significant challenge. Strengthening internal communication, project management, shared protocols and data analysis pipelines across projects will help sustain coherence, reproducibility and efficiency as the team grows.

Attention should be given to balancing supervision load and maintaining high-quality mentoring, particularly for PhD students and postdocs, as the number of trainees increases.

To mitigate technical and logistical risks, the team should consolidate its technological platforms and secure stable technical staff to support complex imaging and biosensor development.

The team should anticipate long-term funding challenges by diversifying grant sources, e.g. EU programs and industrial partnerships. Leadership roles in international consortia, conferences, and high-impact publications will consolidate its reputation.

To maintain its strong translational dimension while safeguarding its excellence in fundamental research, structured interactions with clinical partners and industry are encouraged, but with clear delineation of priorities and deliverables.

Team 11: Purinergic signaling and brain inflammation

Name of the supervisor: Mr François Rassendren

THEMES OF THE TEAM

The team investigates the cellular and molecular mechanisms of neuroinflammation, with a particular focus on purinergic signalling pathways in microglia and their involvement in neurodegenerative and neuroinflammatory diseases. Its main research axes include (1) the role of P2X receptors in chronic pain and Alzheimer's disease, (2) microglial dynamics during disease progression using transcriptomic and imaging approaches, and (3) the development of biosensing technologies to monitor inflammatory mediators such as ATP and IL-1β in real time. The team combines transgenic mouse models, single-cell sequencing, in vivo imaging, and biosensor engineering to bridge mechanistic, functional, and translational insights in brain inflammation.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Following previous recommendations, the team has made significant progress in publication quality, outreach, and strategy. It produced 33 articles (16 with the PDC as senior author), including high-impact papers in *Nature Communications*, *Journal of Neuroinflammation*, and *Brain, Behavior and Immunity*. A patent on bioluminescent biosensors was obtained and collaborations with industry (Intra-Cellular Therapies, NBX) were established. The team also actively participate in public outreach programs (DECLICS, Brain Awareness Week).

The team implemented weekly meetings, young investigator seminars, and an open discussion on leadership succession. Hélène Hirbec was nominated as the next team leader. This transition ensures continuity and strengthen the research on glial biology in the IGF unit.

Scientifically, the team refined its focus on microglial purinergic signalling and biosensor development, while developing state-of-the-art techniques (Cre-Lox models, in vivo imaging in freely moving animals, single-cell RNA-seq). Despite competitive pressures in the AD/microglia field, the team is very well positioned in the field by centering its activity ton P2X4 receptor signalling, microglia transcriptomic remodeling and biology in disease.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	5
Praticien hospitalier	0
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**7**
Total personnels	**16**

EVALUATION OF THE TEAM

Overall assessment of the team

Overall, the team is excellent with a leadership on neuroinflammation and purinergic signalling in glial cells. The scientific output has greatly increased, with 33 publications during the reporting period. It has also strengthened the workforce through the recruitment of a Junior Professor. The team is very well integrated in national networks, including the GDR "Microglia and Neuroinflammation" and the French Glial Cell Club. Societal impact has grown through R&D collaborations with private companies and a patent on bioluminescent biosensors.

Context-related strengths and opportunities

This is a well-established team with five permanent researchers, including a recently recruited Junior Professor with a CPJ CNRS position. During the reporting period, the team published 33 articles, about half as a senior author. It has made major contributions to understanding neuroinflammation and neurodegeneration, combining a multidisciplinary expertise from molecular biology to systems neuroscience. Their key achievements include: 1) identifying the role of P2X4 receptors in chronic pain (*Ulmann, iScience*); 2) uncovering microglial mechanisms in Alzheimer's disease, such as transcriptional remodeling (*Hirbec, J Neuroinflamm*), 3) the involvement of P2X4 receptors (*Ulmann/Rassendren, CMLS*); 4) the deregulation of *Clec7a* (ongoing). In parallel, the team developed advanced biosensor technologies to monitor inflammatory mediators, elucidating ATP release mechanisms (three publications, including one in *Nature Communications*) and IL-1β processing (*Compan, J Inflamm*). The team benefits from robust national funding, with 300–400 k€ annually, and secured resources for the next mandate (4 ANRs, Fondation Recherche Alzheimer). The leadership transition to H. Hirbec should offer a renewed dynamic and continuity of the team.

During the reporting period, four PhD students obtained their degrees, and another six are currently pursuing their thesis work. One post-doc was also trained during this period. Members of the team actively participate to national networks (GDR Microglia, Purines Network, Glial Cell Club), reinforcing the team's visibility in France. The team's technological expertise (biosensors, single-cell omics, transgenic models, in vivo imaging) provides a competitive advantage, and the biosensor invention is protected by a patent. They also regularly participate to outreach activities such as Declics, the Brain Awareness week or University of the Third Age.

Context-related weaknesses and risks

Despite excellent national visibility, participation in European programs and organization of international conferences should improve the team's international visibility. Engagement at national and international scientific committees and meetings should be encouraged for all team members, particularly the new team leader.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team's trajectory demonstrates a clear coherence and consolidation of its research and the emergence of innovative lines combining purinergic signalling, microglial dynamics, and neuroinflammation. Its project for the upcoming mandate is ambitious and comprises two orientations (1) elucidating purinergic mechanisms underlying microglial activation in chronic pain and neurodegeneration, and (2) developing biosensor-based platforms for in vivo monitoring of inflammatory molecules.

The leadership transition ensures scientific continuity and diversification, while the integration of a CNRS Junior Professor brings new competences in inflammation and therapeutic targeting. The adoption of cutting-edge imaging and single-cell technologies reflects the ambition to maintain international competitiveness. The project's success will depend on sustained technical staffing, international collaborations, and effective valorization of technological developments.

RECOMMENDATIONS TO THE TEAM

Submit european and international proposals on neuroinflammation and glial signalling to expand collaborative networks.

Promote the new leadership (H. Hirbec) through active engagement in committees and international meetings, enhancing the team visibility at the international level.

Promote the biosensor platform toward academic, translational and/or industrial partnerships to enhance the value of intellectual property and improve technology transfer.

Team 12: Neuroreceptors: dynamics and functions

Name of the supervisor: Mr Philippe Rondard

THEMES OF THE TEAM

The team's research focuses on structure, function and physiology of class C GPCRs, in particular mGlu and GABAB receptors. In collaboration with Cryo-EM and biophysics teams, they have solved structures of several mGlu and GABAB receptor oligomers in different gating states, as well as deciphered the molecular dynamics of mGlu gating at the single molecule level. The team has furthermore continued its development of light-based sensors for tracking GPCR gating and oligomerization through its ARPEGE platform and the company Revvity Cisbio Bioassays. The team has finally reinforced its axis around nanobody development. These powerful tools allowed the team to reveal unexpected features around mGluR oligomerization, interactome and physiopathological roles with translational potential.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Previous recommendations were:
"*The committee recommends to continue the excellent work*": The team has indeed continued doing excellent work by unraveling new knowledge on the structure, function and pathophysiology of class C GPCRs and providing new tools (nanobodies, light-based sensors) to the GPCR community.

"*Strategy to attract PhD students should be implemented. Current and future team leaders should pay attention to the future strategy of management, especially after the departure of 3 scientists and considering the deep commitment of the team in the collaborations with the Sino-french laboratory and the collaborative lab Eidos with Cisbio*.": Over the 2019-2024 period, the team has trained 11 PhD students. However, Anais Menny does not co-direct any PhD student for the moment. The departure of the 3 scientists has not impacted the productivity of the team, with > 30 publications and 5 patents. The team has refocused its efforts on three axes: mGlu and GABAB receptor structure-function, nanobody development to investigate mGlu in vivo oligomery and pathophysiology, and light-based biosensors (Revvity-CisBio). Balancing commitment between the lab at IGF and the Sino-French laboratory in Wuhan remains a point of attention.

"*The work on mouse will probably have to be strengthened by recruitment of an expert or establishment of new collaborations.* ": A new permanent research engineer has been recruited and new collaborations have been made.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	7
Praticien hospitalier	0
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	6
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**9**
Total personnels	**20**

EVALUATION OF THE TEAM

Overall assessment of the team

The team work is outstanding, with major impacts on the structure, function and pathophysiology of class C GPCRs. The team has produced over 30 publications and filed 5 patents. It has strong Fundraising capacity, visibility, and recognition, reflected in the obtained grants (European Union, ANR, FRM), invited talks and scientific responsibilities. The capacity of the team is reinforced by strong collaborations with expertise in structural biology, biophysics, molecular simulations, chemistry and animal behavior.

Context-related strengths and opportunities

This is a well-established team with four permanent researchers, including a CNRS CRCN recruited in 2023. The research capacity of the team is reinforced by two full-time engineers and one at 40% with a permanent position, including a new recruit, with expertise in *in vivo* studies. This will allow to expand the team research scope to behavior. They have produced > 30 publication, most of them in prestigious journals (Nature, Nature Chem Biol, Nature Comms, PNAS, ...). Major achievements from the team include: (1) tool development: the team has pioneered the development of nanobodies to target specific mGlu assemblies. These are now used to investigate mGlu function at the molecular, cellular and behavioral levels. The team has furthermore a long-standing expertise in light-based assay development to detect protein-protein interaction and GPCR activity. (2) Understanding the molecular mechanisms of mGlu and GABAB receptor signaling using a combination of Cryo-EM (collab with partners in Wuhan, China and the University of South California, USA) and single molecule FRET (collab with CSB, Montpellier); (3) Discovery of new mGlu assemblies in the brain, using a nanobody-based FRET assay. The team has revealed that the large majority of mGlu4 subunits in the forebrain are incorporated in mGlu2-mGlu4 heteromers. This discovery is a major breakthrough and should fuel future drug discovery programs. (4) Therapeutic potential of nanobody-based pharmacology: using their nanobodies as highly specific allosteric modulators, the team has recently demonstrated their therapeutic potential in a mouse model of schizophrenia, in collaboration with experts in mouse behavior in Tours (Oosterlaken et al., Nature 2025). The team has benefited from robust national and international funding, with two grants from the European Union, many national grants (ANR, FRM...) and industry funding (Revvity). Funding is secured until 2029. They have established many collaborations (e.g. Université Paris-Cité, Paris, CBS in Montpellier, University of South California, USA) and have been invited to several prestigious conferences like GRCs, and hold scientific responsibilities. The team has trained 11 PhD students over the evaluation period. 6 out of the 8 PhD students who defended their PhD have published as first authors. The two others are in the process of publishing. PhD students and post-docs largely come from France but the group also hosts a few international doc/post-docs (Netherlands, China). The team maintains strong links with society and the socio-economic world, with collaborations with industry (CisBio-Revvity, Dassault Systems). They have furthermore submitted 5 patents. Finally, Jean-Philippe Pin is highly involved in teaching, since he coordinates the "double cursus Santé Sciences" of Université de Montpellier and école de l'Inserm. All team members are involved in outreach activities.

Context-related weaknesses and risks

Despite the international recognition of the team work, the team has recruited only a few international trainees. Some permanent researchers of the team cumulate several positions (academic lab in IGF, private company, lab in China). This does seem to be an issue so far but there remains a risk that one or the other activity might be left aside.

The outsourcing of some research activities in China (nanobody development, Cryo-EM studies) might pose issues of intellectual property.

ANALYSIS OF THE TEAM'S TRAJECTORY

During the next period, the team will be composed of 6 permanent staff (4 researchers and 2 engineers (one at 50% and one at 80%). Funding is secured until 2029. P. Rondard is planning to apply for an ERC advanced grant in the coming years. The team will continue its longstanding studies on class C GPCR structure-function, oligomery and pharmacology with an evolution towards Cryo-EM studies (thanks to collaborations with their lab in China) and single molecule studies. They will strengthen the nanobody axis by building new nanobody-based tools for imaging and allosteric modulation of specific mGlu assemblies. They furthermore plan to move to in vivo studies to investigate the therapeutic potential of anti-mGlu nanobodies for the treatment of schizophrenia and Alzheimer's disease. This new direction is supported by their latest publication showing rescue of mouse

behavior in mouse models of schizophrenia. They have furthermore recruited an engineer to perform in vivo studies, and are in direct contact with IGF teams to help them set-up in vivo studies. All these conditions should allow the successful transition of the team from molecular and cellular biology to mouse behavior.

Within this team, Anais Menny, holding an ERC starting grant, will lead her independent line of research. She currently manages two post-docs and two engineers. Her goal is to understand (i) how the nature and physical properties of the membrane influence mGlu receptor signaling, and (ii) how heteromerization mGluRs with other GPCRs, or how heteromerization within mGluR, influence the receptor gating and signaling properties. She plans to solve these issues using a combination of Cryo-EM, single molecule FRET and receptor biophysical studies. This is a challenging project that should lead to very important insights into the physiology of native mGlu receptors.

Altogether, the team aims at understanding class C GPCR function from the atomic to the behavioral level, with translational potential. This is an ambitious trajectory that will require careful, strategic allocation of resources and close coordination among those managing projects across different scales.

RECOMMENDATIONS TO THE TEAM

The team should build on this momentum and keep leading the way in membrane protein structure-function and pharmacology. They should apply to international grants and try to recruit more international docs and post-docs.

While Anais Menny will operate as a fully independent researcher, she should still receive support from other permanent researchers. For instance, there could be more synergy between her projects and the other team's projects. In addition, she should receive support to co-supervise PhD students before obtaining her HDR.

Permanent researchers should remain cautious to appropriately manage their commitment between the lab, the Revvity CisBio company and the collaborative lab in China.

Team 13: Appetitive and Aversive Memory Circuits

Name of the supervisor: Ms Stephanie Trouche

THEMES OF THE TEAM

The team was created in 2023 and the main topic is understanding how appetitive and aversive neuronal circuits are shaped by past experiences, environmental and internal states and how they interact in order to select appropriate behaviors (approach and avoidance). Two questions drive the team's research: 1) identify novel neuronal circuits for fear memory expression, with a focus at the circuit level on BLA to NAc pathway and 2) dissect the neural mechanisms for relative aversive value coding in mice. The collaborative project between the Trouche and Perisse labs aims to tackle the mechanisms underlying aversive value coding in mice and flies.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Team created in 2023 following a competitive internal call.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Praticien hospitalier	0
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**1**
Total personnels	**4**

EVALUATION OF THE TEAM

Overall assessment of the team

This is a relative new team with a very exciting research question and with an excellent to outstanding output. The team leader has shown excellent capacity to obtain grants and secure fundings as well as to deliver high profile publications. She has solid national and international collaborations and recognized expertise in the field. The lack of permanent technical help could be on the longtime a weakness for the team. By mutual agreement, the team of E. Perisse and the team of S. Trouche will merge into a memory circuit team.

Context-related strengths and opportunities

The team leader has shown excellent capacity to obtain grants and secure fundings as well as to deliver high profile publications. She has solid national and international collaborations and recognized expertise in the field. The direction indicated that, by mutual agreement, the teams of E. Perisse and S. Trouche have decided to merge into a unified memory circuits team. This evolution is fully aligned with Inserm criteria, which require a sufficient number of permanent staff per team, and it creates several promising opportunities. By bringing together complementary expertise and resources, the merged team gains the capacity to address shared research questions across species, integrating tools and concepts from both fly and mouse models. This combination of approaches positions the team to develop innovative cross-species strategies and to generate particularly original insights into memory and valuation circuits.

Context-related weaknesses and risks

The merge of the Trouche and Perisse teams will require particular attention to ensure that both team leaders can continue to develop their scientific independence and fully establish themselves as experts in their respective fields.

Within Aim 1, the proposed interlink between the fly and mouse approaches is not yet fully articulated, and the level of integration remains to be clarified. The team will progressively need to define how to co-manage shared research questions and personnel involved in cross-species projects. While this may represent an organisational challenge, it also offers a valuable opportunity for the leaders to build a genuinely synergistic program.

In Aim 2, the interaction between Projects 3 and 4 would benefit from the development of a more explicit integrative framework to strengthen coherence across the proposed lines of research.

ANALYSIS OF THE TEAM'S TRAJECTORY

The newly formed team results from the merger of the Perisse and Trouche groups, a strategic decision aligned with Inserm requirements for a sufficient number of permanent staff. This merger is both a challenge and a major opportunity, bringing together complementary expertise on memory circuits from flies to rodents. The combination of behavioural, genetic, and circuit-level approaches in flies with advanced in vivo methods in mice offers strong potential for original insights into memory and valuation. Its success, however, will depend on the ability of both leaders to preserve their scientific independence while developing a coherent, shared medium-term strategy.

The proposed projects reflect this dual dynamic. Some axes, especially within the second project, are already well integrated with clear cross-species complementarities. In contrast, Project 1—particularly the link between fly and mouse approaches—remains insufficiently articulated, and the operational co-management of shared tools, questions, and personnel requires further refinement. Likewise, Projects 3 and 4 in Aim 2 would benefit from a clearer integrative framework to ensure overall coherence.

The recruitment strategy is ambitious and central to the team's development. Supporting candidates for CNRS/Inserm or lecturer positions each year demonstrates a strong long-term vision. The plan to recruit a computational researcher is particularly relevant, as modelling could provide a unifying framework for the cross-species valuation work. The team has demonstrated its ability to attract strong candidates, even if none have been successful yet. Plans to recruit additional postdocs, assistants, and PhD students are realistic and supported by solid funding, including fourth-year PhD support when needed.

Overall, the trajectory is promising. The merger creates a unique opportunity for a distinctive cross-species programme on memory and valuation circuits. The main risks concern scientific integration and leadership organisation, but these can be mitigated through the recruitment plan and clear definition of shared priorities.

RECOMMENDATIONS TO THE TEAM

Directing a team together is more than collaborating: it means assuming shared responsibility for the scientific vision, the day-to-day operating model, and the people who deliver the work. Beyond aligning on projects, effective co-leadership requires a clear, stable "way of working" (decision rights, how priorities are set, how conflicts are handled, and how communication flows), so the team experiences coherence rather than parallel initiatives. In that spirit, it could be useful to build in regular moments of reflection to assess how the integration is progressing in practice: whether roles remain complementary, whether responsibilities are balanced, and whether the combination of perspectives is still actively enriching (rather than merely coexisting within) the team's scientific agenda.

The idea of integrating a computational researcher is very promising and could, over time, provide a unifying framework for the cross-species investigations. To realize this added value, it will be important to position the computational effort as a strategic connector embedded in the biology and experimental questions, rather than as a purely service-oriented function.

It could be helpful to articulate a few medium-term goals to guide the evolution of the integration, but without requiring rapid restructuring.

The direction should ensure technical support for the team.

Team 14: Molecular and Neural Coding of Behavior

Name of the supervisor: Mr Emmanuel Valjent

THEMES OF THE TEAM

The team investigates how brain circuits allow animals to learn predictive relationships between stimuli and positive or negative outcomes, and how these circuits drive approach or avoidance. Key themes include: the contribution of dopamine population heterogeneity to motivated behaviour; interactions between monoaminergic and glutamatergic systems in reward, aversion, and adaptation; circuit alterations in psychiatric disorders; circuit mapping using molecular and cell-type–specific tools; D2R signalling in interneurons and its impact on hippocampal learning; regulation of social behaviours by monoaminergic/glutamatergic pathways; and the identification of molecularly distinct dopamine-responsive striatal neurons.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team has taken the points raised during the previous evaluation and has implemented several of the recommended adjustments. While securing international funding has proven challenging in the current competitive context, the group has continued to pursue opportunities and to strengthen the elements that eventually will improve competitiveness in future calls.

In line with the recommendation to foster autonomy, team members have been given greater freedom to lead and develop their projects. This has had positive effects in terms of scientific ownership and leadership development, and has also revealed a natural maturation of individual research directions.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Praticien hospitalier	0
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**5**
Total personnels	**10**

EVALUATION OF THE TEAM

Overall assessment of the team

The team ranks as outstanding. It has built coherent and complementary research lines centered on monoaminergic and glutamatergic regulation of motivated behaviours. These axes are conceptually strong and have yielded sustained, high-impact output, including influential field-shaping papers. The team leader is widely recognised as a leader in this area, and although he has not obtained major international grants, the team's achievements remain very strong. The team has left the institute for another research center in Montpellier.

Context-related strengths and opportunities

The team benefits from a strong scientific identity centred on the neurobiology of motivated behaviours, with several coherent research lines that integrate molecular, cellular, and circuit-level approaches. The long-standing expertise in dopamine, noradrenaline, and glutamate signalling provides a solid conceptual framework and positions the team at the forefront of a very competitive field. The team has produced a sustained output of influential publications, reflecting both methodological excellence and the ability to address complex question with innovative tools. The diversity of expertise among team members has facilitated the development of complementary projects and has created opportunities for cross-fertilisation across models and techniques. The reputation of the team leader and the visibility of the team's work create favourable conditions for partnerships, including national and international collaborations. The team has also demonstrated a strong commitment to training. During the evaluation period, the team has hosted a total of nine PhD students, with five theses successfully completed and four currently ongoing. In parallel, the team secured significant funding during the period, providing a solid basis for sustaining ambitious research lines, supporting personnel, and maintaining a competitive technical environment. Beyond academic outputs, the team actively engaged with the general public and contributed to societal debates related to brain function, mental health, and behavioural neuroscience, thereby strengthening its links with society and enhancing the visibility and relevance of its research. Finally, the team maintained an international profile in its human resources, with international doctoral and postdoctoral researchers contributing to the team's scientific dynamism and reinforcing its attractiveness within the broader research landscape.

Context-related weaknesses and risks.

Following the previous recommendation, tenured researchers in the team were given full autonomy to develop their own projects. This approach aimed to foster initiative and diversify expertise. This high level of independence encouraged several researchers to use the team as a stepping stone to establish their own groups. As a result, common scientific efforts may appear as more fragmented, and the construction of shared programmes proved more difficult. The main risk is a dilution of the team's scientific identity and a reduced critical mass on key research axes.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team has not been reconducted. Since January 2025, five members of the team have relocated to the Institut de Neurosciences de Montpellier. One member has chosen to remain at the IGF and has joined team 3. In April 2023, one member left the team to establish her own team, "Appetitive and aversive memory circuits," following an international recruitment at IGF; her project investigates how appetitive and aversive circuits are shaped by past experience, spatial or social context, and internal states to guide approach–avoidance decisions. Jeanne Ster joined this group in November 2023 to carry out a project on the PVT–vCA1 circuit and its contribution to thirst-related internal states and emotional memory modulation. Finally, Zoé Husson resigned from her position as associate professor at the University of Montpellier in 2022.

RECOMMENDATIONS TO THE TEAM

None

Team 15: Cardioprotection, pathophysiology of heart rhythm and ischemia

Name of the supervisors: Mr Matteo Mangoni & Ms Stéphanie Barrere-Lemaire

THEMES OF THE TEAM

This team develops its research strategies along two main axes: the elucidation of the physiological and pathophysiological aspects of ion channels involved in cardiac cell automaticity, and the identification of strategies that favor cardioprotective processes that are able to contrast cell death following myocardial infarction. The molecular elements that represent the focus of the research of the groups are GIRK4, HCN4 and Cav1.2, and Cav1.3 channels and the FAS-DAXX interactions. An important perspective that emerges from the themes investigated is the attempt to use the findings gathered by basic research studies as a solid platform to build translational ideas projected towards practical applications in the biomedical field.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Previous recommendations suggested: 1) to increase scientific production; 2) to better define the relative roles of team members within each project, and 3) to implement an additional study model (old animals) to gain further translational insights. The team has carefully considered and properly addressed each of these points.

Point 1: The scientific production of the team consists of 44 indexed research articles and reviews; many of them in high-ranking journals. In consideration of the delicate issue of balancing quality and quantity, the team has reached a remarkable status.

Point 2: The specific role of each team member has been defined. Importantly, it should be noticed that, in addition to his focused contributions to the mainstream project of the group, A.T. has also started a new line of research on cardiac physiology of marine mammals and birds which may unveil important information on cardiac heart rate modulation (for example marine mammals during diving reach extreme bradycardia).

Point 3: This important suggestion had a very impressive impact on the strategic scientific development of the group. Indeed, the team has developed several sub-projects devoted to study the impact of the ageing process on the cardiac automaticity and performance.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	5
Praticien hospitalier	0
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels non permanents d'appui à la recherche	1
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**11**
Total personnels	**21**

EVALUATION OF THE TEAM

Overall assessment of the team

The team work is considered outstanding by the committee. Over the years, this team (and particularly MM) has gained a world recognized status as preeminent expert in the field of cell physiology of cardiac pacemaking. In particular the team has published with continuity seminal papers on the role of L-type calcium channels as well as ACh-activated potassium channels. Also important is the growing role (SBL) in the cardiac field of cell therapy and the recent reviews published in the Physiological Reviews journal confirm this aspect. The team is well balanced in its composition and the integration of competence ensures a positive admixture of ideas.

Context-related strengths and opportunities

The Team has a relevant scientific productivity; indeed, when compared to the previous period (15) the publications are now tripled (44) with some in top ranking journals. In addition, team leaders have published book chapters (3 MM and 1 SBL). The Team is particularly successful in fund raising; 5 grants (4 as PI) were obtained by the two team leaders, and 1 grant (as partner) by one member of the team. Of notice, MM is the European Coordinator of the prestigious Fondation Leduq grant. Overall, the money raised is over 2.3 kEuro and this has been properly capitalized in important scientific achievements and publications. The team leaders are international leading experts in their fields and this is verified by invitations as speakers to international meetings (7). PM (researcher) has also been invited to speak in 2 international conferences. The solidity of the team is also reflected by its national/international attractiveness towards young scientist (12/3 Ph.D. students). The composition of the team is appropriate in size, and the distribution of the internal roles is clear. This Team has largely contributed to define the role of Ca2+ L-type and GIRK4 channels in cardiomyocytes. Studies on Ca2+ channels have highlighted the relative contribution of two isoforms (Cav1.2 and 1.3) to the Excitation Contraction coupling process (Cav1.2), and in impulse generation and conduction (Cav1.3). The focus on GIRK4 has provided proof of principle that pharmacological or genetic inhibition of this channel represents a valuable tool to counteract the clinical manifestations of the Sinus Node Dysfunction (SND). This past trajectory of the group and the consistency of high-quality scientific production over the years represents a sure strength of the group since it ensures the success of present and future projects. Indeed, this profound competence forms a solid basis for future advancement and particularly for the attempt to bridge basic scientific knowledge to applicability studies. Indeed, the most recent work of the groups has evolved in this direction. In addition to the electrophysiological focus mentioned above, a second line of research of the Team consists in elaborating molecular strategies to contrast cell death caused by myocardial infarct. This aim has been accomplished by means of pharmacological (Tat-DAXXp) and cell-therapy (PPARβ/δ stimulated MSC cells) strategies. This research has already produced several patents and an additional one in under development. Also positive is the attempt to combine the experiences in ion channels physiology and in cardio-protection. Indeed, the Team reports a correlation between low heart rate and increased cardio-protection after myocardial injury. Overall, the strength of the Team is their solid background in basic science and the ability to start from basic mechanism and "interpret" them in the logic of therapeutic exploitation.

Context-related weaknesses and risks

No major scientific weaknesses are identifiable in this Team. However, one general consideration is applicable because of the molecular and cellular nature of their studies. In the last decades, the reductionist approach has brought to the scientific community a large array of information mostly derived from different study models (cells and animals). This transition from reductionist frameworks to integrative approaches will be an important priority in the years ahead. In this respect it is paramount to consider that this step forward may require a different approach in the choice of study models. One suggestion is therefore that, when translational studies are attempted, the models must and should move closer and closer to human physiology. In this respect the KO and KI mouse models have demonstrated some sort of limits, and, while they still are and will be valuable tools, other models should be considered. iPS cells are one opportunity provided that the large intrinsic variability and the lack of proper recapitulation of native adult cells is taken into account (and this is unfortunately not often done in the field!). Other possibilities such as mammals with cardiac physiology more similar that of humans may be considered if compatible with the 3R approach. An additional challenge is AV's teaching time and university responsibilities, which present an important time-management challenge for the team. In addition, space availability and future funding for this large active team are a possible challenge.

ANALYSIS OF THE TEAM'S TRAJECTORY

The trajectory of the Team is to turn basic knowledge into translational perspectives in relation to pathologies such as HF, heart rhythm disorders, acute myocardial infarction as well as to cardiac derailments associated with ageing. Three main avenues (axis) are presented.

GIRK4 inhibition by genetic intervention (anti-GIRK4 AAV) or pharmacological blockade (NTC-801) will be tested to rescue arrhythmias using in-vitro (hiPS-CMs) and in-vivo (Cav1.3 KO mouse, age-dependent bradycardic lemur) models. These studies should pave the way for further testing on isolated human heart (by a collaborator) in the perspective of future clinical trials. The team also intends to elucidate the role of inflammatory cytokines during age-related SND (lemur model), and the association between the age-dependent decline in ion channels in SAN and the PI3K/AKT canonical pathway.

Cardiac repair and interventions to limit cardiac injury following reperfusion is also a primary aim of the trajectory. The inhibition of the FAS:DAXX interaction is a target to limit cardiac damage in the presence of diabetes and myocardial (but also other organs) infarct. hMSC cell-therapy based on preconditioned media (variously composed by PPARβ/δ, oligomycin, and Tat-DAXXp) will be tested.

Ectopic ventricular beats represent the trigger for potentially lethal arrhythmias. These ectopic beats likely arise from pathologically-driven expression of Cav1,3 channels in the failing post MI ventricle. The suppression of Cav1.3 currents in different study models may prevent these triggers of arrhythmia.

The trajectories proposed by the Team are intriguing and promising; most importantly they are based on a wealth of well-documented backbone of data. The economic support and the composition of the group ensure to tackle the trajectory at full force. Not secondary is the scientific context in which this group operates. Indeed, the Leduq network provides fundamental moments of data discussion and confrontation with international leading experts which will ensure to shape and refine the trajectory in a dynamic manner.

RECOMMENDATIONS TO THE TEAM

The proposed future scientific strategy aims to create a condition of "communicating vessels" between basic research and "practical" translational purposes. This approach is exciting, appreciated, and a necessary step in biomedicine. However, basic data have been collected in isolated cells or in animal models and this may make this "translation" a challenge. Indeed, the scientific community is progressively learning that, without lowering their intrinsic values, in-vitro and animal model also demonstrate constraints and limits in translatability for clinical development. This also holds for iPS- derived cells and MSC-based cell therapy. It would therefore be important to strengthen the collaboration with clinical colleagues in order to have a constant and valuable constructive feedback.

Team 16: Innovative therapeutics for diabetes: understanding and correction of insulin secretion dysfunction and loss

Name of the supervisors: Mr Stéphane Dalle & Mr Eric Renard

THEMES OF THE TEAM

The focal point of the team "Innovative therapeutics for diabetes: understanding and correction of insulin secretion dysfunction and loss" is the pathophysiology of type 1 and 2 diabetes with specific consideration to the difference in nature i.e the need for insulin supplementations (T1D) and the need to preserve a functional beta cell mass (T2D). The team is exploring determinant of T2D and therapeutic approaches to protect beta cells function and also, develop new technological to deliver insulin in the context of T1D in an automated way and ways to increase pancreatic transplantation success.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Recommendations were made to the team to leverage the synergy created by the merger to seek higher profile journals and also to ensure competitiveness through both basic/clinal research complementarity and industrial collaboration. A clear momentum is in place that capitalize on the complementarity of the meeting with regular joint meeting, a clinal fellow joint the team for master completion and will pursue with a PhD. A clinical study aiming at studying post prandial GLP-1/GIP/insulin in patient with T2D and Parkinson's disease has been co designed with the merged entity. Clinical collaboration with E. Renard and the "islet isolation platform" and O. Villard for pancreatic islet graft is in place to assess the translational aspect of therapeutic approaches to improve transplantation success. Strategical collaboration with Eli Lilly has been established in the context of GLP-1/IP dual agonist for T2D and T1D. Finally, the team has addressed the need of PhD recruitment with 4 PhD and 1 to come.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Praticien hospitalier	1
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels non permanents d'appui à la recherche	1
Post-doctorants	1
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**11**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent to outstanding. The team combined clinical and basic research to tackle various aspect of T1D and T2D physiopathology including insulin delivery methods and therapeutic approaches. The team has good fundraising activity, excellent industrial partnership and valorization and very good publication records. Public outreach and implication in teaching and mentoring is also very good. Attractiveness and production were considered excellent and inclusion in society outstanding.

Context-related strengths and opportunities

The team is developing both basic and clinical research to tackle approaches to tackle a critical public health issue: diabetes and the merging between basic research and clinical researcher has demonstrated to be a very strong asset. The team has a very good publication record in generalist journal of high level (Cell Death Dis, Cell Rep, Diabetes Care) with 9 basic research articles and 2 preprints in revision in Nat comm and Diabetologia, 14 articles in clinical research and 27 reviews. A PHRC grant aiming at investigating the early use of automated insulin delivery system in people diagnosed with T1D. The team has been very active is structuring locally the diabetes community with the organization of the "Montpellier Diabetes Day". The team has a strong network of both National and international collaboration, a very good training and mentorship activity (13 Master, 4 PhDs + 2PhD visiting and 3 post-docs). The team has good fundraising activity. The team members are actively involved in teaching program, M2 Biologie santé, M2 Biologie santé, DU Diabetology and DU cellular therapies, M2 Biologie santé and DU Diabetology and regenerative medicine, the coordination of coordinates the University Diploma (DU) of Diabetology, the Inter University Diplomas (DIU) of Automated Insulin Delivery and of Diabetes and Transplantation and the Diploma of Speciality Studies (DES) of Endocrinology, Diabetes and Nutrition at the University of Montpellier. The team members benefit from national and international excellent recognition with 12 invited conferences, the "Gilberte et Jacques Tacussel" prize awarded to one member of the team by the Académie Nationale de Médecine. The team members are also very active in scientific committee, study groups, academic/learned society and congress organization. Industrial partnership and valorization are also a very strong asset of the team with active collaboration with Eli Lilly, Human Cell Design, consulting activities with private entities (11 compagnies) and the obtention of a Cifre PhD fellowship. Finally, the team has also strong public outreach activities with participation "Képis Pescalune" for charity for young diabetic children 2022-2023 and various intervention in press/audio public media.

Context-related weaknesses and risks

Not identified

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will undergo reorganization in the future mandate but still with jointly developed basic and clinical research.

At a basic research level, the team will explore how environmental xenobiotic impact onto metabolic and neurodegenerative diseases and how twinagonist GIP/GLP-1 contribute to beta cell mass protection and better efficacy of GLP1- receptor agonist specifically in the context of T2D and neurodegenerative disorders (Parkinson disease). Finally, the team will explore the genetic/molecular mechanism involved Transient Neonatal Diabetes Mellitus (TNDM) using iPSC derived beta cells.

The team will pursue translational research on automated insulin delivery (AID) systems, including AID with onboard AI meal-detection modules, and will evaluate the efficacy of early AID devices in people with type 1 diabetes (T1D). Concurrently, basic research on GLP-1R/GIPR agonists for beta-cell preservation will directly feed the beta-cell transplantation program. At a translational research level, the team will pursue the investigation of the project, which combines clinical and basic research, is highly ambitious. Although a collaborative network and funding are in place, a key risk is whether the programme has the critical mass required to deliver the full scope of the endeavour.

RECOMMENDATIONS TO THE TEAM

The team should continue on their excellent endeavour to articulate basic and clinical research to promote T1D and T2D while trying to improve joint effort in high profile journal. Trajectory is sound and extremely promising but the overall ambition of the project might require adequacy with critical mass.

Team 17: Brain plasticity, Stem Cells and Low grade Glial Tumors

Name of the supervisors: Mr Hugues Duffau & Mr Jean Philippe Hugnot

THEMES OF THE TEAM

The team investigates how diffuse gliomas and IDH-mutant brain tumours interact with and reshape large-scale brain networks, using connectome-guided surgery to map functional plasticity and optimise both survival and quality of life, thereby establishing a dynamic model of brain organisation. The team's goal is to improve prognosis, diagnosis and quality of life of patients. In order to reach this goal, its research spans multiple scales, from brain network organisation to molecular and cellular mechanisms driving tumour initiation and progression. The team gathers clinicians highly involved in the therapeutic management of low-grade gliomas (neurosurgeons, neuro-oncologists and neuropathologists) and researchers specialising in the molecular and cellular aspects of these tumours.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

In the previous report, recommendations were made concerning 1) internal collaboration within the IGF and the application for European grants; 2) the frequency of team meetings; and 3) keeping the team focused on the project.

The team responded positively to these recommendations. It developed internal collaborations with several teams within the institute (Rondard, Journot, Bourinet and Perroy teams). It set up weekly team meetings and bi-monthly meetings between researchers and clinicians. In terms of scientific strategy and projects, it refocused its research primarily on IDH1-mutant gliomas.

With regard to EU grants, although the team recognises their value, due to their complexity, low success rate and the considerable time they require, it has not prioritised these applications to date, but plans to devote more effort to identifying relevant calls and integrating into appropriate research networks during the next contract.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Praticien hospitalier	3
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	0
Post-doctorants	0
Doctorants	8
Sous-total personnels non permanents en activité	**9**
Total personnels	**20**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent. The team enjoys outstanding recognition in the field of characterising IDH1-mutated brain tumours. Its integrated approach linking neurosurgery, neuro-oncology, cell modelling, and cognitive neuroscience is a major strength. Thanks to an exceptional access to patients, the team developed a unique biobank of patient-derived samples, allowing strong national and international collaborations. The scientific achievements and output are excellent.

Context-related strengths and opportunities

The team has worldwide recognition in the field of neuronal plasticity and low-grade gliomas. As many team members are in close contact with the hospital, the team develops an integrated and patient-based research.

Indeed, the team explores different levels of brain plasticity, including cellular, structural and functional. Focusing on brain tumours and stem cells of the brain and spinal cord, the research aims to understand the molecular abnormalities and cellular origins of tumours, while developing innovative treatments and biomarkers.

Over the contract, the team has produced excellent landmark advances in the biology and clinical management of diffuse and IDH1-mutant gliomas. (1) Connectome-guided awake surgery has significantly improved patient outcomes, increased median survival, and reduced the incidence of permanent neurological deficits. This work has reshaped international neurosurgical practice through a dynamic network model of brain organisation; (2) In parallel, the team created a unique biobank of patient-derived IDH1-mutant glioma lines, fully annotated with multi-omics (JOVE, 2025). These models recapitulate tumour heterogeneity and have revealed regulators of cellular states (Notch/Dll3) and pro-neural-to-mesenchymal transition; (3) Work on tumour microenvironment demonstrated mitochondrial transfer as a driver of chemoresistance, reversible via DHODH inhibition (Cancers, 2022; Cancer Res Comm, 2023); The Team also generated a human spinal cord biobank, enabling a single-cell atlas and discoveries on the persistence and differentiation of ependymal stem cells. The team has produced a very high number of papers (n=140), with a majority about the connectome-based awake surgery, attesting the high visibility of the team in this subject. Team-specific publications include some high-impact publications (Brain, Nat Comm, Lancet RH Europe, Cell Mol Life Sci, Cancer Research Communications, JOVE). The team has trained eight PhD students in the lab and 70 visiting professors+80 fellows per year in awake surgery at the hospital. Teaching responsibilities are substantial across medical and scientific faculties. International visibility is exceptional, with >750 invited lectures (Duffau) and major invitations for other senior team members. Prizes include a Doctorate Honoris Causa and the Walter Dandy Medal. The team organises major scientific international meetings. The team was good at raising funds. Competitive fundings include Wings for Life (200 k€) and ARSEP Foundation funding (100k€) as coordinator and INCa PRTK, INCa High Risk High Gain, and ANR as partner. The team develops national and international collaborations (SIRIC Montpellier, CEA, Karolinska, DepMap). It develops partnerships with industry (Synaxys, i-PhD laureate). Public engagement includes specialised courses and outreach lectures for patients and the general public.

Context-related weaknesses and risks

Despite excellent visibility and recognition, the number of foreign postdoctoral researchers attracted remains low.

The most critical limitation is the small number of permanent researchers. Much of the team's scientific activity relies on temporary staff, PhD students, postdocs, and short-term technical personnel, whose presence is dependent on unstable, project-based funding.

Due to the retirement of the team's only CRCN in 2026, there will be no full-time researchers on the team for the future contract. There is no clear strategy for recruiting or attracting new young researchers. There is a risk of losing expertise.

Another weakness lies in the uneven distribution of expertise across disciplines. The limited number of senior scientists dedicated full-time to molecular and cellular glioma biology constrains the team's ability to rapidly integrate new technologies, supervise growing numbers of trainees, or maintain parallel lines of investigation.

Access to high-end technological platforms also presents challenges. Compared with larger international centres with substantial competitive funding, the team may face delays or limitations in implementing cutting-edge approaches such as high-throughput technologies. Dependence on collaborations to access these tools, although valuable, reduces autonomy and can slow scientific progress when external availability is constrained.

Finally, some articles resulting from fundamental research have been published in 'grey area' journals, which may have a negative impact on the team's results and recognition.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team "Brain plasticity, stem cells and diffuse low-grade gliomas," renamed "Neuroplasticity and Neuro-oncology" for the next contract, demonstrates a clear and ambitious trajectory, building on strong clinical–scientific synergies and numerous results have been recently obtained. The project focuses on two well-defined axes: 1/ Mapping the brain connectome and studying the mechanisms of neuroplasticity in glioma patients; 2/ Studying IDH1 mutant gliomas with the identification of diagnostic, prognostic and theranostic biomarkers, the characterisation of cellular mechanisms involved in glioma heterogeneity and plasticity; and the understanding of the response to treatment. The molecular and cellular program focus on elucidating the mechanisms driving IDH1-mutant glioma progression and treatment response. Building on prior work in epitranscriptomics, the team will validate tumour- and blood-based RNA modification signatures and explore spatial transcriptomics of transformation foci to understand cellular dedifferentiation and tumour heterogeneity. The regulation of proliferation and quiescence within defined glioma cell populations will be investigated through GPCR-mediated mechanisms, using CRISPR engineering and multi-omics approaches in collaboration with GPCR specialists. The biobank will be further expanded, and patient-derived glioma cell lines and tumouroids developed to model tumour evolution, interactions with neurons, and therapeutic responses. In parallel, a multi-omics investigation of Vorasidenib's mechanism of action will aim to identify predictive biomarkers of drug response, addressing critical clinical and economic challenges posed by variable patient outcomes.

The scientific project relies on state-of-art methodologies such as multi-omics (epitranscriptomics, spatial profiling, scRNAseq, proteomics…). A particularly distinctive strength is the use of human glioma samples and patient-derived cell lines generated in the team, that reinforce the relevance of the studies. These strengths will enable the team to address biological and clinical challenges to better understand and treat these complex tumors. The project relies on strong local (Rondard's team at IGF), national (IRCM, Montpellier) and international (Karolinska Institute, Sweden) collaborations. Moreover, part of the project on the response to targeted therapy is performed through an industrial collaboration (Servier).

With regard to financial resources, a few grants have been obtained, but new grant applications will be necessary to cover project expenses.

Concerning human resources, a notable weakness is the absence of permanent technical staff, which may pose a risk for continuity in the team's activities. It will be necessary to strengthen technical support in order to ensure the smooth running of projects. Moreover, the absence of a full-time researcher, due to the retirement of the permanent one, could have an impact on the organisation of the team.

RECOMMENDATIONS TO THE TEAM

The team demonstrates exceptional expertise and leadership in the field of low-grade glioma research, integrating neurosurgery and molecular oncology. The committee encourages the team to maintain its dynamic and integrative research strategy, which successfully links molecular mechanisms to translational aspects of low-grade gliomas.

However, due to the retirement of several members of the team, the committee strongly recommends to develop a strategy in order to transmit the expertise so far acquired by the members. The recruitment of international postdoctoral researchers who meet the CRCN's recruitment criteria should be a priority in order to maintain of a full-time research position and equilibrate the researchers/clinicians ratio within the team.

The team has to upgrade their efforts to obtain national and international funding. Given the team's excellent visibility and recognition, the committee recommends applying for competitive grants, including European ones, in order to maintain a high scientific standard. In addition, team leaders should make greater efforts to publish, where possible, fundamental science articles in high-impact journals and avoid publishing in "grey area" journals.

The team should keep an effort on their interactions with the non-academic world and the formation of PhD students.

Team 18: Membrane Protein Structure and Function for Drug Discovery

Name of the supervisor: Mr Sébastien Granier & Mr Bernard Mouillac

THEMES OF THE TEAM

The team studies the structural dynamics and pharmacology of GPCRs, in particular opioid, vasopressin and chemokine receptors. They use a combination of biophysical methods including Cryo-EM/X-ray crystallography, NMR, proton-deuterium exchange, mass spectrometry and fluorescent/FRET/BRET probes. Thanks to the recruitment of new team members, they have extended their research axes to investigating ceramide homeostasis and how pathogens hijack GPCRs to infect cells.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team was praised for the quality of its work but several points were raised:

"The input of structural biology has had a tremendously positive impact on the scientific production and quality over the last contract period. The panel suggests this should remain the main driver for the upcoming contract period.": This advice has been followed since the major part of the team projects currently relies on structural studies.

"The team could increase the number of PhD students (...). It might also be an impetus to hire more international students/post-docs. (...), it would be worth to reinforce the involvement of team members in master lectures": This advice has been partially followed. The team has increased the number of PhD students from 1 to 4 and co-trained two international PhD students during short visits, which is a marked improvement. They have also trained 7 post-docs. However, the ratio permanent researchers/trainees remains low and it seems that some permanent researchers have not trained anyone. Only one person in the team (Cherine Bechara, PU) is involved in teaching.

"The wish to expand to drug discovery is understood, but the team misses the medicinal chemistry/drug discovery background to make that happen. It is advised to do that in collaboration with leading teams outside IGF.": The team has established external and internal collaborations for drug development. Xiaojing Cong, recruited in 2021, is an expert in computational pharmacology.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	4
Personnels d'appui à la recherche	1
Praticien hospitalier	0
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels non permanents d'appui à la recherche	1
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	**6**
Total personnels	**17**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent to outstanding, with key contributions into the structural dynamics and pharmacology of GPCRs. The team uses a combination of advanced biophysical techniques to investigate with high molecular detail the subtle conformational changes that can lead to dramatic changes in receptor signaling. The team has strong fundraising capacity, visibility, and recognition, reflected in the obtained grants (European Union, ANR, FRM), distinctions (IUF for Cherine Bechara) and scientific responsibilities.

Context-related strengths and opportunities

The team has a very strong expertise in biophysical methods to understand membrane protein dynamics. Its force resides in the combination of several experimental techniques and state-to-the-art computational biology. Experimental techniques rely both on purified receptors (Cryo-EM, X-ray crystallography, NMR, mass spectrometry, H/D exchange) and receptors in their cellular environment thanks to the use of fluorescent or FRET/BRET probes. This allows them to validate the physiological relevance of the found conformational changes and ligand binding modes. The team has reached major achievements in the molecular mechanisms of biased signaling of several classes of GPCRs: (1) mu-opiod receptors, with key insights into the design of better tolerated pain killers with fewer side effects; (2) vasopressin receptor activation by the arginine-vasopressin hormone; and (3) atypical chemokine receptors. The team has furthermore explored new axes thanks to the recruitment of new permanent researchers: (1) Understanding how pathogen toxins hijack our immune system by binding to GPCRs. And (2) Understanding the molecular mechanisms of ceramide processing by alkaline type 3 ceramidase (ACER3), a key enzyme in lipid metabolism, combined with the design fluorescent ceramide substrates to allow high-throughput screening of new ACER3 inhibitors. This work has led to more than 30 publications in very prestigious journals like Molecular Cell, PNAS or Angewandte Chemie. The team has been well funded, with an ERC and MSCA contract, several ANR and FRM grants and a grant from Inserm. The team successfully obtained its participation to two Impact Santé projects from Inserm. Dr. Cherine Béchara is highly involved in teaching and has become a member of the Institut Universitaire de France, a prestigious distinction for professor. Finally, the team members have a strong international visibility, as attested by the large number of invited conference s (such as GRC in Switzerland, FEBS meeting in Portugal or two GPCR workshops in USA), and hold many scientific responsibilities in France. During the period, the team trained 3 PhD students and 5 post-docs. They hosted around 20 short-term engineers and attracted 7 young researchers on short-term contract. Among them, 3 were successfully recruited as Inserm or CNRS CRCN (permanent position). The team is highly involved in outreach activities (mentoring of female scientists, conferences to the general public) and has close collaborations with industry (Sanofi), although valorization could be improved.

Context-related weaknesses and risks

Although effort has been made to increase the number of PhD students, the ratio permanent researcher / trainee is still small.

Most of the supporting staff is on fixed-term contract, which might pose issues on know-how transmission.

Although the research conducted by the team has strong potential for biomedical applications, no patents have been filed during the contract.

Finally, one team member is proposed to become deputy director of IGF starting 2027, with a potential impact on the team scientific productivity.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will continue its structural work in GPCRs with a focus on dynamic studies with key discoveries on GPCR biased signaling. They will furthermore develop innovative approaches to decipher the mechanisms of pathogen toxin binding onto GPCR and perform high-throughput drug development of ceramidase inhibitors. The techniques they use are all state-of-the art with incursions into newly developed AI-based drug design and computational biology.

Three researchers have recently obtained permanent positions, showing the strong attractivity of the team. This should help the team to continue to be at the forefront of structural biology and membrane protein biophysics.

The team will be composed of 10 permanent researchers (9 full-time (3 DR and 6 CR) and 1 PU), 1 lab manager and 11 people under short-term contract (3 PhD students, 6 post-docs and 1 engineer).

Several grants have already been secured in order to perform the work such as two ANR grants and participation to two Impact Santé projects.

RECOMMENDATIONS TO THE TEAM

The team should continue its efforts to hire more PhD students. As suggested by the team itself, including doctorate stipends in the budget of ANR grants (or in other funding source) could help fund more PhD students.

The research conducted by the team has strong potential for biomedical applications, as illustrated by the discovery of potential analgesics. The committee believes that the team should intensify its efforts in terms of transfer and valorization.

Given the success in the recruitment and attractiveness of many new members, the committee recommends maintaining the project-focused team in order to maintain its visibility and management. The team should avoid developing multiple sub-projects, while allowing all new young researchers to fulfil their potential.

The team should plan ahead the potential appointment of the PI as deputy director to avoid a drop of scientific productivity.

Team 19: Self-renewal and differentiation of epithelia

Name of the supervisor: Mr Philippe Jay

THEMES OF THE TEAM

The research team's main themes center on the physiopathology of the gastrointestinal mucosa, with a focus on mechanisms governing tissue homeostasis and its disruption in infectious, inflammatory, and cancerous diseases. In particular, the team is involved in advancing the understanding of tuft cell roles in dysbiosis, antiparasitic defense and early tumor immunoregulation. In parallel, they are investigating the contribution of DNA methylation to the initial stages of *Apc*-driven tumourigenesis.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The team has shown a good commitment to implement the suggestions made in the previous evaluation. Regarding the request to increase scientific output, the PI has published three main articles as corresponding author in medium-to-high impact journals. The recommendation to strengthen involvement in PhD training and to enhance interactions within the IGF has been satisfactorily addressed. The team currently supervises two PhD students and plans to recruit an additional student in 2025. They actively contribute to joint scientific meetings involving IGF oncology-oriented teams and maintain productive collaborations with the J. Pannequin, E. Valjent and M. Mangoni teams, thereby broadening both scientific exchanges and methodological expertise. Finally, the team has followed through on the recommendation to sustain strong fundamental research while expanding translational activities. They have reinforced their SIRIC-linked clinical collaborations through ongoing studies with the Avicenne Hospital and the Bordeaux Institute of Oncology, and are establishing a new partnership with the Montpellier CHU for the analysis of biopsies from MICI patients.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent. The team demonstrates strong expertise in intestinal mucosal biology, excelling in tuft-cell research and leveraging advanced models with solid institutional support. Their international presence and commitment to training strengthen their profile. However, integrating emerging technologies, enhancing bioinformatics, expanding collaborations, fostering more trainee exchange, and diversifying funding would further increase impact and long-term sustainability.

Context-related strengths and opportunities

The team is at the forefront of studying tuft cells and their role in regulating intestinal mucosa homeostasis. Their focus on this specific field allows for in-depth expertise and potential for groundbreaking discoveries in the regulation of gut health, host-pathogen interactions, and genetic mutations affecting intestinal function. The team is confident in its ability to achieve significant results, leveraging a high level of expertise in the area of intestinal mucosal biology. Their successful use of cutting-edge models, such as transgenic mouse lines and intestinal organoids, reflects a high level of technical competence and methodological innovation. This enables a comprehensive understanding of intestinal mucosa homeostasis and its dysregulation in diseases as well as the exploration of complex interactions, such as between epithelial cells, immune cells, and microbes. The team has particularly demonstrated a cross talk between Paneth and tuft cells and its involvement in the dysbiosis and inflammation in the gut mucosa (PNAS 2023). Interestingly, they also found that tuft cells are able to release acetylcholine in the gut lumen in order to fight against helminth parasites (Immunity, 2024). The fact that P. Jay serves as the scientific director of the campus animal facilities ensures smooth execution of in vivo experiments. This is a significant strength in maintaining a streamlined, efficient, and well-supported research environment. The team has actively contributed to the academic and research community by training two PhD students, which has fostered knowledge transfer and long-term growth. Furthermore, the PI and other team members are deeply involved in teaching, enhancing the group's educational impact. The research team's international recognition is reinforced by the PI's active participation in national and international meetings, such as a welcome trust meeting in Edinburgh (UK), a symposium in Bern (Switzerland) or a conference in Montreal (Canada), ensuring that their findings gain global attention and contribute to the broader scientific dialogue. The PI of the team was very successful in terms of fund raising with highly competitive grants obtained from national funding agencies (ANR, Aviesan-INCa-Inserm PNP grants) or charities/foundations (Labellisation Ligue and ARC Fondation) as coordinator. Funding is secured for up to 2027/2028 (notably with INCa PLBIO and ANR grants as partner). In terms of link with the society, the team has obtained a contract with a start-up company for evaluation of compounds against colon cancer using their optimized mouse models of intestinal cancer susceptibility.

Context-related weaknesses and risks

Although the team has made significant progress in their research, cutting-edge technologies, such as CRISPR-based gene editing, and advanced imaging techniques could be integrated. These tools could provide new dimensions in studying tuft cells and their intricate interactions with immune cells and pathogens, enabling more precise and high-resolution insights. Moreover, with the increasing volume of data generated from various experimental approaches, the team may benefit from strengthening their bioinformatics infrastructure.

Although the team's focus on understanding disease susceptibility and mucosal homeostasis mechanisms holds great potential, more effort could be directed toward translating these discoveries into clinical or therapeutic applications. Developing new diagnostic tools, biomarkers, or therapeutic approaches could further enhance the relevance of their work in addressing unmet medical needs.

Notwithstanding the team has made strides in mentoring PhD students and involving them in publications, there is a potential to expand these efforts. The team could benefit from increasing the number of visiting students/scientists. Increasing these interactions could also further strengthen the team's position as a leading research group in the field.

Although the PI has successfully secured significant funding in the past, the team's reliance on in vivo experiments, which can be resource-intensive, probably limits their ability to expand their research activities within the current budget. To sustain and expand their research efforts, the team should explore additional funding opportunities, such as EU grants or grants for innovative technology integration or collaborative

partnerships with industry. A more diversified funding strategy would support the long-term sustainability of the team's research.

ANALYSIS OF THE TEAM'S TRAJECTORY

Considering the relevance that tuft cells are acquiring in the last years, the project future aims appear to present novelty and future impact. Since the first marker of tuft cells discovery, the number of studies regarding this matter has significantly improved.

The team will focus on several aspects of tuft cell roles in regulating chronic inflammatory diseases and cancers of the GI tract. In particular, tuft cell-mediated type-2 inflammation and its involvement in the genesis of Crohn's disease; the formation of a tumor permissive microenvironment and lastly the tumor-promoting type -1 inflammation in the context of Helicobacter infection. Moreover, the successful completion of the final aim will benefit significantly from the team's strong collaboration with Helicobacter biology experts in Bordeaux, providing valuable complementary expertise and resources.

Overall, the project is ambitious yet firmly grounded in the team's established expertise and prior achievements. The proposed aims are well defined and build on a strong scientific foundation and established collaborations, making their successful completion highly likely, particularly if the team secures additional funding to support the planned expansion and technological integration.

For the next contract, the team will be composed of three full-time researchers (1 DR and 2 CR), two engineers and one PhD student that just started her thesis work. An additional PhD student and a post-doc should to be recruited.

RECOMMENDATIONS TO THE TEAM

Based on the considerations outlined above, the team would benefit from integrating advanced technologies such as CRISPR-based gene editing, and high-resolution imaging to further deepen mechanistic insights into tuft cell biology. Strengthening bioinformatics capacity is also recommended to meet the growing demands of complex data analysis. Increasing efforts toward translating fundamental discoveries into clinical applications, through biomarker development, diagnostic approaches, or therapeutic strategies, would enhance the medical relevance of the research. Expanding opportunities for visiting students and scientists could enrich the team's scientific environment and strengthen its international visibility. Finally, diversifying funding sources, including grants focused on technological innovation or industry collaboration, would support long-term stability and reduce the constraints imposed by resource-intensive in vivo experiments.

Team 20: Cardiac Development, Disease and Regeneration

Name of the supervisor: Mr Chris Jopling

THEMES OF THE TEAM

The mainstream research of this team regards the processes that control cardiac development. This specific interest is channelled into three highly interrelated subthemes: analysis of the physiological role of the Piezo1 channel (including the evaluation of any arrhythmic profile associated with piezo1 mutants); the effect of environmental toxicology (phthalate and perfluorinated acids) on cardiac (and brain) development; interventions based on genetic (Tfr1 gene) strategies to improve cardiac regeneration. The primary study model is the zebrafish model. Altogether these studies aim to apply basic concepts in cardiac development to translational perspectives.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Previous recommendations suggested to increase the quantity and impact of the scientific production and activities and to focus the efforts of the Team towards projects with increase translability. The team has carefully considered and properly addressed each of these points.

The scientific production of the team consists of 21 articles and 4 reviews (12 as PDC). The quality and consistency of the production indicate a very active group. The impact of the research on the community has been improved by the participation to several programs and events.

Following the recommendations, the group has established productive external collaborations which have allowed them to verify with success the relevance of their basic research studies towards the clinic. The present flow of interactions indeed allows testing on whether some forms of cardiomyopathies may associate with mutations in the proteins investigated by the team.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	5
Praticien hospitalier	0
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels non permanents d'appui à la recherche	1
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	**2**
Total personnels	**10**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent. The team derives its expertise from developmental studies carried out in the zebrafish model. Progress toward clinical translation is likely to be slow and will necessitate sustained, multi-year effort. The team has successfully followed this trajectory and besides having an established reputation in basic zebrafish research it has also successfully attempted to approach a clinically oriented scenario.

Context-related strengths and opportunities

The team has an excellent visibility, and this can be appreciated at different levels: quality of publications, fundraising ability, invitation to conferences. The scientific productivity is consistent (25 referenced publications of which 12 as PDC) and of quality (Nat. Commun., Circ Res). Fundraising activity is very successful since grants for a total of 2.5 kEuro have been raised and cover the 2020-2028 period (3 grants to CJ, 1 as coordinator, and 2 to TMM). One of the team's strengths is its ability to establish important connections with prominent colleagues (for example Matteo Mangoni and Philippe Chevalier) and the development of these collaborations have allowed successful publications and the development of common projects. This aspect reveals the importance of the research carried out by the team. The visibility of the team is also verified by the large number of invitations to conferences (10) and by the organization of meetings (8). The composition of the teams is appropriate in size, and the distribution of the internal roles is clear. The profound expertise of the team Leader in the zebrafish model has also resulted in the installation of the zebrafish facility at the IGF; a platform which is now used by 6 Teams. As previously mentioned, the team focuses its research on the processes overlooking cardiac formation during embryogenesis. The information gathered with this research have an intrinsic value of general knowledge, but the team has also been able to apply this information to the concept of cardiac regeneration and human arrhythmias associated with Piezo 1 variants. The zebrafish model is endowed with the ability of cardiac regeneration; the Team has analyzed some of the underlying mechanisms and identified three glycolytic genes (pdk2, pfkb3, and slc2a3) as well as a key regulator of iron metabolism (tfr1). In particular, overexpression of tfr1 may represent a future tool to induce cardiac regeneration also in humans. The involvement of team members in teaching and training activity is solid. The team also attracts students (5 Ph.D. in the period 2018 to 2026). Overall, the Team is excellent and presents all the elements to foresee a successful future in terms of visibility.

Context-related weaknesses and risks

The Team does not present major weaknesses. The economical support in the year to come is reasonable, however most of the grants expire by 2026. An effort toward fund raising for the following years should therefore be planned.

Although the team is on a growing trajectory, the international position as expert leaders of the field should be confirmed and reinforced. For example, the Teams has organized several meetings, it would be extremely relevant and helpful for the team to internationalize this effort.

Among the weaknesses, identified by the team, is the lack of personnel dedicated to the zebrafish facility. Although this issue is tricky and must be balanced with other priorities of the Institution, it is indeed an important concern.

While the effort toward applicability represents a must in the biomedical field, it should be kept clear that while early developmental process may be similar between humans and zebrafish, the concept of cardiac regeneration is different. A note of warning is therefore to move in this direction with the right amount of caution; the importance of this field is too high to fall into the publish or perish ambush.

ANALYSIS OF THE TEAM'S TRAJECTORY

The trajectory of the Team is in line with its previous research and expertise and it is based on three main projects. The first starts from the evidence that hemodynamic shear stress contributes to shaping the process of cardiac development; alterations in this "coupling" may cause Congenital Heart Defects (CHD) and cardiomyopathies. Previously carried scRNAseq analysis allowed the identification of Crip2, a pleiotropic molecule expressed in the developing heart which may be involved in the mechanosensitive pathway. Crip2 silencing in zebrafish leads to incorrect heart looping and up-regulation of the extracellular matrix, while Crip2 silencing in mice causes Ventricular Septum Defects and Left Ventricular Noncompaction Cardiomyopathy. The team intends to better

characterize the pathway of Crip2 with the aim of elucidating the cause of some forms of CHD likely caused by a mis-regulated "coupling". The possibility to search for Crip2 variants in clinical patients will strongly support the causative role of this molecule.

Myocardial fibrosis is a hallmark of negative cardiac remodelling associated with heart degeneration (I.e. HF). Deposition of extracellular matrix (collaaen I) confers stiffness to the tissue and this hampers inotropism. Reversing fibrosis is therefore a mainstay of therapeutic strategies aiming to promote reverse remodelling (RR). The Team intends to investigate the RR and particularly the role of fibroblasts in a mouse model of TAC-based de-banding RR. These findings will be correlated with the events occurring in zebrafish during cardiac regeneration. Understanding this process may provide insights into future therapy.

Cardiac regeneration, the third scientific challenge, has been tackled by different approaches and the most promising one consists in forcing adult cardiomyocytes to resume the cell cycle and cell proliferation. The authors provide evidence that a critical element favoring cell dedifferentiation and regeneration is glycolytic metabolism. Important molecular elements favoring this process are transferrin receptor 1 (TRFC) and Ucp3. In particular, Ucp3 likely acts as a metabolite transporter that favors the shift toward glycolytic metabolism.

The 3 strategies are scientifically sound, well organized, and challenging. The first one (hemodynamics and Crip2) may bear more immediate consequence since its applicative side is based on the identification of variants in human patients. The second (fibrosis) and third (regeneration) are part of a common theme, that, in the long run, consists in the identification of therapeutic strategies to contrast cardiac degeneration. This field is of capital importance for its large health and socio-economical consequences. However, it is a complex and difficult process with a still undefined time-scale. The authors' proposals are clear and logical. The success of these studies will surely provide elements eventually useful to develop a therapeutic strategy.

RECOMMENDATIONS TO THE TEAM

The Team is stably composed by 4 tenured persons which are proposing high quality and complex research project. The possibility to have a fifth stable position will really reinforce the solidity of the team.

The second and third projects are fully developed in mice and zebrafish; while this is the only possible way to proceed, careful consideration should be given to the interpretation of the data in terms of human applicability. For example, the Team may consider to use human iPS-derived cardiomyocytes stem cell or cardiac organoids to test the relevance of TRFC and UC3. Ideally, blocking their contribution should reduce the intrinsic foetal and proliferative nature of these cells. If this will be verified, the translability of their data will be reinforced.

The quality of the Team leaders should be rewarded by organizing an international forum/discussion on their topics.

Team 21: Systems level and statistical approaches to parental genomic imprinting

Name of the supervisor: Mr Laurent Journot

THEMES OF THE TEAM

The team investigates parental genomic imprinting through statistical, computational, and systems-level approaches. Its research encompasses the development of data-driven statistical tools to infer allelic imbalance from high-throughput genomic datasets, machine-learning strategies to refine gene co-expression modules and modelling of imprinting-related diseases using human induced pluripotent stem cells. The team also studies mechanisms of imprinted gene regulation during neurodevelopment, integrating CRISPR-based perturbations and organoid models.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The previous committee recommended enhancing scientific productivity by shifting efforts from core facility management to research. The team responded by progressively relinquishing long-standing leadership roles in major platforms: L. Journot concluded the directorship of BioCampus Montpellier in 2021 and of MGX–Montpellier GenomiX in 2024, while C. Reynès currently leads the StatABio core facility. This reallocation of effort contributed to the publication of 43 co-authored papers between 2019 and 2024. However, the supervisor's publication activity has remained at a standstill since 2022 (with 2021 as the most recent last-author publication).

The committee also highlighted the need to diversify and expand funding sources. The team successfully addressed this by securing multiple ANR grants (TNDModelling, CORGI, COBIOSTEM), as well as regional and translational innovation funding, often through collaborative initiatives with researchers from IGF and IGMM.

A further recommendation concerned increasing the number of PhD students and postdoctoral researchers. Although two PhD theses are currently being supervised, the planned closure of the team in 2026 constrains additional recruitment. Nevertheless, training activities, including two HDR defences, several supervised PhD projects, and extensive teaching across biomedical and biostatistics programmes, demonstrate a commitment to mentorship and capacity building.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent. The team demonstrates strong expertise in statistical genomics, machine learning, and imprinting biology, producing impactful tools and disease-modelling approaches. Its scientific outputs are coherent and innovative, although the impending dissolution of the team constrains long-term development. Productivity, collaborative integration and methodological innovation remain solid and ongoing projects are expected to yield final publications by 2026.

Context-related strengths and opportunities

The team's principal strength lies in its unique integration of computational, statistical, and biological expertise to investigate parental genomic imprinting. The development of ISoLDE, a robust non-parametric framework to infer allelic imbalance from RNAseq data is an example. By relying on data-driven estimation, the method classified genes as allelically imbalanced, bi-allelically expressed, or undetermined. In addition, the machine learning method TopoFun extends the team's contribution to systems biology by refining co-expression network analysis through machine learning, enabling more functionally coherent gene module identification and supporting the discovery of novel gene functions. Together, these complementary approaches exemplify the team's capacity to generate innovative analytical tools that significantly advance the understanding of imprinting mechanisms and their functional consequences. Experimentally, the team successfully developed cutting-edge tools to model imprinting disorders in vitro, through CRISPR-based engineering of human induced pluripotent stem cells to mimic the epigenetic defects underlying Transient Neonatal Diabetes Mellitus. These models support multi-layered analyses spanning transcriptomics, cellular metabolism, calcium signalling, and insulin secretion, offering the potential for therapeutic screening and mechanistic insights. DRAK-seq further strengthens the methodological tool by providing a cost-effective means of detecting copy number alterations in hiPSC cultures. Finally, the team's work on imprinted gene functions in cortical development illustrates a strong combination of epigenomics, organoid biology, and CRISPR activation/inhibition platforms. The elucidation of Mest/miR-335 promoter dependency and the exploration of convergent antisense transcription at the Mest/Copg2 locus highlight the team's capacity to address highly specialized questions in neurodevelopment through sophisticated experimental pipelines. The team also benefits from well-established collaborative networks, including multiple ANR-funded partnerships, joint projects with IGF and IGMM teams and visibility achieved through methodological dissemination, teaching, and public engagement activities. Training capacity remains high, as demonstrated by recent HDR completions, supervision of PhD students, and extensive teaching in biostatistics, molecular biology, and data science. These elements support the completion of the team's final scientific objectives before its scheduled closure.

Context-related weaknesses and risks

The main limitation concerns the structural trajectory of the team, which is scheduled to close in 2026, constraining its capacity to implement long-term research strategies. This impacts recruitment, particularly of PhD students and postdocs, as acknowledged in the document, and limits the potential to build sustained research lines beyond the current projects. The inability to hire additional PhD candidates could diminish the manpower required to fully exploit the team's innovative methodological frameworks.

Another weakness stems from the involvement of group members in the management of scientific platforms, which has partially diverted efforts from scientific productivity. Although the PI's responsibilities have been scaled back, senior-author publications remain limited, especially since 2022.

Finally, because several members will move to new teams or retire, the fragmentation of expertise could hinder the completion of ongoing projects.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will not be reconducted in the future mandate.

RECOMMENDATIONS TO THE TEAM

Not relevant, since the team will terminate at the end of the mandate.

Team 22: Networks and rhythms in endocrine glands

Name of the supervisor: Mr Patrice Mollard

THEMES OF THE TEAM

The team's scientific work centers on understanding how peptide hormone production and secretion are controlled within the hypothalamic-pituitary axis. Their approach is multidisciplinary and in vivo, utilizing animal models to investigate how hypothalamic neurons—including neuroendocrine cells and those in the central hypothalamic clock—integrate cellular signals. They also examine the interactions between these neurons, pituitary endocrine cells, and the microcirculation, both in normal physiological conditions and in disease states.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Recommendation was made to the team to prioritize some project to improve the capacity to publish in high ranking journals and the team was encouraged to identify leadership for the next contract. While the team will not be reconducted, publication record is very good.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Praticien hospitalier	0
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	0
Post-doctorants	2
Doctorants	0
Sous-total personnels non permanents en activité	**3**
Total personnels	**9**

EVALUATION OF THE TEAM

Overall assessment of the team

The committee considers the team to be overall excellent to outstanding. The team has worldwide recognition in the field of neuroendocrinology. The team improved productivity and publication record in highly visible, benefit from excellent National and international recognition and were successful in fundraising. Both Attractiveness & production, and inclusion in society were considered excellent to outstanding.

Context-related strengths and opportunities

Scientifically, the team demonstrated that migrating GnRH neurons must establish glutamatergic communication within an inter-hemispheric network at the nose-brain frontier to successfully reach the hypothalamus, a critical step for reproductive function and species persistence. Their work also revealed nested calcium dynamics in the suprachiasmatic nucleus (SCN), where short-lived calcium transients overlay ultra-slow circadian oscillations, highlighting cell-specific regulation within a synchronized network essential for maintaining the body's 24-hour rhythm. By studying dopamine (TIDA) neurons, they uncovered sex-specific differences in network organization and efficiency, explaining the dimorphic patterns of prolactin secretion and offering insights into reproductive health and disorders. Additionally, they identified the median eminence vasculature as a key regulator, where contractile mural cells control the passage of gut-derived hormones like ghrelin to the metabolic brain, ensuring rapid adaptation of food intake to energy needs. These discoveries were made possible through pioneering in vivo calcium imaging, optogenetic manipulation, and advanced network analysis, bridging cellular mechanisms with physiological outcomes. The team has excellent publication record in highly visible journals (Sci Adv, PNAS Nexus, Elife, Endocrinology. Mentoring is very good with 3 PhD students and 3 post-docs and one invited PI on sabbatical. Team members are coordinators of the teaching week "Neuroendocrinology" for M2 students at Montpellier University. The team benefit from excellent National and international recognition with 10 invited conferences, an excellent expertise activity (ERC grant, HFSP, MRC, BBSRC…) and reviewing in prestigious journal (Scientific Reports, Frontiers in Endocrinology, The FASEB Journal, Molecular Metabolism; Martin: Endocrinology, Neuroendocrinology, Nature Comm., PNAS, Elife, Endocrinology J.). The team has very good fund-raising ability and interaction with non-academic and social economic world with significant scientific breakthrough in nanobodies utilization targeting breast and gastric system metastases (PRECIRIX®) and also with optical imaging company Inscopix in the development of fat imaging method for brain blood flow.

Context-related weaknesses and risks

Possibly the wide diversity of project could be prioritised to keep the good productivity.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team will not be reconducted, the team leader has retired in 2025.

RECOMMENDATIONS TO THE TEAM

Not relevant since the team will not be reconducted.

Team 23: Signaling, Plasticity and Cancer

Name of the supervisor: Ms Julie Pannequin

THEMES OF THE TEAM

The team studies the molecular mechanisms involved in the different stages of colorectal cancer progression in order to identify new potential therapeutic targets. Translational projects focus on the role of the microenvironment in early tumour heterogeneity, the mechanisms used by tumour cells, including cancer stem cells, to resist treatment, and finally the molecular and cellular bases of tumor dissemination, early detection and characterization of CTCs. To achieve its goals, the team develops close collaboration with clinicians. It uses new technologies (single cell RNAseq, 3rd-generation nanopore-based seq, PROTAC…) and develops *ex vivo* models of tumour organoids derived from patient samples and *in vivo* mouse models (xenografts and spontaneous models of colorectal tumorigenesis).

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

It was recommended that the team leader be more assertive by publishing, as far as possible, articles as lead author in high-impact journals.

The team has addressed the previous evaluation's recommendations by making clear progress in multiple areas. In scientific production, the team leader undertook three major studies: "early dissemination in colorectal cancer" and "translation reprogramming of persister cells upon 5-FU") that are set for publication in high-impact journals (2 x Nature Communications in revision) as (co-)last author, and "identification of progastrin receptor," that was published in Advanced Science (2025) as co-last author, directly demonstrating increased assertiveness.

To increase its international visibility, the previous report recommended applying for EU grants, which was done for doctoral networks, but despite very good scores, the applications were unsuccessful.

In addition, following previous recommendations, the team has developed collaborations with other teams from the IGF unit, as evidenced by joint publications with Philippe Jay and Philippe Rondard's teams (*Immunity*, 2024; *FASEB J*, 2021; *Method Mol Biol*, 2019) or by an internal IGF collaborative grant obtained with Emmanuel Bourinet's team.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	3
Praticien hospitalier	0
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels non permanents d'appui à la recherche	1
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**3**
Total personnels	**12**

EVALUATION OF THE TEAM

Overall assessment of the team

Overall, the team is excellent to outstanding. Its internal dynamism, innovation capacity, international visibility, and achievements in valorisation and fundraising position it as a leading group in the study of colorectal cancer heterogeneity and plasticity. The team is excellent in terms of scientific production and in PhD training and is involved in strong network collaborations. The trajectory relies on an excellent project in the continuation of the previous findings based on robust ex vivo and in vivo models, strong collaborations and potential for translational benefit.

Context-related strengths and opportunities

Over the contract, the team conducted high-quality research on colorectal cancer progression and dissemination. The research team tackles urgent clinical challenges such as tumor recurrence, minimal residual disease, and early metastatic spread by using innovative methods including single-cell RNA sequencing, nanopore liquid biopsy, and studies of persister cell translation. Translational work is clear, integrating PROTACs and resistance models, and drawing on collaborations with chemists and computational biologists for novel therapies. The team has produced several significant publications in high-visibility journals (e.g., Nature Communications, Stem Cell Reports) and more specialised journals (Translational Oncology, Cancers). In total, the team has published 29 articles, 10 as main authorship and 19 as collaborative work (3x Nat Comm; 2x eLife, Oncogene; Br J Cancer). The team has followed a clear and coherent strategy exploring areas of major relevance for patient outcomes, including tumour recurrence, therapeutic resistance, and early metastatic dissemination. In terms of recognition and visibility, the PI is/was member of several evaluation committees (Fondation ARC CN4, Cancéropole GSO, Unicancer digestif and Hcéres). The total number of international (1) and national (12) invitations and contributions to meeting organization are very good (organisation of 3 international SUNRiSE network meetings; CECED meeting; Louise Harel day with SFC). Moreover, supported by these numerous collaborations, the team enjoys excellent national and international visibility. It is actively involved in several scientific networks (SUNRiSE network), illustrating its recognition within the scientific community and its capacity to play a structuring role in the field. Its engagement in these networks significantly enhances its scientific influence and the impact of its work. The PI of the team has an excellent capacity of fund raising with highly competitive grants obtained from local and national funding agencies or charities/foundations, either as coordinator or partner. Funding is secured for up to 2028 (notably with the INCa PLBIO, MCMP, and PNP grants). The team has attracted 1 foreign post-doc, which was recruited as CRCN CNRS. The team invests heavily in training through research: as part of the SUNRISE network, it has organised yearly 2-day-training dedicated to tumour heterogeneity and plasticity. It has trained 9 PhD students and hosted 23 interns. In addition, the team is very good in sharing knowledge with the general public and interacting with the society (fête de la Science, Apprentis chercheurs, femmes et sciences, race for La ligue contre le cancer…). This outcome demonstrates the maturity of the research efforts and the team's commitment to ensuring their societal relevance.

Context-related weaknesses and risks

Despite its robust scientific foundation and its innovative drive within translational oncology, the team contends with a set of context-related weaknesses and risks that must be critically addressed to sustain its progress and long-term impact.

Over the 5-year contract, the number of team-specific papers (n=10, including 1 review, 1 method paper and 2 clinical papers) is modest considering the number of permanent researchers (1 DR and 4 CR).

Despite associated to multiple collaborative papers, the number of last author papers for the team leader remains modest with only two original publications over the period (Cancers, 2021; Transl Oncol., 2021). Furthermore, several doctoral students have not published any articles as first authors.

The number of foreign postdoctoral researchers attracted remains low. Recruitment challenges stand out most prominently: attracting new principal investigators and exceptional PhD/postdoctoral talent, particularly from the international pool, has proven difficult, limiting the influx of diverse expertise and the potential for new perspectives essential for driving innovation and maintaining agility. The national prestige and available advanced technological platforms at IGF, while commendable, may not fully offset the increasingly competitive global landscape, with research institutions worldwide offering more attractive packages, supportive environments, and fewer administrative impediments.

Additionally, the team's funding environment is under pressure, marked by decreasing governmental investment in basic science and a frustrating pattern of near-misses on major European Union training and infrastructure grants—despite outstanding scientific merit and high evaluator scores. This creates both operational uncertainty and potential demotivation among promising early-career scientists who seek reliable support.

Another critical layer of risk derives from bureaucratic constraints within the French academic and research field. Complex legal and ethical frameworks, especially around laboratory animal experimentation, are growing more stringent and time-consuming, which could curtail rapid progress on translational projects and cause delays in the generation of clinically relevant preclinical data. The team's exposure to global competition, particularly from well-funded international consortia in cancer biology, demands continuous renewal and strategic expansion—an endeavor made more difficult given barriers to institutional restructuring and strict rules governing team formation and expansion.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team has demonstrated a clear and ascending trajectory over recent years, firmly establishing itself within the colorectal cancer research field by advancing innovative biomedical projects and adapting to evolving scientific priorities. Its significant scientific contributions encompass identifying critical mechanisms in early tumour dissemination, therapeutic resistance, and the biology of persister cells—issues fundamental to improving recurrence and metastasis outcomes in colorectal cancer. The development of original preclinical models, computational methods for multimodal ctDNA analysis, and translational applications have not only enriched the scientific portfolio but also solidified the team's standing in multidisciplinary collaborations across national and international networks, involving partners from leading centers in Paris, Barcelona, and Nice. The team's prospects for future development are highly promising and rely on solid scientific and organizational foundations.

The team organization will increase in size with the recent recruitment of one CRCN, expert in bioinformatics and the attraction of 2 news members (1 CR and 1 DR), raising the number of full-time permanent researchers up to 6. Thus, the team gathers strong technological and transdisciplinary expertise (cell biology, bioinformatics, epigenetic, clinical aspects, mouse models).

The project is clearly written, in the continuity of the previous work, and promising results have been already obtained. The three proposed axes are well defined, from the characterization of pre-malignant lesions and predictive biomarkers of progression into colorectal cancer to the development of strategies to detect and prevent tumour recurrence. A particularly distinctive strength is the use of a sophisticated mouse model, enabling in-depth analysis of the biological mechanisms underlying early dissemination and the preparation of the metastatic niche in the liver. This model represents a major scientific asset and positions the team as a key contributor in this research area.

In order to address these questions, the team has set up an excellent network of collaborations at the national and international levels (IBIDAPs, Barcelona; IRCAN, Nice; Cordeliers & Curie, Paris; CRCL, Lyon; CRCM, Marseille; IRCM, Montpellier; IPBS, Toulouse).

Several grants have already been secured in order to perform the work, and 2 new students just started their PhD (Oct 2025).

RECOMMENDATIONS TO THE TEAM

The committee strongly encourages the team to maintain its dynamic and integrative research strategy, which successfully bridges molecular mechanisms with translational aspects of colorectal cancers.

Due to the recruitment and attractivity of new team members and, de facto, the multiplicity of sub-projects, the committee recommends maintaining the team's project focused for a better visibility and management.

Indeed, the team should continue fostering the autonomy and mentoring of emerging investigators while preserving coherence and synergy among subgroups, ensuring that diversification remains a strength rather than a source of fragmentation.

For the next contract, it will be necessary to reinforce technical support to ensure the continuity of the team's projects. Moreover, the recruitment of international postdoctoral fellows should also be prioritised to enhance innovation and maintain global visibility.

In addition, we recommend the team leader to continue to be more assertive by publishing, as far as possible, articles as lead author in high-impact journals, and ensure that all doctoral students have at least one article as first author, where justified.

The recruitment and retention of early-career scientists and international students remain a critical area for sustained development.

To address persistent difficulties, the team should intensify efforts in targeted outreach, participation in EU networks, and strengthening the international backgrounds.

Team 24: (New Team) Intracellular Compartmentation and Cell Communication

Name of the supervisor: Mr Julien Villeneuve

THEMES OF THE TEAM

This newly-created team combines their separate areas of expertise to focus on unconventional protein secretion (UPS), a recently-described mechanism independent of the well-known secretion phenomenon involving the endoplasmic reticulum and the Golgi apparatus. The team will investigate the contribution of UPS to various pathological processes underlying neurodegenerative diseases, cancer, and inherited disorders. The team members' prior experience with converging research in membrane trafficking, neurodegenerative disease, ion channel function, neurogenetics, and iPSC culture, will facilitate the success of their research program.

ANALYSIS OF THE TEAM'S TRAJECTORY

The research plan of the team is to explore various different processes that involve UPS. Proteins secreted by UPS appear to have important roles in stress, inflammation, and neurodegenerative diseases. The multidisciplinary expertise of the team members will allow the development of an integrated approach to fundamental cell biology studies and also pathological processes.

The main themes are:

1) molecular mechanisms of UPS involvement in secretion of tau and alpha-synuclein. This axis will take advantage of a newly developed cell-based assay to follow UPS, and has already shown a critical role for lysosomes being recruited to compartments that can fuse with the plasma membrane. Factors involved in tau and/or alpha-synuclein secretion by UPS can now be identified and tested in iPSC-derived neurons or in animal models.

2) possible adaptations of UPS to address channelopathies. Evidence suggests that the channel associated with cystic fibrosis (CFTR variant), which accumulates in the ER, can be restored to plasma membrane expression if conventional protein secretion pathways are blocked. UPS may thus be an appropriate therapeutic target for CF in the future. The team will use multiple cell biology and genetic methods to elucidate these mechanisms.

3) interactions between organelle dynamics and UPS during mitosis and migration. The dynamics of different intracellular components during the cell cycle will be investigated using multiple technical approaches (live imaging, proteomics). During mitosis, some organelles may acquire secretory properties; the mechanisms of this UPS will be particularly interesting in cancer cells. The team will describe these processes, and aim to identify potential diagnostic markers.

These research axes will provide fundamental knowledge about UPS mechanisms in a variety of physiological and pathological contexts, with long-term possible biomedical applications.

RECOMMENDATIONS TO THE TEAM

These research projects having already led to co-signed publications, and thus should continue to be fruitful. The team has current ANR funding; European or international funding applications would be a welcome addition to this, since international collaborations are already established.

The team should consider trying to attract a University lecturer or professor, and to continue their teaching engagement, to increase visibility to students at the Master and then doctoral level. The team has many members with the HDR, so increasing the workforce with PhD students and post-docs will be a priority.

The three research axes are all interesting; but with the currently limited number of team members it may be necessary to prioritize one of them until more doctoral students or post-docs can join. `

However, since each research axis is developed in collaboration with national or international partners, it may be possible to undertake all three.

Team 25:	(New Team) Primary Cilium Signalling in Neurobiology And Chronobiology (CilSNAC)
Name of the supervisors:	Ms Séverine Chaumont-Dubel and Mr Xavier Bonnefont

THEMES OF THE TEAM

The project is very well focused: understanding the dynamics and the physiopathological role of a generally overlooked organelle - the primary cilium - through the gathering of a truly multidisciplinary team. The initial goals based on preliminary data will be to understand the impact of the circadian rhythm on the dynamic morphological alterations of the primary cilium and of axo-ciliary synapses, to then exploit how tinkering with a receptor associated with the primary cilium (5HT6) affects the circadian rhythm.

ANALYSIS OF THE TEAM'S TRAJECTORY

This proposal is highly focused on a subject seldom discussed – the dynamics and role of the primary cilium. Moreover, it thrives knowledge through a new tempting angle of a selective modulation system (apparently) highly enriched in this organelle (5HT6-receptors). Finally, the team was constituted by gathering competent researchers with complementary expertises. Altogether, this project is a unique opportunity to develop research activities that may prompt guiding the team towards a leading position in a well-identified and relevant niche of research. In fact, the preliminary findings that grounds this proposal indicate substantial novelty and interest, namely the new concept of axo-ciliary synapses, the identification a metabotropic receptor selectively located in primary cilia, which join previous studies linking morphological alterations of the primary cilium in models of some neurodevelopmental diseases. Furthermore, the scientists gathered additional preliminary evidence of circadian-related alterations of primary cilium morphology.

The choice of focusing on the relation between the circadian rhythm and the primary cilium may potentially lack sufficiently solid foundations to be the most tempting starting point. Eventually, the exploitation of alterations of morphology and function of the primary cilium in animal models of brain aging and diseases might be more effective bolsters of interest (and funding).

Also, the aim of characterizing axo-ciliary synapses in the basal ganglia and SCN is left short of complementing morphology with function, which might be possible with new tools. In fact, the selective localization of 5HT6 receptors in the primary cilium may open new avenues to devise tools to tinker with the primary cilium by identifying the determinants guiding the trafficking of 5HT6 receptors. Choosing a promising initial angle of approach might be of interest to circumvent an apparent major limitation for this project to strive: the apparent lack of sufficient funding to support the research activities. Thus, a major priority of the team should be seeking for competitive funds to ensure supporting the research activities, as well as to hire manpower to speed up activities (irrespective of the advantage of providing training opportunities in a multidisciplinary micro-environment). A pro-active supportive attitude from the Direction of the Institute would be most welcome to support the initial development of the project, in view of its quality and potential relevance to the institution's image.

RECOMMENDATIONS TO THE TEAM

The potencial of the novelty of the subject and of the gathered expertise should be harmessed to develop the most scientifically tempting and 'fundable' projects to rapidly consolidate the team.

Brainstorming with several colleagues may be an effective way to gain a better perception of the priorities amongst the multiple choices offered by this pleiotropic and hitherto largely unexplored topic.

The committee- would dare recommending a priority in obtaining funds to support whichever projects the team decides to undertake since the committee all sadly know that funding is a decisive hurdle for research efforts.

It also seems important to draw the institute's attention to assessing its interest in actively participating in supporting this team (eventually through in-house collaborative efforts), which could offer an opportunity to place the institute at the forefront of a research area.

CONDUCT OF THE INTERVIEWS

DATES

Beginning: December 8th 2025

Ending: December 10th 2025

Interview conducted: on-site

PROGRAMME OF THE INTERVIEWS

December 8th 2025 (day 1)

14:00-14:15 Brief presentation of Hcéres by the Scientific Advisor, followed by a presentation of the Committee.

14:15-15:15 Presentation of the unit by the present director ***Philippe Marin*** *(past) and the future director* ***Sébastien Granier*** *(trajectory). Plenary session (40' presentation + 20' discussion with the committee)*

15:15-15:45 Presentation of scientific program of the team # **Julie Perroy –** ***future team # Julie Perroy and Jérémie Naudé*** *Title:* ***Physiopathology of neuronal plasticity.*** *(15' presentation (past & trajectory) + 10' questions +5' private meeting)*
15:45-16:00 Coffee break
16:00-16:30 Presentation of scientific program of Team # ***Philippe Marin – future team # S Claeysen and C Bécamel. Title: Neuroproteomics and innovative therapies for brain disorders.*** *(15' presentation (past & trajectory) + 10' questions + 5' private meeting)*

16:30-17:00 Presentation of scientific program of the team # ***François Rassendren – future team # Hélène Hirbec****: Title:* ***Signalling of Neuroinflammatory processes.*** *(15' presentation (past & trajectory) + 10' questions +5' private meeting)*

17:00-17:15 Presentation of scientific program of the team # ***Philippe Lory*** *Title:* ***Ion channels in neuronal excitability and diseases.*** *(10' presentation (past) + 5' questions)*

17:15-17:45 Presentation of scientific program of the team # ***Emmanuel Bourinet****: Title:* ***Calcium channel dynamics and nociception.*** *(15' presentation (past & trajectory) + 10' questions +5' private meeting*

17:45-18:15 Presentation of scientific program of the team # ***Freddy Jeanneteau****: Title:* ***Stress hormones and plasticity****. (15' presentation (past & trajectory) + 10' questions + 5' private meeting)*
18:15-19:15 Debriefing of the committee – team evaluations
20:00 Dinner in town for the committee and the Hcéres Scientific adviser at the restaurant. The address of the restaurant will be communicated by the institute.

December 9th 2025 (Day 2)

08:00 Departure for the IGF by tram. Tickets will be provided by the IGF. An IGF staff will pick up the committee members in the lobby of the hotel.

08:45-9:15 Presentation of the scientific program of the team # ***Emmanuel Perisse:*** *Title:* ***Neural circuits and value coding*** *#* ***Stephanie Trouche:*** *Title:* ***Appetitive and Aversive Memory Circuits – Future team #Stéphanie Trouche and Emmanuel Perisse****: Title:* ***Memory Circuits*** *(15' presentation (past & trajectory) + 10' questions +5' private meeting)*

09:15-09:30 Presentation of the scientific program of the team # ***Emmanuel Valjent****: Title:* ***Molecular and Neural Coding of Behavior.*** *(10' presentation (past) + 5' questions)*

09:30-09:45 Presentation of the scientific program of the team # ***Sylvaine Artero and Philippe Courtet****: Title:* ***Environment, Biomarkers, Neuropsychiatry****. (10' presentation (past) + 5' questions)*

09:45-10:00 Presentation of the scientific program of the team # ***Patrice Mollard****: Title:* ***Networks and rhythms in endocrine glands.*** *(10' presentation (past) + 5' questions)*
10:00-10:30 Coffee break

*10:30-11:00 Presentation of the scientific program of the team # **Guillaume Lebon and Cyril Goudet**: Title: **Molecular and structural mechanisms of neuromodulation.** (15' presentation (past & trajectory) + 10' question +5' private meeting)*
*11:00-11:30 Presentation of the scientific program of the team # **Philippe Rondard**: Title: **Neuroreceptors: dynamics and functions.** (15' presentation (past & trajectory) + 10' questions + 5' private meeting)*

*11:30-12:00 Presentation of the scientific program of the team # **Sébastien Granier and Bernard Mouillac**: Title: **Membrane Protein Structure and Function for Drug Discovery.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*
12:00-13:00 Debriefing of the committee (teams)
13:00-14:00 Lunch (Buffet with the unit's team leaders)
*14:00-14:30 Presentation of the scientific program of the team # **Matteo Mangoni and Stéphanie Barrère-Lemaire**: Title: **Cardioprotection, pathophysiology of heart automaticity and ischemia.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*14:30-15:00 Presentation of the scientific program of the team # **Chris Jopling:** Title: **Cardiac Development, Disease and Regeneration.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*15:00-15:10 NEW TEAM Presentation of scientific program of the team # **Julien Villeneuve:** Title: **Intracellular Compartmentation and Cell Communication** (5' presentation + 5' questions)*

*15:10-15:20 NEW TEAM Presentation of scientific program of the team # **Séverine Chaumont-Dubel and Xavier Bonnefont**: Title: **Primary Cilium Signalling in Neurobiology And Chronobiology (CilSNAC)**. (5' presentation + 5' questions*
15:20-15-45 Coffee break
*15:45-16:15 Presentation of scientific program of the team # **Philippe Jay**: Title: **Self-renewal and differentiation of epithelia.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*16:15-16:45 Presentation of scientific program of the team # **Julie Pannequin**: Title: **Signaling, Plasticity and Cancer.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*16:45-17:15 Presentation of scientific program of the team # **Hugues Duffau and Jean-Philippe Hugnot**: Title: **Neuroplasticity and Neuro-oncology** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*17:15-17:45 Presentation of scientific program of the team # **Stéphane Dalle and Eric Renard – Future team # Magalie Ravier and Eric Renard**: Title: **Innovative approaches of insulin deficiency in diabetes.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*
17:45-18:00 Coffee break
18:00-19:00 Debriefing of the committee (teams)
20:00 Dinner in town for the committee and the Hcéres Scientific Adviser at the restaurant. The address of the restaurant will be communicated by the institute.

December 10th 2025 (Day 3)
08:00 Departure for the IGF by tram. Tickets will be provided by the IGF. An IGF staff will pick up the committee members in the lobby of the hotel.

*8:45-9:00 Presentation of the scientific program of the team # **Laurent Journot**: Title: Systems level and statistical approaches to parental genomic imprinting. (10' presentation (past) + 5' questions)*

*9:00-9:30 Presentation of scientific program of the team # **Amaury François:** Title: **Peripheral and central neuronal mechanism of affective behaviors.** (15' presentation (past & trajectory) + 10' questions +5' private meeting)*

*9:30-10:00 Presentation of scientific program of the team # **Nicola Marchi and Vincent Costalat**: Title: **Translational Neurovascular Research**. (15' presentation (past & trajectory) + 10' questions +5' private meeting).*
10:10-10:30 Coffee break
10:30-11:00 Private meeting of committee (teams)
*11:00-11:30 Meeting with **engineers, technicians and administrative staffs in French***
*11:30-12:00 Meeting with **students** and **post-docs***
*12:00-12:30 Meeting with **scientists**, no team leader or lab directors*
*12:30-13:00 Meeting with **team leaders***
13:00-14:00 Lunch (only committee)
14:00-15:30 Private meeting of the committee (Prepare questions for the director and the representative of the funding bodies based on the points arising from meetings with members of the unit)
*15:30-16:00 Meeting with the **present** and the **future directors** of the unit*

16:00-16:30 Discussion with the ***representatives of the funding bodies (***Mme **Emmanuelle Trevisiol** — CNRS; M. **Vivien Devis** — Inserm; - M. **Jacques Mercier** — Vice-président Recherche, Université de Montpellie)

16:30 End of the visit
19:30 Dinner in town for the remaining experts at a restaurant to be confirmed.
Visit of the IGF platforms by Ms. Emilie PECCHI*, the Hcéres representative of supporting personnel to be organized by the unit*

GENERAL OBSERVATIONS OF THE SUPERVISORS

UNIVERSITÉ DE MONTPELLIER

MONTPELLIER
Le 26 février 2026

Monsieur Arnaud TOURIN
Directeur du Département d'évaluation de la recherche
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OBJET : Rapport d'évaluation - DER-PUR270025800 - IGF - Institut de Génomique Fonctionnelle

Monsieur le Directeur,

Je tiens à remercier le comité de visite HCERES pour la qualité de son rapport d'évaluation concernant l'unité de recherche IGF - Institut de Génomique Fonctionnelle - dirigée par Monsieur Sébastien GRANIER.

Le directeur de l'unité et moi-même avons pris connaissance des recommandations formulées par le comité de visite.

Vous trouverez ci-après les observations de portée générale du directeur de l'unité.

Nous vous prions d'agréer, Monsieur le Directeur, nos salutations distinguées.

La Vice-Présidente chargée de la recherche

Agnès MIGNOT

INSTITUT DE GÉNOMIQUE FONCTIONNELLE

CNRS UMR5203 - INSERM U1191 - UNIVERSITÉ DE MONTPELLIER

Le directeur

Montpellier, le 23 Février 2026

Objet : Courrier d'Observations Générales rapport HCERES DER-PUR270025800-IGF-Institut de Génomique Fonctionnelle

à qui de droit

Madame, Monsieur,
En ma qualité de Directeur de l'IGF, j'ai le plaisir de vous communiquer une observation générale émanant de l'équipe du Dr Freddy Jeanneteau :
Le comité évalue l'équipe comme excellente, avec une production scientifique soutenue et de haut niveau, une bonne visibilité nationale et internationale, ainsi qu'un financement stable et diversifié (NIH, Horizon Europe, ANR, FRM). Les travaux sur les neuromodulateurs, le stress et la résilience sont solides, innovants et appuyés par un réseau étendu de collaborations cliniques et fondamentales, y compris au sein de l'IGF. L'équipe dispose d'outils méthodologiques avancés et d'une trajectoire scientifique claire, désormais orientée vers les interactions entre métabolisme, stress et troubles psychiatriques.
Une fragilité est la taille réduite de l'équipe (deux permanents, absence de personnel technique), ce qui représente un risque pour la pérennité et la faisabilité des projets à long terme. La dynamique scientifique repose sur le PI et ses collaborations.
Malgré ces fragilités structurelles, l'équipe est bien positionnée pour poursuivre une trajectoire scientifique ambitieuse et compétitive axée sur des collaborations diversifiées et productives. Le comité recommande de renforcer l'effectif permanent d'une équipe efficace.
Freddy Jeanneteau
Directeur de recherche CNRS
Leader de l'Équipe Hormones de Stress et Plasticité

Nous n'avons pas d'autres observations.
Je vous prie d'agréer, Madame, Monsieur, l'expression de mes salutations distinguées.

Sébastien GRANIER

Sébastien GRANIER
Directeur
-IGF-

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