Research evaluation

EVALUATION REPORT OF THE UNIT

T3S – Toxicité environnementale, cibles thérapeutiques, signalisation cellulaire

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité,
Institut national de la santé et de la recherche médicale – Inserm,
Centre national de la recherche scientifique – CNRS

EVALUATION CAMPAIGN 2023-2024
GROUP D

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In the name of the expert committee[1] :

Dulce Papy-Garcia, Chairwoman of the committee

For the Hcéres[2] :

Stéphane Le Bouler, acting president

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

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

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

MEMBERS OF THE EXPERT COMMITTEE

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CNRS
Mr Bernard Poulain, DAS neurosciences

CHARACTERISATION OF THE UNIT

- Name: environmental toxicity, therapeutic targets, cell signalisation
- Acronym: T3S
- Label and number: UMR 1124
- Composition of the executive team: composition of the executive team: Xavier Coumoul

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE6 Physiologie et physiopathologie humaine, vieillissement

Panel 1 – SVE3 : Living Molecules, Integrative Biology (From Genes and Genomes to Systems), Cell and Development Biology for Animal Science
Panel 2 – SVE1: Basic and Applied Environmental Biology, Evolution
Panel 3 – SVE4 : Immunity, Infection and Immunotherapy
Panel 4 – SVE5: Neurosciences and Nervous System Disorders

THEMES OF THE UNIT

The 'Environmental Toxicity, Therapeutics Targets, and Cellular Signalling' (T3S) (UMR-S-1124, Inserm/Université Paris Cité/CNRS) is a research Unit that relates environmental stressors of chemical, biological, or social nature (i.e. exposome) to different pathologic conditions. The Unit approach is to explore biological pathways involved in the link between the stressor and the disease. Their aim is to characterise different stressors disrupting those pathways and to identify the most relevant targets for therapeutic interventions. T3S is formed of eight autonomous Teams with different expertise including toxicology, cellular signalling, molecular-structural biology, biochemistry, pharmacology, animal behaviour, genetics, epidemiology, infectious diseases, computational sciences, and clinical research. The Unit uses these expertises to explore biological pathways in a variety of diseases. The T3S Unit shows an important activity in the study of environmental pollutants and infectious agents in metabolic, neurological, joint and musculoskeletal diseases, as well as in allergy and cancer, integrating genetic background and environmental insults.

Team 1 (Signalling in environmental and drug toxicology; Metatox, X. Coumoul) works to identify the mechanisms of action of environmental pollutants to assess their influence on the incidence of pathologies including asthma, allergic diseases, cancer, liver diseases, and neurological diseases. With this aim, the Team uses cellular, animal, computational models in system toxicology, network biology, predictive toxicology, human studies, and genetic epidemiology.

Team 2 (Stem cells, signalling and prions; B. Schneider) works to understand the cellular and molecular mechanisms sustaining brain degeneration in prion diseases and that are common to other neurodegenerative diseases, including Alzheimer, Parkinson, and Amyotrophic Lateral Sclerosis. They develop new pharmacological approaches and explore environmental nanoparticles toxicity in neurons.

Team 3 (Myelination and nervous system pathologies; C. Massaad) works on myelin physiology and in pathologies affecting the nervous system. Their aim is to identify new signalling pathways involved in myelination and demyelination and to study the impact of environmental factors (stress, pollutants) on the normal myelination process and on demyelination exacerbated by comorbidities.

Team 4 (Degeneration and plasticity of the locomotor system; F. Charbonnier) studies normal and pathological locomotor systems by focusing in the motor unit and in the osteoarticular system. Their aim is to identify potential biomarkers and/or pathways involved in the physiopathology of disorders affecting the motor system (Spinal Muscular Atrophy, Amyotrophic Lateral Sclerosis, Low Back Pain and Arthritis).

Team 5 (Cellular homeostasis, cancer and therapies; E. Ségal-Bendirdjian) works in cancer biology with the aim to study how aggressive phenotypes due to tumour cell plasticity can be modulated to re-establish a tumour phenotype, more manageable to treatments. Their aim is to restore an earlier stage of differentiation and thus to improve responses to treatments.

Team 6 (Genetic epidemiology and functional genomics of multifactorial diseases renamed 'Gut microbiota and human diseases'; D. Gauguier) works on the characterisation of genetic, environmental, and epigenetic factors altering genomic regulations with the aim to detect specific and shared risk factors in distinct disorders, including asthma, allergic diseases, obesity, and cancer.

Team 7 (Cell death in host pathogen interactions; J. Estaquier) works on the biochemical and molecular mechanisms of apoptosis in the context of host-pathogen interaction and studies the particular contribution of

mitochondrial function and immune response on these processes. Pre-clinical models are used to test new therapeutic approaches and to analyse microbe persistence in deep tissues after treatment.

Team 8 (Addiction pharmacology and therapy; PharmAddict; F. Noble) studies the molecular mechanisms involved in substance use disorders and comorbid diseases (depression, anxiety, PTSD). Their aim is to understand higher vulnerabilities when one pathology is established and to find new therapeutic strategies by developing integrated omics-based signalling-pharmacological approaches.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

T3S was created in January 2014 at the 'Campus Saint Germain', Université Paris Descartes (former name of Université Paris Cité) with the aim to study signalling and environmental toxicology factors linking environmental stressors to pathology. At the time of its creation, the Unit was formed by five teams issued from the former UMR 747 Inserm Unit (Director: Pr. Robert Barouki) with three other Teams. In January 2019 (current contract), the Unit was composed of eight Teams following some movements including the departure of three Teams (Bastin & Djouadi, Mouillet, and Chelbi teams) due to retirement or change of project, and the integration of three new Teams with expertise in cellular homeostasis, cancer, genetic epidemiology, functional genomics, cell death, and host-pathogen interactions (Segal Team, ex-UMR 1007; Gauguier Team, ex-UMR 946 and ex-UMR 1138; Estaquier Team, ex-FR 3636). From 2019, the number of Teams remained constant in the Unit (N=8). Currently, the Unit activity and researchers are principally located in the Saint German Campus; however, one member of Team 8 is still in Bordeaux.

RESEARCH ENVIRONMENT OF THE UNIT

At the local level, the Campus Saint-Germain hosts five other Research Units and one 'Mix Unit of Service' (UMS). The other local Research Units are LCBPT (Laboratoire de Chimie et Biochimie pharmacologiques et toxicologiques, CNRS/UMR 8601), SPPIN (Saints-Pères Paris Institute for the Neurosciences, CNRS/UMR 8003), MSCmed (Matiere et Systèmes complexes, CNRS/UMR 7057), INCC (Integrative Neuroscience and Cognition Center, CNRS/UMR 8002), and the Centre Borelli (CNRS/9010), allowing multidisciplinary collaborations. The UMS is BioMedTech (CNRS UAR2009/Inserm US36/Université Paris Cité), created on January 2019 and hosting eight platforms that give service to the 6 local Research Units and to other exterior groups in the region. BioMedTech manages eight technological platforms essential to the basic and biomedical science activities. Services include mechanobiology, prototyping, nuclear magnetic resonance, animal facility, sensorimotricité, microscopy, flow cytometry, and a structural and molecular analysis platform. A T3S Unit member is head of the BioMedTech facility. Moreover, in terms of facilities, the Unit has access to an imaging-mass spectrometry equipment (MALDI-Imaging), owns L2 and L3 confinement laboratories; In terms of principal equipment, the Unit has access to a cell sorter (BD FACSMelody Cell Sorter), to a single-cell multi-omic system (BD Rhapsody Scanner), to a 10x Genomics sequencer, and to the necessary equipment to manufacture microfluidic chips. Concerning computing and storage facilities, the Unit owns five servers (132 cores, 1760 Gb of memory) along with 384 Tb of storage, allowing software's development and large-scale analyses.

At the national and international levels, T3S has developed, or belongs to, a large network of collaborations (clusters) and has invested in the creation of structures related to the future project of the Unit (e.g.: France Exposome, "Environmental Exposure Assessment Research Infrastructure" (EIRENE), Inserm-Columbia University collaboration, etc.).

In addition, some T3S Unit members participate to the Scientific Councils of ANSES, ANSM, OPECST, and IRSN; are involved in the 'Ecole Universitaire de Recherche' (EUR) 'Biomedical Engineering' and in EUR – 'Neurosciences » ; are involved in the piloting comity (COPIL) of Microbio'Up (Institut Hors Mur Paris Cité), in the Board of 'Réseau Francophone de la Mort Cellulaire', and in the Executive and Steering Committee of the Institute of Neuroscience and Cognition (CSS5 Inserm, CSS6 Inserm). Concerning international journals editorial boards, some T3S members are part of editorial boards for Biochimie, Scientific Reports, Journal of Addiction, Exposome, and Annual Reviews in Pharmacology and Toxicology.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	15
Maîtres de conférences et assimilés	23
Directeurs de recherche et assimilés	5
Chargés de recherche et assimilés	8
Personnels d'appui à la recherche	21
Sous-total personnels permanents en activité	**72**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	11
Post-doctorants	2
Doctorants	24
Sous-total personnels non permanents en activité	**41**
Total personnels	**113**

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

Nom de l'employeur	EC	C	PAR
UNIVERSITÉ PARIS-CITÉ	33	0	8
INSERM	0	9	11
CNRS	0	4	2
AUTRES	5	0	0
Total personnels	**38**	**13**	**21**

GLOBAL ASSESSMENT

The 'Environmental Toxicity, Therapeutic Targets, and Cell Signalling' (T3S) is a biomedical research Unit created in 2014 at the Saint Germain Campus of the University Paris Descartes (now University Paris Cité). The Unit was reconducted in 2019, endorsed by INSERM, University Paris Cité and the CNRS (Team8), to study the links between environmental stressors of chemical, biological, or social nature, to different pathologic conditions. The Unit aim was to characterise how different stressors disrupt different biological pathways and to identify the most relevant targets to monitor environmental risks. Protecting human health from the T3S studied stressors represents a high biomedical impact, a societal issue and a scientifically relevant objective.

The T3S Unit hosts 113 persons, including 72 permanent staff (at 31/12/2022), with an average budget per year of 3,600 k€, 87% of which comes from external grants and 13% from INSERM and University Paris Cité recurrent funding. The T3S staff is distributed on eight autonomous Teams that study the impact of environmental pollutants, infectious agents, and drugs of abuse, in neurological, metabolic, joint and musculoskeletal diseases, and in other pathological conditions as cancer, allergy, and drug addiction. It is to note that the Unit has implemented state-of-the-art facilities, including a metabolomic MS/MS MALDI-Imaging platform (Team 7), although there is currently no permanent technical staff dedicated to this equipment that has the potential to add a great value to the research of the Unit, and to Units of the region.

The T3S attractiveness and international and national visibility are overall excellent, as indicated by I) the scientific distinctions and prizes obtained by members (the Kernier Prize of the ARC Foundation, the Prix de Recherche Clinique, and the Prix Expanscience, …) and by invitations to several international colloquia and to foreign laboratories; II) The capacity of the Unit to obtain competitive and prestigious european and international research grants is overall excellent, but can be improved for Team 8. During the period, T3S members coordinated three EU programs (Teams 1 and 2) and collaborated to ten others (Teams 1, 4, 6, and 7. Moreover, they coordinated a French-Swedish program (Team 5), 1 France-USA project (Team 1), a France-Japan project (Team 6) and 7 IRSC projects with Canada (Team 7). They collaborated to two international ANR projects (Teams 1 and 6). Regarding national grants, the T3S activity was excellent, as they coordinated seventeen ANR and participated to eleven ANRs (Teams 1, 2, 3, 4, 5, and 8). Moreover, T3S Unit members coordinated 35/42 additional projects supported by different foundations (including FRM, Fondation de France NRJ, and ARC among others). However, the attractiveness for international early career researchers (e.g. postdocs, junior researchers) should be improved.

Concerning scientific production (876 scientific publications, including 287 clinical reports), the T3S Unit is overall excellent, as indicated by publications in leading positions (such as Nat Genet, Nat Commun, Nat Rev Immuno, Lancet Rheumatol, Proc Natl Acad Sci USA, Environ Health Perspect, eNeuro, PloS Pathogen, Environ Int, J Allergy Clin Immunol, Cell Death Diff, Mol Psychiatry, etc..). From those papers, 34 involved at least two T3S Teams. Highlights describe the discovery of novel genes and gene-environment interactions or new biological mechanisms involved in the different studied pathological conditions, or proposed novel methods, novel analysis strategies, and/or focused on specific biological phenotypes underlying pathology. However, very large heterogeneity in level and number of publications is observed among Teams.

The T3S Unit interactions with the non-academic sector have well increased during the period and are excellent for most Teams, as indicated by the number of partnerships and service to industry (Ethypharm, Pharmaleads, Hoffmann La Roche, Sanofi, Air Liquide, ABBVIE, Biophytis, METABRAIN SA, IEEP World, GSK, ViiV, Merck… or advise (Lefebvre, Biogen, Novartis Gene Therapy France), and by the PhD students supported by ANRT or other industrial collaborations (Teams 4, Team 7). During the period, 6/8 Unit Teams have produced patents issued from their research and supported by SATT IDFinnov, SATT ERGANEO, SATT-Lutech (Team 1 patented new methods for quantifying CTP and CTP synthetase acSvity; Team 2 developed ROCK and PDK1 kinases inhibitors as anti-inflammatory drugs; Team 3 developed a new squalene-vectorised siRNA based therapy for Charcot-Marie-Tooth type 1A disease and a microfluidic device and method using it; Team 4 developed a diagnostic tool for joint diseases and a new strategy for the treatment of spinal amyotrophy and other neuromuscular disease; Team 5 developed an anti-neurotensin antibody for preventing weight and muscle loss; Team 6 developed new biomarkers for acute mesenteric ischaemia and Team 7 developed anti-covid strategies. Some of these patents have resulted in start-ups (Team 6) or Spin-offs (Team5). Teams are very involved in societal interactions: media, dissemination in local, national, and international meetings and focus groups, interactions with policy-makers at the local (Paris city), national (Groupe Santé Environnement, health plans, safety agencies), and international levels (the EU commission, the HBM4EU that coordinates and advance human biomonitoring in Europe), the PARC (Partnership for the Assessment of Risks from Chemicals), and the WHO.

T3S Unit members hold responsibilities in societies and national and international regulatory bodies, making this activity excellent. T3S Unit members are part of the Scientific Council of the European Environment Agency (Team 1) are advisors for the WHO and OMS (Team 4), or presides the French 'Institut de Radioprotection et de Sûreté Nucléaire' (IRSN) (Team 1). Some members of the T3S Unit have been invited or are adjunct professors in foreigner universities including in the USA, Canada, Japan, Lebanon, and China. Team 6 was member of the International Peer Review Committee for the Terry Fox Research Institute (Canada). Similarly, the T3S Unit hosted professors from the USA, Canada, and Korea. Some T3S Unit members are part of editorial boards for scientific

journals including, Biochemistry, Exposome Journal, Annual Reviews in Pharmacology and Toxicology, Journal of Addiction, and Conference papers in pharmacology.

However, regardless of these performances, the Unit states a low number of newly hired postdoctoral fellows and early career researchers. Similarly, the Unit's internal organisation needs improvements, specifically in terms of increasing internal scientific animations and hiring full-time and competent staff to support the heavy load of administrative and logistical duties, currently undertaken by other staff members.

In conclusion, T3S is an excellent biomedical research Unit well positioned at the international and national levels, with the potential to further reinforce its current achievements at the European and international levels. The Unit should keep the balance between their different research on the exposome by continuing to carry out basic/translational/valorisation projects. They should maintain or increase the level of external fund-raising to promote competitive and multidisciplinary research. Similarly, the Unit Teams should continue their technology patenting and transfer capacities. Nonetheless, they should increase attractiveness by capitalising their excellence through an increased participation to European research projects and networks and by hiring international post-doctorates and PIs on the main research topics of the Unit.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Previous HCÉRES report commented different issues:
Concerning the comment on '*heterogeneity among the different teams*', the Unit states that 'despite team heterogeneity, objectives were achieved'. These Unit objectives, following previous HCÉRES, were listed as follows: *establish links between environmental stressors in the biomedical field; take advantage of multidisciplinary site (chemists, physicists, mathematicians, neurologists); develop networks at the international, European, and national levels to obtain funding and to increase the visibility; encourage interactions between teams; greater scientific animation; disseminate knowledge to public and media; increase valorisation and expertise, at both fundamental and clinical levels.* Concerning the objective '*Establish links between environmental stressors in the biomedical field*', the objective was achieved, as shown by indicators including publications, granted projects, PhDs projects, valorisation, organisation of seminars or conferences. Globally, it is observed that all Teams contributed to a better understanding of the exposome and of its relevance in biology and health, in their own areas of expertise.

Concerning objective '*Take advantage of multidisciplinary site'*. Several expertises exists in other local Units, complementing the TS3 Unit expertise, including units working with chemistry, cellular neuroscience and imaging, behavioural and cognitive sciences, and physics. Effort to interact with these units were observed through the articles published by some Teams in common with chemistry and neurobiology units.

Concerning objective '*Develop networks at the international, European, and national levels to obtain funding and to increase the visibility'*, several European/international networks/projects were obtained in coordination or in partnership, reflecting visibility. In many projects the Unit has a leader position. However, during the period, a limited number of highly competitive international postdocs joined the Unit, indicating that more efforts should be made for rendering the unit attractive for young high potential scientists.

Concerning '*Encourage interactions between Teams'* comment, efforts were performed as shown by collaborations among the Teams 1 and 3 on the role of AhR in myelin biology; among Teams 1 and 7 with the study of the role of chemicals in efficient vaccination, and among Teams 3, 4 and 8 on mental health and behaviour. Teams 1 and 2 addressed topics related to nanoparticles and pesticide toxicology, and teams 1 and 5 currently have ongoing interactions in the field of cancer.

Concerning '*Greater scientific animation'*, few information on periodic Unit retreats, common seminars, scientific activities clubs, etc. were identified, although only a two-day unit meeting outside Paris was organised to support the cohesion within the Unit Teams members and support their interactions. As this meeting was unique during the period, efforts in scientific animation can be improved.

Concerning '*Disseminate knowledge to public and media',* a great effort was observed with the participation of the Unit members in dissemination activities [brain week, interventions in colleges and high schools, workshops…], interviews in the media, etc.

Concerning '*Increase valorisation and expertise, at both fundamental and clinical levels'* comment, the Unit made great efforts, as shown by the number of patents and current plans to develop Start-up projects related to the research of several Teams. For instance, Team 2 got maturation programs *from SATT ERGANEO and UPCité to improve the Start-up project,* Team 3 has also patented some of its discoveries and decided to also build a Start-up. Team 5 devoted most of its research plan towards translational research, leading to development of an anti-tumour drug to be tested in a phase I assay for neuroblastoma (Start-up 'HaNam Therapeutics' that will be created). Moreover, the Unit provided new lab space for a spin-off that will start working soon. The spin-off will be initially located within the current Team 5 lab space. A collaboration with pharma (METABRAIN SA) was initiated by Team 6 and the lab hosted scientists from that company. Team 6 is also involved in a project of creation of a Start-up (*maturation by SATT-Lutech)*.

Concerning other committee comments on '*disparities in the students' access to meetings*', the Unit made it clear that if a team did not have the funding for such activities, the Unit would compensate to ensure fairness in student participation in international meetings.

Finally, concerning previous HCÉRES committee comment on '*Psychological stress that some students and other unit members may experience*', the Unit sent two surveys to the Unit members on occupational psychological stress and has analysed the answers to improve the follow-up of the identified raised issues: they created a group that brainstorms on psychological stress at work and followed their recommendations. When conflicts appear, attempts are made for internal solutions and if this does not work, external support from INSERM or university is sought.

B – EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

The major scientific objective of the T3S Unit is to link different relevant pathologies to environmental stressors of a chemical, biological and social nature. This is an ambitious scientific objective because of high potential for environmental, health and societal impacts. To reach this objective, the unit gathered eight Teams with different expertise including toxicology, molecular and structural biology, cellular signalling, biochemistry, pharmacology, animal behaviour, epidemiology, computational sciences, preclinical and clinical research.

Assessment on the unit's resources

The T3S Unit resources are partly issued from the two representatives (INSERM and University Paris Cité) and partly from the several grants obtained by the different research teams, which respond to national and international highly competitive calls to perform fundamental and translational research. With these very good financial resources, the Unit teams have the capacity to ensure the undertaking and completion their scientific projects by purchasing the necessary research resources and equipment as well as recruit contractual staff. However, there is a lack in permanent staff supporting administrative, logistical and technical tasks.

Assessment on the functioning of the unit

General functioning of Unit is very good although it could still be improved in terms of scientific animations, organisation, logistics, administration and Health and Safety (H&S) aspects. H&S is indicated to be a future major objective for Unit management and 'Prevention Competent Persons' (PCP and PCR) are involved in promoting and managing regulation and guidelines, chemicals, biological reagents and radiologic safety.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

A central strength of the Unit is its scientific objective, which aims to identify links between environmental stressors and their impact on health. This represents a high impact biomedical and societal issue that can be studied in different biological systems and models of pathology. Environmental stressors can be multiple such as air pollution, noise pollution, chemical exposure, and biological factors can adversely affect human health by increasing the risk of chronic diseases and mortality. Moreover, environmental stressors often co-occur, creating multi-hazard scenarios that can have synergistic or cumulative impacts on human health. To protect human health from these stressors, a comprehensive approach that addresses the multiple hazards people are exposed to and implements policies and regulations limiting exposure is important. More research is needed to identify biomarkers to monitor environmental risks and strategies to reduce environmental stressors and protect health are required. Thus, the scientific objectives of the unit are in line with the policy of the supervisory authorities.

The capacity of the Unit to reach its objectives is supported by the numerous different expertises that exist within the Unit (clinical, *in vivo*, *in vitro* and *in silico*) and by their capacities to develop or become part of national and international networks in their research domains, as shown by the participation of the Unit members in the scientific councils of ANSES, ANSM, OPECST, IRSN, etc. The Unit members are then able to analyse the contribution of their research policies to the resolution of societal challenges. Similarly, the Unit has shown the capacity to create and/or participate to infrastructures and networks related to the research objective (e.g.: France Exposome, « Environmental Exposure Assessment Research Infrastructure » EIRENE, PARC, HBM4EU, WHO, etc.).

Weaknesses and risks linked to the context

The framework of the Unit's project proposal, concerning the multiple pathological conditions that are studied, might be too ambitious and lead to isolation of some teams. Moreover, an absence competent/available administrative staff is a risk, without an available administrative organisational operator involved in the scientific and social animation of the Unit, the time of the scientific personnel assuring administrative tasks will decrease their research time and, additionally, some groups risk to not fully adhere to the Unit's dynamism around the scientific objectives. Furthermore, this may deviate from the overarching direction and goals of the Unit.

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

Strengths and possibilities linked to the context

The Unit has the resources suited to its activity profile and research environment and mobilises them, as reflected by the capacity of most Teams to obtain competitive grants, develop health-related programmes as well as to establish links with the University and hospitals. Most Unit teams show excellent ability to raise funds to perform fundamental and translational research and have access to technological platforms (e.g. BioMedTech facilities, INSERM US36, CNRS UAR2009, UPCité). At the local level, some collaborations exist between Teams and with other Units in the site. T3S Teams use the facilities of the University when relevant. Moreover, because of their involvement in the local academic programmes (e.g. head of Masters programmes), most Teams showed the capacity to hire talented Masters and PhD. candidates.
During the period, Team 3 hosted a new professor (C.B.) and an associate professor (H.S.) and Team 8 hosted 4 associate professors (C.L., V.B., R.M., and A.C.) and one technician (I.N.). These arrivals will allow the unit to strengthen the studies and technical expertise.

Weaknesses and risks linked to the context

In such an attractive environment, it is unclear why the Unit has difficulties to recruit young permanent researchers and outstanding postdocs.
Students and staff are taking on administrative and technical tasks and responsibilities assigned to other members of the team, which impacts their ability to undertake their research activities and affects their mental health.

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

Strengths and possibilities linked to the context

The Unit's practices comply with the rules and directives of the supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage.

Weaknesses and risks linked to the context

Although resources from grants, notably in human resources, are important, it is not clear how these resources are allocated to common interest, for instance supporting activities that can support common values.

Concerning data protection/management and scientific heritage, it should be improved and the Unit is currently establishing strategies to improve. Currently, Teams that have major needs for servers and that collect sensitive data have their own management (e.g. Team 1c manages patients cohort data and Team 1b manages toxicological data; F. Jornod). Moreover, personal computers backup is mainly carried out on external discs. However, a committee of IT managers from the site's various research Units was created (RIB) and actions started to be conduced for an automatic backup system.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The Unit has an excellent scientific reputation and contributes to the construction of the European research area. TS3 attractiveness is reflected by their thirteen prestigious European funding, three of which as PI. Moreover, during the period, the unit teams coordinated other european and international (the USA, Japan, Canada, Sweden, etc.) projects and two international ANRs. Members participated or coordinated seventeen national ANRs. Similarly, international recognition is demonstrated by the number of invitations to international conferences and involvement of unit members in the organisation of scientific events. Several unit members are recognised as they participate to national and international governing bodies. However, the attractiveness for international early career researchers (e.g. postdocs, junior researchers) can be improved and the unit should define a strategy to attract more postdocs (10 hosted).

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

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

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

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

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

1/ The Unit contributes to the development of the international and European research landscape. This is illustrated by the participation of Unit Teams to two University Research Schools (EUR) and to 19 European projects (OBERON, HERA, PrPetPDK1, Kindred, NMTryp, InLeish, IRS, HERA, PrPetPDK1, HEALS, HBM4EU, NEUROSOME, RADONORM, MLFPM2018, ERC-ADDITIIVES, PARC, REDOX SMA, Infect-ERA, METACARDIS), three of which as PI. Furthermore, Team leaders obtained, as PI, 6 grants with Canada, Sweden (145kE), Japan (75kE) and Columbia Univ (116kE). At the European level, the Unit is coordinator of three grants (H2020 OBERON, HERA, PrPetPDK1) on a total of fourteen obtained.

Twenty tenured researchers were involved in the organisation of a total of 60 international congresses. Moreover, several members of the Unit are members of French societies (e.g. SFN, SFBBM, SFN, SFG), international societies or federations (e.g. FEBS, FENS, IGES, SOT and ECNP) and nationally recognised expert committees (e.g. CSS5, CSS6, CoNRS S28, Pesticides, ANSES, PARC, WHO, IRSN, COST, IRESP, etc.).

The T3S Unit has developed a large network of local, national and international collaborations and has invested in the creation of infrastructures and network related to the future project of the Unit (e.g.: France Exposome, EIRENE, Inserm-Columbia University collaboration) and has established strong links with University hospitals and health-related programs with significant capacity to develop translational research.

2/ T3S Unit hosted invited professors from Boston University (USA), Baylor College of medicine (Houston, USA), University of Quebec (Canada), McGill University (Canada), National Institute of Environmental Research (Korea).

During the period, 22 postdoctoral fellows and 71 PhD students worked in the Unit, for a global number of 55 HDRs, making a postdoc/HDR ratio of 0.4 and a PhD/HDR ratio of 1.29/HDR for the whole period, and equivalent to 0.06 postdocs/HDR/year and 0.22 PhD/HDR/year. From the 71 PhD students, 22 of them (31%) were in co-direction with Universities including the Univ Paris Cité, the University of Caen, University of Toulouse III, the University of Lima (Peru), the American University of Beyrut, the University of Beyrut, and the University St Joseph (Liban). Among the PhD students, twelve were issued from foreigner Masters (10 from Liban and 2 from Italy), 46 defended their thesis between 2017 and 2023, two abandoned and the rest (23) are currently working in their research project in the Unit. Globally, graduated PhD students found a position one year after their thesis defence, mostly due to the national and international networks of the Unit.

3/ The average budget per year of the unit is 3,600 k€, 87% of which comes from external grants. These include fifteen European contracts (Team 1, 2, 4 and 6), thirteen international non-European contracts (Team 1, 6 et 7) and numerous national funding. The rest of the budget, 13%, comes from the supervisory bodies.
Globally, the Unit is able to finance its research by obtaining highly competitive national and international grants. During the period, Team 1 coordinated two Horizon Europe programs (OBERON, HERA), Team 5 coordinated a French-Swedish program, and teams 1 and 6 participated to two international ANR projects. This indicates an active participation of the Unit members to the European Research Landscape. Moreover, outside Europe, Team 1 coordinated two France-USA projects (International INSERM-Columbia Univ and NIH), Team 6 coordinated a France-Japan (International INSERM-Kyoto University, Team 6) and a France-Canada project (Genome Quebec). Team 7 coordinated or participated to 7 IRSC (Institute de Recherche en Santé du Canada).

Among national grants, T3S members coordinated (PI) seventeen ANRs (all Teams) and participated to other eleven ANR (Teams 1, 2, 3, 4, 5 and 8) and to several UPC PIA-IDEX programs (Teams 1, 2, 3, 4, 5, 6, and 8). Moreover, T3S obtained 4 contracts FRM (3 as PI/4), 7 contracts ANRS (7 as PI/7); 11 ANSES (5 as PI/11) ; 6 APHP (1 as PI/6) ; 2 ARSEP (2 as PI/2) ; 3 ARSLA (2 as PI/3) ; 18 diverse fondations (Fondation du Soufle, Fondation des Geules cassées, Fondation Institut de France NRJ, Fondation pour la Recherche sur le cerveau, Fondation Univ Paris Cité, Fondation de l'Avenir, Fondation de France/Fondation pour la recherche en alcoologie, Fondation Université Paris Cité Sauver la vie, Fondation Canadienne à l'Innovation (FCI), with 16 as PI/18. Moreover, several Teams obtained eight IDEX (6 as PI/8), two INRA, seventeen INSERM (10 as PI/17), one Ligue contre le Cancer (2 as PI/2), 4 PHRC (2 as PI/4), among others. Some examples of Teams implications in some of these contracts are: ANSES (Team 1, 2 and 3), DIM IDF (Teams 1, 2, 7), INSERM (Teams 1, 2, 4 and 8), INRA, INCA, Fondation de France, and INERIS, Ligue Contre le Cancer (Team 1), LECMA, and ARSLA (Team 2), Fondation des Gueules Cassées, Fondation Institut de France, and Fondation de l'Avenir (Team 3), AFM, APHP, ARSLA, ICM, Institut Jérôme Lejeune, and PHRC (Team 4)....

4/ T3S is one of the Units that support the activities of the BioMedTech facilities (e.g. CNRS UAR2009/INSERM US36/Université Paris Cité). This joint Service Unit (UMS) brings together various local Research Units on the Saints-Pères site and enables exchanges of biotechnological expertise in relation to the disciplines on which each research entity works.
The T3S Unit has developed state-of-the-art facilities including a metabolomic MS/MS MALDI-Imaging platform. However, there is currently no permanent technical staff dedicated to this equipment, which can be of great usefulness for both the Unit and its environment.

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

The international recognition is not equal for all teams and there is no apparent strategy to improve international attractiveness for all teams. Few invited professors are registered (only one professor form Korea is present in the unit characterisation data). Furthermore, the number of PhD students and postdocs is quite low compared to HDR staff. Considering the Characterisation data table, two postdoctoral fellows and 71 PhD students worked in the Unit, for a global number of 55 HDRs, making a postdoc/HDR ratio of 0.06 postdoc/HDR/year and 0.22 PhD/HDR/year. This indicates that recruitment of young permanent researchers should be improved.

There is a disparity in the manner the information is presented by the different teams. Although there are 55 Unit members that hold an HDR in the Unit, the number of PhD students is relatively low and the number of postdocs is quite low for the whole Unit. The lack of recruitment of young permanent researchers is also a weakness.
The number of European grants under coordination is low (only 2 Teams for 3 grants), it can be improved for other Teams.
T3S also uses several other platforms of Université Paris Cité (e.g. genomics, proteomics, epigenomics) but this technological park is not located on the T3S site and is not supported by T3S.
MS/MS MALDI-Imaging platform lacks of permanent technical staff dedicated to this equipment.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

According to the production file, T3S is very productive in scientific publishing in excellent journals such as Nat Commun, Nat Rev Immuno, JAMA Intern Med, Gut, Environ Health Perspect…. They have produced several communications, assured many conferences… From those papers, 34 involved at least two T3S Teams. As for the number of publications, large heterogeneity can be observed among Teams. Overall, the diversity of the production allows a large visibility of the Unit in the scientific community.

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

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

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

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

The Unit provides a list of 876 scientific publications including articles in prestigious journals (Neuroscience, Mol Oncol, J Virol, Lancet Rheumatol, eNeuro, PloS Pathol, Rheumatology, Genomics, Nat Commun, Nat Rev Immuno, JAMA Intern Med, Gut, Environ Health Perspect, Environ Int, J Cell Death Diff, Allergy Clin Immunol, Mol Psychiatry, Proc Natl Acad Sci USA, etc.). The total production of T3S is excellent with 876 scientific publications including basic science reports (N=589) and clinical reports (N=287). The Unit encourages each Team to develop an independent publication strategy. Within Teams, the contribution of each member is acknowledged by co-authorship.

The Unit comprises 51 HDR within the global task force of researchers. Throughout the entire evaluation period, 77 PhDs were defended, resulting in 65 publications in PDC positions (over the 876 publications of the Unit). In total, it gives a ratio of 1.5 PhD/HDR during the period.

The Unit has a member with an important activity of training in scientific integrity, ethics and open science. One Team is particularly involved in raising awareness to the ethics around animal experimentation and in developing new technologies to replace animal models.

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

Covid has impacted the scientific production for several Teams.

It is worth noting that 6 PhD students have yet not published their work.

The Unit member involved in the ethics and integrity strategy will retire and the Unit needs to find a new candidate to follow up on the activity. The candidate will have to implement the means to obtain flawless results, to guarantee their traceability and, where appropriate, their reproducibility (laboratory notebooks, anti-plagiarism software, internal peer-review procedures, data and source code archiving procedures, etc.).

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Globally, the Unit is perceived as an important player in environmental health research and in supporting policies in this field. The Unit management is actively involved in public outreach and engagement activities: media, dissemination of research findings at local, national and international meetings and through focus groups as well as interactions with policy-makers at local (e.g. Paris city) national (e.g. Groupe Santé Environnement, health plans, safety agencies) and internationally (e.g. EU commission and WHO). The Unit also supports NGOs and contributes to the reflection of economic factors on environmental issues (e.g. industry associations, insurance companies, water companies, cosmetics), without any conflict of interest regarding these activities.

The specific strategy of partnerships with cultural, economic and social impacts are clearly important and supported by each team, indicating an excellent inclusion of the Unit's research in societal realms.

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

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

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

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

T3S interactions with the non-academic sector have well increased during the period. The Unit encourages valorisation in general, whether it is targeted to public health and prevention or whether it is related to an economic outcome. Several teams have an important role in the development of patents (e.g. cancer, inflammation, neurological diseases, infections). 6/8 Unit Teams have produced patents issued from their research and patenting was supported by SATT IDFinnov, SATT ERGANEO, SATT-Lutech: Team 1 patented Methods for quantifying CTP and CTP synthetase activity (WO2018/0298420); Team 2 developed ROCK and PDK1 kinases inhibitors as anti-inflammatory drugs (WO2021191460 and WO/2021191455); Team 3 developed a new squalene-vectorised siRNA based therapy for Charcot-Marie-Tooth type 1A disease (WO2020064749) and a microfluidic device and method using it (EP18305185); Team 4 developed a diagnostic tool for joint diseases (EP0758-IDF39) and a new strategy for the traitement spinal amyotrophy (FR 2111920-2022) and neuromuscular diseases (FR3093640-2021); Team 5 developed an anti-neurotensin antibody for preventing weight and muscle loss (PCT/ep2019/073991); Team 6 developed new biomarkers for acute mesenteric ischaemia (EP21305252.5); Team 7 developed anti-covid strategies (BIO20529, BIO20529, NIMES2022). Some of these patents have resulted in the Start-Up projects (Team 6 is involved in the creation of a Start-Up company) or spin-offs (Team 5 is involved in the construction of the Spin-off 'HaNam Therapeutics' from FairJourney Biologics). The Unit supports these teams through support for students and in some cases through the dedication of lab space to spin-offs or collaborating industries.

T3S Teams (most Teams) have partnerships or offered service to industry (Hoffmann La Roche, Sanofi, Air Liquide, ABBVIE, Biophytis, METABRAIN SA, IEEP World, GSK, ViiV, Merck…) or have given scientific advises to companies (Lefebvre, Biogen, Novartis Gene Therapy France). Two PhD students were supported by ANRT (Teams 4, Team 7), supporting industrial collaborations, including with Biophytis.

Each Team is independent in its scientific production strategy and knowledge dissemination policy. Several Teams are involved in communication of scientific advances and popularisation activities. For example, T3S members spoke at several meetings aiming to inform the general public and in schools. Every year, the Unit hosts high-school students interested in learning about research activities. The future Unit director is strongly involved in the communication of scientific culture and its influence at the University level.

The Unit is involved in societal interactions: media, dissemination in local, national and international meetings and focus groups as well as interactions with policy-makers at the local (e.g. Paris city) national (e.g. Groupe Santé Environnement, health plans, safety agencies) and international levels (e.g. EU commission, HBM4EU, PARC, WHO). They also support NGOs and contribute to the reflection of economic actors on environmental issues (e.g. industry associations, insurance companies, water companies, cosmetics). The Unit's role in environmental health research and in supporting policies in this field is one of its major strengths. Unit's topics (e.g. environmental stressors and health) are of major societal and biomedical relevance.

The Unit developed an attractive policy to support the valorisation targeted to public health and prevention as well as to an economic outcome including patents, Start-Ups and collaboration with industry. Strong links to University hospitals and involvement in health-related programs facilitate translational research. Altogether, this results in a strong valorisation activities (e.g. Start-Ups, patents) from several Teams. Each Team has a societal and economic valorisation strategy supporting either prevention and public health and/or the development of new therapeutics or diagnostics (e.g. INSERM expertise on pesticides & health, the banishing of phytosanitary products for consumers, the genetic screening in familial melanoma, patent filing of new leads in therapeutic intervention, Spin-offs projects).

Strong involvement in dissemination to citizens: media interventions, nonacademic interactions and education of the general public. During the time period, this resulted in the development of computational tools shared in open access (Team 1), a total of fourteen patents in cancer, inflammation, neurological diseases (2 by Team 2; 1 by Team 3; 2 by Team 4; 4 by Team 5; 2 by Team 6; 3 by Team 7) and the development of 4 Start-Ups projects (Team 2, Team 3, Team 5, and Team 6) currently in various stages (2 established and 2 in maturation with SATT support). A total of 27 contracts (4 by Team 1, 5 by Team 2, 1 by Team 3, 8 by Team 4, 1 by Team 5, 2 by Team 6, 2 by Team 7, 2 by Team 8) were in collaboration with Industry (e.g. Abbvie 200 keuros, Sanofi 26 keuros, Air Liquide 231 keuros, or IEEP World 7.6 keuros), including a CIFRE PhD fellowship. The Unit supports valorisation through support for students and dedication of lab space to Spin-Offs or to collaborating industries. Finally, Teams within the Unit are strongly involved in the set-up of French infrastructures for exposome assays (e.g. France exposome) and a European ESFRI on exposome (EIRENE).

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

The insufficient consideration of dissemination of knowledge to the public in the evaluation of researchers and professors and the extreme complexity of and amount of time required for valorisation activities may lead to discouraging such endeavours in the future.

ANALYSIS OF THE UNIT'S TRAJECTORY

The new Unit named 'Health-Fex' will be directed by a new director Xavier Coumoul, who is a dynamic and very well-recognised scientist in the exposome field and who has greatly contributed to the development and evolution of the T3S Unit with the current director.

The exposome topic will be at the centre of the new Unit's scientific objective. Reorganisation of the Unit will occur, whereby there will be 6 Teams instead of currently eight. This will reinforce the cohesion of the Unit around the exposome thematic. The committee feels that the new theme will strengthen the collaborations within the Unit.

RECOMMENDATIONS TO THE UNIT

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

The committee recommends that the Unit continues their track record of acquiring competitive national and international competitive grants as PIs.

The Unit is characterised by diverse research activities, with an impact on a range of different public health and environmental conditions. The committee recommends that the Unit remains focused on the currently considered pathological conditions to continue facilitating communication between Teams and to support a welcomed dynamism around the exposome theme by each Team.

There is a clear need for additional full-time and competent administrative staff and trainees within the Unit. The actual INSERM administrative position is not fulfilled and the workload is currently distributed among the other staff members. This situation required to be resolved to improve the work environment for all members.

The scientific animations within the Unit and across the Teams should be improved by implementing regular scientific Unit seminars and PhD/Postdoc workshops. Early career researchers should be strongly involved in organising and participating in these events. The Unit could support social events to gather all staff members together, regardless of career stage.

There is currently no clear Equality, Diversity and Inclusion (EDI) policy and/or committee. There is a brief mention of actions to promote gender equality but they were poorly developed and not adequate. We therefore recommend that the Unit put in place such frameworks that enhance inclusion and diversity (sex, gender, sexual orientation, ethnicity, disability) within the workplace.

Recommendations regarding the Evaluation Area 2: Attractiveness

The Unit should improve its strategy for the recruitment of early career researchers (e.g. permanent researchers/group leaders, postdoctoral fellows). In addition to promoting scientific animations through regular inter-Teams scientific and social gatherings within the Unit, the committee also recommends increasing communication activities at international level, outside from established collaborations, to increase attractiveness. This could for example be achieved by having a logo or a slide that is used by all Unit members when presenting their Team-specific work. An actively maintained Unit social media account that advertises research and public engagement activities across the Unit would also be beneficial.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee acknowledges the high impact of the original research the Unit is involved in. The committee recommends that an integrated research approach be considered producing Unit-level research outputs that span across the Teams. The committee also recommends that a specific effort is invested in recruiting early career researchers (postdoctoral level and early stage principal investigators) into the Unit spanning across all Teams.

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

The committee recognises the Unit's dedication to advance research related to environmental issues and public health. Whilst the Unit is generally internationally recognised well, an imbalance between independent Teams on the contribution to societal and environmental issues and a lack of clarity on how the contribution from each team aligns with the overarching scientific objective of the Unit have been recognised by the committee. Going forward, the committee recommends clear evidence of specific co-projects between the Teams, demonstrating a united effort to advance research in environmental and public health issues as a Unit, rather than as individual Teams.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Signalling in environmental and drug toxicology

Name of the supervisor: Xavier COUMOUL

THEMES OF THE TEAM

The Team studies the mechanisms of action of several environmental pollutants, alone or in mixtures, in order to identify and better understand the effects of exposure to these pollutants on health, using different and complementary models (cellular, animal, computational). The Metatox Team works on several health issues such as cancer, chronic liver diseases, metabolic, and allergic diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendations of the previous report encouraged:

1) to publish in a major generalist scientific journal, particularly on the AhR theme;
2) to develop some interactions *with the socio-economic world and to involve in applied toxicology activities;*
3) *to continue the recruitment of more PhD students, to encourage the HDR holders to supervise PhD students and to precise the future of the former PhD students*

The Team published in the leading journals in the field of environmental health (Environ Int) and toxicology (Annu Rev Pharmacol Toxicol), in particular in 2022 in the AhR theme. In addition to these publications on this specific theme, the Team organised in Paris, an international meeting in 2018; the leader of Team 1 has been invited to several international meetings (Eurotox Meeting 2017, University of Singapore 2018).

According to the Team's research topics (pesticides, endocrine disruptors), interactions with industries are quite complex; although the members are more involved in public agencies at European and national levels, to contribute to public policy decision-making. They developed interaction with the private sector (Start-up, Tech2Heal). Moreover, their expertise is regularly called upon by numerous national and international regulatory agencies (ANSM, ANSES, European Environmental Agency…) and also in different scientific and program committees of international meetings. Finally, they lead or are partners of European and national research projects on the exposome and risk assessment. All these dynamics demonstrate their commitment to applied toxicology activities.

During the period, seventeen PhD students (8 defended) were supervised or are still in progress. To increase the number of PhD students, the Team has diversified the sources of funding for PhD grants. In the Team 1, sixteen members hold the HDR but some of them have just obtained their HDR during the contract. Half of the HDR holders supervise PhD students. Most of the former doctoral students have been successful (postdoctoral position, clinical research associate, vigilant manager).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	7
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**19**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	7
Post-doctorants	0
Doctorants	8
Sous-total personnels non permanents en activité	**18**
Total personnels	**37**

EVALUATION

Overall assessment of the team

Scientific production: The Team has a very high number of publications, more than 250 publications during the contract within 180 articles in PDC position in the leading journals of environment and health (Environment International, EHP, Nat Genet, J Allergy Clin Immunol) and toxicology (Annu Rev Pharmacol Toxicol). They coordinated or participated in eight books in the field of exposome. The scientific production of the Team is excellent.

Attractiveness: Metatox team members have obtained in total 36 grants as PI and 31 as partners (including an international ANR project): they are PI in two on 9 European grants and on 7/10 ANR. Members are regularly invited as a hosted professor in foreign environmental research and genome centers. The Team hosted five visiting professors from the USA and Canada, and one postdoctorant. Thus, the attractiveness is excellent.

Valorisation: Team members participate in debates with citizens and are particularly involved in international and national public or regulatory agencies at European and national levels (on the effect of pesticides on human health). They developed interactions with clinicians and with the private sector. Via artificial intelligence, the Team developed a webserver (AOP-helpFinder). The valorisation of the Team is outstanding.

Strengths and possibilities linked to the context

The Team 1 highlighted the effects of several persistent organic pollutants alone or in mixture on cancer metastasis and aggressiveness, particularly in breast cancer. They developed specific *in vitro* models useful for toxicology studies as co-culture models recapitulating the tumour microenvironment.

They contributed to the emergence of a new field of toxicology research, through artificial intelligence: computational toxicology with a webserver for regulatory assessment (Adverse Outcome Pathway AOP-helpFinder) to identify associations between stressors and key events through a comprehensive analysis of literature (Bioinformatics 2022). Moreover, the Team highlighted the role of the AhR as a physiological regulator of myelination and inflammatory processes during the development of the central nervous system, also identifying the AhR as a potential drug target for demyelinating disease (Scientific Reports 2017). Finally, they identified new genetic factors, gene-environment interactions, and biological pathways for asthma and allergy-related phenotypes. During this contract, the Team developed collaboration with clinical teams from the site with other scientific and research units in different disciplines such as chemistry and neurobiology. They are leaders or coordinators of European projects on exposome (Heals, Hera) and partners in other projects (ERC Additives, Radonorm, PARC).
According to the Team's research topics (pesticides, endocrine disruptors), interactions with industries are quite complex; they developed interaction with the private sector (Start-up, Tech2Heal). Although the members are more involved in public agencies at European and national levels, to contribute to public policy decision-making.

They have scientific expertise activities (INSERM 2021 Pesticides et santé ; ANSES) and participate in scientific councils (ANSES, EEA, ANSM, OPECST, IRSN). They are involved in different scientific committees of international meetings (FEBS meeting, AhR meeting, Am Soc Hum Genet meeting, Int Genet Epi Soc meetings, VisioMel meeting) and organised a national meeting (AhR meeting in Paris 2018, Assises de Génétique Humaine et Médicale) leading to more than 50 invited conferences. For Team 1, almost of the budget comes from grants to support PhD contracts and technical staff (annual budget of 850k€, i.e.> 5,000 k€ over the contract): they obtained 36 grants as PI from international funds (6 contracts including 2 H2020 projects (Oberon, Hera) and also from national competitive calls (4 ANSES, 7 ANR, Ecophyto, Pepper). Moreover, they obtained 32 grants as partners. These results underline the dynamism of each subgroup of the Team, enabling them to have sufficient resources for their activities and showing their great capacity to mobilise different research environment levels.

At last, Team 1 is very involved in public outreach and help decision makers. Four members of the Metatox Team are members of editorial members of leading journals in the fields of environment and health and of exposome (Biochimie, Ann Rev Pharmacol Toxicol). Some have been Guest Editors for special issues (Plos Genetics).

Weaknesses and risks linked to the context

Nearly half of engineers and technical staff are on a non-permanent position. Moreover, the number of PhD students varies according to the subgroup of the Team. There are no postdoctoral scientists, although the team has a great scientific reputation and obtained numerous funding. This situation could become an issue for the long-term potential of the Team.

Analysis of the team's trajectory

The Metatox Team will be reorganised for the next contract: two subgroups ExpTox and Gems will constitute Team 1 Metatox with two co-leaders. Exptox will integrate some members coming from other Teams of the Unit and also with new arrivals to pursue and extend exposome projects (including not only chemical, but also diet and psychosocial stressors) on different issues (cancer, chronic liver diseases, vaccination, and neurodevelopment). Gems subgroup will develop novel insights into genome-exposome relationships in respiratory diseases. One new Team will be created emerging from Systox subgroup. This new team in the field of bioinformatics and artificial intelligence will strengthen the whole Unit. The Metatox team remains a large Team that will play a significant part in the leadership of the Unit in the field of exposome and toxicology.

RECOMMENDATIONS TO THE TEAM

The committee recommends the Team to continue their excellent research activity. The Team has also shown an impressive success at raising EU and national funds in the field of toxicology and exposome. The Team has been done an excellent job at developing bioinformatics, systems biology and AI tools which resulted in the creation of a novel team which will be a great asset for the new unit dynamics. Altogether, the committee strongly encourages the Team to try to further support the emergence of new interactions between Teams in the exposome field and to apply for fundings that will allow recruiting postdoctoral scientists.

Team 2: Stem cells, signalling and prions

Name of the supervisor: Benoit SCHNEIDER

THEMES OF THE TEAM

This Team's work is basic science related with three overarching aims: 1) to understand the sequence of events explaining how normal physiological prion protein transforms into abnormal pathological prion protein leading to neurodegeneration; 2) understanding to what extent other misfolded proteins associated to neurodegenerative diseases (such as AD, PD, ALS) mimic events characteristic of prion diseases, 3) to find out the role of environmental nanoparticles in the development of neurodegenerative diseases. The Team is also developing novel pharmacological approaches targeting downstream prion protein signalling effectors to combat these diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations HCÉRES 2018: (1) The Team is small in size and should seek to strengthen itself, particularly in terms of researchers and teacher researchers. (2) The Team's projects need to be prioritised. It is recommended to focus more particularly on the relationship between PrPc, neuronal death and stem cells. (3) Certain aspects of the research project could be carried out in collaboration with other Teams in the unit.

Answer of the Team: Given that the previous HCÉRES report was riddled with inaccuracies, the recommendations made by the HCÉRES committee were biased…

(1) Pierre Nioche, assistant professor at UPC joined the Team in 2019, Aurélie Alleaume-Butaux was recruited to the Team in 2020 as an INSERM Research Engineer, and Nathalie Evrard, assistant professor at UPC, joined the team in 2020 for professional reconversion.

(2 and 3) The work on PrPc was fruitful and done with national and international collaboration (publication: Nat Commun 2019, Plos Pathogens, 2021). The work on neurodegenerative mechanisms induced by prion infection and the comparison with other amyloids, unfortunately, was stopped in July 2021 because of the prion moratorium after the death of two technicians in Inrae laboratories accidentally contaminated with prions. They thus focused their work on the physiological implication of PrPc in neuronal functions and the in-depth characterisation of two kinases, ROCK and PDK1, in neurodegenerative diseases. They further evidence that inhibiting ROCK or PDK1 with pharmacological compounds exerts anti-inflammatory action, opening the road for the design and development of new ROCK/PDK1-targeting approaches for dampening inflammation in neurodegenerative and other inflammatory diseases (2 patents deposited during the 2020–2023 period – WO2021/191460; US patent n° 1,790,735; FR2110122).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**4**
Total personnels	**14**

EVALUATION

Overall assessment of the team

Scientific production: The team produced fifteen original research publications and three reviews as PIs in the time period 2017–2022 (highest-ranking publication in Nature Communications in 2019). The Team members have also contributed to 4 book chapters. The scientific production of the Team is excellent.

Attractiveness: The Team lead is coordinator of a European Program on Neurodegenerative Diseases and obtained funding from 2ANR. The team obtained funds from DIM Mal Inf for equipping the P2 facility for prion studies. The Team lead has given multiple talks as an invited speaker at conferences mainly in France, but also at several conferences internationally. The Team in total has participated at various meetings, nationally and internationally, with fifteen poster presentations and in total seventeen invitations to participate at scientific conferences. They organised one international symposium (Paris, France), supervised 7 PhD students, 6 MSc students and had three postdoctoral research fellows, although not all of them were indicated in the Unit characterisation Table. The attractiveness of the Team is excellent.

***Valorization*:** The Team has two patents and have made plans to develop a Start-up project related to the design and development of a new class of anti-inflammatory drugs. They have received financial support from companies including Sanofi and Air Liquide. The valorisation of the Team is excellent.

Strengths and possibilities linked to the context

Team 2 in the time period 2017–2022 generated eighteen publications as PIs. From these, fifteen were original scientific papers and three invited reviews. The three major publications as listed by authors are directly related to the research aims of the Team, such as in Nature Communication, PloS Pathogen, Particle and Fibre Toxicology. The Team also contributed to 4 book chapters.

The scientific highlights of the Team are the study the cellular prion protein interaction with other amyloidogenic proteins, in particular amyloid beta, work on dichloroacetate as potential treatment for prion diseases and in-depth characterisation of kinases ROCK1 and PDK1as potential pharmacological targets for treatment of inflammatory diseases.

The Team consists of ten permanent staff members, but it is growing: N Evrard (MCU Université Paris Cité, expert in NMR) joined the Team in 2020 to work on the structure-function relationships of signalling intermediates involved in neurodegenerative diseases. A. Alleaume-Butaux was hired at Inserm as Research Engineer in 2020. H. Ardila-Osorio was promoted Engineer Assistant at Université Paris Cité in 2022.

The Team successfully obtained competitive funding. Notably they coordinated a European Joint Program on Neurodegenerative Diseases project (PrP&PDK1, 2014–2019, 356kE) and 2/4 ANR research program (Targeting PDK1 in AD, 2016–2021, 320kE; SAMENTA, 2013-2018, 181kE) and they received financial support from two companies: Sanofi (2015–2020, 26kE) and Air Liquide (2021–2023, 21kE). They have also collaborated on other grants (ANR, ANSES). As coordinator of a European Program on Neurodegenerative Diseases, the Team lead B. Schneider formed an international laboratory network. The Team obtained funds from DIM Mal Inf to equip the P2 facility for prion studies. The team was granted by foundations (LECMA Vaincre Alzheimer and ARSLA) and obtained maturation contracts (ERGANEO, Université Paris Cité) for result valorization.

Team members have participated in many conferences with seventeen invited oral presentations and fifteen poster presentations at various national and international meetings. The Team has two patents related to their work.

The Team also organised one international symposium (Paris, France) and the Team lead was the coordinator of a European Joint Program project on neurodegenerative diseases. The Team is also involved in public outreach through various media sources.

The Team 2 is actively involved in education and student supervision: 7 PhD students (2 foreign students from Peru and Brazil) defended; 6 Master students (Brazil, Italy, UK) were supervised for three HDR in the Team. The Team hosted one foreign postdoc (ANR fellow) and foreign student for short period (ERASMUS).

Weaknesses and risks linked to the context

Major risk for future success of the Team is in relation to the infrastructure to have access to P3 level laboratory facilities to enable continuation of research with infectious materials. Currently in France there is prion

moratorium that stopped team's research on prions since July 2021. To continue research on prions, the Team must establish or join existing P3 level laboratory. The Team acknowledges the urgent need to restart research in prion diseases, and the team by joining CNRS Unit 7654 (Ecole polytechnique), equipped with a P3 laboratory, plans to restart the research in prion diseases in near future. Estimated start of the experimental prion work at Ecole polytechnique is provided as the end of 2024/beginning of 2025, after minor but essential modifications of the P3 laboratory to adapt it for the work involving prions.

Analysis of the team's trajectory

The Team will not be part of the Unit for the next period. The Team lead has accepted the proposal to move the Team to Ecole polytechnique (CNRS Unit 7654), which will enable them to access P3 laboratory and restart their research on pathological prion protein, with the estimated start date at the end of 2024/beginning of 2025.

RECOMMENDATIONS TO THE TEAM

The Team will not be part of the future Unit. The main concern is related to the infrastructure in relation to the need of having P3 level laboratory facility for the Team to carry out their research work; however, the team has a plan in place to enable them to continue work on prion diseases in appropriate laboratory facilities by start of 2025 as the latest.

Team 3: Myelination and nervous system pathologies

Name of the supervisor: Charbel MASSAAD

THEMES OF THE TEAM

Team 3 uses an interdisciplinary approach to research the process of myelination and related pathologies affecting the nervous system. The three overarching aims that guide the research programme within Team 3 are:

(1) Identify new signalling pathways involved in myelination and demyelination;
(2) Determine the contribution of these signalling pathways to the pathophysiology of several conditions that affect the nervous system (e.g. Multiple Sclerosis (MS), spinal cord injuries, Diabetic peripheral neuropathies and traumatic brain injuries);
(3) Study the impact of environmental factors (e.g. stress, pollutants) on the normal process of myelination, on demyelination and relevant comorbidities.

Deciphering the signalling pathways involved in myelination and demyelination as well as the extrinsic factors that influence their dysregulations will open up new therapeutic avenues for the treatment of myelin-related pathologies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the previous report, Team 3 was encouraged to make changes around the supervision of PhD students such as increasing the number of CIFRE PhD students with industrial partners, increasing the number of co-supervised PhD students and equalise the number of PhD students per HDR Team member. In the current contract, there is one reported CIFRE PhD student and nine co-supervised PhD studentships (2 national, 7 international).

In addition, the previous report recommended that Team members participate in the development of a massive open online course (MOOC) capable of accommodating a large number of French and foreign participants. As the Covid pandemic placed a large importance on remote learning, various team members, including several Professors and Associate Professors, played an active role in the remote delivery of educational activities.

The previous report also suggested that Team 3 reduces the large amount of educational and administrative duties undertaken by members of the team. The team therefore started to do so in 2021, whereby C. Massad stepped down as UFR Director. Nevertheless, Team 3 has also stated that these additional educational and administrative duties contribute to the strengths of the team in terms of building and establishing scientific and industrial networks.

Finally, the last recommendation was for Team 3 members to enhance their interactions with clinical collaborators to enable the successful achievement of their objective to develop new pharmacological therapeutics. Team 3 is presently initiating a Phase 1 clinical trial with the Neuropathies Reference Center of the Kremlin-Bicêtre Hospital.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**7**
Total personnels	**19**

EVALUATION

Overall assessment of the team

Scientific production: Team 3 has been involved in the publication of 51 manuscripts, 31 of which are with a Team member as last corresponding author, including original research articles (e.g. highest-ranking publication in PNAS), specialty journals (e.g. Neuropharmacology) and invited reviews (e.g. Nature Rev Immunology). The scientific production of the Team is excellent.

Attractiveness: Members have obtained funding as PIs from regional (e.g. 7 from Fondation des Gueules Cassées) and national (e.g. ANR) funding agencies. Furthermore, Team 3 members have given multiple talks as invited speakers at conferences, mainly in France, as well as poster presentations at various conferences (6 national and 8 international). Team 3 hosted 4 postdocs (one ongoing) and twelve PhD students defended and passed their viva. The attractiveness of the Team is excellent.

Valorization: Team 3 has five patents, one of which relates to the development of a new therapy for a genetic neuropathy (Charcot-Marie-Tooth type 1A (CMT1A)). IP licensing was sought for this CMT1A patent, which will drive further development as well as potential approval and marketing of this therapy through the preclinical studies and Phase 1 clinical trials. Team 3 members have participated in thirteen public engagement and awareness activities (e.g. Interview, YouTube, afterwork, Radio). The valorisation of the Team is outstanding.

Strengths and possibilities linked to the context

Team 3 is currently composed of thirteen permanent staff that include 4 principal investigators (Full Professors), 6 associate senior scientists (MCU-PH, 1 CRCN Inserm, 4 MCF) and three technicians/research engineers. The team is well structured into several subgroups and each PI conducts a specific work package and has an excellent visibility and capacity to obtain funding (40–50 k€ per year and per work package). Team 3 is growing in size, whereby one CNRS researcher and their current lab members (PhD students and post-doc) will soon be joining the current Team. Team members have successfully and consistently obtained competitive peer-reviewed funding as PIs from regional and national funders (e.g. ANR, Fondation des Gueules Cassées, Fondation NRJ – Collège de France, ARSEP – Multiple Sclerosis, Federation for the Research on the Brain (FRC), Ligue française contre l'Epilepsie (LFCE – seizure), Idex Emergence for new projects – UP Cité). More specifically, 108 kE were obtained from ANSES, 258 kE from ANR and 310 kE from Fondations des Gueules Cassées (7 awards).

Team 3 is growing in size, whereby one CNRS researcher and their current lab members (PhD students and postdoc) will soon be joining the current Team.

Team 3 has demonstrated active and consistent research outputs as well as international dissemination of their research findings. Furthermore, the team has acquired niche expertise, experimental models (e.g. *ex vivo* model of toxin-mediated demyelination as an MS model) and equipment (e.g. Locotronic) that leads to collaborative and/or training opportunities with external laboratory researchers.

Team 3 members have been involved in more than 30 publications as senior/corresponding author, the majority of which are original research articles (e.g. Sci Rep, Neuroscience, Diabetes) while the rest being reviews (e.g. View, Nat Review Immnuol). The three major publications (PNAS, eNeuro and Neurobiol Dis), as listed in the report, are directly related to the research aims of the Team. Their publication in eNeuro 2019 was taken as a reference publication to introduce the concept of new statistics and was the subject of the editor's choice of Science.

Team members have participated in many national (e.g. 12ème rencontre annuelle du Club de Neuroprotection, Conference on Multiple Sclerosis, ARSEP) and international (e.g. Neuroscience Institute Cavalieri-Ooolenghi) conferences and meetings, where their research was presented via oral and poster presentations.

The interaction of the team with the private sector was demonstrated by the establishment of five patents and one IP license (applied for in the 2017–2022 period) that enabled the creation of a start-up (MAAsiRNA, created in 2023). The Team has developed a new therapy for a genetic neuropathy (CMT1A) and the start-up will drive further development as well as potential approval and marketing of this therapy through the preclinical studies and Phase 1 clinical trials.

Team 3 members are also involved in several public outreach and engagement activities through different media outlets and have participated in open debates in the field of ethics.

As chairs of three Master's programmes (Neuroscience, Clinical Research and Biomedical engineering), coordinators of two Graduate Schools and one ERASMUS exchange programme, Team 3 members are strategically placed to welcome talented international and national Masters and PhD students within their Team.

Together, Team members have supervised twelve PhD students (5 HDR in the Team) that have successfully passed their viva and five students are currently undertaking a PhD project supervised by a Team 3 member. Two members of the team have been promoted to HDR.

Weaknesses and risks linked to the context

As described in the report, there is an imbalance of positions/roles within Team 3, whereby it is mainly composed of members at the level of Professor or Associate Professor and they all have high loads of educational and administrative duties (e.g. Dean/Vice-Dean of UFR Biomedical sciences, in charge of International Relations and student mobility) with minimal support from permanent and designated administrative staff within the Team.

Although the team brings 400,000 euros/year in grants, there is currently no competitive international and/or European funds, as most awards are from local and national charities and organisations. Finally, although Team 3 members do participate in various public engagements and outreach activities, the strategies to disseminate their research to the general public have not been optimised.

Analysis of the team's trajectory

Current team members are remaining within the team and an additional member and their trainees will be joining Team 3.
The future research programme will be developed through five axes, which align with work undertaken by team members during the previous 2017–2022 period:

(1) Define Schwan cell lineage progression and its contribution to peripheral nerve development as well as impairment of motor and sensory functions.
(2) Define the role of oligodendroglial ADAM10 on myelin in health and disease and following exposure to different stressors.
(3) Develop microfluidic compartmentalised chips to recapitulate physiological and relevant *in vitro* models of myelination, demyelination and remyelination.
(4) Define the role of stress in the aggravation and the development of comorbidities (e.g. cognitive impairments, depression) in myelin-related pathologies.
(5) Define the pathophysiology and develop treatments for diseases and lesions of the peripheral nervous system.

Team 3's future trajectory proposes a strong multidisciplinary approach based on expertise in various areas such as myelination, myelin-related pathologies, biophysics, experimental models and animal behaviour. There are also several national, international, clinical, academic and industrial partnerships (e.g. ERASMUS, Columbia University, Mater Epilepsy Unit in Australia) that are in place that will support the delivery of the research programme and recruitment of trainees.

The organisation and scientific animations of Team 3's future trajectory are made clear. The Team have stated that they will limit the number of PhD students per PI due to the majority of the permanent Team members being Professor and Associate Professors with large amounts of teaching and administrative duties.

RECOMMENDATIONS TO THE TEAM

The committee recommends that Team 3 continues their excellent bench-to-bedside translational research activities, outputs and collaborations with clinical and industrial partners.

The committee also recommends that Team 3 enhances their attractiveness to hire new postdocs or young researchers by perhaps utilising timely and relevant social platforms (e.g. X, TikTok, YouTube, webpage) to advertise their day-to-day research activities and public engagement activities as well as use conference poster and oral presentations to advertise available posts.

Finally, the committee acknowledges the ability of Team 3 members to consistently acquire financial support from regional and national funding agencies. The committee recommends that this be continued alongside attempts to acquire funding from additional international and EU funding organisations as well as from industrial partnerships.

Team 4: Degeneration and plasticity of the locomotor system

Name of the supervisor: Frédéric CHARBONNIER

THEMES OF THE TEAM

Team 4 investigates the basic mechanisms involved in the physiopathology of several human disorders affecting the motor system, including spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), low back pain and arthritis, in order to identify potential biomarkers and/or pathways that could be modulated, pharmacologically or through personalised exercise protocols, to improve the symptoms associated with these conditions.

Specifically, the research programme of Team 4 is divided into 4 defined work packages:

1. The development of normal and pathological neuromuscular and osteoarticular systems.
2. The interplays between energetic metabolism, oxidative stress and inflammation in osteoarticular and neuromuscular diseases.
3. The role of RNA metabolism in neuromuscular diseases.
4. The nuclear signalling pathways in RNA metabolism, cellular differentiation and diseases.

The ultimate objective of their research programme is to identify new therapeutic targets and related treatment options for osteoarticular and neuromuscular diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the previous report, Team 4 was encouraged to publish a greater number of publications with Team members as first or last authors. They have since published 32 research articles with a team member as first author, 52 research articles with a team member as last author and 69 research articles with a Team member as corresponding author.

It was also recommended that they develop their international collaborations, which was done via new co-supervision of PhD students with partners in Lebanon and Spain.

In addition, they have followed the recommendation of increasing Team 4's attractiveness to postdocs and foreign researchers as well as enhance its interactions with non-academic communities by initiating a collaboration with a Team at Sheffield University (UK), with the company Biophytis as well as with the RHU SMART network, composed of several companies with a shared goal of therapeutic development for muscle atrophy. Furthermore, F. Rannou, a member of Team 4, has recently been appointed as a member of the WHO.

To follow the recommendation of reducing their expertise/consulting and administrative duties, members of Team 4 have limited their teaching management duties and F. Rannou and F. Charbonnier have absorbed most of the supervisory and management activities.

Finally, the previous recommendation concerning the organisation and scientific unity of the Team was also taken into consideration through the appointment of a defined lab manager and the holding of weekly and monthly Team meetings and social events that bring together all members if Team 4. Members of the team are also encouraged to attend the same conferences to promote Team building.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**6**
Total personnels	**18**

EVALUATION

Overall assessment of the team

Scientific production: Team 4 members have contributed to the publication of over 140 journal articles, including original research (48), clinical research (84) and review articles (9), with approximately 50% having a Team member as last or corresponding author (e.g. J Clin Med, Sci Rep), mostly in speciality journals**.** The scientific production of the Team is excellent.

Attractiveness: The Team currently has twelve permanent staff members and together, they have acquired funding as PIs from various funders, including national federal agencies (e.g. ANR MIRROR, 256 kE), international funders (e.g. partner in Horizon 2020, 73 kE), clinical calls (e.g. 2 PHRC awards), patient organisations (e.g. partner in AFM, 23 kE) and industry (e.g. Biophytis, 269 kE). Team 4 is also successful in attracting new students (10 trainees), PhD students (5 defended and passed their viva) as well as technical staff (2 hired on short-term contracts) to the Team. The attractiveness of the Team is excellent.

Valorization: Team 4 members have filed three patents and lead 26 clinical trials. Team members have also participated in dissemination of knowledge with the general public via national TV and radio programmes. The valorisation of the Team is outstanding.

Strengths and possibilities linked to the context

Team 4 is composed of academics (4 MCF, 2 PR and 1 CR INSERM) and clinicians (1 MCUPH and 2 PUPH) that together, have an excellent track record in terms of publications, clinical trials, patents and funding. The Team will be further supported by the upcoming arrival of an INSERM Research Director.

Members have contributed to the publication of over 140 journal articles, including original research, clinical research and review articles, with approximately 50% having a Team member as last or corresponding author. These publications are in both specialty (e.g. Cartilage, J Rheumatol) and generalist (e.g. J Clin Med, Sci Rep) journals. In those publications, the Team has contributed to the identification of new molecular pathways involved in spinal muscular atrophy (SMA)-induced neurodegeneration, a potential treatment for muscle atrophy in SMA, a new therapy for osteoarthritis and a new method based on surface-exalted Raman spectroscopy to diagnose joint diseases. Finally, Team members have developed niche expertise in exercise models and investigations in both preclinical models and humans.

There is a clear bench-to-bedside collaborative framework within the Team members, highlighted by 26 clinical trials currently being driven by team members. Members acquired funding as PIs from national federal agencies (e.g. ANR MIRROR, 256kE), and clinical calls (e.g. 2 PHRC awards), patient organisations (e.g. 2 awards from

Arthritis Recherche & Développement, 1106 kE) and industry (e.g. Biophytis, 269 kE). They were also partners in other awards such as international funders (e.g. Horizon 2020, 73 kE) and patient organisations (e.g. AFM, 23 kE).

Team members have disseminated their research findings at numerous national (e.g. 7th International Myology Congress) and international (e.g. Cure SMA) meetings and conferences. The expertise of team members in their respective fields in further highlighted by their positions on advisory boards of several national (e.g. ANR, AFM) and international (e.g. OMS, CNAM) organisations, funding agencies and/or pharmaceutical companies.

The translational strength of Team 4 is further supported by the recent filing of three patents aimed at diagnosing and/or treating osteoarticular and neuromuscular diseases.

Some Team members also undertake impact activities that either directly influence global policies and/or enhance the dissemination of research outputs to the general public. Furthermore, one member of the team (F. Rannou) is a member of the WHO.

Team 4 has filed three patents, covering both the osteoarticular and neuromuscular diseases that are the research focus of team members. One patent is in collaboration with the company Biohytis, as it stems from a CIFRE PhD thesis supported by the company. Another patent is financially supported by the public valorisation company SATT Erganeo.

Weaknesses and risks linked to the context

As described in the report, there is currently an imbalance in positions/roles within the Team, whereby there are a greater number of Team members with teaching and/or clinical duties than full-time researchers.

Furthermore, the clinical Team members currently have a stronger track record than the academic researchers (although this was not distinguished in the DAE).

Finally, although Team 4 members do participate in public engagement and outreach activities, this is only undertaken by a select few that also have additional educational and administrative duties.

Analysis of the team's trajectory

Team 4 will remain in the proposed Unit transition from T3S to Fun-Expo and will be composed of fourteen permanent Team members. One team member has recently been recruited and promoted at another University while a new Assistant Professor and Inserm Research Director will be recruited. The research programme will be divided in three work packages/research themes, which will be under the leadership of different Team members:

1. Plasticity of the normal and pathological osteoarticular system.
2. Motor neuron diseases.
3. Diseases of the neuromuscular junction.

The overall goal of the team's trajectory is to build on the recent successes (publications, patents, clinical trials, academic and industrial collaborations) to ultimately provide novel insights on the structure and physiology of the locomotor system and on new therapeutic approaches for the associated pathologies.

RECOMMENDATIONS TO THE TEAM

The committee recommends that Team 4 continues their excellent bench-to-bedside translational research activities, outputs and collaborations with clinical and industrial partners.

The committee also recommends that Team 4 enhances their day-to-day public outreach and engagement activities by utilising timely and relevant social platforms (e.g. X, TikTok, YouTube, webpage) to reach a greater number of people.

Finally, the committee recommends that Team 4 carefully consider how they will strategically make themselves visible in the competitive research field of ALS, ensuring that their novel research avenues are recognised and valued.

Team 5: Cellular homeostasis cancer and therapies

Name of the supervisor: Evelyne SEGAL-BENDIRDJIAN

THEMES OF THE TEAM

The work of the Team is based on both fundamental and translational research. The research is focused on a better understanding of the mechanisms of cancer progression and potential therapeutical intervention, by identifying new therapeutic targets, which would modulate the aggressivity of tumours by re-establishing the phenotype more amenable to treatments. They focus of the Team is on two pharmaceutical targets: the telomerase and derivatives of neurotensin named Long Form Neurotensin (LF-NTS) and its high affinity receptor NTSR1.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

No specific recommendation from the previous evaluation was presented.
The Segal-Bendirjian team moved in 2019 from UMR 1007 to T3S with a reduction from seventeen to ten ETP.

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

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

EVALUATION

Overall assessment of the team

Scientific production: The Team has produced 30 research articles, with in total 559 citations. In fifteen of these publications, the Team members were in lead positions (first or last authors). The Team was also involved in 145 clinical publications. The research articles have been published in excellent journals of oncology, such as Mol. Oncol, and Mol. Cancer. They have produced translational work related to treatment of acute promyelocytic leukemia, lung cancer and neuroblastoma. Notably, the Team has developed a monoclonal antibody, which is ready to be used in a clinical trial for neuroblastoma treatment. Scientific production of the Team is excellent.

Attractiveness: The Team has obtained funding at national (one ANR as partner) and international level (LUND University Suède as Coordinator). They also obtained a major maturation contract with SATT-Erganeo. The Team supervised 6 PhD students. The attractiveness of the Team is excellent.

Valorization: Team has 4 patents and they have created a start-up. The start-up will be involved in using the LF-NTS antibody developed by the Team in a clinical trial for treatment of neuroblastoma. The valorisation of the Team is outstanding.

Strengths and possibilities linked to the context

Team 5 has a strong expertise in cancer biology with the research focus on both basic science and translational aspects. Over the last five years, they published 30 basic original research articles, including in high impact journals in leading positions including Molecular Cancer 2018, Molecular Oncology 2020, Cancer Letters 2019, Cancer Research 2017.

One of the main research focus of their work is the investigation of cooperative interplay between hTERT promoter methylation, chromatin accessibility, and histone modifications that give new insights in the epigenetic regulation of hTERT. This is important for the potential development of therapies targeting expression of telomerase in cancers. The other main research focus is related to the evaluation of the impact of cisplatin treatment on PD-L1 expression, a protein involved in tumour escape from immune response. They analysed the clinicopathological characteristics of patients who received cisplatin-based neoadjuvant chemotherapy followed by surgery and showed that cisplatin-based induction treatment significantly increased PD-L1 staining in both tumour and immune cells. Importantly, the Team has also developed an anti-tumour agent targeting LF-NTS that blocks NTRS1 receptor that restores of cisplatin-based therapies responsiveness and decreasing metastatic processes.

Importantly, both tenured researchers have contributed to the scientific production of the Team and PhD students have published as first authors. The PI wrote several reviews (2 as invited) and participated at five internationals meeting with oral presentation as an invited speaker.

During this period, the PI obtained one ANR as partner and one researcher of the Team obtained one European contract with Lund University (145kE, Sweden) as a coordinator and one maturation contract with SATT-Erganeo (267kE) to promote the development of antibodies targeting LF-NTS (long form neurotensin) for human therapy to decrease metastatic processes. The Team also obtained funds from Gefluc, Fondation du souffle and LNCC.

Team 5 has produced four patents, and have developed an anti-tumour drug ready to be tested in a phase I and then II assays for neuroblastoma treatment. This will be done within the Start-up 'HaNam therapeutics' that has been created in collaboration with INSERM Transfert and Université Paris Cité. The start-up will also form part of Team 1 in the future reorganisation of the Unit.

The PI is co-coordinator of the UE 'Pharmacology Applied to Cell Biology' of Master 1 Santé parcours Physiologie Pharmacologie et Toxicologie (Faculté de Pharmacie).

Finally, the Team 5 is active in communicating their findings and knowledge to mass media on TV and radio and participated in open debates on topics of nutrition and cancer.

Weaknesses and risks linked to the context

The Team will not be reconducted for the next five-year contract HEALTH-FEX. The Team moved in 2019 from UMR 1007 to T3S with a reduction from seventeen to ten ETP. This loss was not compensated by fresh recruitment of researchers.
No organisation of meeting was reported. Only the PI participates to meetings

Analysis of the team's trajectory

The Team will not be reconducted for the next five-year contract. However, some of the members will join other teams in the Unit, specifically the Spin-off Start up will be part of Team 1. Those Team members not joining the future Unit will retire.

RECOMMENDATIONS TO THE TEAM

To ensure successful integration of the research, the committee recommends that the Unit will pay particular attention to the team members of Team 5 that will join other Unit Teams in the HEALTH-FEX project. It is important to note that there is a clear plan provided and agreed between the Team members on how specifically the current and planned research work of Team 5 and prospective research work of the start-up will align with the Unit's overarching goals and direction and what will be specific interactions within the Unit.

Team 6: Genetic epidemiology and functional genomics of multifactorial diseases

Name of the supervisor: Dominique GAUGUIER

THEMES OF THE TEAM

At the beginning of the former contract, the Team was developing statistical tools and mathematical models to characterise genetic, environmental factors and epigenetic marks altering genomic regulations and disease manifestations (asthma and obesity). The Team was reorganised following director's request, and part of the personals went to Team 1.

Since 2020, the research has focused on analyses of the architecture and function of the gut microbiota in health and cardiometabolic diseases. The Team has developed omics approaches in collaboration with international laboratories (Japan, Canada). The Team has a strong physiological expertise and develops software tools for analysis of omics data. They generate metabolomics profiling and metagenomics sequencing data.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The document was not sent to the committee by the Team leader.

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

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

EVALUATION

Overall assessment of the team

Scientific production. The Team has a high international visibility relative to the size of the Team. They published 25 publications, and appear first, last or corresponding author in excellent journals including Cell Reports and Diabetologia. The scientific production is excellent.

Attractiveness. The team has a remarkable capacity to obtain funding, as PI, in two ANR BACTOCRESOLDIAB (248kE) and METABASTHMA, 250kE) and international (INSERM International Research Project Kyoto, 75kE) research grants and a grant with Satt Lutech (391kE).
The level of attractiveness is excellent.

Valorisation. The Team is in process of creating a Start-up (*maturation by SATT-Lutech)* and obtained two patents, one selected by the SATT-Lutech (maturation project). A collaboration with pharma (METABRAIN SA 216kE) was initiated and the lab hosted scientists from that company. Therefore, the valorisation is excellent.

Strengths and possibilities linked to the context

The Team has 25 publications during the period, with original research articles signed as first last or corresponding author, five with PhD students. Some of the articles were published in excellent journals such as Cell Reports and Diabetologia.

The Team has a high international visibility, with several invited lectures (RIKEN Yokohama Campus, Yokohama, Japan, 19–20 February 2018; Interna1onal symposium on disease genomics. Kyoto, Japan, 06 October 2018) and participation to international boards, such as Research Grant Committee of the Academia of Finland in 2019, International Peer Review Committee for the Terry Fox Research Institute, Canada in 2018. Moreover, several periods were performed as a visiting researcher in foreign laboratories. There is an effective recruitment of postdocs and two PhD defences occurred during the period (for 1 HDR).

The team obtained Funding, as PI, by national (2 ANR BACTOCRESOLDIAB (248kE) and METABASTHMA, 250kE)) and international research grants (INSERM International Research Project) and a grant with a pharma company (Total amount 763k€). Two patents illustrate the valorisation activity, together with the creation of a Start-up company (in 2022) which will contribute significantly to the research activity of the Team. For the future, the team chose to join another group and unit with complementary expertises in the field of metabolism and metabolic diseases. This looks like a very good idea.

Weaknesses and risks linked to the context

The size of the Team, with only one permanent researcher, appears as a strong limitation. Also, there is no interaction with the educational system or with the general public.

Analysis of the team's trajectory

The Team will not be reconducted for the next five-year contract of HealthFex. It will join another Team with whom it already collaborates (BFA) to continue the same line of research, on probiotic effects, as well as on proteins mediating cellular function of metabolites.

RECOMMENDATIONS TO THE TEAM

The committee recommends the Team to continue their excellent research activity and projects, and try recruiting new researchers, when joining their new Team BFA.

Team 7: Cell Death in host-pathogen interactions

Name of the supervisor: Jérôme ESTAQUIER

THEMES OF THE TEAM

The work of Team 7 has been dedicated to study the programmed cell death (PCD) and particularly apoptosis, in the context of host – pathogen interactions. The studies have been conducted on HIV/SIV, leishmania and more recently on SARS-Cov-2. The specificity of their research lies in an upstream research aimed at clarifying the biochemical and molecular mechanisms involved in the process of PCD, in particular the contributing role of bioenergetics in reprogramming immune cells, and a downstream research studying these mechanisms *in vivo* by using Non-Human Primates (NHP). These models, highly relevant and unique in Europe for Leishmaniasis, allowed the opportunity to evaluate drug therapeutic approaches and analyse microbe persistence in deep tissues despite treatment in SIV model. Moreover, the Team has taken advantage of its strong experience in monitoring PCD and lymphopenia to investigate these aspects in SARS-Cov-2 infection in human since the beginning of the pandemic and is now leading international consortium on Covid-19.

These activities are highly relevant to public health and INSERM policies. The Team is involved in an International Cure program proposing to define persistent viral reservoirs and new therapeutic and vaccine strategies to improve immunity in patients.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The Team successfully addressed all recommendations made in previous evaluation.

- One postdoctoral fellow has been recruited to the Team during the time period, she co-authored publications on Covid-19.
- The Team produced 34 publications were produced during the period.
- The Leishmania project, considered by previous HCÉRES committee as with limited industrial impact, has led to several publications, integration in European program COST, and strongly funded by European contracts (INFECT-ERA), IDF OneHealth program/ANRS-MIE (equipment fundings, 800,000 euros). These demonstrated the interest of funding agencies for this project and indirectly its potential.
- Communication in general media were recommended: Results on Covid have been presented to general population through general media (press, TV, 40 interviews), and social network (X). The PI has been implied at the level of the Ministry about long Covid, demonstrating the societal impact of the research.
- The PI is member of the CSS5 commission, demonstrating its implication in the academic institution.
- The Team regularly used e-learning and videoconference because of its international nature (Paris and Laval QC).
- The size of the Team in Paris is limited as the whole team is spread between two locations (Paris and Laval QC), nevertheless it is sufficient for excellent publication records (34 publications on the period), and all students published.

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

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

EVALUATION

Overall assessment of the team

Scientific production of the Team in the evaluated period consists in 23 original papers in excellent journals (J Clin Invest, Cell Death Differ, J Allergy Clin Immunol, J Immunol, J Virol, Cell report, Mucosal Immunol, etc.) and eleven reviews or chapters covering the three main topics of the Team. Members of the team are clearly on leading position in thirteen of the published papers and are invited to conferences (N=22) and students to give talks in meetings (N>30). Scientific production is Excellent.

Attractiveness: In the evaluated period, the academic reputation allowed the Team to obtain high level of funding at the national level (ANRS, FRM, ANR-Covid, Sidaction, 800 k€) and at the international level (IRSC, 1500 k€). In addition, the Team received funding for the acquisition of up-to-date single cell analysers, MALDI imager and cell sorter to support studies on the three scientific topics (1800 k€, FCI and DimOneHealth). Additionally, the Teams also obtained funding from the private sector on Covid-19 biomarkers studies (AbbVie, 300 k€), and GSK, ViiV, Merck as drug providers. Concerning the formation through research, the HDRs of the team have been involved in ten PhD theses, 6 as directors and 4 as co-directors. All the students have been associated to an average of 3.2 papers (range 2 to 7) and except two students have at least published one paper as first author.
Despite the small size of the French Team (permanent staff are 1 DR and 1 TR), its national and international visibility is very high: in terms of recognition, the Team leader is INSERM DR1 and occupies a Canada research Chair at Laval University. He is member of CSS5 INSERM, member of Réseau Francophone de la Mort Cellulaire, expert for different agencies (ANR, ANRS, IRSC, Institut McGill, Institut Armand Frappier). Lab members have been promoted during and after their period in the lab (3 postdoctorants recruited as assistant professor, CRCN, and Start up and one technician promoted CE, one DR2 took the direction of INSERM Unit in Tours). Attractiveness is outstanding.

Valorization: The Team produced three patents, and one clinical trial in NHP. Results related to long-Covid-19 had very important public outreach. Valorization is excellent.

Strengths and possibilities linked to the context

The Team leader developed a very strong expertise over more than twenty years in the field of cell death and HIV infection, that has been more recently successfully extended to Sars-Cov2 and Leishmania infection.
Despite the small size of the French Team (permanent staff are 1 DR and 1 TR), its national and international visibility is very high: in terms of recognition, the Team leader is INSERM DR1 and occupies a Canada research Chair at Laval University. He is member of CSS5 INSERM, member of Réseau Francophone de la Mort Cellulaire, expert for different agencies (ANR, ANRS, IRSC, Institut McGill, Institut Armand Frappier). Lab members have been promoted during and after their period in the lab (3 postdoctorants recruited as assistant professor CRCN, and Start up and one technician promoted CE, 1 DR2 took the direction of INSERM Unit in Tours).
The Team developed pre-clinical models very relevant for human diseases that are very rare (VIH) and unique (Leishmania visceral infection). The Team recently obtained major funding to implement MALDI imaging, that will constitute a very strong asset for the Team, and hopefully the entire Unit, to study the impact of exposome on animal physiology. The international nature of the Team between France and Canada and strong collaboration with former postdocs in Portugal are also a strong asset.

Weaknesses and risks linked to the context

Despite an important scientific production, the main weakness is the size of the Team (1 DR and 1 TR). However, the Team trajectory clearly address this issue with the arrival of 4 FTE including two assistant professors. Others weakness are the lack of space to accommodate lab member and several maintenance issues, particularly on the BSL3 facility. A more difficult weakness to address is the difficulty to stabilise human resources in Paris.

Analysis of the team's trajectory

In the HEALTH-FEX project, the Team will be in charge of the biological exposome. The two main aims 1/microbe reservoir establishment and its impact on immune defences and 2/mitochondrial damage and immunometabolism consequences in Host/Pathogen interactions) are clearly in line with the expertise and the production of the Team. With the strong investment policy of the past period, the up-to-date equipments are present in the lab or on close platforms (MALDI imager, sorters), or in the canadian lab. The local and international collaboration network involving bioinformaticians, clinicians will be of particular importance to

identify and validate biomarkers and to obtain new funded projects. The arrival of 4 ETP with expertise in protein structure, cellular pathways and particularly PCD is a clear opportunity. Also, the arrival of assistant professors will be of interest to recruit talented students in the Team.

RECOMMENDATIONS TO THE TEAM

The committee recommends the Team to continue their excellent research activity and projects. The integration of 4 FTEs and the opportunities created by the double location of the laboratory is a clear opportunity to develop their attractiveness and to hire postdocs and permanent researchers (CR and assistant professors). The committee recommends taking advantage of arrival of FTE to increase inter-teams collaborations on immunosuppressive impacts of chemicals. More generally, the committee recommends administrative assistance from the Unit.

The committee recommend to employ a permanent staff member (e.g. engineer) to maintain and run the new technologies platform and to mutualise this resource with all the other Teams of the Unit, thus increasing scientific competitiveness and collaborations of the Units.

Team 8: Addiction pharmacology and therapy

Name of the supervisor: Florence NOBLE

THEMES OF THE TEAM

The Team identifies the molecular pathways involved in substance abuse and comorbid diseases such as depression, anxiety and post-traumatic stress disorder with the aims to understand the crossed vulnerability and to propose new therapeutic strategies. For this goal, the main lines of research seek to determine:

(1) the reasons for therapeutic failures of opioid substitution treatments and propose new therapeutic approaches;
(2) how and why post-traumatic stress disorder leads to a high prevalence of addictive behaviour;
(3) the factors responsible for relapses and particularly stress and depression;
(4) the role of two candidate pathways, namely ghrelin and CRF systems, in the vulnerability to substance abuse and comorbidities.

Their ultimate goal is to define new treatments for psychostimulant addictions. All questions have been addressed with the constant motivation of using multidisciplinary approaches ranging from subcellular measures to integrated animal behaviour.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Regarding the publication standards, the Team 8 managed to increase publication number and quality and for the last period, between one to four articles signed as first, last or corresponding author by a Team member were published per year, in very good to excellent journals of neuropharmacology. The expertise of one Team member in genetics allowed to contribute to outstanding articles in genetics. Team members published rather independently suggesting that the team cohesion and homogeneity can be improved. This could be easily achieved by combining Team member expertise in common projects and joined publications.

Concerning the few numbers of patents produced, efforts have been made to initiate projects of tech transfer and valorisation, notably with the local SATT, during the period. But still unsuccessfully. This recommendation must be reiterated.

In terms of application to calls for projects, international funding, the Team has a moderate global amount of self-generated resources, but it may be insufficient to carry out the projects proposed for the next term. Indeed, these latter are ambitious for both preclinical and clinical research. Several attempts were done during the past period, particularly to attract EU or Canadian funding, but unsuccessfully. More funding must be actively secured that will also rely on publication success.

Concerning the strategic integration of the Team in the Unit, it must be pointed out that only one publication with members of the other Teams has been finalised yet. New projects are proposed in interaction with other Teams that must be incorporated to confirm the Team integration in the Unit. This will be a double challenge, as the Team will be in the reorganisation during the next contract and research themes of the Team members must also be integrated together.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	1
Sous-total personnels non permanents en activité	2
Total personnels	**11**

EVALUATION

Overall assessment of the team

Scientific production. The Team is involved in 43 total publications with seventeen signed as first, last or corresponding author (but 6 by a staff member signing in another laboratory). Articles were published in excellent journals of the neuropsychopharmacology field (Neuropharmacology, Br J Pharmacol, Prog Neuropsychopharmacol, Biol Psychiatr, Int J Neuropsychopharmacol, Neurotrauma, J Neurosci Res...) and contributions to consortium in genetics studies published in outstanding journals (Biol Psychiatr, Brain…). The Team production during the period is very good to excellent.

Attractiveness. The Team has recruited eight PhD students during the period for a total of 6 permanent staff with HDR. A majority of them (5) published at least one article as first author during their PhD. Five teaching researchers (with one still in Bordeaux) joined the Team during the period. Major funding obtained during the period as PI include mainly the ANR BIOSCIENCE. No international postdocs were hired during the period. The Team attractiveness is very good to excellent.

Valorisation. The Team has developed an important activity of valorisation with two pharmaceutical companies (EthyPharm and Pharmaleads). The theme of addiction, being a relevant public health issue, brings the team to undertake numerous outreach actions such as 'Apprentis Chercheurs MAAD' (MILDECA-INSERM action), or press interviews. The Team valorisation is very good to excellent.

Strengths and possibilities linked to the context

The team is composed of two CNRS researchers (FN, NM), one INSERM researcher (JP), 4 MCU (LC, AC, BB V, RM) and two PAR (1 tech INSERM, and 1 AI CNRS). AC is located in Bordeaux University and no mention for his move to Paris was provided.

The Team contributed actively in understanding the molecular pathways and pharmacological targets involved in substance abuse and their interactions with comorbid diseases such as depression, anxiety, eating disorders or post-traumatic stress disorder. Both preclinical and clinical studies were conducted with excellent expertises in behavioural pharmacology or genetic studies.

The Team has published 43 scientific articles during the period corresponding to seventeen (40%) original research articles signed as first, last or corresponding author, five review articles and 21 co-authorships. The articles were published in very good or excellent journals of neuropsychopharmacology (Neuropharmacology, Br J Pharmacol, Prog Neuropsychopharmacol Biol Psychiatr, Int J Neuropsychopharmacol, Neurotrauma, J Neurosci Res...). Contributions in large collaborative genetic studies allowed a Team member to co-signed as collaborators (Nat Genet, Biol Psychiatr, Brain…).

The Team has a visibility at the national level, with invitations to national colloquia (such as organized by the Société Française de Nanomédecine, Société Cerveau et Maladies Cérébrovasculaires, or Société Francophone de Tabacologie). The team has international visibility as well with participation to international conferences (Drug Discovery and Therapy World Congress) and the organisation of an international symposia (European College of Neuropsychopharmacology). The Team obtained two ANR (1 as PI by the member in Bordeaux, and 1 Partner) + partner in one ANR for PhD and engineer, one IDEX (projet émergence), and one FHU. The Team has had three foreign PhD students and one French postdoc.
A good support is offered to research-support staff, both in terms of promotion and recognition such as co-authorship in publications; three Team members got promoted during the period (1 PAR, 1 MCU, 1 DR CNRS).

Several Team members have excellent implications in research management with implication in national society and university panels, including juries for MCU/PU selection, in national committees such as CoNRS section or CNRS direction, or ITMO. The Team members have teaching duties, being in charge of responsibilities in Master courses, PhD training, Master student training.
Of note, eight PhD and one HDR were defended during the period. Six Team members have therefore the HDR (which give a ratio of 1.3 PhD/HDR). The PhD students were recipient of several prizes and awards. There were 9 PDC publications (1.1/PhD).

The Team reports regular team's meetings (every 2 weeks) with all the members of the Team (permanent, non-permanent, IT, students), which represents an excellent opportunity to discuss results, perspectives and practical strategies with all the Team members.

The Team is involved in interaction with pharmaceutical partners (Ethypharm, Pharmaleads, InnoPain) and in the dialog with La Fondation des Gueules Cassées, the Start-up Nanosep Therapeutics. The Team largely contributes to scientific outreach (Apprentis chercheurs MAAD, Université Ouverte) and participates to several media communications (Express, Ouest France, Mag de la science, Libération, Science et Avenir).

Weaknesses and risks linked to the context

The Team will continue to evolve for the next contract and an effort must be put on internal collaborations. Individual expertise is valued in the different research themes, however, there is not enough collective projects based on strong and complementary axes of research within the Team itself. Team members still publish separately with very few contributions gathering all Team members. A teaching researcher is still in the process to finalise his arrival from Bordeaux. The Team dynamics need to be strengthened.

The Team applied but did not succeed in getting international research contract or EU grants. Considering its human, technological and financial means, the Team might have too many distinct research axes around drugs of abuse and comorbid pathologies. The research conducted is rather ambitious, and may lead to difficulties with both human resources (few PARs, the team does not present the time-share within the Team). Moreover, the multisite organisation might be an additional issue in the dynamic of the Team.

Only one publication with other teams were reported, probably due to the specific research theme of the Team.

Analysis of the team's trajectory

The Team scientific project for the HEALTH-FEX Unit is in the direct continuation of the present projects with ambitious new axes:

(1) the investigation of long-term pathophysiological consequences of drug exposures and relapses, particularly through the prism of comorbidities with high prevalence;
(2) the development of epigenetic and transcriptomic analyses to identify new pathways and biomarker;
(3) to explore the roles of two candidate signalling, corticotropin-releasing factor, through CRF1 and CRF2 signalling, and ghrelin, through GHSR signalling.

A new recruitment scheme has been in place for the past three years: 'Junior Professorships'. This year, the Team applied to the 'Institut Thématique Santé Publique INSERM', and a chair was favourably selected on the theme: Risk reduction strategy for chronic opioid use. Candidates competition will open in 2024.

The Team will have access to pertinent animal models of addiction, PTSD, or transgenic lines, as well as molecular tools to perform high-class neuropharmacology and genetic studies. The Team will concentrate efforts on both cocaine and opiate drugs of abuse (heroin but new opioid drugs too). Additionally, molecular biology and bioinformatics analyses in collaboration with other Teams of the Unit are planned to enhance originality. Mechanistic approaches will dig into the role of CRF and ghrelin systems.

RECOMMENDATIONS TO THE TEAM

The Team dynamics would benefit from a prioritisation of its research projects to avoid dispersion, reinforce originality by specifying the focus of projects, maintain/increase productivity and funding levels. In addition, they should further develop international collaborative activities on their main research axes in order to enhance the Team's international visibility and improve attractiveness to foreign students and postdocs.

The Team would gain from a focus on projects that bring together the various expertise of the Team members and the optimisation of technical support. In particular, hiring a permanent research support staff to oversee long-term experiments, instead of relying on PhD students to avoid losing the expertise, would be beneficial.

CONDUCT OF THE INTERVIEWS

Dates

Start: 20 décembre 2023 à 9 h

End: 21 décembre 2023 à 16 h

Interview conducted: on-site

INTERVIEW SCHEDULE

Day 1. 20 December Morning: Room R229 (2nd floor)

8:45 a.m. – 9:05 a.m. Arrival/Welcome Coffee and pastries

9:05 a.m. – 9:15 a.m. Introduction of the Committee to the Unit

9:15 a.m. – 10 a.m. Unit overview by the head of the lab:
Past: Robert Barouki 12 minutes
Trajectory: Xavier Coumoul 12 minutes
Discussion: 15 minutes

10 a.m. – 10:15 a.m. Closed-door meeting of the committee

Team Leader Presentations:

10:15 a.m. – 11:25 a.m. Team 1 – Xavier Coumoul (past)

F. Team 1 – Etienne Blanc/Emmanuelle Bouzigon (traj.)

F. Team 2 – Karine Audouze (trajectory)

Discussion

Team 5 – Evelyne Segal (past, trajectory, disc.)

11:25 a.m. – 12 p.m. Closed doors: Break/Coffee and pastries

12 p.m. – 12:30 p.m. Team 6 – On Visio Zoom-Dominique Gauguier (past, trajectory, disc.)

12:30 p.m. – 1 p.m. Team 7 – Jérôme Estaquier (past, trajectory, disc.)

1:15 p.m. – 2 p.m. Closed doors lunch

2 p.m. – 3 p.m. Debrief of the morning sessions

Day 1. 20 December Afternoon: Room R229 (2nd floor)

Team Leader Presentations

3 p.m. – 3:30 p.m. Team 2 – Benoit Schneider (past, trajectory, disc.)

3:30 p.m. – 4 p.m. Team 8 – Florence Noble (past, trajectory, disc.)

4 p.m. – 4:15 p.m. Break/Coffee and pastries

4:15 p.m. – 4:45 p.m. Team 3 – Charbel Massaad (past, trajectory, disc.)

4:45 p.m. – 5:15 p.m. Team 4 – Frédéric Charbonnier (past, trajectory, disc)

5:15 p.m. – 7 p.m. Closed-door meeting of the committee

7:30 p.m. Closed doors DINER

Day 2. 21 December Morning: : Room Leduc (Ground floor)

8:30 a.m. – 9 a.m. Arrival of the experts/Coffee and pastries/Installation

9 a.m. – 9:30 a.m. Closed doors meeting with BIATSS/ITAs (Engineers, technicians, administrative staff)

9:30 a.m. – 10 a.m. Closed doors meeting with young researchers (PhD students and postdocs)

10 a.m. – 10:30 a.m. Closed doors meeting with researchers without team leaders

10:30 a.m. – 11 a.m. Meeting with institution representatives

Inserm:
* IT Santé Publique Arnaud de Guerra :
* Déléguée régionale Sabrina Sahnoun
:
Université Paris Cité (Faculté des Sciences) :
* Vice-doyenne recherche, Nathalie Eisenbaum :

CNRS
* Directeur Adjoint Scientifique Neuroscience, Bernard Poulain

11 a.m. – 12:30 p.m. Debrief of the morning sessions, preparation of the Q to the head of the lab

12:30 p.m. – 1:45 p.m. Closed doors lunch

1:45 p.m. – 2:30 p.m. Meeting with the present and future head + deputies

2:30 p.m. – 6:30 p.m. Closed-door meeting of the committee

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 4 mars 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024248 – T3S – Toxicité environnementale, cibles thérapeutiques, signalisation cellulaire**

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **T3S – Toxicité environnementale, cibles thérapeutiques, signalisation cellulaire.**

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

Adresse
85 boulevard St-Germain
75006 - Paris

www.u-paris.fr

Ce rapport a été lu avec attention par la direction de l'unité qui signale des erreurs à corriger (cf document joint), la vice-doyenne Recherche et le doyen de la Faculté des Sciences d'UPCité (cf courrier joint), par la vice-présidente Recherche d'UPCité et par moi-même.

J'adresse mes remerciements au comité HCERES pour la qualité du rapport d'évaluation et vous indique ne pas avoir d'observations de portée générale à apporter.

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

Édouard Kaminski

Sciences
Université Paris Cité

Référence
MC/NE/EB/2024-014

Faculté des Sciences
Université Paris Cité
5 rue Thomas Mann
75013 Paris

Objet : DER-PUR250024248 - Évaluation HCERES de l'UMR-S 1124 T3S – Retour Tutelle Université Paris Cité

Chères et Chers Collègues,

Nous souhaitons par ce courrier remercier les membres du comité de visite pour le temps qu'ils ont consacré à l'évaluation du T3S, ainsi que pour leur écoute et le travail considérable qu'ils ont accompli.

La Faculté des Sciences est fière de compter le T3S parmi ses unités de recherche et rappelle la grande qualité de la recherche menée par tous les membres du laboratoire.

Après lecture du rapport provisoire d'évaluation de l'UMR-S 1124 T3S, la Faculté des Sciences ne souhaite ajouter ni remarques générales, ni remarques factuelles.

En vous priant, chères et chers collègues, d'accepter nos chaleureuses salutations.

Maximilien CAZAYOUS
Doyen
Faculté des Sciences
Université Paris Cité

Nathalie EISENBAUM
Vice-Doyenne recherche Faculté des Sciences
Université Paris Cité

Université Paris Cité

Environmental Toxicity
Therapeutic Targets
Cellular Signaling
& Biomarkers

Inserm
La science pour la santé
From science to health

Observations générales sur le rapport d'évaluation

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We really appreciated the quality of the committee's work, both upstream and downstream of the visit; the unit particularly appreciated the interactions with committee members, with a large part of the discussions devoted to scientific issues. In the report, we particularly appreciated the "SWOT work" which has been delivered: we will use it to correct certain weaknesses in the unit that we can act on now (e.g.: scientific animation), but also to call on our institutions to improve the life of the unit (e.g.: lack of administrative staff).

For the unit, we would like to make the following comments:

- "The attractiveness for international researchers at the start of their careers (e.g. postdocs, junior researchers) should be improved". One of the difficulties we face on this specific topic, is the incompatibility between salaries and life in the Paris area, and the very strong tendency of PhD students to opt for the private sector (with salaries at least 2x higher than those of young CRs or MCUs, again in a region where the cost of living is particularly high). Note that in certain fields of the unit such as toxicology and bioinformatics, the private sector is very active and attracts many young researchers, which is good for their careers. The committee also pointed out that doctoral graduates find jobs one year after their thesis is defended, mainly thanks to the unit's national and international networks (p12). A more aggressive policy will be undertaken within the unit to increase its visibility and thus attract new foreign talents, thanks to 1) the "Animation scientifique, communication et médiation scientifique" and "Cellule Internationale" thematic groups. The expertise of several members of the Inserm CSS unit will be used to introduce interested candidates to the competition.

- "There is no apparent strategy to improve international attractiveness for all teams." We do not completely agree with this statement; indeed, our unit is well known at the international level. The current director received the "étoile de l'Europe" prize from the ministry of research for our involvement in EU programmes. The creation of a national and international (Europe and others) "Calls for projects" thematic group will be a strategy for the future unit on this point. As early as 2023, the future director has begun to include 4 teams of the future mandate in the setting up of an EU project (Dominoes project). This strategy will be extended to all teams, and the management team will encourage coordination of EU projects by members of the unit.

- "Specific co-projects need to be developed between teams", and this has already been undertaken within the current unit with the BOOSTER Inserm Exposome program, which includes 3 teams from the future unit.

- Hiring competent, full-time staff to support the heavy load of administrative and logistical tasks (currently carried out by other staff members) is an issue (p8, 10, 11). Encroaching on the unit's budget to recruit someone would put a considerable strain on all the other activities we aim to implement (the recurrent budget has decreased this year despite the inflation rate). We are firmly convinced that this dramatic situation for both administrative and scientific staff (transfer of workload) must be addressed first and foremost with the governing bodies (University, Inserm), and we will be sure to stress this issue to them repeatedly.

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- “The protection/management of data and scientific assets should be improved.” As the committee points out, the unit is in the process of establishing strategies to improve this (IT security training for staff from 2024, interaction with digital vice-president Thomas Patzak). Until now our strategy has been to dissociate the different data repositories. But a more structured approach will be taken shortly.

- “The member of the unit involved in the ethics and integrity strategy is due to retire, and the unit needs to find a new candidate to follow up this activity”. The unit's current director organized 3 webinars on this theme last year (all of them international), and is particularly committed to it, as demonstrated by the creation of a dedicated thematic group.

- “The fact that the dissemination of knowledge to the public is taken into account in the evaluation of researchers and professors is insufficiently considered.” Although this could demobilize the unit, we have for many years continued to perform this function of "science for and with society". A large number of unit members have already volunteered to join the "scientific animation" thematic group, which is proof that this remains a major challenge for the unit's staff. In fact, we believe this is one of our important assets.

- “We need to increase in-house scientific activities”: following the COVID19 crisis, we have given priority to organizing scientific workshops and summer schools (3-4 per year). Furthermore, we have contributed to animation at the center level (in neuroscience or dedicated to students). In addition to this activity, which will continue (Exposome summer school with UPEC in 2024), we will reorganize seminars from 2025 onwards.

- “There is currently no clearly defined policy and/or committee for equality, diversity and inclusion”. A thematic group is also being set up in this area.

We thank the committee for noting:

- That there is currently no permanent technical staff dedicated to the MS/MS MALDI metabolomics imaging platform (team 7), which as you have pointed out, has the potential to bring great added value to the unit's research and to units in the region (p7, 13).

- That the unit clearly needs additional competent full-time administrative staff (see also above) and trainees. The current INSERM administrative position is not filled, and the workload is currently shared between other staff members. This situation needs to be resolved to improve the working environment for all members. Actions will be taken with Inserm and the university.

- the new theme ("Functional Exposomics") will strengthen collaborations within the unit with a positive trajectory.

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For team 1,

We really appreciated the comments made by the committee. As weakness it mainly points the fact that

- regarding the recommendation: “Altogether, the committee strongly encourages the Team to try to further support the emergence of new interactions between Teams in the exposome field”, we will continue to develop inter-teams projects: as an example, team 1, the future team 2 and team 3 will be part of the INSERM booster project on Exposome (2024-2027). Interaction with the Systox team spin-off (future team 2) will of course keep going, given the tight relationships the members of those teams already have.

- regarding the recommendation: “Altogether, the committee strongly encourages the Team …. to apply for fundings that will allow recruiting postdoctoral scientists”. The team are partly composed of engineers and technical staff with non-permanent position; the team does not hire post-doctoral scientists. The two points are somehow linked. To get grants with human resources and related functioning budget, we often choose to ask for technicians/engineers instead of post-doctoral position. We will pay attention to ask for postdoctoral fellowship, which could, as mentioned, which could allow us to welcome future candidates to postulate as INSERM researcher or Ass. Prof. We are also in contact with the university administration to open soon an engineer position in our team. It is also important to note that one of the difficulties we face on this specific topic, is the incompatibility between salaries and life in the Paris area, and the very strong tendency of PhD students to opt for the private sector (with salaries at least 2x higher than those of young CRs or MCUs, again in a region where the cost of living is particularly high). Note that in the fields of toxicology and bioinformatics, the private sector is very active and attracts many young researchers, which is good for their careers. The expertise of several members of team (regarding CSS Inserm) will be used to introduce interested candidates to the competition.

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For team 8:

- Regarding valorization, we are currently in the 2nd round of a prematurity project, which could lead to the proof-of-concept of an easy-to-use diagnostic test to assess the activity of the ghrelin system. As for the team's own resources, we have obtained €1,020,000 over the last 5 years. We will continue to build on this momentum. Additionally, we have already attempted to secure international funding, but without success, despite having several collaborators abroad. We are expanding our network of foreign collaborators with the arrival of Eleni Tzavara and the recruitment of a CPJ with extensive experience abroad.

- Regarding our integration into the unit, we have one publication in collaboration with Team 5. However, interactions cannot solely be measured by publications. We have contributed our expertise in animal behavior to three of the unit's teams, without being listed as co-authors. On the other hand, we currently have an article in BioXriv for which we are completing functionality experiments and preparing for resubmission to Nature Neuroscience. This article is co-authored by former members of the unit. Additionally, we have collaborative projects with the bioinformatics team (from Team 1) and with Team 3 on neuroinflammation. These projects are expected to result in publications in the coming years.

- Regarding the dispersion of the team's projects and interactions between different members: We have recently secured funding from Idex UPcité, which involves 5 researchers and teaching-researchers from the team. Additionally, we have an FRC project under evaluation, which also includes 5 researchers and teaching-researchers from the team along with a teaching-researcher from Team 3. Furthermore, we are in the process of submitting an ASTRID application involving 6 researchers and teaching-researchers from the team.

- Regarding the comment about the team possibly having too many distinct research axes focused on drugs of abuse and comorbid pathologies, and dispersion: In our various projects, we have identified clear links. We use the same behavioral protocols, with only 3 different protocols utilized by the entire team. Additionally, we employ identical OMICS approaches and analyses, and we are actively searching for common biomarkers between isolated pathologies and comorbidities. Across all our projects, we maintain an integrated approach, spanning from behavior to molecular regulation. However, the pattern remains consistent, allowing us to optimize our strengths.

On behalf of T3S members and team leaders, " We would like to thank the committee for its overall very positive assessment, its constructive comments and advices"

Pr Robert Barouki — Pr. Xavier Coumoul
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