Research evaluation

# EVALUATION REPORT OF THE UNIT

BSC - Biotechnologie et signalisation cellulaire

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

Université de Strasbourg - Unistra

Centre national de la recherche scientifique - CNRS

**EVALUATION CAMPAIGN 2022-2023**

GROUP C

Rapport publié le 13/04/2023

In the name of the expert committee[1] :

Juliette Azimzadeh, Chairwoman of the committee

For the Hcéres[2] :

Thierry Coulhon, President

Under the decree n° 2021-1536 of 29th November 2021:
[1] The evaluation reports "are signed by the chairperson of the expert committee". (Article 11, paragraph 2);
[2] The president of the Hcéres "countersigns the evaluation reports established by the expert committee and signed by their chairperson." (Article 8, paragraph 5).

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

## MEMBERS OF THE EXPERT COMMITTEE

| | |
|---|---|
| **Chairperson:** | Ms Juliette Azimzadeh Centre national de la recherche scientifique — CNRS, Paris |
| **Experts :** | Ms Susan Chan, Inserm, Illkirch<br>Ms Catherine Etchebest, université Paris Cité (representative of CNU)<br>Ms Isabelle Landrieu, CNRS, Villeneuve d'Ascq<br>Ms Laurence Molina, CNRS, Montpellier (representative of supporting personnel)<br>Mr David Pignol, CEA (representative of CoNRS)<br>Mr Lucas Jacques Waltzer , CNRS, Clermont-Ferrant<br>Mr Nicolas Vodovar, Inserm (representative of CSS) |

## HCÉRES REPRESENTATIVE

Ms Marie José Stasia

# CHARACTERISATION OF THE UNIT

- Name: Biotechnologie et Signalisation Cellulaire : Intégrité du génome, biologie tumorale, récepteurs, outils thérapeutiques
- Acronym: BSC
- Label and number: UMR 7242
- Number of teams: 10
- Composition of the executive team: Mr Jean-Luc Galzi

## SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE3 Molécules du vivant, biologie intégrative (des gènes et génomes aux systèmes), biologie cellulaire et du développement pour la science animale

## THEMES OF THE UNIT

The UMR 7542/Biotechnology and Cellular Signaling depends on the University of Strasbourg and the CNRS (INSB). The work of the unit is organised around three scientific themes (genome integrity and cancer, pathogens and infection, pain and inflammation) and three technological domains (chemobiology, functional genomics, synthetic biology and organoids).
The unit is currently composed of ten teams, eight of which will seek renewal in the next term.
—Team 1 'Poly (ADP-ribosyl) ation and genome integrity', directed by Françoise Dantzer, studies the role of PARP family proteins in the maintenance of genome integrity and the impact of their inactivation on tumour progression.
—Team 2 'Nuclear signalling and cancer', led by Katia Zanier, studies the protein-protein interactions that regulate the p. 53 and NF-kB tumour suppressor pathways using proteomic and structural approaches.
—Team 3 'Replisome dynamics and cancer', led by Bruno Chatton, studies different aspects of the DNA damage response (DDR). This team will not be renewed in the next term.
—Team 4 'Chemobiological intervention', led by Guy Zuber and Etienne Weiss, develops antibody-based technologies, aiming in particular at their intracellular delivery. This team will not be renewed.
—Team 5 'Epigenetic regulation of cell identity', led by Michaël Weber, studies the role of DNA methylation in mammalian development and in tumour progression.
—Team 6 'GPCRs, pain and inflammation', directed by Frédéric Simonin, is interested in the role of G protein coupled receptors (GPCRs), in particular opioid receptors, in pain and inflammation.
—Team 7 'Metals and microorganisms: biology, chemistry and applications', led by Isabelle Schalk and Gaëtan Mislin, studies iron homeostasis in bacteria as well as applications such as the vectorisation of therapeutic molecules by siderophores and bioremediation.
—Team 8 'Neuroimmunology and peptide therapy', led by Sylviane Muller, studies immune reactions and their dysregulation during autoimmune diseases such as lupus, and the development of adapted therapeutic pathways.
—Team 9 'Biosystems chemistry', directed by Vladimir Torbeev, studies intrinsically disordered proteins, protein misfolding and aggregation, and develops methods for protein design.
—Team 10 'Therapeutic peptides', led by Dominique Bagnard, works on the development of transmembrane therapeutic peptides for the treatment of cancer or nervous system diseases.

## HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The unit results from the fusion of three pre-existing units (two UPR and one UMR) in 2004, which became effective in 2009. All the teams, except one, are located within the building of the Strasbourg Graduate School of Biotechnology (ESBS) on the Illkirch campus. The team 8 is located in the USIAS building (University of Strasbourg Institute for Advanced Study) on the Strasbourg campus. The ESBS building itself is part of the Pôle API site together with the Télécom Physique Strasbourg School and the Computer Science Department of the University of Strasbourg.

## RESEARCH ENVIRONMENT OF THE UNIT

The BSC unit is located close to the Faculty of Pharmacy of the University of Strasbourg, and to the IGBMC (Institute of Genetics, Molecular and Cellular Biology), institutes with which it collaborates extensively.
The unit also works very closely with the ESBS, which hosts the unit on its premises. This integration has been achieved by reorienting the unit's research themes towards chemistry-biology interface, focusing on the use of small molecules for the study of life and in therapeutic approaches. The ESBS faculty joined the unit at the time of its creation, and the ESBS has developed a curriculum (ChemBioTech) in line with the unit's research themes.

The BSC unit is part of the IDEX Unistra, and members of the unit are founding members of two ITIs (Instituts thématiques interdisciplinaires) in the field of medicine. ITI IMS (Institut du Médicament de Strasbourg ; 2021-2029), which involves teams 1, 6, 8, and 10, is dedicated to the discovery and development of bioactive molecules. ITI InnoVec (2021–2024), which involves teams 2, 3, 4, 5, and 7, aims at the development of vectorisation methods. The unit also participates in the ITI SysChem (Chemistry of complex systems; team 9). In addition, the unit participates in the EUR Euridol focused on the study of pain (team 6).
BSC is also involved in the creation and coordination of the network GIS (Groupement d'intérêt scientifique) ChemBioFrance (created in 2018 and renewed in 2021).

## UNIT WORKFORCE: in physical persons at 31/12/2021

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 6 |
| Lecturer and associate lecturer | 7 |
| Senior scientist (Directeur de recherche, DR) and associate | 8 |
| Scientist (Chargé de recherche, CR) and associate | 12 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 22 |
| **Subtotal permanent personnel in active employment** | 55 |
| Non-permanent teacher-researchers, researchers and associates | 5 |
| Non-permanent research supporting personnel (PAR) | 12 |
| Post-docs | 3 |
| PhD Students | 35 |
| **Subtotal non-permanent personnel** | 55 |
| **Total** | 110 |

## DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: NON-TUTORSHIP EMPLOYERS ARE GROUPED UNDER THE HEADING 'OTHERS'.

| **Employer** | **EC** | **C** | **PAR** |
|---|---|---|---|
| CNRS | 0 | 17 | 18 |
| Université de Strasbourg | 13 | 0 | 4 |
| Inserm | 0 | 3 | 0 |
| **Total** | 13 | 20 | 22 |

## UNIT BUDGET

| | |
|---|---|
| Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years) | 339.0 |
| Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.) | 1470.0 |
| Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.) | 1752.0 |
| Own resources obtained from international call for projects (total over 6 years of sums obtained) | 0.0 |
| Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.) | 523.0 |
| **Total in euros (k €)** | 4084.0 |

# GLOBAL ASSESSMENT

The unit has developed a very good scientific policy, with a common theme 'from genes to drugs' to which all the teams contribute actively. Most of the teams conduct both basic and translational research. The Unit belongs to two ITIs (interdisciplinary thematic institutes) in the field of medicine: IMS (Institut du médicament de Strasbourg) and Innovec (Innovation and vectorisation). Despite an important effort to harmonise the research topics within the unit, there is still a significant diversity in themes, which likely results in part from the fact that BSC is the result of the merger of three units. This clearly affects the visibility of the unit and complicates the scientific interactions between its members.
The functioning of the unit is excellent. All the personnel (technical and administrative staff, students and postdocs, and staff scientists) have expressed their satisfaction with the working conditions, whether from the point of view of interpersonal relations, material conditions, or support in career progression and training. However, it must be pointed out that career progression is very limited for university staff, but for reasons that are beyond the control of the members of the unit and its management.
The unit has demonstrated an excellent capacity to mobilise its own financial resources during the period under consideration, up to about 90% of its total budget, salaries not included, which represents about 3.75 million euros over the period under review. These resources came mainly from national (35%) and regional (31%) competitive calls. The partnerships with industry also contribute of the unit's budget with up to 5%. The unit has also demonstrated a remarkable capacity to seize the opportunities offered by the PIA programs. IMS and InnoVec are both directed by BSC members. IMS succeeded to the Labex Medalis, which has also been extremely beneficial to the unit in terms of financial support and scientific outreach. The capacity to obtain funding via competitive calls is excellent. During this term, 36 national funding were obtained (ANR/INCA/plan Cancer), of which twenty are coordinated by members of the unit. The majority of the teams (8/10) have benefited from this type of funding. In addition, 24 projects were funded by the PIA programs, with the Labex Medalis providing> 1,300 k€ of funding to the teams involved, and the ITIs IMS and InnoVec which are now taking over. An additional 49 projects were funded by charities. This high level of success in the various calls have allowed a significant investment in terms of human resources, with 21 PhD grants (out of the 66 carried out during the evaluated period), twelve postdoctoral contracts and 26 ITA contracts funded this way. Thus, the attractiveness of the unit is excellent, as illustrated by the arrival of two new teams, including an ERC award-winning team, and eleven new researchers in the unit during the period under review. The recruitment in 2021 of these two new teams also reinforces the scientific strategy. Despite the intermediate size of the unit, the success in the creation of the two ITIs, is also a strong sign of its scientific recognition. . BSC has taken advantage of the environment offered by the Illkirch campus (access to a panel of cutting-edge platforms) and has in turn contributed to the creation of the UAR 3286 (Plateforme de chimie biologique intégrative de Strasbourg, PCBIS facility), to which it has transferred some of its competences and with which it maintains close links. This platform hosts and gives access to a copy of the national chemical library, in full adequacy with the theme 'from genes to drugs' developed by the BSC unit.
However, the current absence of a scientific advisory board deprives BSC of an important tool to help define its scientific policy specifically to access more European grants and to prepare its future mandates. In addition, the unit currently has a common limited budget to implement its scientific policy. In the future this point could be addressed by pooling some of the financial resources of each team.

Overall, the scientific production is very good to excellent, with 196 articles published in peer-reviewed journals and the majority of teams published one or more papers in top journals and some of them in prestigious journals (Nature, Nature Comm, Nature reviews in drug discovery, Journal of the American Chemical Society…). These publications concern both basic and translational studies, reflecting the research topics of the unit. However,

the number of inter-team publications remains limited, which suggests that there are not enough internal collaborations. There is also a certain level of disparity between teams in terms of visibility of the publications, but this can be explained in part by the specificities of the different disciplines. Doctoral students and postdocs sign publications as the first author, and staff scientists within teams publish as last or corresponding author. Technical staff are properly included as authors in publications.
The emergence of innovative themes has been favoured at the unit level by the creation of teams 2 and 4 in 2018, and the arrival of teams 9 and 10 in 2021. Thus, the present dynamics will likely lead to a further increase in the proportion of publications in leading journals in the coming years.

Finally, the interaction of the unit with the non-academic world is excellent. The Unit has interactions with industry (Roche Pharmaceuticals, Biosynex, Servier, Novalix…) and developed academia/industry partnerships (Somez, SATT Conectus). The unit is also involved in the development of molecules marketed for research (Enzo life sciences, Roche, Euromedex…) and of therapeutic molecules (Domain Therapeutics, Green Pharma, Biomérieux…). It also offers consulting services (Astra Zeneca, ImmuPharma, Servier…), and participates in the creation of start-up companies (Pregnomics, Adaptherapy).
During the period under review, fifteen industrial contracts and four industrial partnerships have been established, fifteen patents have been filed, of which five were associated with a license, and two start-ups have been created. The members of the unit are also involved in different communication actions with the general public (Pint of Science, Fête de la science, MT180, village des sciences…). There are few interactions with clinical research, which is surprising when considering the heavy focus on drug discovery and vectorisation.

# DETAILED EVALUATION OF THE UNIT

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

*Scientific quality:*
The previous committee advised that the unit adopts a more focused research program to further improve its scientific quality and visibility. This recommendation has been taken into account by orienting the research work developed within the teams towards a common theme, 'From genes to drugs'. Furthermore, nine out of ten teams are now part of ITI IMS or ITI InnoVec, both of which are dedicated to drug discovery.
The unit was also encouraged to attract more international students and postdocs, to participate to more international meetings, and to apply to more competitive international funding to increase its scientific reputation. Overall, these recommendations were followed. Fourteen international students (out of 39) and ten international postdocs or technical staff (out of 52) have been trained within the unit in 2016–2021. The unit welcomed in 2021 the Team 8 who obtained an ERC starting grant in 2017. A researcher recruited in 2021 in Team 7 is currently applying to an ERC starting grant. Members of the unit are part of international networks (European Chemical Library, IMI New Drugs for Bad Bugs, SWAFS Hybrida, Transautophagy European network, Ecos-Sud Argentine). Members of the unit have presented their results in more than 50 international conferences during the considered period of time.

*Social and economic interactions:*
As advised by the expert committee, the unit has maintained strong collaborative links with the other units on the Illkirch campus, in particular the IGBMC and the Faculty of Pharmacy.
The expert committee also recommended to develop a unified training framework for early-career researchers to improve links between them and help in their employability. This has been addressed by the organisation of a different series of seminars more specifically aimed for postdoctoral fellows (Work in Progress seminars twice a year, Illkirch campus day once a year, internal or invited seminars).

*Involvement in training:*
The committee suggested maintaining contact with former postdocs and PhD students to evaluate training success and offer networking opportunities to the current young researchers. This has led to the organisation of a meeting with former students and postdocs, an initiative that is to be repeated at a frequency of one per five-year mandate.
Full-time researchers were also encouraged to increase their participation to teaching, both on campus and outside of the campus. Overall this has been taken into account, as about half of the full-time researchers (10/18) were involved in teaching during the evaluation period, mainly in the context of PIA programs (ITIs IMS, InnoVec and CSC; EUR Euridol).

*Strategy:*
The previous committee recommended a more focused overall research program, which was achieved by defining the common theme 'From Genes to Drugs' and by involving most teams in ITIs IMS and InnoVec. The unit was also advised to recruit a young researcher to continue the research themes carried out within Team 8, which has not happened. Finally, it was suggested to stabilise bioinformatics within the unit by assigning permanent staff members and developing stronger links with bioinformatics expertise present on the campus. This has been addressed since a bioinformatics engineer was hired on a permanent position (IE CNRS) in 2019.

## B – EVALUATION AREAS

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

#### Assessment on the unit's resources

The unit has demonstrated an excellent capacity to mobilise resources, since about 90% of its budget comes from funding through European, national, or regional calls and partnerships with industry. As evidence of its strong commitment in seeking additional funding, the unit has contributed to the creation of two ITIs. The unit has also taken advantage of the environment offered by the Illkirch campus by actively participating in the effort of mutualising platforms with neighbouring institutes. BSC has in particular played a driving role in the creation of the UAR 3286 with which it continues to interact closely.

## Assessment on the scientific objectives of the unit

The scientific policy of the institute is very good. The unit has defined a common theme, 'from genes to drugs', to which the different teams have committed. This is reflected in the fact that most teams are now involved in both basic and translational research, and in the foundation of the IMS and InnoVec ITIs to support this research. This strategy has also been consolidated by the recruitment of two new teams in the unit. However, the unit did not appear to implement strong proactive actions to develop its scientific policy, for instance by increasing team resources mutualisation.

## Assessment on the functioning of the unit

The functioning of the unit is excellent. All the personnel have expressed a high degree of satisfaction with their working conditions and with the support they receive for their career progression and training. However, it should be highlighted that these efforts in terms of career progression do not pay off as far as the university personnel (Biatss) are concerned, for reasons that are independent of the unit's staff and direction, but rather depend on how this issue is managed by the university.

### *1/ The unit has resources that are suited to its activity profile and research environment.*

#### Strengths and possibilities linked to the context

The unit has demonstrated an excellent capacity to mobilise its own financial resources during the period under consideration, up to about 90% of its total budget, salaries not included. These resources result mainly from national (35%) and regional (31%) calls, and also include industrial partnerships (5%).
The members of the unit have been remarkably proactive in exploiting the opportunities provided by the PIA programs within the Idex Unistra. All the teams of the unit participate in an ITI, two of which (InnoVec and IMS) were founded by and are directed by members of the unit. This has allowed not only to generate important financial resources but also to reinforce the links with teams present on other sites.
The unit has also actively taken advantage of its environment by investing in a mutualisation effort with neighbouring institutes. Many services essential to the unit's activities (sequencing, cell sorting, confocal imaging, structure resolution, high field NMR, proteomics, molecular imaging and analytical chemistry) are provided by the IGBMC or at the Faculty of Pharmacy. Conversely, the unit has largely contributed to the setting up of the UAR 3286 (PCBIS facility), to which it has transferred some of its competences and with which it maintains close links. This platform hosts and gives access to a copy of the national chemical library, in full adequacy with the theme 'from genes to drugs' developed by the BSC unit.
The unit has been able to mobilise its resources to support the installation of new researchers (11 in total) through the development of infrastructure adapted to their activities. This includes for instance the recent installation of a large L2 laboratory dedicated to microbiology. The unit has been able to maintain, and in some cases extend and upgrade, its premises by devoting 10% of its annual budget to this purpose.

#### Weaknesses and risks linked to the context

While the unit's budget is excellent overall, the resources available to management, such as those that could be generated by systematic sharing of financial resources by teams, are limited. This reduces the flexibility of the unit's management to deal with emergency situations related to equipment failures or for funding new infrastructure.

### *2/ The unit has set itself scientific objectives, including the forward-looking aspect of its policy.*

#### Strengths and possibilities linked to the context

BSC has defined a clear scientific strategy by focusing on the common theme 'From genes to drugs'. This has been implemented in part by reinforcing the chemistry-biology interface, for which the unit has remarkable expertise. The research topics have been restricted to three main axes (genome integrity and cancer,

pathogens and infection, pain and inflammation), developing a continuum between fundamental research and translational research to address pathologies that constitute major public health problems. To illustrate the extent to which this strategy has been implemented, projects aiming at identifying new therapeutic targets include those on PARP3 (Team 1), on the regulation of the p. 53 and NF-kB pathways (Team 2), of the DNA damage response (Team 3) and DNA methylation (Team 5) in the context of cancer, on the opioid receptors and associated regulators in the context of pain (Team 6), or on the mechanisms of autophagy in the chronic autoimmune response (Team 8). Most of the teams are working in parallel on the identification or characterisation of therapeutic molecules (small molecules, peptides, antibodies – Teams 1, 3, 4, 6, 8, 10) and their vectorisation (Teams 5, 7), or methodologies for the study of cancer-related proteins (Team 9).
The strong involvement of the members of the unit in the ITIs allows to further consolidate this common scientific strategy, and to develop high-risk projects.
The unit has been able to mobilise resources to develop emerging themes via the recruitment of researchers and teams. This has led to the arrival of two new teams (9 and 10) thus reinforcing the chemistry-biology interface, which is a major asset for the unit. Additional methodological expertise of major interest for the unit (bioproduction, organoid culture…) has also been acquired through the recruitment of new researchers and financial support from the unit.
Finally, the unit has also developed numerous links in the socio-economic sector, with 13 industrial contracts, 15 patents filed, and the creation of one start-up (Immu-Pharma).

### Weaknesses and risks linked to the context

Despite an important effort to harmonise the research topics within the unit, there is still a significant variability, which likely results in part from the fact that BSC is the result of the merger of three previous units. As mentioned in the self-evaluation report and in the previous Hcéres evaluation, this can hinder the visibility of the unit and it also complicates the scientific interactions between its members.
Furthermore, the limited resources available to the direction of the unit also limits its capacity to further develop its scientific policy, for example by funding inter-team collaborative projects or installation packages for new teams.

## *3/ The functioning of the unit complies with the regulations on human resources management, safety, the environment and the protection of scientific assets.*

### Strengths and possibilities linked to the context

All the categories of the Unit personnel met by the committee expressed the fact that they were generally very satisfied with their working conditions. The unit encourages the training. Training needs are identified during annual interviews with staff and prioritised in line with the unit's technical requirements. The team leaders contribute to promoting the careers of support personnel (ITA and Biatss) by participating in a dedicated internal committee which prioritises the demands to improve the rate of success. Both technical and administrative support staff can easily switch teams, although care is taken to respect the balance between teams. Work from home is being made broadly accessible.
The members of the common services are involved in the functioning of the unit via weekly meetings.
Health and safety training is adequate.
The management of the computer network security is ensured by the IT service of the API pole, and the unit has developed means for the automatic backup of workstations.
Adequate measures have been taken to manage environmental risks (storage of chemical products and waste, decay chamber for radioactive isotopes, etc.).
The activity continuity plan to allow, among other things, the securing of isolated workers and the monitoring of the animal facility is regularly updated.

### Weaknesses and risks linked to the context

Although the staff is globally very satisfied with their working conditions, some strategic decisions, in particular concerning the development of new infrastructure, have had a negative impact on their work environment, the lack of space being a serious problem in this unit. A total transparency in the decision process is necessary in order to better involve the staff and anticipate potential issues. In addition, if the committee understands the gain in efficiency that it represents to associate all the team leaders to the laboratory council, it wishes to draw attention to the fact that this can make it more challenging for the representatives of the other categories of personnel to make their voice heard.
Another point that is important to mention is that while the career progression of the technical and administrative staff of the CNRS is judged satisfactory, it is not the same for those who depend on the University of Strasbourg. These staff members (Biatss) do not successfully advance in their career and this has been going on for years. In

spite of their repeated efforts, the Biatss, the team leaders and the unit's director have not found the way to resolve this problem with the university.
Another point that emerged was that the majority of the teams (8 out of 10) are located on two different floors, and that the staff on the two floors rarely cross paths on a daily basis. Another team is located in another wing of the building, and another on another campus. This has an impact on young researchers, for whom it is important to interact with their peers, especially since not all of them have direct access to a common lunch/break area.
Finally, the reflection on the question of data storage has not yet been initiated at the level of the unit.

## EVALUATION AREA 2: ATTRACTIVENESS

### Assessment on the attractiveness of the unit

The attractiveness of the unit is excellent, as shown by the arrival of two new teams, including an ERC laureate team, and eleven new researchers in the unit. The unit has participated in the creation of the ITIs IMS and InnoVec, which together with other PIA initiatives provided 35% of the unit's budget, and has been successful in numerous competitive calls at the national and international levels, representing 41% of the budget. Finally, the unit has access to a range of state-of-the-art platforms on the Illkirch campus, and has itself developed the impress platform (integral membrane protein research and services) and contributed to the creation of UAR 3086.

### *1/ The unit has an attractive scientific reputation and contributes to the construction of the European research area.*

#### Strengths and possibilities linked to the context

The unit has an excellent scientific reputation, with numerous communications (275) in national and international conferences (>50 for the latter, including the prestigious CSHL, EMBO and Gordon conferences). Members of the unit also contributed to the organisation of seventeen conferences, including twelve international conferences. BSC members participated in the scientific committee of fourteen peer-reviewed journals, as well as in national committees (CNRS sections 20 and 28, Inserm CSS1 – four persons in total) and other evaluation committees (Hcéres, La Ligue Nationale contre le Cancer, University of Mainz). In addition, several members have been distinguished by important awards or nominations (CNRS Bronze Medal, nominations to the European Academy of Sciences and finalists of the European Inventor Awards in the research category).

#### Weaknesses and risks linked to the context

In spite of the progress realised during the period under consideration, the identity of the unit is still difficult to grasp because of the diversity of research topics, which hinders its visibility.

### *2/ The unit is attractive for the quality of its staff hosting policy.*

#### Strengths and possibilities linked to the context

BSC has achieved remarkable results in attracting new researchers. Two new teams (teams 9 and 10) were recruited during the mandate, one of which (Team 9) is funded by an ERC starting grant. In all, two professors (who lead teams 9 and 10), five assistant professors (in teams 2, 4, 5, 7 and 10), and four CNRS/Inserm researchers (teams 5, 7 and 10) have joined the laboratory during the evaluation period.
The unit has committed resources to support the installation of new researchers by providing premises and equipment, and by helping in the search for funding, in particular funding for the adaptation of premises and the purchase of equipment from the Idex Unistra. Shared space and equipment have also been made available for students and postdoctoral projects.
The unit has taken appropriate steps to promote open science and raise awareness of good science practices.

#### Weaknesses and risks linked to the context

There are currently more full-time researchers than professors and associate professors (19/13) in the unit, but this proportion is evolving to the detriment of the former, which could eventually limit the availability of researchers for the management of projects and the supervision of young scientists.

### *3/ The unit is attractive because of the recognition gained through its success in competitive calls for projects.*

#### Strengths and possibilities linked to the context

The capacity to obtain funding via competitive calls is excellent. During this term, the unit has obtained one ERC grant, and 36 national funding (ANR/INCA/plan Cancer), of which twenty are coordinated by members of the unit. The majority of the teams (8/10) have benefited from this type of funding. In addition, 24 projects were funded by the PIA programs, with the Labex Medalis providing> 1,300 k€ of funding to the teams involved, and the ITIs IMS and InnoVec which are now taking over. These results reward the strong investment of the different teams in setting up the Labex and now the ITIs, and underline the relevance of their strategy. An additional 49 projects were funded by charities. This high level of success in the various calls have allowed a significant investment in terms of human resources, with 21 PhD theses (out of the 66 carried out during the evaluated period), twelve postdoctoral contracts and 26 ITA contracts funded this way.

#### Weaknesses and risks linked to the context

There is a strong potential for participation in European networks that is not fully exploited.

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

#### Strengths and possibilities linked to the context

The unit benefits from an excellent environment in terms of equipment on the Illkirch campus, with the proximity of many common platforms within IGBMC (sequencing, cell sorting, confocal imaging, proteomics, structure resolution, NMR) and the faculty of pharmacy (molecular imaging, analytical chemistry), the impress platform within its premises and the PCBIS platform (UAR 3086) hosted in the same building. Shared equipment is also widely available, including both standard (ultra-pure water, liquid nitrogen…) and more specific pieces of equipment (LS-MS, circular dichroism spectroscopy, fermenters…).

#### Weaknesses and risks linked to the context

A large part of the equipment is available on facilities external to the unit, which can make it vulnerable to access to services in the event of high demand within the hosting institutes, or an increase in user costs.

## EVALUATION AREA 3: SCIENTIFIC PRODUCTION

#### Assessment on the scientific production of the unit

Overall, the scientific production is very good to excellent. For the period under review, 196 scientific papers have been published in peer-reviewed journals, with highlights in Nature, Nature communications, and the Journal of the American Chemical Society. Reflecting the thematic profile of the unit, these publications relate to both basic and translational research. The present dynamics will likely lead to a further increase in the proportion of publications in leading journals in the coming years.

### *1/ The scientific production of the team meets quality criteria.*

#### Strengths and possibilities linked to the context

For the period 2016–2021, 196 scientific papers, 57 journal articles and 6 book chapters have been published in peer-reviewed journals. The majority of teams published one or more papers in top journals (Team 1: Cell Death and Differentiation, 2019; Team 2: Nature 2016; Team 4: Journal of Cell Biology; Team 5: Genome Research 2016, Nature comm, 2020, 2021; Team 7: Nature comm, 2019; Team 8: Trends in Molecular Medicine 2019, Nature Reviews in Drug Discovery 2019; Team 9: Journal of the American Chemical Society). Important fundamental advances in the unit include elucidation of the structure of the E6/E6AP/p53 complex (Team 2, Nature 2016), global analysis of the impact of DNA methyltransferases and DNA methylation on transcription in the mouse

embryo (Team 5, Nature Comm 2020), elucidating the role of E2F6 in targeting and initiating epigenetic germline gene silencing in early embryogenesis (Team 5, Nature Comm, 2021), identifying the role of PARP3 in tumour aggressiveness of BRCA1-associated breast cancers (Team 1, Cell Death Diff, 2019), or demonstrating the phenotypic plasticity associated to the expression of iron uptake pathways in *P. aeruginosa* (Team 7, Molecular & Cellular Proteomics, 2020). On the other hand, the work developed in the unit allows proposing promising technological advances, such as new therapeutic strategies in the management of pain and autoimmune response (Teams 6 and 8), innovative processes of de novo enzyme synthesis (Team 9) or tools to reveal or regulate the activity of protein targets in living cells (Teams 3 and 4). The emergence of innovative themes has been favoured at the unit level by the creation of teams 2 and 4 in 2018, and the arrival of teams 9 and 10 in 2021.

### Weaknesses and risks linked to the context

The number of inter-team publications remains limited, which suggests that there are not enough internal collaborations. Furthermore, the use of preprints is not yet widespread, whereas this practice is becoming generalised elsewhere and is strongly supported by the supervising bodies.

#### *2/ Scientific production is proportionate to the research potential of the unit and shared out between its personnel.*

### Strengths and possibilities linked to the context

The work of the unit is published in peer-reviewed journals. There is a certain level of disparity between teams in terms of visibility of the publications, but this can be explained in part by the specificities of the different disciplines. Doctoral students and postdoctoral fellows sign publications as the first author, and staff scientists within teams publish as last or corresponding author. Technical staff are properly included as authors in publications.

### Weaknesses and risks linked to the context

None obvious.

#### *3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science.*

### Strengths and possibilities linked to the context

The guidelines for the production of high-quality data are adequately implemented by the different teams. A discussion on good scientific practices is initiated with new PhD students using the charter established by the University of Strasbourg. The work is on the whole published in reliable peer-reviewed journals. The mouse animal facility has approval until 2025 and all projects are carried out in compliance with the 3R rules.

### Weaknesses and risks linked to the context

The questions related to data storage and open science have not yet been addressed at the unit level.

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

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

The unit's interactions with the non-academic world are excellent, the main strength of the unit being its interactions with industry. During the period under review, fifteen industrial contracts and four industrial partnerships have been established, fifteen patents have been filed, five of which are associated with a license, and two start-ups have been created. The members of the unit have also been regularly involved in communication with the general public.

### *1/ The unit stands out by the quality of its non-academic interactions.*

#### Strengths and possibilities linked to the context

Interactions with industry are excellent. They include the financing of industrial contracts (Roche Pharmaceuticals, Biosynex, Servier, Novalix, EDF, Prestwick Chemical, DomainTherapeutics, Green Pharma, Transgene, Pregnomic, Immupharma, Adaptherapy, Peptimimesis, Find Therapeutics, Chiome), academia/industry partnerships (Somez, SATT Conectus), molecules marketed for research (Enzo life sciences, Roche, Euromedex, Sigma, Tocris, Bachem), development of molecules (Domain Therapeutics, Green Pharma, Biomérieux, Immupharma), consulting services (Astra Zeneca, ImmuPharma, Imcyse, Servier), and participation in the creation of start-up companies (Pregnomics, Adaptherapy).
In addition, there are numerous interactions with non-profit organisations, for expertise or for the financing of research work (IARC-WHO, Vaincre la mucoviscidose, ARSEP, ARC, La Ligue contre le cancer, AFM, FRM).

#### Weaknesses and risks linked to the context

There are few interactions with clinical research, which is surprising when considering the heavy focus on drug discovery and vectorisation.

### *2/ The unit develops products for the socio-economic world.*

#### Strengths and possibilities linked to the context

The unit's involvement in the development of products for the socio-economic world is excellent. The majority of the teams have either already filed a patent or initiated maturation projects with SATT Conectus. In total, fifteen patents have been filed by six teams, five of which have been licensed for exploitation. This includes licences for a single domain antibody that can detect replicative stress in live cells (Team 4), molecules for the treatment of pain (Team 6), gold-based compounds with antibiotic properties (Team 7), a process for the bioremediation of asbestos waste (Team 4), and transmembrane peptides for the treatment of multiple sclerosis (Team 10). Members of the unit have also participated in the creation of two start-ups: Pregnomic (Team 4), which provides diagnostic and prognostic solutions for the management of pre-eclampsia, and Adaptherapy (Team 10), which develops software that helps identify the most effective individualised treatments for cancer.

#### Weaknesses and risks linked to the context

None identified.

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

#### Strengths and possibilities linked to the context

The interactions with the general public are excellent, as the majority of the teams were involved in actions of diffusion to the public (Pint of Science, Fête de la science, MT180, village des sciences…) and associations of patients (Vaincre la mucoviscidose, Lupus France, fondation Maladies rares…) during the period under review.

#### Weaknesses and risks linked to the context

None identified.

## C – RECOMMENDATIONS TO THE UNIT

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

The committee strongly recommends that the unit acquires a scientific advisory board to help define its policy. This is all the more important as the unit still needs to ascertain its scientific identity. A SAB would help assess the unit's functioning and achievements, and define its strategy for future terms, at both the global and team levels.

It would also help in the selection of new teams, which is instrumental for the implementation of the unit's scientific policy.
Another point that has emerged is that the budget of the unit as it is defined does not give it many means to animate its scientific policy. The provision of additional resources, via recurring, even if moderate, contributions from the teams, could help achieve this goal. This would enable the unit to further help the installation of new teams and fund internal collaborative projects to increase the thematic cohesion of the unit. It could also help to support teams encountering transitory funding problems.
Finally, the committee also recommends greater transparency and/or communication with respect to decision-making, particularly concerning the allocation of space and the recruitment of new teams. All staff should be involved in these processes, especially when the decisions affect their working conditions. Attention should also be paid at the team level to involve technical staff at a very early stage in the decision to take on students for internships. The technical staff is very often involved in the supervision of these students, in addition to all their other responsibilities, which can sometimes cause them a significant work overload.

## *Recommendations regarding the Evaluation Area 2: Attractiveness*

The unit has demonstrated its attractiveness in a number of ways, in particular through its ability to recruit new teams, including an ERC funded team during the last term. To further increase its visibility, the committee recommends that it makes greater use of open calls for the recruitment of new teams, and that the future SAB should be associated with this. As several members of the unit are part of European research networks (Réseau européen Autophagies, SWAFS – Hybrida program, ECOS avec l'Argentine… – , we recommend applying to international calls for proposals – ERC, Horizon H2020… – .
A policy of shared resources, as well as the opportunities provided by the PIA programs, should make it possible to offer competitive funding for the installation of new teams.

## *Recommendations regarding Evaluation Area 3: Scientific Production*

The committee recommends continuing its efforts to increase the proportion of publications in leading journals and making greater use of preprints to accelerate the dissemination of its work.

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

The committee was impressed by the number and quality of interactions with industrial partners, and can only recommend that the unit continue in this direction.

# TEAM-BY-TEAM ASSESSMENT

**Team 1:** Poly [ADP-ribosyl] ation et intégrité du génome

Name of the supervisor: Ms Françoise Dantzer

## THEMES OF THE TEAM

The team has a longstanding interest in the role of PARP proteins in the DNA damage response, where it has studied the biochemical and physiological roles of PARP one and two as therapeutic targets in cancer. In this period, it has worked on the role of PARP3 in: 1) breast cancer and the possibility of developing PARP3 as a therapeutic target, through chemical inhibition, and/or bi-conjugated antibodies that couple a siRNA against PARP3 with a drug to target cell microtubules; 2) astrocyte differentiation and during cerebral ischaemia; 3) muscle stem cell differentiation and centronuclear pathologies.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation recommended that the newly reduced team remain focused, publish in journals with higher impact, get involved as editors and experts for international organisations, increase socio-economic interactions, and increase the number of permanent team members.

The team has followed the most important part of these recommendations and specifically focused on PARP3, which is appropriate for its current size, and allowed it to be productive in this period. The PI participated in various scientific committees and did not overstretch herself with editorial or international responsibilities. The team has established valuable interactions with industry by selling its generated resources (purified proteins, antibodies) and acting as an expert for the PI. One permanent researcher (MCU) arrived in 2018.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 0 |
| Lecturer and associate lecturer | 1 |
| Senior scientist (Directeur de recherche, DR) and associate | 1 |
| Scientist (Chargé de recherche, CR) and associate | 0 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 2 |
| **Subtotal permanent personnel in active employment** | **4** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 0 |
| Post-docs | 0 |
| PhD Students | 4 |
| **Subtotal non-permanent personnel** | **4** |
| **Total** | **8** |

# EVALUATION

## Overall assessment of the team

**The team has obtained diverse and interesting results that led to a very good scientific production. Their results have given the team an excellent reputation in the PARP field, and opened up numerous invitations to speak at highly visible international conferences and to act as scientific consultants. The team's attractiveness is very good: it recruited a permanent researcher in the past period, but its financial support is tenuous and needs to be fortified. The ability of the team to produce and sell its reagents has helped its budget, and contributed to its very good impact on society. The involvement in training through research is excellent.**

### Strengths and possibilities linked to the context

By focusing on the role of PARP3 in normal and pathological states and its use as a therapeutic target, the team has published three solid articles in very good journals to show that: PARP3 promotes tumour aggressiveness and favours the epithelial-mesenchymal transition (Oncotarget 2016); PARP3 activates the mTORC2 oncogenic pathway in breast cancer cells (Cell Death Diff 2019); PARP3 promotes astrocyte differentiation and in response to cerebral ischaemia (Cell Death Dis 2020). These studies have revealed important functions of a lesser-known PARP protein, and continues the team's interests at the interface of fundamental science and biomedical implications. These results have been well received and have led to numerous invitations (25, e.g. CSHL, EMBO, Gordon, FEBS) to present the work by the PI as well as poster presentations by students (3). The team has also published eight reviews (Methods Mol Biol, Semin Cell Dev Biol, Biochem Pharmacol, Cell Cycle, FASEB J). In addition, thanks to its expertise and the valuable tools it developed (mouse models, antibodies, etc.), the team benefits from a strong network of national and international collaborations resulting in eleven publications as co-authors (Oncogene, Redox Biol, PNAS x2, Nat Commun, Cell Death Diff, Sci Rep, Cancer Lett). The team has attracted many PhD students (3 completed PhD, 4 ongoing) and one foreign postdoc, which is remarkable given the supervising capacity of the team. The three PhDs and the postdoc have published at least one paper or review as the first author, and the training seems excellent.

The PI is an internationally recognised expert on PARP molecules and is sought after as a scientific consultant (AstraZeneca). The PI has also sat on numerous national committees (ANR, Inserm CSS1 2017-2021, Hcéres, Ligue, EDF). The team's first contact with SATT Conectus to explore patent applications is in preparation, and the overall implication of the team in translational research aimed at developing PARP3-targeting molecules for therapeutic purposes has significantly increased. The PI has coordinated one CNRS International Joint Research Project (PICS: NTNU Trondheim 2016–2018), one similar Hubert Curien (PHC) Aurora program: NTNU Trondheim 2015. The PI is a partner of one PICS: CSIC Grenade 2018–2020. The team's grants for this period have included: ITI IMS (Institut du Médicament) 2019–2022 – Drug Discovery Development challenge on antibodies coupling an siRNA against PARP3 and a drug targeting microtubules; EDF 2020-2022 – Impact of PARP3 disruption on tumour aggressiveness in glioblastomas; USIAS fellowship; project grants from Association Française Contre les Myopathies, Ligue Régionale Contre le Cancer, Fondation ARC. The team has also generated income by selling its purified proteins and antibodies to biomedical companies (>30K € over 5 yrs).

### Weaknesses and risks linked to the context

Although the team received grants from numerous local and national sources (100–200 K€/year until 2020), it has not been able to obtain money from larger entities such as ANR, INCa, Equipe Labellisée programs (e.g. Ligue, ARC, FRM) in recent years. This has forced the team to work with a tight budget that could limit its scientific ambitions. As the only senior researcher in the team, the PI feels a heavy burden from the administrative tasks that she has accepted (evaluation committees, congress organisation, CSS1 Inserm). The small size of the permanent team limits its capacity to engage in outreach activities.

# RECOMMENDATIONS TO THE TEAM

Overall, the team is doing solid work and should be commended for successfully transitioning to a more focused topic following the departure of a co-PI at the beginning of the review period. It will need to somehow combine different biological questions under an attractive project in order to obtain more substantial funding, which is critical. Team projects can be consolidated through closer collaborations to obtain co-first and co-senior authorship, or by recruiting additional permanent researchers. The PI should consider scaling down the outside responsibilities to have more time to consolidate her projects. It will be important to fine-tune the balance between fundamental research, which lies at the heart of the team expertise, and valorisation.

**Team 2:** Nuclear signalling and cancer

Name of the supervisor: Ms Katia Zanier

## THEMES OF THE TEAM

Team 2 research is focused on the characterisation of protein-protein interactions related to tumour suppressor pathways (p. 53) to gain knowledge on deregulation that drive the oncogenic processes. In addition, regulatory interactions in the NF-kB signalling pathway are studied to better understand how sustained inflammation promotes cancer. To address these questions, the team use proteomic approaches to define interactomes and structural biology to obtain molecular detail of complexes. Concerning the proteomic approach, a particular focus is devoted to the interactions of the ubiquitin-proteasome system. For the structural aspects of research, the team has developed a specific interest in characterising the role of Small Linear Motifs in p. 53 and NF-kB regulatory cascades.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Project of Team 2 was evaluated at the last Hcéres interviews and officially emerged in its new configuration in 2018.
Establish a distinctive research profile/translating the excellent quality of research: an original and distinctive project is led by the team. This project has, however, not yet reached its full potential and a maturity stage allowing translation towards clinical projects.
Enhancing international visibility: one international postdoc and two PhD students were attracted to join the team – communication to international audiences still needs to be increased.
Evaluations as reviewers: scientific evaluations were provided by the team (1 national for IdEx Grenoble and 1 international for the Greek Research minister for a five-year period) but there is room for a larger contribution.
Technical support: there is no apparent improvement in the technical support available.
Raising the number of PhD students: a PI defended her HDR in 2018. Two PhD students were funded and joined the team since 2018. Difficulties remain at the local level, as these PhD were funded on the team own resources (and not with University fellowships).
Low number of permanent people: one MCF has joined the team in 2020 but one PI is leaving.
Seeking international funding: not yet achieved.
The team should focus on one of the proposed projects unless the team attracts additional researchers (postdocs, PhD students): the team has attracted early-stage researchers but the risk remains of research lines dispersion within a small team.

# WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 1 |
| Senior scientist (Directeur de recherche, DR) and associate | 0 |
| Scientist (Chargé de recherche, CR) and associate | 2 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 0 |
| **Subtotal permanent personnel in active employment** | **4** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 0 |
| Post-docs | 0 |
| PhD Students | 2 |
| **Subtotal non-permanent personnel** | **2** |
| **Total** | **6** |

# EVALUATION

## Overall assessment of the team

**The activity profile of the team is strongly focused on basic research with a high-risk high-gain strategy. Although it has not yet published major results on its new axes of research, this is a promising team that showed a very good productivity on the period. The research is of quality and relevance, supported by an original high-end technical expertise. Visibility of the team at the national and international levels is very good to excellent. The team is small but with a very positive scientific dynamic and very good attractiveness. The relevance of the project in cancer research is obvious and might lead in the future to exploitation of some of the results.**

## Strengths and possibilities linked to the context

The team has an original and relevant research that is well focused and benefits from the specific technical expertise developed in the team. The integrated approach between proteomic, using high-end approaches such as cross-linking mass spectrometry, and original resources such as in-cellulo interactome of the UPS pathway, coupled to X-ray crystallography/NMR spectroscopy of challenging complexes is excellent. The approach is particularly well suited to the team research challenges that have an impact in the field of cancer, and more specifically viral and inflammation-fuelled oncogenesis. The strategy is clearly high risk – high benefit, but despite this, PhD students and postdocs are in good position to publish their results as main authors (first or co-first). Previous work of the team on the oncoprotein E6 of papillomavirus HPV16 led to an important breakthrough (Nature in 2016, with team PI as last author) by revealing the structural basis by which the virus hijacks the cellular proteasome machinery to induce p. 53 tumour suppressor degradation. Eight additional original publications have been produced since 2016, with one as main author (Febs J. 2017) and one review (cell cycle 2016). Three manuscripts are under preparation or submitted and interesting line(s) of research paved for the future. The team has established several collaborations with excellent international lab, with a two-way exchange: to find complementary expertise more particularly on functional aspects or to offer technical expertise, mainly in proteomic. Internal collaborations have been established. The team has funded one postdoc and two-PhD students on international mobility since 2018, contributing to the overall dynamism. To

support the effort, the team PI obtained an HDR in 2018. The team has shown its capacity to renew its resources and was very well funded. 2 ANR financial supports have been obtained in the contract, including an ANR jeunes chercheuses (2014–2017) and one as partner. The team also benefited from a consequent 'équipes FRM' grant (2018–2022) and one additional project coordination starting this year (2022) is funded by INCA with the PI as coordinator. Two financial supports were received from Idex, including one for equipment. Six projects were funded by national or regional anti-cancer charities. Notably, recognition at the national and local level of the research excellence resulted in two awards to the PI from the CNRS (médaille de bronze) and the University of Strasbourg (Les espoirs). The PI has also been invited to present work in other institutions and to an EMBO conference. The arrival of a newly recruited MCF is an opportunity for additional expertise and shows the institutional support.
At the international level, the team interacts with the WHO international agency for research on cancer and benefits from access to its biobanks. Preliminary contacts have been engaged with CNRS and SATT Conectus to develop more translational projects. Noticeable efforts have been made towards communication with the general public, with two vulgarisation seminars covering the link between viral infection and cancer and participation in outreach activities, notably with the 'Alsace contre le cancer' association.

### Weaknesses and risks linked to the context

The team has difficulties attracting local students and PhD funding support.
They are no formal international network initiatives and presentations in international congress could be increased. International visibility has yet to come, specifically given the quality of the research. Efforts in that direction might have been hindered by the coincidence of the team emergence and sanitary restrictions.
The research project is at high risk. The scientific production per researcher is lower than the average production of the other unit teams. Production linked to the current research project has been delayed.

The synergy between the research axes led by each of the two researchers is not fully apparent. The arrival of a newly recruited MCF, with her own research interest, might create some risk of dispersion. The upcoming departures of a PI and a support staff member with their specific expertise will reduce the operational capacities of the team.
No mention is made of the potential use of cryo-EM microscopy approaches, despite the availability of local infrastructure and the high potential of this technique.

## RECOMMENDATIONS TO THE TEAM

Keep up the dynamism of an emerging team and preserve a strong and focused basic research. Publication of results issued from the original current project is a priority and will be a crucial milestone to establish the team's reputation. All the seeds for increased international visibility are there and need some additional efforts to flourish. Support should be offered to favour the recruitment of students from the University of Strasbourg and obtain local PhD grants as well as to allocate some technical support. Arrival in the team of a new MCF researcher is an important opportunity but the team should avoid dispersing its projects and resources. Internal collaborations within the unit should be sought whenever relevant as well as stronger integration in the exceptional local environment, notably with the ITI.

**Team 3:** Dynamique du réplisome et cancer

Name of the supervisor: Mr Bruno Chatton

## THEMES OF THE TEAM

The team is interested in understanding the molecular characteristics of the DNA damage response, such as the DNA repair and DNA damage tolerance pathways, with emphasis on the DNA polymerases of translation DNA synthesis, and damage avoidance through homologous recombination. The goal of these studies was to identify potentially novel targets for drug development which will sensitise cells to chemotherapy and prevent cell proliferation.

The team is composed of four researchers and two MCUs. Two PhD students graduated during the reporting period. The PI is the deputy director of BSC.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation recommended that, for the scientific progress of the team, it should increase international visibility by participating in international meetings, increase interactions with industry, increase collaborations with DNA damage response labs and continue its collaborations with the newly created offshoot Team 4. The team has continued a productive collaboration with Team 4, which led to co-publications, but the other points remain to be addressed.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 1 |
| Senior scientist (Directeur de recherche, DR) and associate | 0 |
| Scientist (Chargé de recherche, CR) and associate | 3 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 1 |
| **Subtotal permanent personnel in active employment** | **6** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 0 |
| Post-docs | 0 |
| PhD Students | 0 |
| **Subtotal non-permanent personnel** | **0** |
| **Total** | **6** |

# EVALUATION

### Overall assessment of the team

**The team scientific production is good for the number of researchers, and very good for its collaborations. Its attractiveness and reputation are good, and could be helped with more synergy among team projects. The committee appreciates the team's efforts to link its work to biomedical opportunities; the interactions with the non-academic world are very good.**

### Strengths and possibilities linked to the context

The team has published regularly in good journals (10 in the reporting period; Biotechniques, Bioconjug Chem x2, RSC Chem Biol x2, J Immunol Methods, Mutat Res, J Med Chem, Proteomics, J Cell Sci), the majority of which are method- or resource-based. One member has studied the Replication-Associated Proteins during NHEJ (Proteomics), and the possible mechanism of Polη retention in UV-induced replication foci (J Cell Sci). The team has also published about 15 articles in collaboration with international groups as co-authors (e.g. NAR, Mol Cell, Nat Commun). In particular, the team has maintained a productive long-term collaboration with a Japanese group over the past two reporting periods. The team has provided a very good training environment for students, and both PhD students had published their work as first authors.

### Weaknesses and risks linked to the context

Some projects appear to have obtained considerable funding while others have suffered from a chronic lack thereof. It is regrettable that the team projects could not have been more synergistic in order to take advantage of common tools and resources. This makes the team look less like a cohesive entity and more like a federation working under a common theme. The group has also had difficulty in attracting more students.

# RECOMMENDATIONS TO THE TEAM

As the team is closing due to the upcoming retirement of the PI, no recommendations are proposed. In the time remaining, the team might want to coalesce around the projects that are funded and define the goals that it wants to achieve there.

**Team 4:** Intervention chémobiologique

Name of the supervisor: Mr Guy Zuber

## THEMES OF THE TEAM

The team conducts original research focused on the development of new nucleic acid and protein intracellular delivery systems in order to detect targets and diagnose the presence or location of specific biomarkers; to interfere and modulate the functional activity of intracellular proteins; or to transport biomolecules inside cells.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation recommended that the team should increase its international visibility, its capacity to attract PhD students and its interactions with the biologists of the unit.
The international collaborations were limited to those already existing (University of Freiburg, Germany). Two PhD students were recruited during the period, which remains a limited number for 2 PI. The interactions with the other teams of the unit are not specified in the report.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 1 |
| Senior scientist (Directeur de recherche, DR) and associate | 1 |
| Scientist (Chargé de recherche, CR) and associate | 0 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 2 |
| **Subtotal permanent personnel in active employment** | **5** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 0 |
| Post-docs | 0 |
| PhD Students | 0 |
| **Subtotal non-permanent personnel** | **0** |
| **Total** | **5** |

## EVALUATION

### Overall assessment of the team

**The academic output is very good with 22 publications during the period. The reputation and the visibility of the team are good with room for improvement in student recruitment (only 2 PhD students) and in the search for grants. The interactions with the non-academic world are very good thanks to a successful collaboration with private companies.**

## Strengths and possibilities linked to the context

The production is very good for the size of the team (1DR, 1PU, 1MCU) with twenty scientific articles in international journals and two reviews, including thirteen first/last author publications in very good journals (J. Control Release 2017; Adv. Healthcare Mater 2018; J. Cell Biol 2018; Cancers 2019, 2021). The two PhD students of the team have participated in the scientific production of the team. The major works developed allowed to (i) demonstrate the use of chemically modified oligoethylenimines for the intracellular delivery of nucleic acids (DNA, mRNA and oligonucleotides) in vitro and in vivo (ii) the use of gold particles of controlled sizes to manufacture antibody-gold particle conjugates for use inside living cells and as electron microscopy probes and (iii) the development of nanobody library and the discovery of an anti-gammaH2AX nanobody that can be used to diagnose DNA damage.

The involvement of the team in relations with the socio-economic world is very good, the team having established a partnership with the company Biosynex to develop diagnostic reagents. The team is also involved in the creation of the start-up Pregnomic.

The team is also strongly involved in teaching activities (participation in the professional licenses of the Faculty of Pharmacy, participation in the Challenge Telecom Physique Strasbourg).
G. Zuber is one of the founding members and the current coordinator of ITI InnoVec.

## Weaknesses and risks linked to the context

The team will not be renewed, so there are no recommendations.

# RECOMMENDATIONS TO THE TEAM

The team will probably close. No recommendation.

**Team 5:** Régulation épigénétique de l'identité cellulaire

Name of the supervisor: Mr Mickaël Weber

## THEMES OF THE TEAM

The team focuses its research on the epigenetic regulation of genome expression by DNA methylation. More specifically, it combines mouse genetics with molecular biology approaches, next generation sequencing techniques and bioinformatics analyses to define the role of the different DNA methyltransferases during mammalian development and to understand how DNA methylation is regulated.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report did not make particularly strong recommendations even though it advocated that the team publish in even higher impact journals, increase its international exposure (e.g. international conferences), develop valorisation and teaching activities, and pursue its well balanced (although diverse and ambitious) projects. It is not clear that specific actions were put in place to reach these goals. Nonetheless, the production of and ongoing projects of the team are still of very high quality and the arrival of one assistant professor could facilitate access to students. Valorisation activities and international exposure do not seem strongly improved yet.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 0 |
| Lecturer and associate lecturer | 1 |
| Senior scientist (Directeur de recherche, DR) and associate | 1 |
| Scientist (Chargé de recherche, CR) and associate | 2 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 3 |
| **Subtotal permanent personnel in active employment** | **7** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 0 |
| Post-docs | 0 |
| PhD Students | 4 |
| **Subtotal non-permanent personnel** | **4** |
| **Total** | **11** |

# EVALUATION

## Overall assessment of the team

**Team 5 has obtained very interesting results of fundamental interest. Its scientific production is of excellent quality and relies on state-of-the-art technologies. The team attractiveness is excellent: it has hosted a high number of Postdoc/PhD and recruited new researchers. It had extremely strong financial support from diverse research agencies, which allowed it to develop various ambitious and original research lines, but its current funding trend is not as strong. While the reputation of the team is very good, it has not yet fully capitalised on its expertise and high scientific profile to gain strong international visibility.**

### Strengths and possibilities linked to the context

Team 5 has developed very strong research lines revolving around the role of DNA methylation in mammals. This research is of fundamental importance and takes place in a very competitive field. The team uses a valuable combination of state-of-the-art techniques and has a well-established expertise in the field of epigenomics. During this period, team 5 has made some prominent discoveries. Notably, it established the respective role of DNMT3a/3b and DNMT1 in de novo DNA methylation and maintenance at the genome-wide level, and revealed the consequences thereof on the regulation of genome expression and integrity. This elegant study resolved some outstanding questions in the field and illustrated the important regulatory roles of this epigenetic modification. Team 5 also showed that the histone lysine methyltransferase EHMT2 and the transcription factor E2F6 contribute to gene repression via the DNA methylation machinery. These original findings were published by the team in high-profile journals (Nature Comm 2020, 2021 & Genome Res 2016). The recognised expertise of the team in 5mC cartography on the genome also led to productive collaborations as demonstrated by co-authorships on five very good publications (Genome Biol 2016, Leukaemia 2016, BMC Genomics 2018, Int J Cancer 2019, Cancer Res 2020) and redaction of a method paper (Methods Mol Biol 2020).

Thanks to exceptional financial resources obtained as coordinator in the early phase of the project (ERC Consolidator Grant 2014–2019; INCa 2014-2018 ; Plan Cancer 2014–2018), the PI was able to deploy several ambitious research lines, including a CRISPR/Cas9-based screen for new players in DNA methylation or, more recently, the development of organoid models to study methylation in rare diseases. The PI also obtained support from charities (Ligue contre le Cancer, ARC, FRM) and, as partner, from the Labex Medalis, ITI InnoVec, INCa (2x), Plan Cancer and ANR. The team attracted five postdocs and five PhD (2 ongoing). The CNRS (bioinformatician) researcher recruited in 2017 contributed to 3 publications of the team, including one as senior author in NucleicAcids Res (2020), and obtained strong funding support (Plan Cancer, Idex). Moreover, 1MCU and 1CR joined the team in 2019 and 2020 respectively. Together with the three engineers (2 IE +1AI), they strongly reinforce the permanent staff of the team. Training has been excellent: the three PhD students who graduated during the review period are co-authors in publications and two have been published as first authors; Three of the five postdocs also published as first authors, in papers published during this period and in 2022.

### Weaknesses and risks linked to the context

The financial resources of the team are getting thinner, raising concerns for the future.

The high scientific profile of the PI is not fully apparent at the international level, for instance through the participation in European networks or invitations to highly reputed conferences, as acknowledged by the PI.

Apart from the recently arrived MCF, the team does not seem strongly involved in teaching, which may limit its local visibility and access to the (best) students.

The link with the ITI InnoVec does not seem fully exploited to increase the valorisation potential of the team.

The recent departure of the CNRS researcher to a neighbouring institute might lessen the expertise of the team in bioinformatics.

# RECOMMENDATIONS TO THE TEAM

The team should maintain and if possible increase the high scientific standards and quality of its production.

It is essential that the team obtains new funding from the main French and/or international agencies. A redefinition of the extent/scope of the project or underlying biological questions could be envisioned to better fit the different calls (as well as the resources of the team).

The PI should strive to gain further visibility at the international level via proactive participation in conferences and development of international collaborations.

The team could take further advantage of the exceptional local environment and of its own expertise in epigenomics to develop some translational and/or valorisation projects.

**Team 6:** RCPG, douleur et inflammation

Name of the supervisor: Mr Frédéric Simonin

## THEMES OF THE TEAM

The team is investigating the role of G protein-coupled receptors (GPCRs) related to inflammation and chronic pain. Their studies are focused on three research axes:
1- Identification and characterisation of selective antagonists for the RF-amide receptor family. These receptors are involved in the development of analgaesic tolerance and hypersensitivity to pain induced by chronic opiate treatments.
2- Characterisation of the GPRASP1 protein role, member of a new family of G-protein associated sorting proteins (GPRASP). The GPRASP1 protein is essential in the development of the tolerance associated with the repeated administration of agonists of different RCPRs.
3- Study of the CXCL12 role: Development of small molecules, which can neutralise in vivo the action of CXCL12.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous committee mainly recommended that the team should achieve more comprehensive studies in order to publish in high-visibility journals should focus on the most promising projects to avoid overloading resources, and may attend key conferences and try to recruit a permanent young scientist.

The team focused on the quality publications rather than the quantity as recommended by the previous committee. They published in high visibility journals in the field such as PNAS, JCI or Pharmacology&Therapeutics. The team carried on working on the three projects. However, the valorisation of the results and the collaborations seem to be focused on the two subjects mentioned by the Hcéres committee (axes 1 and 3) and less on the GASP subject.
A permanent researcher (professor) has recently joined the team.
Regarding attendance at key conferences (as Gordon and Keystone meetings), no information was found in the report. Altogether, the actions fit the recommendations of the previous committee.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 0 |
| Senior scientist (Directeur de recherche, DR) and associate | 2 |
| Scientist (Chargé de recherche, CR) and associate | 1 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 7 |
| **Subtotal permanent personnel in active employment** | **11** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 3 |
| Post-docs | 0 |
| PhD Students | 4 |
| **Subtotal non-permanent personnel** | **7** |
| **Total** | **18** |

# EVALUATION

## Overall assessment of the team

**The team has excellent visibility and experience in the fields of RPCGs and the chronic pain which is of great interest.**
**The know-how and expertise on pharmacological and genetic tools is a real asset of the team which has enabled them to identify pain antagonists or molecules neutralising chemokines.**
**The high-level scientific expertise is acknowledged by very good international publications.**
**The team has an excellent interaction with its socio-economic environment and in particular with several industrial partnerships.**
**The team attractiveness is excellent. It recruited a new professor and PhD students.**

## Strengths and possibilities linked to the context

The team performed excellent scientific research by studying the RPCGs and their role in chronic pain and inflammation. They have identified a new potent opioid analgaesic compound that has attenuated side effects. They also identified and characterised the GPRASP1 protein which in involved in analgaesic tolerance. Finally, the team showed that CXCL12 is essential for the development of persistent pain and could be used as a biomarker for pain.
Their whole project could potentially lead to great progress in the field of pain treatment.

The overall output of the team has been very good, with a total of 26 articles and 8 reviews during the period under review with very good publications (*PNAS, JCI, 2x Pharmacology&Therapeutics, BrJPharmacol*). This project benefits from well-established national and international collaborations and led to several co-publications (25% of the team's publications).

National and International visibility is excellent: the team has reached its visibility through its position as coordinator of the ChemBioFrance infrastructure, its membership in Euridol (EUR on pain), and its membership in national and international networks on RPGR or membrane proteins.
Members of the team were invited as reviewers in many (13) high quality journals (Science, Journal of Neurochemistry, Frontiers in Pain Research, …), they were evaluators for national and international grant committees (Région Centre-Val de Loire, UKRI Research Medical Council, …). As well, they participated in multiple thesis (7) or habilitation (HDR; 4) juries.
The team also participated in the organisation of twelve meetings (2021 conference of the Neuroscience Society, an annual meeting of the GDR3545, …) and are frequently invited to conferences. Team members participated in communication events with the general public through seminars (Pint of Science, Middle School) and interviews in the general public scientific press and local television (7).

A large part of the team's funding comes from national grants (ANR, Labex Medalis, Région Grand-Est) or charitable foundation (Fonds Roche,…), in particular in 2021. In 2021, the team was also well funded by industrial partnerships.
This team has excellent interaction with economical partners. During the period of interest, the team filed 4 patents, to be licensed with the company Domain Therapeutics, and 4 maturation projects are funded by SATT-Conectus. In 2021, the team was significantly funded by industrial partnerships.

The doctoral students training has been excellent: all PhD students co-authored at least one publication in the first author position. Three thesis students received awards and the majority of PhD students (5/6) were hired as researchers by companies in the health and biotechnology field or started a postdoc abroad. The team currently has six PhD students, three of whom started their thesis in 2021.
The arrival of a newly recruited professor is an opportunity to strengthen the pain project and the team's involvement in teaching.

## Weaknesses and risks linked to the context

The team leader is involved in time-consuming administrative tasks. The PI of the CXCL12 project also has a strong involvement in the management of the unit, but this should change, as he will no longer lead the unit in the next term. Another permanent member of the team is responsible for a technology platform.
The team develops many innovative molecules that lead to patents. This slows down the publication of results and can raise problems for PhD students to promote their thesis.

Some of the important results in terms of translational research, such as the identification of antagonist or neutralising small molecules, were so far only validated in mice. Clinical studies in humans have yet to be initiated.
The team should continue its efforts to publish in outstanding journals.
The team should strengthen the funding requests to international partners and should consider leading a European project.

## RECOMMENDATIONS TO THE TEAM

It could be of great interest to get in touch with pharmaceutical companies in order to prepare toxicology and preclinical studies.
Another recommendation would be to get in touch with patent offices in order to optimise and accelerate the publication of the patent.
The results obtained with CXCL12 are encouraging and show that CXCL12 could be used as a biomarker of chronic pain. This innovative approach should be developed with clinical partnerships.
Attracting permanent young scientists, who would be involved full-time in one of the projects, would be a crucial asset for the team.

**Team 7:** Métaux et microorganismes : biologie, chimie et application

Name of the supervisor: Ms Isabelle Schalk and Mr Gaëtan Mislin

## THEMES OF THE TEAM

The team focusses on the metabolism of metals in Gram-negative bacteria, including the characterisation of iron uptake systems, the development of antibiotics by the Trojan horse strategy, and asbestos waste remediation systems. — The research activity of the team is divided into three axes:
1) Iron homeostasis in Gram negative bacteria for which the team has an international reputation.
2) Therapeutic applications of vectorisation by siderophores. Iron assimilation pathways are gateways through the bacterial envelope for those who have the keys. These pathways can be used to efficiently deliver antibiotics to the target pathogen using a Trojan Horse strategy.
3) Bioremediation of asbestos-containing waste.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

No strong recommendation in the previous evaluation

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 0 |
| Lecturer and associate lecturer | 2 |
| Senior scientist (Directeur de recherche, DR) and associate | 2 |
| Scientist (Chargé de recherche, CR) and associate | 2 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 4 |
| **Subtotal permanent personnel in active employment** | **10** |
| Non-permanent teacher-researchers, researchers and associates | 2 |
| Non-permanent research supporting personnel (PAR) | 1 |
| Post-docs | 0 |
| PhD Students | 7 |
| **Subtotal non-permanent personnel** | **10** |
| **Total** | **20** |

# EVALUATION

## Overall assessment of the team

**The team has a very good to excellent scientific production and a fundamental scientific project of quality. The team has a strong network of international collaborations and an excellent international visibility in the field shown by its involvement in 3 large European projects. The attractiveness of the team is excellent as demonstrated by three in-coming researchers. The interaction with non-academic partners is excellent since the team capitalises on its original fundamental research to address relevant societal challenges, i.e. antibiotic resistance or environmental decontamination through partnerships with companies and patent filing. The team had an excellent activity of public outreach.**

## Strengths and possibilities linked to the context

The size of the team allows maintaining a very good level on these various axes and an excellent balance between basic science and applications. A young researcher has been recruited by the CNRS in 2021 to work on axis 1 of research with the objective of expanding its investigations to *Salmonella* and into the field of microbiota.
The scientific production is very good (42 articles and 9 reviews) with numerous international collaborations and an important reputation of the team in the field of siderophores and iron homeostasis in bacteria. Over the period concerned, the members of the team were 22 times first author and 25 times last author or corresponding author on research articles in well-esteemed journals. The PhD students of the team, who defended their thesis during the evaluated period, signed an average of 3.6 publications during their thesis.
The team has been excellent at attracting funding, from diverse sources: at the local level (Idex, Unistra), on the national level (2 Prime CNRS, one PRC ANR as coordinator and one JCJC ANR) and on the European level, 2 large programmes (New Drugs for Bad Bugs) and one Joint programme initiative (JPI). The team also had a research contract with the association Vaincre la Mucoviscidose for vectorisation projects.

The work published on the first axis has allowed the study of the adaptation of the expression of the different iron import pathways according to environmental stimuli, the characterisation of catecholamine-type neurotransmitters capable of chelating iron and being used as siderophores by *P. aeruginosa*, the characterisation of the spatial distribution of Non-Ribosomal Peptide Synthetases partners involved in the biosynthesis of the pyoverdine siderophore, demonstrating the existence and dynamics of multienzyme complexes involved in the synthesis of a siderophore and finally the characterisation of the molecular mechanism of iron dissociation from the siderophore nocardamine in *P. aeruginosa*. The work deployed on the Trojan Horse strategy based on metalloantibiotics focused on Au (I) and Ir (III) complexes and showed that these molecules are generally very active against Gram-positive pathogens and led to three publications and a patent. The bioremediation process based on axis 3 research concerns the alteration of asbestos fibres by using pyoverdin-producing *Pseudomonas* to extract the iron present within the fibres, an innovative technology that was the subject of a national patent in 2017, extended to Europe in 2018. Proof of concept on native asbestos and flock waste showed that they could be a source of iron and magnesium for *Pseudomonas*.

The team has proved to be particularly attractive since during the period concerned one IR, one CRCN and one MCU have joined the team.

The team's involvement in partnerships with non-academic actors is excellent. In total, the team members have 4 patents over the period evaluated. In addition, the team has benefited from a research contract with Roche Pharmaceuticals to study at the molecular level the iron import pathway via the pyochelin siderophore in P. aeruginosa. The team has also had regular research contracts with the association Vaincre la Mucoviscidose for vectorisation projects. The team also has a partnership with the Société Méditerranéenne des Zéolithes (Somez, Montpellier) to study the feasibility of using the potential of siderophores to extract iron from asbestos fibres.

The involvement of the team in participatory science activities and actions towards the general public is excellent. The project, developed in collaboration with the Maison pour la Science en Alsace, aims to study the microbial biodiversity of Alsatian soils and to raise awareness among the general public about the identification of bacteria with high added value (antibiotic producer, agricultural fertilizer, soil decontamination, etc.). For two years (2020 and 2021), the team members have also been very active in the participation of the science village set up by the team to promote the research conducted at the University of Strasbourg around microbiology. The theme concerning the degradation of asbestos-containing waste has been the subject of several popularisation articles as well as interventions by the team's researchers in local television media.

### Weaknesses and risks linked to the context

The team does not develop any scientific or technical collaboration with the other teams of the Unit.

## RECOMMENDATIONS TO THE TEAM

The team must continue its research in the continuity of the previous years with a balance between fundamental research in molecular microbiology and more applicative fields. The opening to other strains and to microbiota is encouraged and will allow each PI to have his own thematic while preserving the visibility of the team and sharing the long experience of the team in the field of iron metabolism.

**Team 8:** Neuroimmunologie et thérapie peptidique

Name of the supervisor: Ms Sylviane Muller

## THEMES OF THE TEAM

The basic and translational research carried out by the team is focused on the chronic autoimmune response. The research carried out in patients and several autoimmune mouse models, aims at i) understanding the complex molecular and cellular mechanisms involved upstream of the loss of immune tolerance ii) defining innovative therapeutic pathways, based on the development of synthetic peptides and peptidomimetics, capable of intervening in a targeted manner in the restoration of tolerance to the self.
The team is focusing on lysosome defects that often appear to be involved in the pathophysiological patterns examined. Thus, the patented P140 peptide offers new applications in chronic inflammatory but also metabolic diseases.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As the team had proposed two research axes, the committee recommended focusing on the long-term expertise of the team, i.e. the development of therapeutic peptides. The neuroimmunological orientation, while very interesting, was judged riskier and the articulation between the two axes would have needed to be clarified. This recommendation was followed.
The permanent human resources of the team consist of two researchers (1 CR and 1 Emeritus PR), 1 Technician. It was recommended to increase the size of the team and to attract postdoc and PhD students. Five PhD students were recruited in the period 2016–2018 and have defended their thesis. Postdoc, engineers were hired, but unfortunately on short-term contracts. Thus, the size of the team has not increased.
Note that the PI who was supposed to head the team is not the PI indicated in the present report. The present PI is a professor emeritus since 2018.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 0 |
| Lecturer and associate lecturer | 0 |
| Senior scientist (Directeur de recherche, DR) and associate | 1 |
| Scientist (Chargé de recherche, CR) and associate | 1 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 1 |
| **Subtotal permanent personnel in active employment** | **3** |
| Non-permanent teacher-researchers, researchers and associates | 2 |
| Non-permanent research supporting personnel (PAR) | 4 |
| Post-docs | 0 |
| PhD Students | 3 |
| **Subtotal non-permanent personnel** | **9** |
| **Total** | **12** |

# EVALUATION

## Overall assessment of the team

**Considering the size of the team, the scientific production, its success in grant applications, its links with the non-academic world are considered as excellent. Its visibility is excellent. The attractiveness was very good. The administrative status of the PI should be clarified.**

### Strengths and possibilities linked to the context

The team has pursued its productive research on therapeutic peptides and has published 23 original papers in high impact journal (Nature Medicine, J. Autoimmunity – 4 –, Angiogenesis – 1 –, Autophagy – 2 –, Cell Death and Differentiation – 1 –, Scientific Reports – 1 –, Frontiers in Immunology – 2 –, Cells – 2), with twelve in leading position and eleven in collaboration. Team members also published 25 reviews and contributed to congress proceedings.
All PhD students co-authored at least one publication in the first position.
Fruitful collaborations have been maintained with international research teams and were assessed by co-publications.
Industrial collaboration is also the hallmark of the team.
The team was also successful in research grant applications and got more than 1 M € over the last four years, which clearly shows the quality of the projects.

### Weaknesses and risks linked to the context

The size of the team was previously identified as a major risk, with a loss of expertise due to the PI retirement. Actually, the co-PI who was supposed to head the team during the past period, is no longer involved in the team.
A major issue rose by the committee has concerned the administrative status of the present PI, who is a CNRS director emeritus.
As a consequence, the original expertise, the international network of collaborations and the strong link with industry and clinicians will definitely be lost.

# RECOMMENDATIONS TO THE TEAM

Since 2020 and the departure of the co-PI, the team has been led by an emeritus researcher. This unusual situation, generally forbidden by the institutions, will continue at least until 2023. It is therefore likely that the team will have to close, and there is therefore no recommendation for the team as such. A solution would be for the PI to join another team in the institute, which would allow her very productive research to continue. In any case, particular attention should be paid to the follow-up of the two students who started their thesis in 2022 in a team with no active researcher.

**Team 9:** Chimie des biosystèmes : protéines intrinsèquement désordonnées

Name of the supervisor: Mr Vladimir Torbeev

## THEMES OF THE TEAM

The team utilises state-of-the-art methodology for chemical synthesis of proteins based on solid-phase synthesis of peptide segments and their ligation by chemoselective ligation chemistry. The synthesised proteins and protein libraries are studied by various biophysical and biological methods. The team is able to produce homogeneous protein molecular constructs of high molecular weight, to synthesise protein libraries containing non-canonical amino acids, to design and synthesise new catalysts for the amide bond formation. Its research area covers a large spectrum from protein aggregation, structure-function studies of intrinsically disordered proteins and protein design.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was not evaluated in the previous period.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 0 |
| Senior scientist (Directeur de recherche, DR) and associate | 0 |
| Scientist (Chargé de recherche, CR) and associate | 0 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 0 |
| **Subtotal permanent personnel in active employment** | **1** |
| Non-permanent teacher-researchers, researchers and associates | 0 |
| Non-permanent research supporting personnel (PAR) | 2 |
| Post-docs | 2 |
| PhD Students | 4 |
| **Subtotal non-permanent personnel** | **8** |
| **Total** | **9** |

## EVALUATION

### Overall assessment of the team

**This young team recently joined the unit (2021) and is headed by an ERC starting grant laureate. Its research is considered as excellent, original and highly competitive at the international level. The scientific production, the international visibility and the attractiveness are excellent. The relation with the non-academic world is ongoing. Importantly, the integration in the unit looks successful.**

## Strengths and possibilities linked to the context

This young team recently has joined the unit (2021) and is headed by an ERC starting grant laureate. Hence, its research project is considered as excellent, original and highly competitive at the international level. The scientific productivity is high considering the team size (3 papers/year on average) in high reputation journals (JACS, Angew. Chem. Int. Ed, Chem. Science, Biophysical Journal). The team has significantly contributed to PhD training with four PhD students who defended their thesis between 2018 and 2020 and authored publications.
Since then, six PhDs (1 co-supervised) and two postdocs have been recruited, which confirms the excellent attractiveness of the team.
Despite its recent arrival, the team appears very well integrated with productive internal collaborations (e.g Team 2 and Team 4)
Besides, the team is involved in national (e.g. IGBMC) and international collaborations (University of California San Francisco, USA, Wroclaw University of Science and Technology, 2 joined publications). The team has also acquired an international visibility with seven invited Lectures in international conferences (e.g Gordon Research Conference 'Intrinsically Disordered Proteins', E. T. Kaiser Memorial Symposium, MIT, Boston, Etats-Unis, 7th Chemical Protein Synthesis – CPS – ', Haifa, Israel, International School-Seminar on Computer-Aided Molecular Design, Kazan, Russia to name a few).
Finally, the team has developed a partnership with a company (Inoviem Scientific SAS on the development of artificial biomaterials for aorta prosthesis).
Overall, the team equilibrates basic and applied research with innovative applications that could be of major interest for companies.

## Weaknesses and risks linked to the context

The only weakness that was identified lies on the human resources, who are hired on short-term contracts, except for the PI. The absence of technical support is also a major risk.

# RECOMMENDATIONS TO THE TEAM

The team is strongly encouraged to pursue its productive and original work and to strengthen its emerging network of collaborations within the Unit. Recruitment of permanent staff is recommended, which would help in establishing collaborations with the non-academic world.

**Team 10:** Peptides thérapeutiques

Name of the supervisor: Mr Dominique Bagnard

## THEMES OF THE TEAM

Because the team arrived at BSC in September 2021, the description of research activities and especially the fundamental part is missing from the document. The committee appreciated the scientific oral presentation which described the research activities in detail.

The team designs and develops therapeutic peptides targeting the transmembrane domains of bitopic receptors. A peptidic antagonist was identified to reduce demyelination in multiple sclerosis. A software platform has also been developed by the team to assist doctors in prescribing the most adapted personalised treatment for cancer patients.
The team applied its technologies to different preclinical disease model (cancer and CNS diseases). The team also develops a lot of industrial interaction to proof the concepts that emerge from the team's work.

## CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was not present in the BSC unit during the last evaluation.

## WORKFORCE OF THE TEAM

| **Permanent personnel in active employment** | |
|---|---|
| Professors and associate professors | 1 |
| Lecturer and associate lecturer | 0 |
| Senior scientist (Directeur de recherche, DR) and associate | 0 |
| Scientist (Chargé de recherche, CR) and associate | 0 |
| Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées) | 0 |
| Research supporting personnel (PAR) | 0 |
| **Subtotal permanent personnel in active employment** | **1** |
| Non-permanent teacher-researchers, researchers and associates | 1 |
| Non-permanent research supporting personnel (PAR) | 1 |
| Post-docs | 1 |
| PhD Students | 4 |
| **Subtotal non-permanent personnel** | **7** |
| **Total** | **8** |

# EVALUATION

## Overall assessment of the team

**The team runs its activities on a very promising field with successful research and industrial partnerships that led to a very good scientific production. The visibility of the team is excellent, they are a leader in the field and have applied their technologies on relevant models. The technologies and concepts they developed are also appreciated by the community. The interaction with its socio-economic environment is excellent and their discoveries have been successfully transferred to national and international companies. The team has recruited two new researchers, its attractiveness is excellent.**

### Strengths and possibilities linked to the context

The technological advance and the capacity of the team to organise and secure its processes is a strength. Indeed the team control its process from peptide design to preclinical validation including production of peptides, studies of biodistribution or toxicity.
The team's research is based on technology transfer with innovation criteria leading to the creation of two start-ups (Adaptherapy, Peptimimesis) and two licenses.
Many industrial partnerships were carried out in the form of service or co-development contracts with shared intellectual property.
The team has different sources of national funding: public funding (ANR, Labex Medalis, Région Grand-Est, and one maturation project funded by SATT-Conectus) and charitable foundations (Ligue contre le cancer,…). The team also benefits from an important part of financial resources resulting from valorisation, transfer and industrial collaboration.

The scientific recognition of the team is also demonstrated by the high number of publications in collaboration with national or international groups (18 publications since 2016) leading to publications in well-ranked journals (Cells, Frontiers in Cell and Developmental Biology, …). This represents a good ratio compared to the number of members in the team (1.5 full-time equivalent researchers).

D. Bagnard is editor-in-Chief of Cell Adhesion & Migration and has co-organised the workshop Neurex/Medalis (2 years).
The team has very recently recruited an assistant professor who will strengthen student supervision and research.

The team collaborates with a clinician to develop its preclinical validation projects, which is essential for the development of therapeutic peptides.

### Weaknesses and risks linked to the context

The balance between technological developments and related basic science must be equilibrated over time in order to keep the current team's competitiveness in the future. There is a point of attention on the team's human resources and the risk of loss of expertise in the future. The permanent recruitment of two scientists to the team should consolidate the team in the long term.
The team should strengthen the funding requests to international partners and should consider leading a European project.
The team leader is involved in other time-consuming tasks: head of the research pole at ITI IMS, director of the ESBS (École supérieure de biotechnologie de Strasbourg), co-founder of the start-up, editor-in-chief of a scientific journal), and supervises three PhD students.
During the evaluation period, the team was invited to speak at national and international meetings only four times.
There is no dissemination of knowledge to the general public.
Data related to the expertise work of the team members are not reported in the document.

# RECOMMENDATIONS TO THE TEAM

The team should balance basic research and technological development/transfer to keep its current strength. In particular, such useful technologies for therapy can also provide great tools to investigate transmembrane molecular functions in biology.
It is requested to reinforce the team with permanent positions to face the dynamics and potentialities of the field. As well, it would be great to expand scientific communication to the public and public authorities to stimulate the common interest (and investments) in a probably key future area of therapy.

Strengthening links with the clinic will also be essential in the future to assess the therapeutic effect of transmembrane peptides in humans.

The team should aim at increasing its national and international visibility by being more regularly invited to conferences and by publishing articles in outstanding scientific journals.

# CONDUCT OF THE INTERVIEWS

## Date

**Start:** 05 octobre 2022 à 9 h

**End :** 05 octobre 2022 à 18 h

**Interview conducted: on-site or online**

## INTERVIEW SCHEDULE

### BSC – Wednesday 5 October, 2022

8:00 – 8:15 Testing Zoom connections

8:15 – 8:30 Closed session Expert Committee (EC) – Scientific Officer (SO)

**Assessment of the Unit, Scientific Plenary session**

8:30 – 8:45 Presentation of the EC to the staff members by SO

8:45 – 9:15 Presentation of the unit by Jean-Luc Galzi (20 + 10 min discussion with the committee)
Attending: EC, SO, all the unit members

***Presentation of the teams***

9:15 – 9:40 **Team 1:** Poly (ADP-ribosyl) ation and genome integrity (F. Dantzer)
(15 min presentation+5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

9:40 – 10:05 **Team 2: Nuclear signalling and cancer (K. Zanier)**
(15 min presentation +5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

10:05 – 10:30 **Team 10: Therapeutic peptides (D. Bagnard)**
(15 min presentation +5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

10:30 – 10:55 **Team 4: Chemobiological intervention (G. Zuber/E.Weiss)**
(15 min presentation +5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

**Break 20 min**
**Meeting of the EC and SO (closed hearing)**

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|---|---|
| 11:15 – 11:40 | **Team 5: Epigenetic regulation of cell identity (M. Weber)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| 11:40 – 12:05 | **Team 6: GPCRs, pain and inflammation (F. Simonin)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| 12:05 – 12:30 | **Team 7: Metals and microorganisms: biology, chemistry and applications (I. Schalk/G. Mislin)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| 12:30 – 1 p.m. | **Meeting of the EC and SO (closed hearing)** |
| 12:30 – 2 p.m. | **Lunch Break** |
| 2 p.m. – 2:25 p.m. | **Team 8: Neuroimmunology and peptide therapy (S. Muller)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| 2:25 p.m. – 2:50 p.m. | **Team 9: Proteins with disordered domains (V. Torbeev)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| 2:50 p.m. – 3:15 p.m. | **Team 3: Replisome dynamics and cancer (B. Chatton)**<br>(15 min presentation +5 min questions)<br>Attending: Team members, EC, SO, director of Unit<br>+5′ private discussion with the PI; attending: EC +SO |
| | **Break 15 min**<br>**Meeting of the EC and SO (closed hearing)** |
| 3:30 p.m. – 4 p.m. | Meeting with the representatives of CNRS and University<br>Attending: expert committee, representatives of Institutions, SO |
| 4 p.m. – 4:30 p.m. | Technical and administrative personnel<br>Attending: Technicians, Engineers, Administrative staff, EC |

***parallel meetings:***

| | |
|---|---|
| 4:30 p.m. – 5 p.m. | #1: Thesis students and postdocs<br>Attending: PhD students and postdocs, **EC1** |

4:30 p.m. – 5 p.m. #2: Researchers and professors
Attending: Researchers except group leaders, **EC2**

5 p.m. – 5:30 p.m. Meeting of the EC and SO (closed hearing)

5:30 p.m.-6 p.m. (if required) Meeting of the Committee with the head of the unit.
Attending: Unit Direction, expert committee, SO

**Meeting of the Committee (closed hearing) 0ctober 6, 9:00 – 11:00**

# GENERAL OBSERVATIONS OF THE SUPERVISORS

Université de Strasbourg

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

Strasbourg, le 28 mars 2023

Objet : Rapport d'évaluation DER-PUR230022989 - BSC - Biotechnologie et signalisation cellulaire

Réf. : RB/FF/ 2023-195

**Rémi Barillon**
Vice-Président Recherche, Formation doctorale et Science ouverte

Cher Collègue,

L'université de Strasbourg vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « Biotechnologie et signalisation cellulaire » (BSC – UMR 7242).

Nous n'avons aucune observation de portée générale à formuler sur le rapport d'évaluation transmis.

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

Rémi Barillon

**Affaire suivie par :**
Florian Fritsch
Responsable du département Administration de la recherche et accompagnement des chercheurs
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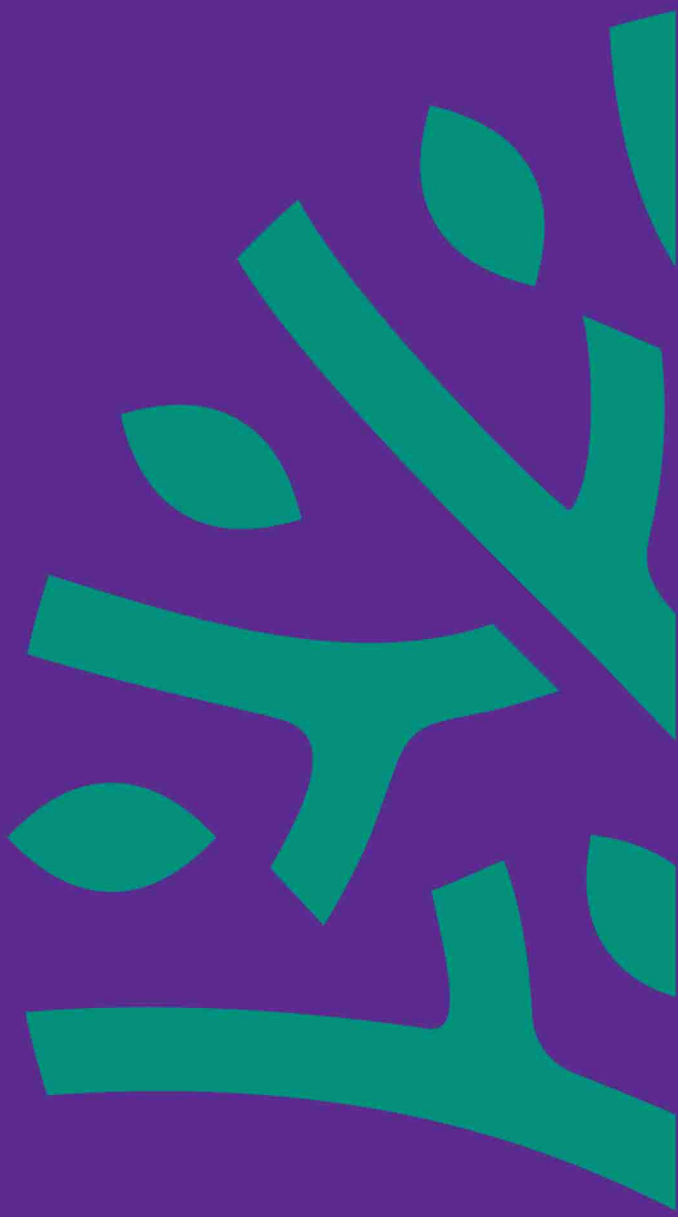

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